PHYSIOLOGICAL AND PHARMACOLOGICAL INFLUENCES UPON INTRAOCULAR PRESSURE

W. MORTON GRANT

Howe Laboratory of Ophthalmology, Harvard Medical School and Massachusetts Eye and Ear Infirmary, Boston, Mass.

TABLE OF CONTENTS

INTRODUCTION

This review presents a survey of current and recent investigations into the control of intraocular pressure, particularly with respect to the action of drugs. Previous reviews in this field have placed emphasis upon the pharmacology of pupillomotion and accomodation rather than upon mechanisms of regulation of intraocular pressure (53, 71, 96, 169). In recent clinical and experimental work the emphasis has shifted to the study of ocular hydrodynamics. The effect of drugs on intraocular pressure continues of interest not only from the purely scientific standpoint, but also from the practical standpoint. Scientifically, problems concerning the pharmacology and physiology of blood vessels and smooth muscle, secretion and water movement have been particularly important. Practically, the problem of control of glaucoma, which is still the most prevalent cause of blindness in adults, remains foremost. In this disease drugs offer the only alternative to treatment by surgery, or to loss of vision. Some helpful drugs are available, but more effective substances are needed. Certain drugs cause an increase in intraocular pressure, and the basis for their undesirable effect requires elucidation.

I. HYDRODYNAMIC CONSIDERATIONS

Intraocular pressure may be defined as the pressure of the watery fluid which fills the globe and permeates the vitreous humor. The pressure of this intraocular fluid is determined by the relationship between the volume of the ocular contents and the tension of the walls of the globe. The latter is in turn dependent upon the volume of the ocular contents and the elasticity of the tissues of which the walls are composed, and, to a small degree, upon the constraining influence of the extraocular muscles. The elasticity, or rigidity, of the cornea and sclera varies somewhat from eye to eye but in individual eyes is relatively constant. The intraocular volume, on the other hand, varies with the volume of the intraocular fluid and with the state of the vascular bed.

In the hydrodynamics of the eye the role of the aqueous humor is of foremost significance. Normally there is a continuous flow of aqueous humor into and out of the eye. The aqueous humor is secreted into the eye with sufficient potential energy (osmotic) to produce an intraocular pressure greater than 100 mm. mercury, but ordinarily the pressure is much less because of continuous escape of aqueous humor from the eye through special outflow channels (12, 58, 110, 159). The aqueous humor encounters capillary resistance to flow while passing through the outflow channels (78, 82, 88, 90). Moreover, in its course through these channels the aqueous humor enters the venous circulation and encounters venous hydrostatic opposition to outflow (14, 78, 88, 135, 184). The rate of escape of aqueous humor from the eye is proportional to the outflow pressure (intraocular pressure minus recipient venous back-pressure) and is inversely proportional to the capillary resistance of the outflow channels (78, 82, 83). On the other hand, the rate of formation of the aqueous humor appears to be independent of change in intraocular pressure over a moderate range (82, 193). When the parameters of rate of formation, resistance to outflow and venous back-pressure are constant, the intraocular pressure spontaneously stabilizes at a steady state with outflow equal to inflow. The relationship in the steady state is believed to be expressed by the following equation (78, 79, 81, 82, 87):

$$F = F_{in} = F_{out} = \frac{P - P_v}{R} \text{ or } C(P - P_v) \qquad \text{(Equation 1)}$$

(F is the rate of flow of aqueous humor in the steady state, F_{in} is rate of flow in, F_{out} is rate of flow out, P is intraocular pressure, P_v is the recipient venous pressure, R is resistance to outflow, and C is the coefficient of facility of outflow.)

The total volume which is maintained within the eye in the steady state is determined by the relationship between the intraocular pressure and the elasticity of the ocular walls. The volume of the aqueous humor is the difference between the total intraocular volume and the volume of the lens, iris, choroid, ciliary body, retina, and vitreous humor. The relationship between intraocular volume and intraocular pressure (for ordinary pressures) is expressed by the following equation (61):

$$E(V_2 - V_1) = \log \frac{P_2}{P_1} \qquad \text{(Equation 2)}$$

(E is the coefficient of scleral rigidity, V_1 and V_2 represent two different volumes of ocular contents, and P_1 and P_2 represent the corresponding intraocular pressures.)

The distinction between sustained and transient alterations of the steady state will be discussed first, since for elucidation of physiological and pharmacological effects upon the intraocular pressure it is essential that such a distinction be made. It is apparent from equation 1 that a sustained change in the rate of formation of aqueous humor, in the resistance to outflow or in the recipient venous back-pressure results in a sustained alteration of the steady state and the

intraocular pressure. If these parameters are not changed, only transient alterations of the steady state are caused by changes in the intraocular volume or in the elasticity of the walls of the globe. A change in either of these two factors causes an immediate corresponding change in intraocular pressure, but at the same time the rate of outflow of aqueous humor becomes altered and there is gradual retention or expulsion of a compensatory volume of aqueous humor, eventually bringing the intraocular pressure back to its original value, with the inflow and outflow again equal and the same as before. In other words, the intraocular pressure is determined directly by the rate of formation of aqueous humor, the resistance to outflow and the recipient venous back-pressure, but the intraocular pressure is modified only transiently by change in volume of ocular contents or elasticity. These considerations are particularly significant with regard to vascular influences upon intraocular pressure, since the only intraocular structure subject to rapid variation in volume is the vascular bed.

The fundamental difference between normal eyes and glaucomatous eyes is that in glaucoma the resistance to outflow and the intraocular pressure are greater than normal (78, 84, 141, 199). The rate of formation of aqueous humor appears to be approximately the same in glaucomatous as in normal eyes (79, 88, 196). As a consequence of the greater resistance to outflow in glaucomatous eyes, any variation in rate of formation of aqueous humor causes a greater alteration in the intraocular pressure in glaucomatous eyes than in normal eyes (88). Furthermore, when the steady state is disturbed by an increase in intraocular pressure as, for instance, by an increase in the volume of the vascular bed, a compensatory loss of aqueous humor takes place less promptly from glaucomatous eyes than from normal eyes.

The various parameters of equations 1 and 2 have been evaluated experimentally for human eyes, both normal and glaucomatous. The intraocular pressure has been determined repeatedly and several investigators have measured the pressure in the episcleral veins (8, 77, 136, 138, 158, 184). Goldmann has estimated the rate of flow of aqueous humor in human eyes by measuring the rate of change of concentration of fluorescein in the anterior chamber and in the circulating blood after intravenous injection (76, 79). Grant, employing tonography, which will be described in the section on methods, has evaluated the coefficient of facility of outflow (83, 88). Friedenwald has determined the relationship between intraocular volume and pressure (61). Approximate values for normal eyes are: intraocular pressure 14–15 mm. Hg, episcleral venous pressure 9–11 mm. Hg, rate of flow of aqueous humor 1–2 microliters/min., coefficient of facility of outflow 0.23 microliters/min./mm. Hg of intraocular pressure, coefficient of scleral rigidity 0.0215.

An idea of the temporal relationships may be obtained from the following examples based upon data obtained largely by tonography. In the average normal eye when the intraocular pressure is increased from the 15 mm. Hg of the normal steady state to 30 mm. Hg by increase of 14 microliters in the volume of ocular contents, the ensuing spontaneous return to the original pressure, which is accomplished by accelerated outflow of aqueous humor, is half complete in 2 to 3

minutes. For comparison, in a representative glaucomatous eye having a steady state intraocular pressure of 30 mm. Hg and a coefficient of facility of outflow of 0.06 microliter/min./mm. Hg an increase of 14 microliters in the volume of ocular contents would cause an increase of the pressure to 60 mm. Hg, and the ensuing spontaneous return to original pressure would be half completed in 4 to 5 minutes. In a more complex case in which the volume of ocular contents gradually increases or decreases (*e.g.*, from progressive vasodilation or constriction) the return to steady state conditions may be delayed. However, the potential duration of the disturbance of intraocular pressure is in each case limited by the extent to which the intraocular vessels can distend or contract.

The maximum change which can be induced physiologically or pharmacologically in the volume of the intraocular blood vessels has not yet been established. Ingenious attempts have been made to determine intraocular blood volume by means of radioactive thorium; however, for these determinations the eyes had to be enucleated, and the blood volume may have been different from what it was *in vivo* (170). Experimental determination of variations of intraocular blood volume *in vivo* would aid considerably in analyzing the influence of drugs on intraocular pressure.

The temporal relationships of spontaneous recovery from the decrease in intraocular pressure which follows a decrease in the volume of ocular contents can not yet be presented on as satisfactory an experimental basis as the effect of increase in volume. Qualitatively, however, the recovery from diminished ocular volume is more rapid in the glaucomatous eye than in the normal (182).

Obviously, in an analysis of pharmacological and physiological influences upon ocular blood volume one must take into consideration the damping influence of spontaneous compensation for changes in the volume of the aqueous humor and the consequent tendency to return to the steady state. Only sustained effects, such as those resulting from change in rate of formation, in resistance to outflow, or in recipient venous pressure, are significant in long-term alterations of intraocular pressure.

II. ANATOMICAL CONSIDERATIONS

The anatomical features which are principally concerned with the regulation of intraocular pressure are the secretory structures, the channels through which the intraocular fluid escapes to the outside, and the vasculature. Secretion of hydroxyl and ascorbate ions which causes the movement of water and other substances into the eye takes place in the processes of the ciliary body (62, 110). This structure is located directly behind the iris and encircles the lens. Morphologically, the muscles, stroma, and epithelium of the ciliary body have no particular attributes suggestive of a glandular structure, except that the leaf-like processes do present an extensive area of epithelium. However, the evidence that formation of the aqueous humor is initiated in these processes is convincing and currently undisputed.

The principal route taken by the aqueous humor after its entry into the eye is as follows. It is first received from the ciliary processes by a small approxi-

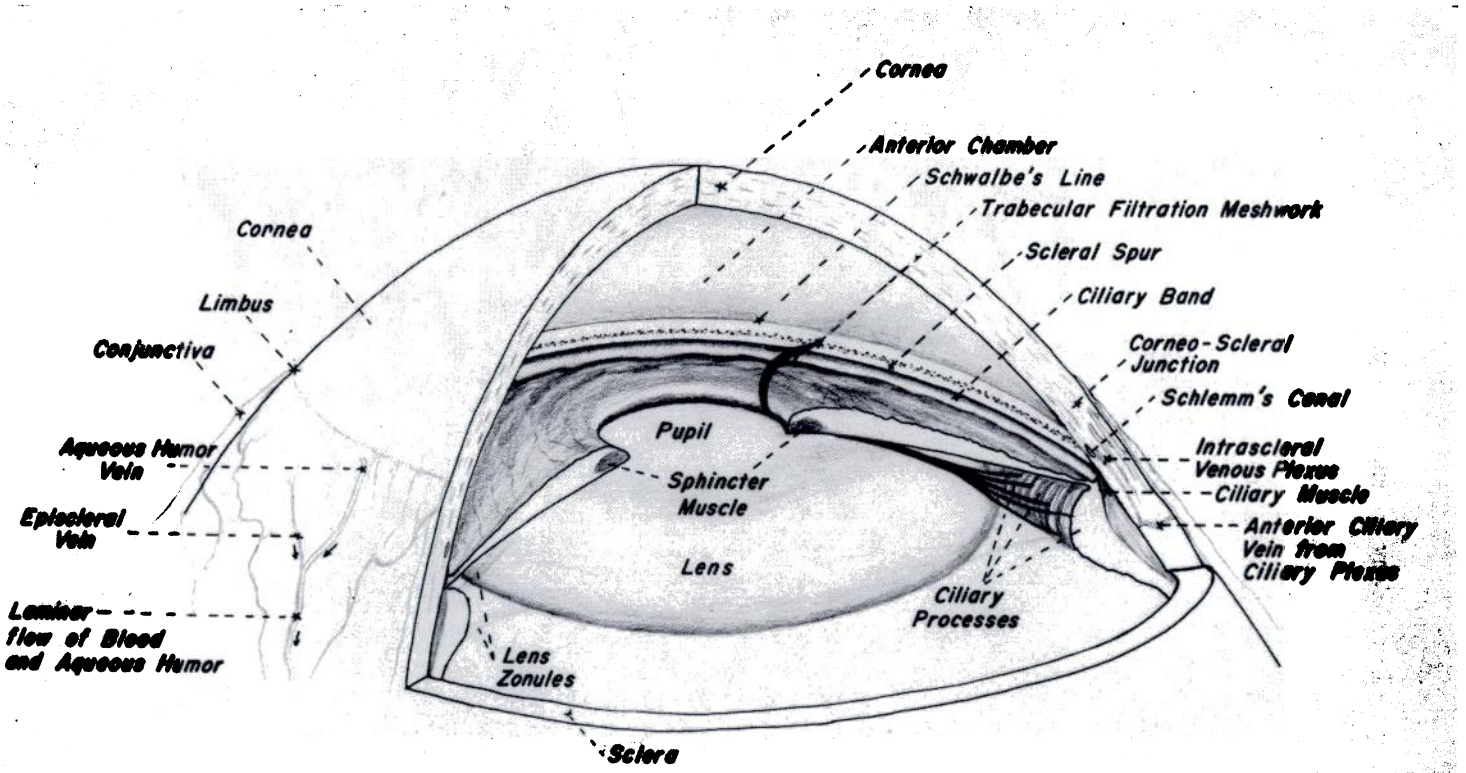

FIG. 1. Diagram of the anterior segment of the human eye, with portions of the cornea and iris cut away. The direction of flow of aqueous humor from the ciliary processes to Schlemm's canal is indicated by a heavy black arrow. The flow of blood and aqueous humor in the episcleral veins is indicated by small black arrows.

mately annular space bounded by the ciliary body, the back of the iris, the lens and the face of the vitreous humor. From this space, known as the posterior chamber, the aqueous humor flows forward between the lens and the back of the iris to emerge through the pupil into the anterior chamber.

The only established route for escape of aqueous humor from the anterior chamber is by way of channels which lead from the tissue in the angle of the anterior chamber and out through the sclera to make connection with intrascleral and episcleral veins. In the human eye a circumferential annular space in the sclera (Schlemm's canal) is interposed between the tissue in the angle of the anterior chamber and the veins. Schlemm's canal is separated from the anterior chamber only by a trabecular meshwork of tissue consisting principally of strands of protein thickly covered by so-called endothelial cells (20, 34). Microscopic study of sections of this meshwork indicates that there are continuous fine passages through it between the trabeculae of which it is composed (179). Measurement of the size of particles which will pass through this meshwork at normal pressures indicates that some of the passages have a diameter of at least 1 micron (21, 56). The peripheral outlets from Schlemm's canal consist of some 20–35 "collector channels" which break up into a rich plexus within the sclera, anastomosing with small veins from the ciliary and intrascleral venous plexus (9, 10, 11, 12, 179). Many of these vessels extend through the sclera, some carrying aqueous humor ("aqueous veins") and some both aqueous humor and blood side by side ("laminar veins"). Histologically, the vessels which carry aqueous humor away from Schlemm's canal are indistinguishable from the small veins which carry blood (12). Biomicroscopically, some of the aqueous veins are to be seen on the surface of the eye carrying clear aqueous humor and making connection with blood-carrying veins in the conjunctiva (8). The clear stream and the blood stream may then be seen to flow side by side in the same vessel for some distance before mixing. Multiple interconnections of the aqueous veins and blood veins have also been found within the sclera at the exits from Schlemm's canal, suggesting that some mixing of aqueous humor with blood must also take place within the intrascleral plexus (12, 50, 51, 189). The aqueous veins which are seen on the surface of the eye were discovered clinically by biomicroscopic examination, and were identified as channels for escape of aqueous humor from the anterior chamber to the veins in the episclera and conjunctiva by tracing the outflow of fluorescein (4, 5, 72). The most noteworthy study of the anatomy of the channels for aqueous humor and for blood in the anterior segment of the eye has been made recently by Ashton, utilizing neoprene injection casts (9, 10, 11, 12). The histology has been reviewed by Carpenter (34).

The possible relationship of arteries to Schlemm's canal and to the venous outflow channels has been investigated with conflicting results (11, 12, 57, 58). Direct arterial connections to Schlemm's canal could influence the hydrostatic pressure and the colloid osmotic pressure of the fluid in this canal. Friedenwald has postulated that the trabecular meshwork is impervious to proteins and that a continual supply of plasma proteins to Schlemm's canal would promote the outflow of protein-poor aqueous humor from the anterior chamber into Schlemm's

canal even against a small pressure gradient (57, 58). However, most investigators have failed to find direct arterial connections with, or blood in Schlemm's canal, except the blood which may be made to reflux into the canal artificially by obstructing the veins. Most recently, in a thorough search by Ashton, no direct arterial connections with Schlemm's canal were found, although many arteries were identified with walls in close contact with Schlemm's canal (11, 12).

In animals the anatomic relationships in the aqueous outflow channels differ slightly from those in the human eye. In the angle of the anterior chamber of animals the aqueous humor must pass through a coarse "pectinate ligament" before reaching the trabecular meshwork of the sclera. (Vestiges of this pectinate ligament may be seen in most human eyes.) Moreover, instead of a well-defined canal of Schlemm there are irregular anastomosing spaces in the tissue just peripheral to the trabecular meshwork. However, from these spaces the collector channels lead outward, interconnecting with venous channels, apparently as in the human eye. Outside the sclera, aqueous veins are observable biomicroscopically in animal eyes as in human eyes (8, 91).

The vascular bed within the eye consists of two essentially separate parts, the retinal and the uveal. Of these, only the uveal vascular bed need be considered in relation to the control of intraocular pressure. It is comprised of the interconnecting blood vessels of the choroid, ciliary body, and iris. The arterial supply comes from the posterior ciliary and long anterior ciliary arteries, and the venous outlet is principally by way of the four vortex veins through the sclera near the equator of the globe. There is also some venous outflow by way of the small anterior ciliary veins which emerge through the sclera of the anterior segment of the globe in association with the outflow channels for aqueous humor. This uveal vascular network may influence the pressure of the eye in several ways. It constitutes a variable volume within the eye. It may control the supply of necessary materials for the secretory functions of the ciliary body. And it may modify the composition of the aqueous humor through interchange by diffusion between vessels of the iris and the aqueous humor. Furthermore, the anterior venous outlets of the uveal vascular bed are found in such close connection with the channels by which the aqueous humor escapes from the eye as to suggest some potential controlling influence on the outflow of the aqueous humor (8, 49, 50, 183, 186, 189, 198). Mention has already been made, in connection with equation 1, of the influence of the recipient venous back-pressure in opposing aqueous outflow.

The pressure within the veins of the uveal vascular bed must just exceed the intraocular pressure if the veins are not to collapse. When the intraocular pressure is increased, the initial tendency to collapse is overcome by an automatic build-up of the venous blood pressure toward the arterial pressure to achieve the necessary excess of venous pressure over intraocular pressure for the continued outflow of blood. This is a simple hydraulic phenomenon requiring no special controlling apparatus. No glomus cells could be found on choroidal veins by Ashton, and no special controlling apparatus has been demonstrated where the vortex veins

pierce the sclera, although occasionally some regulatory function has been ascribed to the obliquity of the course of these veins through the sclera (12).

III. PHYSIOLOGICAL ASPECTS OF INTRAOCULAR PRESSURE

1. Inflow of aqueous humor. The formation of the aqueous humor is believed to be accomplished by a combined process of secretion and diffusion. The secretory part of the process is probably accomplished by an energetic redox mechanism in the ciliary body based upon transport of oxygen and formation of hydroxyl ions at the surface of the epithelium of the ciliary processes (59, 110). Evidence for the production of hydroxyl ions is the presence of a significantly higher pH in the aqueous humor than in the blood (112). Evidence for a secretory mechanism in the ciliary processes was originally obtained from study of the transport of anionic and cationic dyes (67, 68). In addition, enzyme systems for oxidation-reduction reactions have been identified in the ciliary body, and the redox potentials of the ciliary epithelium and stroma have been measured (64, 65, 68). The electromotive redox chain of the secretory mechanism appears to have several links. In some species, ascorbic acid and adrenaline appear to be essential for secretion (59, 62, 63).

Some of the hydroxyl ions which are formed at the surface of the ciliary epithelium are converted to bicarbonate ions by reaction with carbonic acid (59, 111, 112). The carbonic acid is formed by hydration of carbon dioxide, which is thought to diffuse between blood and aqueous humor. Both hydroxyl and bicarbonate, and also ascorbate, are found in higher concentration in the aqueous humor of the posterior chamber than in the blood (116, 121). As an osmotic consequence of the relatively high concentration of these substances in the posterior chamber, there is a net movement of water from the blood into the posterior chamber (110, 114, 116). The secretion of anions also necessitates a migration of the cations of the blood, in particular sodium, into the posterior chamber (116). However, this fluid which is formed by the movement of ions and water into the posterior chamber is deficient in some of the other constituents of the blood, *e.g.*, glucose, phosphate, urea, and chloride (114). Those substances in the blood which appear not to be secreted but which can diffuse across the blood-aqueous barrier by virtue of their solubility and molecular size, tend to diffuse from the blood to the newly secreted fluid (114). The ultimate concentration attained by each substance in the aqueous humor is a function of the rate of transport of the secreted ions and of the movement of water. It is limited by the rate of flow of the new-formed aqueous humor away from the site of secretion to the outlets in the angle of the anterior chamber (114). Normally, there is a steady movement of substances into the eye, a flow from posterior to anterior chamber, and a flow out. As the aqueous humor passes from posterior chamber to anterior chamber, there is some interchange with vitreous humor and lens, probably resulting in some depletion of glucose and accumulation of lactate in the aqueous humor due to metabolic processes (116). However, contrary to former beliefs, there is no gain of ascorbic acid from the lens (109, 116). Apparently there is some interchange with the blood vessels of the iris during passage of the aqueous

humor through the anterior chamber, and this results in some decrease in bicarbonate and increase in chloride concentration. However, any dilution of the aqueous humor as it passes from posterior to anterior chamber, is too slight to detect by comparative measurements of osmotic pressure of aqueous humor taken from the posterior chamber and from the anterior chamber (112).

The modern dynamic concept of the aqueous humor contrasts with the concept, prevalent a decade or two ago, of a stagnant fluid in equilibrium with the blood. The older concept provided no satisfactory explanation for the great increase in intraocular pressure which is possible in glaucoma. The present concept has developed from measurements of the osmotic pressure of the aqueous humor and from experimental investigations of the kinetics of formation of the aqueous humor (16, 17, 29, 42, 48, 103, 104, 111, 159, 160, 161, 163). Various substances have been administered systemically to animals, and the rate of accumulation in the eye, or the rate of later disappearance from the eye, has been determined (22, 113, 115). An analysis of the rate of change of concentration of each substance in the eye, taking into consideration the concentration in the blood and the loss due to continual bulk outflow has demonstrated that different substances enter the eye at different rates (110, 114). The analysis has provided evidence that most substances enter the eye by diffusion in proportion to the differences between their concentrations in the blood and aqueous humor. Under steady state conditions these same substances are always found to be in lower concentration in the aqueous humor than in the blood. On the other hand, substances which are introduced into the eye through secretory or metabolic processes (*e.g.*, ascorbate, hydroxyl, bicarbonate, lactate and hyaluronate) may be found in higher concentration in the aqueous humor than in the blood (109, 111). In some instances the analysis has been complicated by the potential influence of blood proteins on the distribution of ions between blood and aqueous humor (Gibbs-Donnan effect). This influence has figured most prominently in the cases of sodium and chloride, but it now appears that the concentration of sodium achieved in the aqueous humor is greater than could be accounted for by diffusion, unless the high concentration of hydroxyl, bicarbonate and ascorbate ions within the eye provide a special motivating force (110). The mode of entry of chloride is still somewhat obscure.

2. Outflow of aqueous humor. Surprisingly little is known of the physiological or pharmacological control of the escape of aqueous humor from the eye, although the anatomical character of the outflow channels and the general hydrodynamics of outflow have been fairly well elucidated. It is known that the aqueous humor flows out of the eye in proportion to the intraocular pressure, encountering capillary resistance in the outflow channels and hydrostatic back-pressure in the recipient blood-containing veins (78, 82, 141). Furthermore, it has been found that the resistance to outflow in normal human eyes is not much different after enucleation from what it is *in vivo* (89, 90). Unfortunately, present clinical measurements of the resistance to outflow, and of the decrease in resistance induced by drugs do not in any way indicate the anatomical locus of this resistance. Anatomical investigations coupled with measurements of resistance to outflow

have not yet definitely established whether the resistance to outflow in normal and glaucomatous eyes resides predominantly in the trabecular meshwork or in the outlets from Schlemm's canal, although the possible sites have been narrowed to these structures. The author of this review, at present, favors the concept that the main resistance to outflow in non-glaucomatous human eyes is peripheral to Schlemm's canal, since he has recently obtained evidence that the meshwork of tissue between the anterior chamber and Schlemm's canal offers a relatively slight resistance. These observations were made in enucleated normal human eyes which had nearly the same overall resistance to outflow as normal eyes *in vivo* (86, 89). This overall resistance was not significantly altered by extensive incision of the trabecular meshwork of the anterior chamber from within the eye, nor, in another set of eyes, by dissecting away the outflow channels of the outer two-thirds of the sclera from outside the eye (86, 90). The same inference regarding low resistance in the meshwork of the angle of the anterior chamber has been drawn from preliminary cannulation experiments by Perkins (51). These observations indicate that the pressure in Schlemm's canal in the living monkey eye is essentially the same as in the anterior chamber. Of course, neither of these sets of experiments indicate where the site of resistance may be in open-angle glaucomatous eyes, and both sets of experiments require elaboration and confirmation.

The distribution of pressures and resistance to flow in the intrascleral plexus of aqueous and blood-containing veins has not been elucidated. A knowledge of these factors would obviously be helpful in study of the site and mode of action of drugs which may influence either the resistance or the venous back-pressure.

3. Physiological variations of the intraocular pressure. The intraocular pressure is subject to a number of physiological influences which are imposed upon the hypothetical steady state. These influences in some cases have obvious connection with activities of other parts of the body. However, in the case of certain small cyclic variations of intraocular pressure the connection is obscure. In general, the pressure may be modified physiologically by variations in the intraocular vascular bed, or by changes in the rate of formation of aqueous humor, and possibly by variations in the resistance and venous opposition to outflow.

The most conspicuous physiological fluctuations of intraocular pressure are caused by variations in the intraocular vascular bed. These fluctuations are rapid and of short duration. Changes in volume of the vascular bed, either as a consequence of vasomotor phenomena or as a result of changes in blood pressure, are immediately reflected in changes in the intraocular pressure. However, alteration of the volume of the vascular bed has only transitory influence on the intraocular pressure, owing to the gradual compensatory adjustment of the volume of aqueous humor which was discussed in the section on hydrodynamics. The arterial pulse is normally transmitted to the intraocular fluid producing an ocular pulse with an amplitude of 1 to 3 mm. Hg. Ordinary respiratory influences on blood-pressure also are reflected in small variations of intraocular pressure. Rapid transient rises of as much as 20 mm. Hg may be produced by increase in venous pressure through the Valsalva experiment. Vasodilatation during blushing causes an increase of the order of 5 mm. Hg (86).

Physiological variation of the rate of formation of aqueous humor with consequent modification of intraocular pressure is best established by observing the effect of a change in osmotic pressure of the blood which alters the rate of movement of water into the eye and consequently modifies both the volume of aqueous humor and the intraocular pressure (28, 44, 48, 125, 163). Hemodilution from drinking, or hemoconcentration from exercise cause, respectively, an increase and a decrease in intraocular pressure. In normal eyes, the change in pressure from these causes is rarely more than 8 or 9 mm. Hg (131). The effect lasts only so long as an osmotic difference is maintained and until the intraocular volume has returned to its original value. The rate of formation of aqueous humor may also be governed physiologically by the supply of materials to the secretory cells of the ciliary body, or by hormonal regulation of the secretory process itself, but very little is known concerning possible influences of this sort (55).

Physiological variation of the resistance to outflow of aqueous humor is reported to occur in association with the menstrual cycle (27). Moreover, some decrease in resistance has been found during pregnancy (27). In explanation of the action of miotic drugs which lower the pressure by decreasing the resistance to outflow, it has been proposed that the porosity of the trabecular meshwork may be modified mechanically by the pull of the muscles of the iris and of the ciliary body (55). A corollary to this theory would be that physiological variation of tone of these muscles might influence the resistance to outflow. Any such influence must be small, for no lasting effect on intraocular pressure is produced either by parasympathetic or sympathetic denervation. Cycloplegic drugs occasionally exert a slight influence. This will be discussed in section VI, A 2, p. 166.

Spontaneous physiological diurnal variations in the width of the column of blood in the episcleral veins have been observed, and the pressure in these veins is said to increase prior to a rise in intraocular pressure, and to decrease prior to a decrease in intraocular pressure (8, 185, 186). A hypothesis has been advanced that small diurnal variations in intraocular pressure are the result of variations in the recipient venous pressure under some systemic influence (8, 49, 185). The hypothesis has been extended to explain variations of intraocular pressure in glaucoma and in response to drugs (8, 14, 46, 49, 50, 51, 137, 184, 186). At present, however, the majority of investigators consider the variation of episcleral venous pressure to be insignificant (27, 60, 78, 79, 134, 135, 136, 158, 194, 197, 198). Further investigation and comparison of techniques are required to settle this point.

The influence of ocular innervation upon intraocular pressure has been the subject of much investigation, executed mostly under quite unphysiological circumstances. No adequate demonstration has been made of any sustained controlling influence of the ocular innervations upon the intraocular pressure either in normal or glaucomatous eyes, except for the mechanical relief of angle-closure glaucoma by the miosis resulting from decrease in sympathetic or increase in parasympathetic nervous influences. Many transient effects of nerve section or nerve stimulation have been observed, and these may well be analogous to transient effects of some drugs. In general, the transitory changes observed in intraocular pressure are those which would be expected to result from alterations

in intraocular blood volume due to change in innervation of the vessels. Sympathetic stimulation has been found to minimize the influence of variations of systemic blood pressure upon the intraocular pressure. When the extraocular muscles are stimulated, the intraocular pressure also temporarily increases, as would be expected (92, 93). In many instances, observations of the influence of ocular innervation were made upon cannulated, or otherwise irritated, eyes in which the blood aqueous humor barrier was at least partially broken down (1, 41, 43, 102). Under these abnormal circumstances, sympathetic stimulation was observed to cause transient decrease in intraocular pressure and to ameliorate somewhat the leakiness of the barrier (1, 43, 132, 176, 177, 178). Further reference to studies of this type will be made in section IV and in section VI.

IV. PATHOLOGICAL ASPECTS OF INTRAOCULAR PRESSURE

Pathologically the intraocular pressure may be found above or below the normal range of approximately 10 to 22 mm. Hg. When the pressure is abnormally high the condition is called glaucoma, and when low, hypotony. Since glaucoma is the more thoroughly studied and more common condition, it will be the principal subject of discussion. Hypotony has been little investigated, although under certain circumstances it does present a serious clinical condition. At present, we can go little beyond outlining the nature of the problem of hypotony.

1. Hypotony. The clinical significance of hypotony is greatly influenced by the state of the anterior chamber. The anterior chamber may, on the one hand, contain aqueous humor and be "formed", or, on the other hand, the anterior chamber may be collapsed or "flat" with the iris touching the cornea. In the case of hypotony with the anterior chamber present, low pressure may be a simple consequence of abnormally easy escape of aqueous humor from the eye through a fistula such as may be produced surgically, or the hypotony may be due to a subnormal rate of formation of aqueous humor (83, 195). When the anterior chamber is "formed", this condition is ordinarily not serious, unless the formation of aqueous humor is depressed as the result of widespread degeneration and impending atrophy of the eye. On the other hand, hypotony with "flat" anterior chamber is a more serious condition which may follow ocular surgery and may lead eventually to glaucoma, owing to the formation of adhesions between the iris and the entrance to the channels for outflow of aqueous humor. In some instances, this type of hypotony is associated with escape of aqueous humor from the eye through a leaky surgical or traumatic wound; here the problem is a mechanical one which may be corrected surgically. In other instances, no abnormal leak of the wound may be discoverable. In these cases, there is always collection of fluid between the sclera and choroid ("separation of the choroid") adjacent to the ciliary body. This subchoroidal fluid occupies considerable space, and apparently displaces forward the vitreous humor and iris. This is particularly notable in eyes from which the lens has been removed. In those cases which have no known leak the hypotony is probably due to subnormal formation of aqueous humor. Nothing is known of the basis for the apparent dysfunction of the ciliary body under these circumstances. Surgical drainage of fluid from the subchoroidal

space helps in restoring normal conditions, but the reason for this is not known. An effective medical treatment for the condition is needed. Diamox administered orally is said to show promise (187). The evaluation of medical measures is difficult because, in some cases normal conditions return without treatment, and evaluation must be statistical. A technique for producing hypotony experimentally in animal eyes would greatly facilitate investigation.

2. Pathogenesis and classification of glaucoma. At present the pathogenesis of glaucoma is better understood than the mechanisms by which physiological and pharmacological factors influence intraocular pressure. This is partly because the insensitivity of present investigative methods constitutes less of a limiting factor in the study of the relatively large changes which occur in glaucoma than in the study of the comparatively small changes produced by physiological or pharmacological influences in normal eyes.

In glaucoma the intraocular pressure is elevated because of an increase of the resistance to outflow of aqueous humor, seldom, if ever, by increase in the rate of formation (27, 29, 60, 78, 79, 83, 88, 105, 119, 147a, 162, 193). This is indicated both by tonographic measurements and by measurements utilizing fluorescein as a tracer (see section V). No sustained elevation of the intraocular pressure results from alteration of the blood pressure, of the concentration of the constituents of the blood, or of the innervation of the eye, although, as mentioned in section III, these factors may cause transitory elevation. Furthermore, no abnormality of the osmotic pressure of the aqueous humor has been detected in glaucoma (104). Quantitative determinations by means of tonography have shown that the increased resistance to outflow in glaucoma is sufficient to account for the increase in intraocular pressure. This increase in resistance has the hydrodynamic characteristics of a constrictive or frictional factor, not the characteristics of an increased hydrostatic back-pressure (82, 88). In support of this conclusion, most investigators have found the venous back-pressure in the episcleral vessels, into which the aqueous veins discharge, to be practically the same in glaucomatous eyes as in normal eyes, or possibly slightly lower in glaucomatous eyes.

Analysis of the cause of increased resistance to outflow in glaucoma indicates that different causes are associated with different clinical types of glaucoma. For clinical classification, glaucoma is generally divided into the two major categories of primary and secondary, depending upon whether or not some antecedent pathological process is recognizable in the pathogenesis of the glaucoma.

Most significant from the standpoint of incidence are the primary glaucomas. The terminology has changed gradually from a symptomatic to a functional basis. Angle-closure glaucoma (also called closed-angle and narrow-angle glaucoma) has in the past been known as congestive glaucoma; open-angle glaucoma has been known as simple or non-congestive glaucoma. The highly important functional differentiation of the primary glaucomas into angle-closure and open-angle glaucoma has long been a controversial matter, but recently has gained almost universal acceptance as the result of correlated biomicroscopic examination of the angle of the anterior chamber and measurements of the resistance

and rate of aqueous humor outflow (51). In angle-closure or closed-angle glaucoma the outlets for aqueous humor from the circumferential angle of the anterior chamber are obstructed by a valve-like action of the periphery of the iris which closes the angular space. This type of glaucoma can occur only in eyes having the anatomic predisposing feature of an abnormally narrow angle. Abnormal narrowness of the angle appears to be an innate, possibly genetic, feature in some individuals, and this narrowness may be rendered critical by enlargement of the crystalline lens during its lifelong growth and increase in thickness. Under these circumstances the iris is more closely opposed to the front surface of the lens than ordinarily, with the result that the aqueous humor encounters greater than normal resistance in its passage from the posterior chamber through the pupil into the anterior chamber. A small gradient of pressure exists across the resistance to flow, with the result that the pressure in the posterior chamber is slightly higher than in the anterior chamber, tending to bulge the base of the iris still further forward. The resistance to outflow of aqueous humor from the anterior chamber remains entirely normal until the iris comes into actual contact with the trabecular meshwork in the angle and obstructs it. The important role of the resistance to flow from posterior to anterior chamber is clearly demonstrable by the effect of providing an extra-pupillary route for aqueous through the iris. If a tiny hole is made through the iris, directly connecting the posterior and anterior chambers by perforating the iris with the point of a knife or by removing a tiny piece of iris, the tendency for the iris to bulge forward and to close the angle is permanently eliminated. In fact, angle-closure glaucoma is completely cured by such a surgical procedure (35, 97). The influence of pupillary size on both the precipitation and the relief of closed-angle glaucoma is of great theoretical and practical interest. It will be discussed in section VI.

In the other type of primary glaucoma, so-called open-angle glaucoma, there is also abnormally great resistance to the outflow of aqueous humor, but the iris is not implicated (79, 83); the angle of the anterior chamber remains open at all times and neither biomicroscopic examination of the angle of the anterior chamber nor microscopic study of stained sections has established the cause for the abnormal resistance (147a). In this form of glaucoma the intraocular pressure characteristically rises slowly and progressively over a period of years with a minimum of symptoms, except that there is a gradual loss of vision, and eventually complete blindness if treatment is unsuccessful. Characteristically, there are no acute attacks of high pressure such as occur in angle-closure glaucoma, although considerably greater fluctuations in intraocular pressure may occur than in normal eyes (50). The anatomical site of the abnormal resistance to outflow in open-angle glaucoma has not been established. It may conceivably be found in the meshwork of tissue separating the anterior chamber and Schlemm's canal, or it may be in the outflow channels from Schlemm's canal. Obviously it will be important for the investigation of the therapeutic action of drugs as well as to the determination of the etiology of the disease to discover the nature and location of the hindrance to outflow. Up to now attempts to localize the obstruction to outflow in open-angle glaucoma have been almost wholly restricted to

rather ambiguous clinical observations on Schlemm's canal and the aqueous veins (8). It has been observed that in normal eyes blood may be made to reflux into Schlemm's canal by slight compression of the outflow vessels on the surface of the eye, but that in glaucomatous eyes this is more difficult to accomplish (7, 74). However, in normal eyes, when a laminar vein is compressed locally, the aqueous humor is generally seen to reflux into adjacent venous connections, whereas in glaucomatous eyes the blood stream may displace the clear fluid from the aqueous veins. Various observers are in agreement regarding the reality of these phenomena, but not regarding their significance (8, 46, 49, 74, 75, 134, 184, 186, 197). There is real need for more direct experimental investigation. Unfortunately, eyes having primary open-angle glaucoma rarely are available for investigation in the laboratory. Although this is the most common form of glaucoma, there is seldom an indication for removal of an eye having this disease. Pain is rare in primary open-angle glaucoma even after complete blindness.

3. Pathologic variation of the intraocular pressure. The intraocular pressure is susceptible of variation through influences which in each type of glaucoma are rather special and characteristic. In glaucoma due to bulging of the iris against the trabecular meshwork with valve-like obstruction of aqueous outflow, variations in pressure are characteristically brought about by the relative miosis and mydriasis induced by changes in illumination, accomodation and emotion, and by sleep (35). In open-angle and secondary glaucoma the mechanism of variation of intraocular pressure is more complex, yet worth considering for the light it may shed on the mechanism of action of drugs.

In open-angle glaucoma the chronic elevation of the resistance to outflow causes the intraocular pressure to be abnormally high, and renders it abnormally susceptible to variation. Variation in the rate of formation of aqueous humor, whether due to a transient change in the tonicity of the blood or to a variation in the rate of secretion, affects the intraocular pressure in an exaggerated manner when the resistance to outflow is elevated (88). Decrease in rate of formation, such as that produced by certain drugs, causes a more substantial decrease in the pressure in glaucomatous eyes than in normal eyes (87).

Tonographic measurements have indicated that spontaneous diurnal variations of intraocular pressure may occur in open-angle glaucoma without appreciable change in the resistance to outflow (88, 162). The episcleral veins have been observed to broaden when the intraocular pressure is low and to narrow when the pressure rises spontaneously (8, 46). The narrowing has been thought to represent constriction and increase in resistance of the veins, but the postulated increase in resistance has not been demonstrated. Equation 1 indicates that this variation of intraocular pressure might be accounted for hydrodynamically by altered rate of flow (F) or altered recipient venous pressure (P_v). Moreover, change in volume of the intraocular vascular bed could influence the intraocular pressure according to equation 2. The possible role of the recipient venous pressure in the variation of intraocular pressure in open-angle glaucoma remains obscure. A number of investigators have been unable to detect significant variation in the episcleral venous pressure (60, 78, 79, 134, 136, 159, 193, 197.

198), while others, Thomassen in particular, report that the episcleral venous pressure does vary and that a small decrease or increase in this pressure precedes a larger decrease or increase in intraocular pressure (8, 20, 50, 138, 184, 186). (The manner of measurement is described in section V.) No special device or arrangement has been discovered in the outflow channels which could cause small variations of recipient venous back-pressure to have an inordinate effect on intraocular pressure. Hydrodynamic considerations, supported by experiment, indicate that increase in venous pressure can cause an equal increase in intraocular pressure (77, 90, 194). Conceivably, the small fluctuations in episcleral venous pressure which have been reported may be but a reflection of greater changes in pressure in the intrascleral portions of these veins where they communicate directly with the collector channels at Schlemm's canal (51). These matters remain to be elucidated.

In glaucoma secondary to inflammation a phenomenon is occasionally noticed which seems worth describing, since it illustrates an effect which may be observed in the testing of drugs. In glaucoma secondary to iritis, there is, as in other glaucomas, an increased resistance to outflow due to some abnormality of the outflow channels. Under these conditions, the intraocular pressure usually is elevated. However, in some instances the rate of formation of aqueous humor is depressed, and this may prevent elevation of the intraocular pressure, or may even cause the pressure to be subnormal despite the increased resistance to outflow (83). The formation of aqueous humor is depressed because intraocular inflammation causes the osmotic barrier between blood and aqueous humor to break-down and become permeable even to molecules as large as proteins (110). Owing to this abnormal leakiness of the tissue barrier separating blood from aqueous humor, the osmotic force for movement of water into the eye is lost. A similar break-down of the blood-aqueous humor barrier may be induced by cannulation or other irritation of the eye, especially in rabbits (113, 115). This phenomenon must be taken into consideration in connection with the testing of drugs in animals.

The possible influence of ocular innervation on the intraocular pressure in glaucoma has been subject to much speculation and to some clinical investigation. Speculatively, there has been some tendency to attribute the occurrence of glaucoma to an abnormality of autonomic innervation, particularly to sympathetic hyperactivity (200). This thought appears to have arisen from occasional clinical observation of increased pressure in association with emotional states, and also from observation of mydriasis in attacks of acute angle-closure glaucoma. However, no convincing evidence has ever been presented in support of this assumption. A number of attempts have been made to treat glaucoma by means of cervical sympathectomy or stellate ganglion block, but without significant benefit, except possibly in cases of angle-closure glaucoma in which miosis is mechanically advantageous (140, 151). The influences of ocular innervation on the intraocular vascular bed and on the intraocular pressure have been discussed in section III.

V. METHODS FOR EVALUATING THE INFLUENCE OF DRUGS ON INTRAOCULAR PRESSURE

Selection of a suitable type of eye, as well as choice of appropriate investigative procedures, presents some difficulties. Unfortunately, the eyes of animals other than primates differ in significant anatomical detail from human eyes; the blood-aqueous barrier may be more sensitive to irritation in animals than in human beings; and in animals there is no satisfactory counterpart of human primary open-angle glaucoma. Glaucoma, induced in animal eyes by injection of particulate material to obstruct the drainage channels, causes progressive enlargement of the animal eye and is unlike the glaucoma of the adult human being. In normal human eyes the pressure is characteristically less influenced by drugs than is the pressure of the human glaucomatous eye (54, 87). Normal animal eyes may evidence little change in intraocular pressure under the influence of drugs which cause a decrease in pressure of human glaucomatous eyes. From consideration of hydrodynamic and physiologic concepts certain simple principles in evaluating the action of drugs are evident. For instance, it is helpful to know whether a drug is capable of sustained influence on the intraocular pressure or has only a transitory influence. Sustained influence may be attributable to an effect upon the rate of formation of aqueous humor, upon the resistance to outflow or upon the venous back-pressure to outflow. On the other hand, an increase or decrease of the intraocular pressure which cannot be maintained even by continuing administration of the drug may represent an effect upon the volume of the intraocular vascular bed, for which, it may be recalled, there is an automatic compensating mechanism.

Errors in evaluating the influence of drugs on the intraocular pressure most commonly arise from ignoring, or accidentally eliminating, some of the normal controlling factors, particularly the slow readjustments in pressure due to compensatory changes of the aqueous humor volume. The perspective for the whole picture is commonly lost in observations which are too brief, and a distorted picture is obtained from methods of measurement which in themselves derange the normal processes. Both of these difficulties are encountered in experiments involving brief manometric measurements in cannulated eyes. The literature contains many examples of doubtful experiments of this type.

1. Manometry of cannulated eyes. This is no doubt the most direct method for measurement of the intraocular pressure in animal eyes (95). However, cannulation, or other irritation of the eye, may cause a break-down of the blood-aqueous barrier and profoundly derange the normal processes of formation and outflow of the aqueous humor. In intact eyes, both normal and glaucomatous, a change in the volume of the vascular bed is slowly compensated by an equal and opposite change in the volume of the aqueous humor. This compensatory mechanism is impaired by break-down of the blood-aqueous barrier. The cannulated eye may be employed as a sort of plethysmograph for study of the influence of drugs on the intraocular blood vessels, but it should be kept in mind that the phenomena

observed under these circumstances may be only remotely related to the regulation of intraocular pressure in the intact eye.

Measurements by cannulation of the eye after death or enucleation present simpler conditions which are appropriate to investigation of the physical properties of the eye. In this case, the influence of blood supply and formation of aqueous humor are purposefully eliminated. Perfusion of enucleated eyes is currently being profitably employed in analyzing the functional characteristics of the outflow channels (20, 21, 89, 90). This technique is useful for investigating the physico-chemical influence of substances on the resistance in the outflow channels (21, 90, 98).

2. Tonometry in intact eyes. Various mechanical tonometers are available for indirect determination of intraocular pressure. They have the advantage of avoiding damage or disturbance of the eye from insertion of a needle or cannula. Tonometers, generally, suffer from several disadvantages, *i.e.*, they have inferior sensitivity, they are difficult to calibrate, and they elevate the intraocular pressure during measurement. However, particularly for clinical investigation, their advantage far outweighs their disadvantages. The most commonly employed instrument is the Schiotz tonometer, of which mechanical and electronic models are available. The electronic type has the greater sensitivity. With this instrument measurement is made of the depth to which the cornea is indented when a metal plunger of standard weight and dimensions is rested upon it. From this measurement an estimate is made of intraocular pressure, taking into consideration the weight, the area of support, the volume of indentation and the relationship between the volume and the intraocular pressure (61). Much effort has been put into the calibration of the Schiotz tonometer for human eyes. Animal eyes require separate calibrations. To keep track of the intraocular pressure by tonometry the usual practice is to make periodic measurements, each sufficiently brief to avoid excessive alteration of the intraocular pressure.

3. Tonography. The resistance to outflow and the rate of outflow, as well as the intraocular pressure, may be determined by extending the period of application of the Schiotz (electronic) tonometer to the eye for several minutes. As noted previously, application of the tonometer artificially elevates the intraocular pressure. In ordinary tonometry this is a disadvantage, but in tonography advantage is taken of the measurable acceleration of outflow which is caused by the artificially increased intraocular pressure (27, 82, 84, 85, 88, 119, 141, 199). The acceleration of outflow is evaluated quantitatively from the rate of fall of the pressure which is correlated with the rate of decrease in intraocular volume. Then, by relating the increment of intraocular pressure caused by the tonometer to the resultant acceleration of outflow, a quantitative evaluation of the resistance to outflow is obtainable. Determinations based on tonography are valid only if the formation of aqueous humor is insensitive to small elevations of intraocular pressure, and this appears to be the case (79, 82). Perhaps the best evidence that the rate of formation is essentially uninfluenced by tonography has been the demonstration by Weekers that, given sufficient time, the eye returns to its initial steady state pressure even with the tonometer remaining on the eye, and

that furthermore, the value for resistance to outflow remains constant throughout (193).

Using tonographic data, the rate of flow in the steady state may be calculated, in accordance with equation 1, from the steady state intraocular pressure, the resistance to outflow, and the venous back-pressure. The episcleral venous back-pressure must be separately determined. Determination of resistance to outflow by tonography is believed to be independent of recipient venous pressure, and the episcleral venous pressure is little affected by tonography (82, 135, 194).

Tonography is primarily suitable for clinical investigation, and during the past five years it has been widely employed in studies on patients. Tonography has contributed information concerning the pathogenesis of glaucoma and the mechanism by which certain drugs influence the intraocular pressure. Unfortunately, the experimental usefulness of tonography is limited by inadequate sensitivity when analyzing changes of less than 30–50 per cent in the intraocular pressure.

4. Observations on vessels containing aqueous humor. Biomicroscopy of the vessels which emerge from the sclera permits qualitative and semi-quantitative observation of the outflow of aqueous humor and of the influence of drugs. However, fundamental uncertainties in techniques and interpretations remain to be worked out, for upon observations of this sort are based the present principal disagreements among investigators concerning the mechanism of control of the intraocular pressure.

The vessels which emerge from the sclera can be conveniently examined undisturbed in human beings and in animals by means of a low power binocular microscope. A convenient instrument for this purpose is the slit-lamp biomicroscope or corneal microscope which is standard equipment wherever clinical or investigative ophthalmology is practiced. Certain vessels which emerge from the sclera appear to carry only effluent aqueous humor, and others only blood. Certain other vessels, particularly those continuing from the junction of an aqueous vein and a blood vein, appear to contain both aqueous humor and blood flowing side by side. Observations have been made on the influence of drugs on the width of the stream of aqueous humor or blood in these vessels (6, 8, 46, 91). The pressure in these vessels and the influence of drugs has been estimated by means of a tiny transparent bladder connected to a manometer (14, 50, 73, 74, 75, 77, 78, 135, 136, 138, 139, 158, 171, 184, 185, 186, 193, 198). The bladder is held against the vessel while the pressure within the bladder is raised until the vessel is just occluded. It is assumed that there are sufficient anastomoses among the effluent vessels to prevent significant increase in the back-pressure as a result of the experimental occlusion. Measurements by this technique have, to the present, yielded fundamentally different results in the hands of various investigators.

These disagreements may be ascribable to differences in the variety of vessel upon which the measurements have been made. Also, the material which has been employed for construction of the bladder is known to have varied from mouse or rat urinary bladder to rubber or plastic, and this may have influenced the sensitivity of measurement. Because of the possibly critical significance of circumstances in the effluent vessels further investigation is indicated.

5. Determination of rate of flow by means of tracer substances. Several methods have been devised utilizing fluorescein for estimation of the rate of flow of aqueous humor through the eye (26, 76, 78, 79, 105, 107, 122, 123, 193). In most instances, fluorescein has been administered intravenously or by mouth, but topical application has occasionally been employed. The rate of change in concentration in the aqueous humor has been estimated by means of various special devices for continuous fluorimetry of the anterior chamber in patients and animals. The manner in which the estimate has been made has varied widely among different investigators. Under what appear to be the best circumstances the concentration of free fluorescein in the blood has simultaneously been determined and this has been taken into consideration in evaluating the rate of change in concentration in the aqueous humor (78, 79). In all methods the assumption has been made that the movement of fluorescein affords an indication of the movement of the whole aqueous humor. Unfortunately, the kinetics of transfer of fluorescein into and out of the eye has not been studied as carefully as it should be. Moreover, the influence of alteration of the permeability of the blood aqueous barrier on the kinetics of transfer of fluorescein has not been adequately analyzed. A change in the permeability of the barrier, it may be recalled, may influence interchange of substances between blood and aqueous humor. Since the permeability of the blood-aqueous humor barrier to fluorescein appears normally to be rather limited, any inflammatory or irritative process which increases the permeability of this barrier may be expected to increase the rate of transfer of fluorescein between blood and aqueous humor. An increase in rate of change in concentration of fluorescein from this cause constitutes a potential source of error of the method, for it may be misinterpreted as a change in the rate of flow of the aqueous humor (27). Despite these considerable technical difficulties the results obtained by various investigators are reasonably consistent. Also estimates of rate of flow of aqueous humor in normal and glaucomatous eyes are similar to those obtained by tonography (27, 60, 79, 88). Similar conclusions regarding the mode of action of drugs have been reached by both methods, except when a disturbance of the permeability of the blood-aqueous barrier may be suspected.

A number of substances other than fluorescein have been employed for determination of rate of flow of aqueous humor in animals. They have been reviewed by Ross (164).

6. Estimation of the permeability of the blood-aqueous humor barrier. The penetration of substances from the blood into normal eyes is influenced by molecular size. Large molecules, such as the proteins of the blood normally pass into the eye at so low a rate that only traces are found in the aqueous humor. Even substances of moderate molecular size, such as inulin, normally pass the blood-aqueous humor barrier very slowly (144, 175). An abnormal increase in permeability of the barrier may be detected by examining the aqueous humor for an increase in concentration of these substances. Abnormal permeability to protein may be detected chemically or biomicroscopically from the intensity of the Tyndall effect in the aqueous humor (177, 178). Visual detection of protein in

the aqueous humor may be facilitated by staining the blood proteins with Evans blue (166). Inulin may be injected intravenously and measured chemically in the fluid withdrawn from the anterior or posterior chambers (175). These methods have been widely employed for detection of abnormal permeability of the barrier under pharmacological influences. However, some criticism may be made that through use of large molecules these tests may lack sensitivity for detection of slight changes of permeability.

Possibly a more sensitive index of permeability may be obtainable by utilizing fluorescein, which is small enough to enter the normal eye at a moderate rate but enters more rapidly when permeability is increased. However, the concentration which is achieved in the aqueous humor is influenced by other factors besides permeability, *e.g.*, by the rate of loss from the eye by diffusion or by outflow (which in turn is dependent upon intraocular pressure), by the concentration in the blood, and by the proportion of the fluorescein in the blood which is bound by proteins. Furthermore it has not been satisfactorily established for normal eyes in what proportion fluorescein enters by way of the ciliary body compared with the iris, or by secretion as compared with diffusion. Accordingly, it is evident that analysis of the effects of pharmacological agents upon the concentration of fluorescein in the eye may be quite complex unless a gross change is produced such as could result only from a large increase in the permeability of the barrier between the blood and aqueous humor (19, 32, 76, 79, 107, 132).

7. Gonioscopy. Inspection of structures in the periphery of the anterior chamber of intact human and animal eyes encounters an optical difficulty due to internal refraction of obliquely incident light rays within the cornea. This difficulty may be easily overcome by altering the effective curvature of the surface either by immersing the eye in a solution (*e.g.*, physiological salt solution) or by applying a gonioscopic contact lens to the cornea. Through such a device all the structures in the recess of the angle between the back of the cornea and the iris may be examined microscopically. Clinically this examination is commonly carried out utilizing a binocular microscope of 20 to 30 power and a well-focused small light.

By this method one can inspect in the human eye the posterior surface of the cornea in the periphery, the trabecular meshwork of tissue through which the aqueous humor must pass to gain access to Schlemm's canal, the scleral spur to which the ciliary body is attached, a narrow band of ciliary body to which the iris is attached, and the iris itself. In animal eyes these structures are partly obscured by the pectinate ligaments.

For investigation of factors which influence the intraocular pressure, gonioscopy is of great value in detecting possible obstructions to outflow of aqueous humor (35, 56, 83, 118). Closure of the angle of the anterior chamber by forward bulging of the iris or by abnormal forward attachment of the iris may be seen, or deposits of pigment, of inflammatory cells, or of material resembling exfoliated lens capsule may be distinguished. In normal eyes blood may be seen in Schlemm's canal in back of the trabecular meshwork (8, 120). Gonioscopy

has, so far, yielded much more valuable data in clinical investigation than in animal studies.

VI. PHARMACOLOGICAL INFLUENCES UPON INTRAOCULAR PRESSURE

The influence of specific drugs upon the intraocular pressure can now be considered in the light of what has been presented concerning hydrodynamic, anatomical, physiological, pathological and methodologic aspects of the intraocular pressure. The aim will be to discuss the influence of drugs from an investigative standpoint, rather than from an historical or clinical therapeutic standpoint. Other reviews have covered many of the therapeutic aspects (53, 71, 96, 169).

A. Autonomic drugs

1. Parasympathomimetic drugs. Many of the drugs in this group have been utilized in the treatment of glaucoma because of their effectiveness in lowering the intraocular pressure. Miotic drugs such as pilocarpine, carbachol and physostigmine, applied to the glaucomatous eye, characteristically cause a decrease of intraocular pressure of several hours' duration. The decrease of pressure may be maintained for long periods, even for many years, if these drugs are applied regularly several times a day. On the basis of ocular hydrodynamics this sustained effect obviously can not be explained by an influence of these substances upon the volume of the intraocular vascular bed. Rather, as has long been suspected, the principal action of these substances is a lowering of the resistance which the aqueous humor encounters in flowing out of the eye (26, 79, 83, 119, 141, 156, 193). How this is accomplished has been established only in the case of angle-closure glaucoma (35, 53, 83). In this type of glaucoma, it may be recalled, the access of aqueous humor to the trabecular meshwork and Schlemm's canal is blocked by forward bulging of the iris. Gonioscopy, correlated with measurements of resistance to outflow and of rate of flow of aqueous humor has made it evident that parasympathomimetic substances relieve the mechanical block to outflow by causing the sphincter iridis muscle to contract and to withdraw the iris from contact with the trabecular meshwork, thus permitting the aqueous humor to leave the eye by its normal channels.

In the case of open-angle glaucoma the parasympathomimetic drugs also decrease the resistance to outflow, but how this is accomplished has not been established. Theoretically, a decrease in resistance to outflow could be accomplished either by an increase in the number of open channels or by a slight increase in the diameter of these channels (60). There are two main theories: one attributes the effect to a mechanical action on the trabecular meshwork; the other, to a dilating action on the veins peripheral to Schlemm's canal. According to the first theory, the sphincter muscles of the ciliary body and of the iris contract and pull upon the scleral spur, exerting some mechanical influence upon the trabecular meshwork which is also attached to the scleral spur (53, 55, 71, 96, 169, 187). This action is thought to spread open the channels in this meshwork. According to the vascular theory, parasympathomimetic substances dilate

the collector channels and aqueous humor veins peripheral to Schlemm's canal, thus causing a decrease in resistance in these vessels, as well as a fall in the venous pressure opposing aqueous outflow (6, 8, 14, 50). Obviously, knowledge of the actual site of the resistance to outflow will be crucial in deciding which of these two theories is valid.

Measurements of the pressure in episcleral veins, by methods which have already been described, have yielded conflicting results. One group of reputable investigators reports that the episcleral venous pressure is abnormally high in glaucoma and that the veins are dilated and the pressure lowered by pilocarpine (8, 50, 138, 139, 184, 186). Another and somewhat larger group of equally reputable investigators finds that the episcleral venous pressure is not abnormal in glaucoma, nor is it significantly influenced by pilocarpine (74, 77, 78, 135, 136, 159, 193, 196). Broadening of the stream of aqueous humor in dilated effluent veins after application of pilocarpine has been described and supported by photographic evidence, but this observation is compatible with a transient increase in the rate of escape of aqueous humor, resulting from either of the mechanisms which have been mentioned (8, 14).

A different mode of action of parasympathomimetic drugs, less common than the action on resistance to outflow, is encountered occasionally under special conditions. In patients having high intraocular pressure as a result of permanent obstruction of the outflow channels, a temporary lowering of the pressure occasionally is brought about by intensive local administration of parasympathomimetic drugs. Tonographic measurements in such cases indicate decreased flow of aqueous humor (83, 86). Similar treatment of animal eyes has been known for some time to increase temporarily the permeability of the blood-aqueous humor barrier (18, 166, 175, 176, 177). Probably, intensive treatment in certain clinical cases similarly causes a temporary increase in permeability of the barrier and a decrease of the osmotic effectiveness of the aqueous humor, resulting in diminished flow and lowered intraocular pressure.

In rabbit eyes, a transient rise in intraocular pressure may be observed after application of parasympathomimetic drugs. The rise is associated with conspicuous vasodilation and occurs despite temporary increase in the permeability of the blood-aqueous humor barrier (18, 166, 175, 176, 177). The response is greatest to the initial application of parasympathomimetic agents, and gradually disappears on repeated application (18). This type of transient rise in pressure is commonly provoked in rabbit eyes by substances which cause inflammation or vasodilation, as will be noted further in section VI. B. 7 and 8, pp. 173–174. In human eyes, a rise in pressure after application of parasympathomimetic drugs is relatively uncommon, although it is occasionally observed. The increase in vessel calibre, blood-aqueous humor permeability and intraocular pressure, which is provoked by parasympathomimetic drugs and by irritative agents in general, may be antagonized by parasympatholytic and sympathomimetic agents, as well as by stimulation of the sympathetic nerve supply to the eye (3, 18, 19, 41, 43, 132, 144, 166, 169).

Interestingly enough, the intraocular pressure in normal eyes is usually little influenced by application of pilocarpine (54), although some decrease in resistance to outflow is reported to occur (26).

In enucleated eyes, no action of parasympathomimetic drugs on the resistance of the outflow channels has been detected although some miosis may be observed (86, 90).

No fundamental differences in influence on the intraocular pressure have been established among the various parasympathomimetic drugs despite known pharmacological differences. Parasympathomimetic drugs which cause a decrease in intraocular pressure in human glaucomatous eyes are pilocarpine (53, 169), carbachol (147, 192), methacholine (53, 169), furfuryl trimethyl ammonium (148), urecholine (69), arecoline (53, 169) and trimethyl (2-methyl-1,3-dioxolan-4-methyl) ammonium iodide (86). Among the cholinesterase inhibitors which have similar effect are physostigmine (53, 169), neostigmine (53, 169), diisopropylfluorophosphate (124), tetraethylpyrophosphate (80, 81, 133) and diethyl-p-nitrophenyl phosphate (180, 201). Approximately half of these substances have been investigated by means of tonography and found to lower the resistance to outflow (26, 83, 193). Probably all have fundamentally the same mode of action. Variations in clinical characteristics among these drugs are attributable to differences in intensity and duration of action, and to differences in ability to penetrate into the eye, when topically applied.

2. Parasympatholytic drugs. Substances which cause mydriasis with or without cycloplegia may induce a dramatic rise in pressure in eyes with abnormally narrow angles (35, 118, 119, 120, 126, 129, 131), but little or no rise in normal eyes, or in eyes having primary or secondary glaucoma with wide and open angles (119, 120, 126, 131, 175). Similarly, interruption of the third cranial nerve with its parasympathetic supply to the eye has little or no effect on the pressure in normal eyes (93).

Among the various parasympatholytic agents no fundamental differences are recognizable in mode of action, but the hazard of protracted closure of the angle and severe elevation of pressure appears to be minimized by using substances which have a particularly short duration of action, *e.g.*, eucatropine (euphthalmine) and methyl atropine (eumydrine). These short-acting agents, when applied to the cornea, commonly block the sphincter iridis muscle more effectively than the more deeply situated ciliary muscle, and this could also, at least theoretically, influence the tendency to closure of the angle.

In the case of homatropine, administration to normal human eyes causes no consistent change in intraocular pressure, although sporadic increases, or decreases, of as much as 8 mm. Hg may be observed (129). In glaucomatous eyes the influence of homatropine upon the intraocular pressure has been found to be related principally to the width of the angle between the iris and the trabecular meshwork of tissue in the angle through which the aqueous humor normally escapes from the eye. In most cases of open-angle glaucoma, the effect of homatropine is not significantly greater than in normal eyes. However, in eyes in which the angle is narrow and which are subject to angle closure glaucoma, a significant

rise of intraocular pressure is commonly, but not uniformly, observed upon dilatation of the pupil by homatropine. This rise of pressure, generally, has been ascribed to mechanical blocking of the angle by the iris (129).

Agents having greater duration of action, such as atropine and scopolamine, have fundamentally the same effect as homatropine. These drugs, whether administered topically or systemically, induce little or no change in pressure, except occasionally in eyes having abnormally narrow angles they may bring about angle-closure and acute glaucoma (35, 119, 129, 131).

A noteworthy paradox in the action of mydriatic agents may occasionally be observed in certain eyes which, upon slight mydriasis, are subject to angle-closure glaucoma, but which may tolerate wide mydriasis without elevation of the pressure. In these eyes, it appears that the resistance to flow of aqueous humor from the posterior chamber to the anterior chamber, and the associated tendency for the iris to bulge forward, is critically related to the size of the pupil. Generally, conditions are at an optimum for angle-closure when the pupil is semi-dilated. When the pupil is widely dilated, the flow from posterior to anterior chamber may be so easy that the tendency to forward bulging of the iris is practically eliminated (35). In the treatment of iritis and iridocyclitis, parasympatholytic drugs, particularly atropine and scopolamine, are regularly employed, even when secondary glaucoma is present. Ordinarily, if the angle is of adequate width no aggravation of the glaucoma is caused. However, the factors controlling the intraocular pressure are particularly complex under these circumstances. The permeability of the blood-aqueous humor barrier which is greater than normal in intraocular inflammation may be returned at least partially to normal under the influence of parasympatholytic agents. If, before treatment, leakiness of the barrier has caused the intraocular pressure to be low through loss of secreted substances back to the blood stream, a rise in pressure may result under the influence of parasympatholytic agents, owing to improvement of the barrier (83, 110).

3. Sympathomimetic drugs. Epinephrine (52, 154, 169), neosynephrine (phenylephrine) (102), hydroxyamphetamine hydrobromide (paredrine, 3-hydroxyphenylisopropylamine), paredrinol hydrochloride (veritol, 4-hydroxyphenylisopropylmethylamine) and naphazoline hydrochloride (privine, 2-(1-naphthylmethyl)imidazoline) (108), have a slight but therapeutically valuable influence on the intraocular pressure in glaucoma. In normal eyes these drugs exert little effect on the pressure, but in open-angle glaucoma, and in glaucoma secondary to uveitis they often cause a decrease of 5 to 15 mm. Hg. When epinephrine is applied topically in the form of a 1.8 per cent solution of the bitartrate salt a brief mydriasis and vasoconstriction result, but the intraocular pressure may be lowered for many hours following a single application. The lowering of pressure may be maintained for months, or years, by application 2 or 3 times a day. Epinephrine and other sympathomimetic drugs are commonly employed in conjunction with pilocarpine or carbachol; the effects of these drugs upon the intraocular pressure are roughly additive. Under these conditions, the pupil is usually maintained in miosis. Norepinephrine has effects similar to epinephrine (106).

The mechanism by which the intraocular pressure is lowered by the sympathomimetic drugs has not been established. The duration of effect appears to be considerably greater than the apparent duration of the vasoconstriction or the mydriasis. Studies of the influence of sympathomimetic drugs on ocular blood vessels have generally been concerned with the initial brief phase, and any relation to long-term control of intraocular pressure has remained obscure. Injections of epinephrine subconjunctivally or retrobulbarly in animals has been observed to induce only a transient drop in pressure in cannulated eyes (41, 43). Studies of the influence of sympathomimetic drugs, particularly epinephrine, on the permeability of the blood-aqueous humor barrier have not revealed the basis for the pressure-lowering action, although an interesting protective or reparative influence on abnormally permeable blood-aqueous humor barriers has been demonstrated in numerous experiments. This influence has been observed in the eyes of animals in which the barrier was rendered abnormally permeable to fluorescein, ascorbate, or proteins by exposure to an irritating or inflammatory stimulus, such as cannulation of the anterior chamber, subconjunctival injection of 10 per cent sodium chloride solution, or intramuscular injection of theophylline (1, 32, 43, 107, 132, 175, 178, 191). Epinephrine, applied under these circumstances, has been found to preserve essentially normal permeability despite the noxious stimuli. The change in permeability appears to be a function of the degree of dilation of the uveal vessels. The transitory influences of systemically administered epinephrine and norepinephrine on the systemic blood pressure and its reflection in the intraocular pressure have been examined in animals, but these studies have shed little light on the enduring influence of epinephrine on the intraocular pressure of glaucomatous human eyes (167).

Tonographic investigation of the action of sympathomimetic drugs has been hampered by the rather small changes which they produce. However, epinephrine has been found to cause some decrease in the resistance to outflow of aqueous humor, and, in some instances, also a decrease in the rate of formation of aqueous humor (26, 86, 100, 193). Further study is needed to corroborate these findings and to determine the influence of sympathomimetic agents on the pressure in the veins which receive the outflow of aqueous humor.

To explain the lowering of resistance and the lowering of intraocular pressure by sympathomimetic drugs, a mechanical hypothesis may be entertained analogous to one of the hypotheses concerning the mechanims of action of the parasympathomimetic drugs. The radial and circular sets of smooth muscles of the iris and ciliary body which are innervated by the sympathetic and parasympathetic nervous systems respectively may both act upon the scleral spur to modify the channels for aqueous humor through the trabecular meshwork. The tension resulting from contraction of the sphincter or circular muscles may be transmitted to the scleral spur through the radial muscles, and, when the radial fibres also contract, the tension upon the scleral spur may be enhanced (53). However, this mechanical hypothesis has little or no experimental evidence either to support or to oppose it. Furthermore, it does not explain a lowering effect upon intraocular pressure which is of greater duration than the mydriatic effect.

Sympathomimetic mydriatic drugs occasionally cause an increase in intraocular pressure, and may induce an attack of acute glaucoma. This effect occurs in eyes with abnormally narrow angles. However, in some eyes which have narrow angles and which are subject to spontaneous attacks of angle-closure glaucoma it is possible to dilate the pupil maximally by means of sympathomimetic drugs without causing closure of the angle or elevation of intraocular pressure (35, 86, 126, 129). In these cases, it appears that by wide mydriasis the flow of aqueous humor from posterior to anterior chamber is rendered so easy that there is no significant pressure differential and no tendency to bulge the iris forward into contact with the trabecular meshwork. Usually the tendency of the iris to bulge forward is maximal when the pupil is only semi-dilated (35). A clinical impression exists that sympathomimetic mydriatic drugs are somewhat less likely to precipitate angle-closure glaucoma than are parasympatholytic mydriatics. If this is true, it may be conjectured that contraction of the radial fibres of the iris may oppose forward bulging of the iris.

4. Sympatholytic drugs. Neither sympathectomy nor pharmacological block of the sympathetic supply of the eye has more than a brief influence on the intraocular pressure (140, 190, 151), although slightly lower pressure occasionally has been noted in the eyes of patients with spontaneously occurring Horner's syndrome (200). Ergot, and the alkaloids derived from ergot, have no consistent or enduring influence on the intraocular pressure (2, 149, 150, 153, 181). Piperoxan hydrochloride (benodaine hydrochloride) has also been ineffectual (142); and dibenzyline, administered orally in a dose of 20 mgm. per day, does not significantly lower the intraocular pressure in glaucoma (190). On the other hand, dibenamine does cause a definite decrease in intraocular pressure (36, 37, 39, 45, 142, 145). This effect has been demonstrated to be due to partial inhibition of the formation of aqueous humor (45). Since there have been indications that epinephrine is a link in the redox chain of the mechanism for secreting aqueous humor, it appears likely that secretion is interfered with at this point (45).

Dibenamine has been shown to have some usefulness in emergency treatment of acute glaucoma, either primary or secondary, but not in continuous treatment (36, 37, 39, 45, 142, 145). This substance must be administered parenterally, and it has unwanted side-effects on the general circulation which outlast the influence upon the intraocular pressure. Direct application of dibenamine and related substances to the eye is impractical because they are irritating.

Another group of sympatholytic agents raises intraocular pressure, an action which may be associated with the conspicuous vasodilation evoked when these substances are applied to the eye. Priscoline (tolazoline hydrochloride) and vasculat (p-hydroxyphenylethanolbutylamine), in particular, cause a slight rise in intraocular pressure when injected subconjunctivally (127, 128, 130, 131). The rise is greater in glaucomatous eyes than in normal eyes, and provides a provocative test for early glaucoma (130, 131). It is not known why the effect is greater in glaucomatous eyes than in normal. The pressure may remain elevated by several mm. Hg for more than an hour after injection, which suggests that some temporary alteration of the rate of aqueous humor formation, or of the resistance

to outflow, or of the recipient venous pressure must be responsible rather than a simple change in the volume of the intraocular vascular bed. When priscoline (tolazoline hydrochloride) is administered parenterally no significant influence upon intraocular pressure is observed (203).

5. Ganglionic blocking drugs. The effects of blocking the autonomic ganglia of the eye itself have already been mentioned in discussion of the autonomic drugs, indicating that slight influences are observed in intact eyes, but that in inflamed, or irritated, eyes the sympathetic innervation may influence the permeability of the blood-aqueous barrier, and to some extent the intraocular pressure, through control of the state of the blood vessels. Blocking of the sympathetic ganglia by means of local procaine, and actual removal of the ganglia have slight or no effect upon the intraocular pressure in glaucoma.

Generalized ganglionic blocking, which causes a rapid fall in blood pressure, causes also a small fall in intraocular pressure (22, 23, 47, 137). However, the fall is transient even if the systemic hypotension is maintained. Hexamethonium has been observed to cause a prompt fall of blood pressure and a decrease of several mm. Hg in the intraocular pressure of both normal and glaucomatous eyes (23, 33, 165). However, despite repeated administration of the drug and persisting decrease of blood pressure, the intraocular pressure returns to its original level within a few hours. The short duration of the response suggests that the effect is primarily attributable to a change in volume of the intraocular vascular bed, and that if hexamethonium has any influence upon the formation or outflow of aqueous humor it must be rather brief. Insufficient information is available on the distensibility and contractibility of the intraocular vascular bed to permit realistic estimation of the possible duration of an alteration of intraocular pressure due to a change in vascular volume alone.

B. Non-autonomic drugs

1. Amyl nitrite. Inhalation of amyl nitrite commonly causes a rapid and brief rise of a few mm. Hg in intraocular pressure, coincident with vasodilation and flushing of the face (13, 86, 117). The changes closely resemble those observed in emotional blushing. The change in intraocular pressure in both instances is presumably a reflection of a transient increase in the volume of the intraocular vascular bed. A small secondary decrease in intraocular pressure has also been described, but no influence upon the inflow or the outflow has been demonstrated (40).

2. Histamine. Topically applied histamine causes dilatation of the vessels visible on the surface of the eye and also some miosis. A decrease in intraocular pressure has been induced in cases of acute angle-closure glaucoma by means of histamine, but little is known of its mode of action (52, 99). It is not known whether the reduction of pressure should be ascribed to the miotic action or to some influence on the blood-aqueous humor barrier. For some years histamine was employed in the form of a 10 per cent solution for emergency treatment of acute glaucoma, but such severe conjunctival reactions were evoked that it has largely been abandoned in ophthalmic practice. At one time a misconception was

entertained regarding the miotic activity of histamine; actually histamine has a rather weak miotic effect compared to that of the parasympathomimetic drugs, but because atropine fails to antagonize the miotic action of histamine this was interpreted as a sign of superior activity rather than as an indication of pharmacological dissimilarity (99). Injection of histamine intraocularly in animals produces a transient rise in pressure, owing presumably to dilation of vessels within the eye, but this is followed by increased permeability and subnormal pressure (66).

3. Drugs depressing or stimulating the central nervous system. Clinical observations that the intraocular pressure in glaucoma may be elevated when the patient is under emotional stress, and that the pressure may be decreased in periods of relaxation have led investigators to attempt to influence the intraocular pressure by depressing or stimulating the central nervous system. The results have been disappointing, for so far no definite pharmacological influence of this nature has been established.

General anesthesia with ether has no special influence on the intraocular pressure. However, the intraocular pressure may be affected secondarily to alteration of the blood pressure or the osmotic pressure of the blood (3, 29).

Narcosis and sedation are commonly employed in treatment of acute glaucoma, but a systematic study would be required to evaluate their effect satisfactorily. Particularly with morphine and to a lesser degree in natural sleep the possible mechanical influence of miosis would also have to be taken into account (53). The influence of the so-called tranquilizing agents such as chlorpromazine (thorazine) and the alkaloids of *Rauwolfia serpentina* are being investigated (190).

Among the stimulants of the central nervous system, caffeine has received most attention, but neither this nor other stimulants have yet been convincingly demonstrated to have an effect on the intraocular pressure through action on the central nervous system. Although a brief rise of intraocular pressure has often been found to follow ingestion of coffee or a solution of caffeine, this effect has been demonstrated to be due to the water rather than to the alkaloid (3, 131). Ingestion of water causes a slight rise in intraocular pressure, owing to temporary lowering of the osmotic pressure of the blood (30, 48, 103, 125, 163), but administration of caffeine by itself induces no consistent response.

4. Local anesthetic agents. Of the local anesthetic agents only cocaine is known to have an influence on the intraocular pressure when applied to the eye, and this only as a consequence of its mydriatic activity. The possibility of precipitating an attack of angle-closure glaucoma due to mydriasis has long been recognized as a real hazard if cocaine is employed in the presence of an unusually narrow angle (3, 71, 169).

Retrobulbar injection of other local anesthetics, blocking the sensory, motor and autonomic innervation of the eye and its adnexa, has been observed to cause a temporary decrease of intraocular pressure (70). In a recent analysis of this effect it was observed that injection of 1.5 cc. of 2 per cent procaine hydrochloride or 1 per cent lidocaine hydrochloride (xylocaine hydrochloride) behind the normal human eye caused a decrease of pressure in 5 minutes averaging 2 mm. Hg and

ranging from 0 to, occasionally, 8 mm. Hg. This effect was slightly enhanced by addition of epinephrine 1:50,000, but no effect was obtained when isotonic saline solution was substituted (174). No relation was found between the degree of paralysis of extraocular muscles and the reduction of pressure. No satisfactory explanation has been established for the effect.

5. Diamox. The secretory mechanism which has been conceived by Friedenwald (59), as the motivating factor in the formation of aqueous humor involves the production of hydroxyl ions at the ciliary epithelium and the reaction of these ions with carbonic acid to yield bicarbonate. Presumably, the carbonic acid is derived from the carbon dioxide of the blood, probably through a series of reactions catalyzed by the enzyme carbonic anhydrase, which has been found to be present in the ciliary processes (202). As a corollary to these considerations, it has been postulated that inhibition of carbonic anhydrase might slow the process of secretion. Sulfanilamide investigated as a potential inhibitor by Kinsey (unpublished) had no appreciable influence on intraocular pressure, but definite lowering of pressure has been obtained utilizing the more effective inhibitor, diamox (acetazoleamide) (24, 25, 87). This substance administered systemically in a dose of 250 to 500 mgm. causes prompt gradual fall of intraocular pressure of the order of one-third of the initial pressure in most types of glaucoma. In some eyes the decrease may be maintained for many months by administering 250 mgm. of the drug two to four times daily.

Determination of the resistance to outflow of aqueous humor by means of tonography, and estimation of the rate of flow by means of fluorescein indicate that the formation of aqueous humor is suppressed (24, 25, 26, 87). Attempts to induce a decrease of pressure by application of diamox to the eye, by means of drops or by subconjunctival or retrobulbar injection, have been ineffectual. Thus, it has not been established with certainty that the primary site of action is in the eye, although it is regarded as highly probable.

Diamox has already become a valuable drug in the treatment of acute glaucoma, but further investigation is required to elucidate its influence on the formation of aqueous humor and also to determine whether or not related substances might produce a greater effect.

Diamox has also a diuretic action which does not seem to account for the lowering of intraocular pressure. The effect on intraocular pressure can be maintained for many months while the diuretic action may be of much shorter duration unless periodic recovery periods are provided. Apparently other agents which produce diuresis have not been investigated systematically for influence on intraocular pressure, but no pressure lowering effect has been discovered in the ordinary course of clinical experience. Theophylline, administered systemically, has been noted to increase briefly the permeability of the blood-aqueous humor barrier in animals, but little is known of its influence on the intraocular pressure (3, 32).

6. Hormones. Occasional apparent association of change of intraocular pressure with emotional conditions and with physiological variations of body hormones has suggested to many observers the possibility of hormonal control of

intraocular pressure. Also, the administration of certain hormones, experimentally and clinically, has been observed to have an influence on the intraocular pressure (3). In open-angle glaucoma the intraocular pressure may vary somewhat as a consequence of variation of the rate of formation of aqueous humor, and in some instances this variation has appeared related to the emotional state (49, 50, 88, 162). A slight change in resistance to outflow of aqueous humor from normal eyes has been detected in association with the menstrual cycle and in pregnancy (27). Alterations of the intraocular pressure in animals have been reported to result from experimental disturbance of the gonads, the hypophysis, and the hypothalamus, but the significance of these observations remains to be established through experiments on larger numbers of animals with adequate controls (30, 143, 157, 200). There is indeed a need for systematic clinical and experimental investigation of the intraocular pressure where definite hormonal abnormalities are known to exist.

The influence of certain hormones on the intraocular pressure in glaucoma has been investigated by administering these substances to patients. The adrenocorticotropic hormone (ACTH) appears to have no influence, except in cases in which glaucoma is due to intraocular inflammation, and in these instances the pressure may be influenced secondarily to modification of the inflammation (31). Similarly, cortisone and hydrocortisone do not directly influence the intraocular pressure. On the other hand, progesterone, administered systemically in glaucoma, lowers the intraocular pressure appreciably, but despite continuing administration the effect is not sustained for more than a few days or weeks (27, 146, 155).

Pituitrin, injected subconjunctivally, has been reported to cause a small decrease in intraocular pressure, and some therapeutic application in cases of glaucoma has been made in the past (168). However, pituitrin has not proven to be a useful therapeutic agent, and nothing is known of its mode of action.

7. Argemone oil and sanguinarine. Possibly as the result of ingestion of oil from the seeds of *Argemone mexicana*, an unusual type of glaucoma may occur in association with "epidemic dropsy" in India. In this condition the intraocular pressure is sufficiently elevated for some weeks to cause cupping and atrophy of the optic nerves. Histologically no inflammatory cellular or fibrotic changes have been found in the angle of the anterior chamber, or in the drainage channels for aqueous humor, but considerable dilation of the uveal vessels has been observed. The cause for the increased intraocular pressure has not been established.

In a search for evidence for the cause of this glaucoma, the ocular effects of argemone oil and of an alkaloid obtained from it, sanguinarine (ψ-chelerythrine, or 7,8,2′,3′-dimethylenedioxy-1,2-benzphenanthridine methochloride) have been investigated by Hakim (98). He succeeded in producing transient acute rises in intraocular pressure in animals by injection of these derivatives of argemone seeds into, or about, the eye, but he did not succeed in inducing a glaucoma resembling that which occurs in patients with epidemic dropsy. Subconjunctival injection of 0.1 to 0.2 ml. argemone oil or 0.04 to 0.4 mgm. sanguinarine chloride in rabbits was found to produce a rise of approximately 25 mm. Hg in intraocular

pressure in 15 to 20 minutes, usually with return to the original level in 40 to 90 minutes. Similar results were obtained by injection of smaller doses of the same substances directly into the anterior chamber of the eyes. In all instances, a severe iritis and corneal edema were provoked. The inflammatory response and the rise in pressure were found to be suppressed by prior local medication with epinephrine, or systemic administration of ephedrine, BAL (dimercaprol), or cysteine.

The elevation of intraocular pressure which was produced by argemone oil or sanguinarine in animal eyes may not represent any specific pressure elevating property of these substances, since numerous other agents which cause intense local inflammation and vasodilation also cause a transient rise in intraocular pressure (3, 66). This phenomenon is, for example, exhibited by some parasympathomimetic drugs, especially diisopropylfluorophosphate in the eyes of rabbits (166). This effect too is suppressed by epinephrine. Priscoline (tolazoline hydrochloride) and vasculat (p-hydroxyphenylethanolbutylamine) (see section VI. A. 4.) appear to have a similar action in human eyes, which likewise is antagonized by epinephrine (127, 130, 131). Even physical irritation, such as that caused by removal of a small quantity of aqueous humor from rabbit eyes, is followed by vasodilation and a temporary increase of intraocular pressure which can be suppressed by epinephrine. Transient rises of intraocular pressure were also noted by Hakim (98) to be induced by various irritating substances other than argemone oil or sanguinarine, *e.g.*, by the alkaloids chelerythrine, quinidine, berberine and by extracts and seed oils from a series of papaveraceous plants; however, no rise was produced by bland, nonirritating substances.

The mechanism by which vasodilating substances cause the intraocular pressure to increase transiently has not been satisfactorily established. In some instances, the pressure rises despite increased permeability of the blood-aqueous humor barrier and even passage of plasma proteins into the aqueous humor. Epinephrine is known to oppose both the vasodilation and the increase in permeability. It remains to be determined whether the intraocular vascular bed is capable of volume changes sufficient to account for the rise in pressure, or whether vasodilation may through some influence on the outflow channels impede the escape of aqueous humor from the eye.

8. Miscellaneous agents. The enzyme hyaluronidase has been found by Bárány to cause a decrease of approximately 50 per cent in the resistance to outflow from the anterior chamber of excised animal eyes (20, 21). The enzyme was added directly to the fluid with which the eyes were perfused. Comparable addition of hyaluronidase to the aqueous humor *in vivo*, or injection of hyaluronidase outside of the eye, has not, however, been observed to lower the intraocular pressure (94, 152). Intraocular injection of the enzyme *in vivo*, unfortunately, evokes an inflammatory response, and this may obscure any influence on the resistance to outflow. The results in enucleated eyes are of interest in relation to attempts to discover the anatomical site of resistance to outflow of aqueous humor from the eye. However, as yet, the site of action of the enzyme has not been determined, and this in itself presents some problems. Hyaluronic acid has not been identified

in the structures of the outflow channels, nor is it necessarily only hyaluronic acid which is affected by the hyaluronidase. Comparison of the action of other enzymes and examination of the effect in glaucomatous eyes should furnish further interesting information.

Certain toxic cyanine and styroquinoline dyes injected into the carotid artery in rabbits cause, among other effects, decrease of intraocular pressure (15). These agents interfere with oxidative phosphorylation and oxygen-uptake in the ciliary processes, and reduce the content of ascorbic acid in the aqueous humor. However, these metabolic effects are less consistently induced than decrease of intraocular pressure. Furthermore, the dyes cause edema of the ciliary processes and severely destructive changes in the retina and choroid. Presumably, decrease in intraocular pressure is, at least in part, due to interference with secretion in the ciliary processes, whether directly inhibited or secondarily impaired by the inflammatory response.

Various substances which incite an inflammatory response, or provoke considerable ocular vasodilation may, on the other hand, cause a transient rise in intraocular pressure (3). This response is much more commonly noted in rabbit eyes than in human eyes. The phenomenon has already been referred to particularly in connection with argemone oil and sanguinarine, and, in that connection, it was pointed out that the mechanism has not been satisfactorily elucidated (98). To those substances which have already been listed as capable of inciting a transient rise in intraocular pressure upon local application to rabbit eyes may be added barium chloride (170), and nitrogen mustard (43).

Nicotine administered intravenously to rabbits at a dose of 0.28 mgm./kgm. is reported to cause a transient rise of a few mm. Hg in intraocular pressure. This may be a reflection of a change in blood pressure; but the mechanism has not been identified (30).

Curare and curare-like agents, administered systemically, do not appreciably alter the pressure in normal animal eyes. This suggests that the intraocular pressure is little influenced normally by the tone of the extraocular muscles, at least when the eye is at rest (38).

Some other substances, claimed to influence the intraocular pressure, have been omitted from discussion in this review because the significance, or the validity of the observations appears dubious. A more complete listing has been compiled by Ascher (3).

SUMMARY

The physiology and pathology of the intraocular pressure have now been explored to the stage of development of good working hypotheses. General hydrodynamic principles governing the intraocular pressure have been formulated and experimentally tested. Good evidence indicates that the aqueous humor is formed by a secretion-diffusion mechanism. Energy from metabolism in the ciliary processes accomplishes transport from the blood and concentration within the eye of hydroxyl, bicarbonate and ascorbate ions, thereby furnishing the osmotic driving force for movement of water into the eye. Sufficient potential osmotic

energy is available to produce an intraocular pressure of more than 100 mm. Hg, but in normal eyes the pressure is limited by continual escape of aqueous humor through special channels. The rate of escape of aqueous humor is governed by the resistance to flow which is encountered in these channels, and by the difference between pressure in the eye and the pressure of the blood in veins into which the escape channels drain. In normal eyes, the various parameters governing the intraocular pressure are such that a steady state with equal rates of inflow and outflow of aqueous humor obtains at pressures in the neighborhood of 15 mm. Hg. In glaucomatous eyes, an abnormally great resistance is encountered in the outflow channels and the intraocular pressure is elevated although the rate of inflow is not increased. Various causes for obstruction to outflow in glaucoma appear to characterize different forms of the disease. The most obvious obstruction is presented by the iris in eyes which have abnormally narrow spaces between the outflow channels and the dome of the iris. However, in the most prevalent form of glaucoma this space is ample and the iris is in no way implicated. In this case neither the anatomical site nor the cause for the abnormal resistance to outflow has been identified.

Attempts to correlate the influence of drugs on the intraocular pressure with the present concepts of physiology and pathology have succeeded to the extent of having achieved some distinctions between influence on rate of inflow of aqueous humor and influence on resistance to outflow. However, in few instances have the mechanisms by which drugs exert these influences been satisfactorily elucidated. In the case of mechanical opening, or closing, of an abnormally narrow space between iris and outflow channels, the mechanism of control of the obstruction by miotic or mydriatic drugs is evident, but in practically all other instances the manner of control of outflow or inflow remains obscure.

Development of the pharmacology of the intraocular pressure approximately parallels the development of its physiology and pathology. Progress in these three fields is to a considerable extent dependent on solution of the same problems. For instance, for elucidation of the mode of action of autonomic drugs in open-angle glaucoma, there is need of fundamental information on the site and nature of the resistance to outflow and on the basis for its increase in glaucoma. Furthermore, the relationship of outflow of aqueous humor to the condition of the meshwork of the tissue in the angle of the anterior chamber and to the pressure and flow of blood in the anastomosing outflow channels must be elucidated, in the interests of physiology and pathology, as well as pharmacology. More detailed knowledge of the secretory process for formation of aqueous humor would be valuable in relation to the pharmacology of control of intraocular pressure.

The approach to further investigation must be governed somewhat by the availability of suitable eyes, as well as by the objectives. For fundamental studies of mechanism of formation and control of aqueous humor, various animal eyes are convenient and probably well suited. Similarly, animal eyes may be useful for investigation of the dynamics of outflow and of the relationship to venous pressure, as well as for estimates of variability of the intraocular blood volume. However, the anatomical and possibly physiological differences between animal

eyes and human eyes, and the lack of a suitable counterpart of human glaucoma in animals, necessitates that studies which are to relate to human disease be carried out, as far as feasible, on human eyes. Clinical investigations, of course, offer valuable opportunity, especially for studies of hydrodynamics and testing of drugs, but the experimental possibilities are naturally limited to non-injurious procedures. Studies post-mortem on eyes left for scientific purposes by altruistic individuals can furnish much additional information concerning outflow of aqueous humor. Most valuable, at the present time, should be the study, post-mortem or post-enucleation, of glaucomatous eyes. This would be particularly valuable if these eyes were thoroughly studied clinically beforehand. Unfortunately, although many individuals who have glaucoma die daily, it is extremely rare that the eyes are donated for the scientific study of their disease.

Methods of study currently available have not yet been fully exploited, but there is need for methods with greater sensitivity and wider clinical applicability for determining rate of secretion, rate of outflow, and resistance to outflow of aqueous humor and for the measurement of intrascleral, as well as extrascleral vascular pressures.

BIBLIOGRAPHY

1. Adler, F. H., Landis, E. M. and Jackson, C. L.: The tonic effect of the sympathetic on the ocular blood vessels Arch. Ophth., 53: 239–253, 1924.
2. Agarwall, L. P.: Treatment of glaucoma with hydergine. Ophthalmologica, 127: 25–33, 1954.
3. Ascher, K. W.: The intraocular pressure. Tabul. biol., Hague, 22: 331–384, 1947.
4. Ascher, K. W.: Aqueous veins. Preliminary note. Am. J. Ophth., 25: 31–38, 1942.
5. Ascher, K. W.: Aqueous veins. I. Physiologic importance of visible elimination of intraocular fluid. Am. J. Ophth., 25: 1174–1209, 1942.
6. Ascher, K. W.: Aqueous veins. II. Local pharmacologic effects on aqueous veins. III. Glaucoma and aqueous veins. Am. J. Ophth., 25: 1301–1315, 1942.
7. Ascher, K. W.: Backflow phenomena in aqueous veins of normal and of glaucomatous eyes. Am. J. Ophth., 27: 1074–1089, 1944.
8. Ascher, K. W.: Aqueous veins (review). A.M.A. Arch. Ophth., 49: 438–451, 1953.
9. Ashton, N.: Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. Part I. Aqueous veins. Brit. J. Ophth., 35: 291–303, 1951.
10. Ashton, N.: Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. Part II. Aqueous veins (continued). Brit. J. Ophth., 36: 265–267, 1952.
11. Ashton, N. and Smith, R.: Anatomical study of Schlemm's canal and aqueous veins by means of neoprene casts. Part III. Arterial relations of Schlemm's canal. Brit. J. Ophth., 37: 577–586, 1953.
12. Ashton, N.: Some anatomical aspects of the problem of glaucoma. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
13. Baillart, B. and Bollack, J.: De l'action comparée de certaines substances médicamenteuses sur la tension intraoculaire et sur la pression artérielle. Ann. ocul., 158: 641–654, 1921.
14. Bain, W. E. S.: Variations in the episcleral venous pressure in relation to glaucoma. Brit. J. Ophth., 38: 129–135, 1954.
15. Ballintine, E. J. and Peters, L.: Effects of intracarotid injection of a basic dye on the ciliary body. Am. J. Ophth., 38, Part II: 153–163, 1954.
16. Bárány, E.: The influence of intraocular pressure on the rate of drainage of aqueous humor. Stabilization of intraocular pressure or of aqueous flow? Brit. J. Ophth., 31: 160–176, 1947.
17. Bárány, E.: The relative importance of ultrafiltration and secretion in the formation of aqueous humour as revealed by the influence of arterial blood pressure on the osmotic pressure of the aqueous. Acta physiol. scandinav., 13: 81–86, 1947.
18. Bárány, E.: The action of atropine, homatropine, eserine and prostigmine on the osmotic pressure of the aqueous humour. Acta physiol. scandinav., 13: 95–102, 1947.
19. Bárány, E.: The influence of gum arabic and dextran on the blood-aqueous barrier and intraocular pressure. Ophthalmologica, 116: 65–79, 1948.
20. Bárány, E.: In vitro studies of the resistance to flow through the angle of the anterior chamber. Acta Soc. med. upsalien., 59: 260–276, 1953.
21. Bárány, E.: Factors affecting the hydrodynamic resistance of the filtering angle. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications, Oxford. To be published in 1955.

22. BÁRÁNY, E. AND KINSEY, V. E.: The rate of flow of aqueous humor. I. The rate of disappearance of para-amino-hippuric acid, radioactive rayopake and radioactive diodrast from the aqueous humor of rabbits. Am. J. Ophth., 32: Part II: 177–188, 1949.
23. BARNETT, A. J.: Ocular effects of methonium compounds. Brit. J. Ophth., 36: 593–602, 1952.
24. BECKER, B.: Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, diamox. Am. J. Ophth. 37: 13–15, 1954.
25. BECKER, B.: The short-term administration of diamox in the therapy of the glaucomas. Internat. Congress of Ophthalmology, New York, 1954, in press.
26. BECKER, B.: The evaluation of glaucoma therapy by tonography. Internat. Congress of Ophthalmology, New York, 1954, in press.
27. BECKER, B. AND FRIEDENWALD, J. S.: Clinical aqueous outflow. A.M.A. Arch. Ophth., 50: 557–571, 1953.
28. BELLOWS, J., PUTENNEY, I. AND COWEN, J.: Use of sorbital in glaucoma. Arch. Ophth., 20: 1036–1040, 1938.
29. BENHAM, G. H., DUKE-ELDER, W. S. AND HODGSON, T. H.: Osmotic pressure of aqueous humor in normal and glaucomatous eyes. J. Physiol., 92: 355–360, 1938.
30. BIETTI, G. B. AND CIMA, V.: Experimentelle Untersuchungen über die Rolle der Hypophyse bei der durch Nikotin- und Wassergaben erzeugten Augendrucksteigerung. Klin. Monatsbl. Augenh., 124: 386–392, 1954.
31. BLAKE, E. M., FASANELLA, R. M. AND WONG, A. S.: The effect of ACTH in glaucoma. Am. J. Ophth., 33: 1231–1235, 1950.
32. BUSCHKE, W.: Blutsirkulation im Auge und Vitamin C. Arch. Augenh., 109: 691–705, 1936.
33. CAMERON, A. J. AND BURN, R. A.: Hexamethonium and glaucoma. Brit. J. Ophth., 36: 483–491, 1952.
34. CARPENTER, R. L.: Eye. In: Histology, ed. by Greep, R. O., pp. 844–889. Blakiston, New York 1954.
35. CHANDLER, P. A.: Narrow-angle glaucoma. A.M.A. Arch. Ophth., 47: 695–716, 1952.
36. CHRISTENSEN, L., SWAN, K. C. AND GOULD, J.: Hypotensive action of dibenamine in glaucoma. Northwest Med., 47: 731–733, 1948.
37. CHRISTENSEN, L. AND SWAN, K. C.: Adrenergic blocking agents in the treatment of glaucoma. Tr. Am. Acad. Ophth., 1949, pp. 489–497.
38. CIOCATTO, E. AND GARZINO, A.: Osservazioni oftalmologiche sull'azione del curaro somministrato per via endo-carotidea in soggetti non anestetizzati. Rass. ital. ottal., 22: 184–191, 1953.
39. CLARK, W. B. AND DUGGAN, J. W.: The use of dibenamine in the treatment of acute congestive glaucoma. Am. J. Ophth., 34: 535–542, 1951.
40. CRISTINI, G. AND PAGLIARANI, N.: Amyl nitrite test in primary glaucoma. Brit. J. Ophth., 37: 741–745, 1953.
41. DAVSON, H.: Nervous control of the intraocular system. J. Physiol. 3: 55P, 1950.
42. DAVSON, H., DUKE-ELDER, W. S. AND MAURICE, D. M.: Changes in ionic distribution following dialysis of aqueous humor against plasma. J. Physiol., 109: 32–40, 1949.
43. DAVSON, H. AND MATCHETT, P. A.: The control of the intraocular pressure in the rabbit. J. Physiol., 113: 387–397, 1951.
44. DAVSON, H. AND THOMASSEN, T. L.: The effect of intravenous infusion of hypertonic saline on the intraocular pressure. Brit. J. Ophth., 34: 355–359, 1950.
45. DELONG, S. L. AND SCHEIE, H. G.: Dibenamine: an experimental and clinical study. A.M.A. Arch. Ophth., 50: 289–298, 1953.
46. DOBREE, J. H.: Vascular changes that occur during the phasic variations of tension in chronic glaucoma. Brit. J. Ophth., 37: 293–300, 1953.
47. DRUCKER, A. P., SADOVE, M. S. AND UNNA, K. R.: Ocular manifestations of intravenous tetraethyl ammonium chloride in man. Am. J. Ophth., 33: 1564–1567, 1950.
48. DUKE-ELDER, W. S.: The reaction of intraocular pressure to osmotic variation in the blood. Brit. J. Ophth., 10: 1–39, 1926.
49. DUKE-ELDER, W. S.: Fundamental concepts in glaucoma. A.M.A. Arch. Ophth., 42: 538–545, 1949.
50. DUKE-ELDER, W. S.: The phasic variations in the ocular tension in primary glaucoma. Am. J. Ophth., 35: 1–21, 1952.
51. DUKE-ELDER, W. S.: Discussion. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
52. DUKE-ELDER, W. S. AND LAW, F. W.: Treatment of glaucoma by adrenaline and histamine (the so called "glaucosans"). Brit. Med. J., 1: 500–502, 1929.
53. DUNPHY, E. B.: Some observations on miotics. Am. J. Ophth., 32: 399–407, 1949.
54. FANTA, H.: The effect of pilocarpine on normal eyes. Ophthalmologica, 115: 338–353, 1948.
55. FORTIN, E. P.: Action du muscle ciliaire sur la circulation de l'oeil; insertion du muscle ciliaire sur la paroi du canal de Schlemm. Signification physiologique et pathologique. Compt. rend. Soc. biol., 102: 432–434, 1929.
56. FRANCOIS, J.: Discussion. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
57. FRIEDENWALD, J. S.: Circulation of aqueous. V. Mechanism of Schlemm's canal. A.M.A. Arch. Ophth., 16: 65–77, 1936.
58. FRIEDENWALD, J. S.: Dynamic factors in formation and reabsorption of aqueous humour. Brit. J. Ophth., 28: 502–510, 1944.
59. FRIEDENWALD, J. S.: The formation of the intraocular fluid. Am. J. Ophth., 32, Part II: 9–27, 1949.
60. FRIEDENWALD, J. S.: Discussion. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
61. FRIEDENWALD, J. S.: Committee on standardisation of tonometers. Am. Acad. Ophth. & Otol., Decennial Report, 1954.

62. Friedenwald, J. S. and Buschke, W.: The role of epinephrine in the formation of the intraocular fluid. Am. J. Ophth., 24: 1105–1114, 1941.
63. Friedenwald, J. S., Buschke, W. and Michel, H. O.: The role of ascorbic acid (vitamin C) in secretion of intraocular fluid. A.M.A. Arch. Ophth., 29: 535–574, 1943.
64. Friedenwald, J. S. and Herrmann, H.: Enzymatic oxidations in tissue fractions of ciliary processes. Bull. Johns Hopkins Hosp., 78: 119–125, 1946.
65. Friedenwald, J. S., Herrmann, H. and Moses, R.: Distribution of certain oxidative enzymes in the ciliary body. Bull. Johns Hopkins Hosp., 73: 421–434, 1943.
66. Friedenwald, J. S. and Pierce, H. F.: The pathogenesis of acute glaucoma. II. Experimental study. A.M.A. Arch. Ophth., 3: 574–582, 1930.
67. Friedenwald, J. S. and Pierce, H. F.: Circulation of the aqueous. II. Mechanism of secretion of the intraocular fluid. A.M.A. Arch. Ophth., 8: 9–23, 1932.
68. Friedenwald, J. S. and Stiehler, R. D.: Circulation of the aqueous. VII. A mechanism of secretion of the intraocular fluid. A.M.A. Arch. Ophth., 20: 761–786, 1938.
69. Frisch, F. and Leopold, I. H.: Evaluation of the urethane of beta-methylcholine chloride in chronic glaucoma. Am. J. Ophth., 36: 442–445, 1953.
70. Gifford, H. Jr.: A study of the effect of retrobulbar anesthesia on the ocular tension and the vitreous pressure. Am. J. Ophth., 32: 1359–1368, 1949.
71. Gifford, S. R.: Some modern preparations used in the treatment of glaucoma. Arch. Ophth., 57: 612–637, 1928.
72. Goldmann, H.: Abfluss des Kammerwassers beim Menschen. Ophthalmologica, 111: 146–153, 1946.
73. Goldmann, H.: Weitere Mitteilung über den Abfluss des Kammerwassers beim Menschen. Ophthalmologica, 112: 344–349, 1946.
74. Goldmann, H.: Über Abflussdruck und Glasstabphänomen. Ophthalmologica, 116: 195–198, 1948.
75. Goldmann, H.: An analysis of primary glaucoma. Tr. Ophth. Soc. U. Kingdom, 69: 455–476, 1949.
76. Goldmann, H.: Über Fluorescein in der menschlichen Vorderkammer. Ophthalmologica, 119: 65–95, 1950.
77. Goldmann, H.: Der Druck im Schlemmschen Kanal bei Normalen und bei Glaucoma simplex. Experientia, 6: 110–111, 1950.
78. Goldmann, H.: Abflussdruck, Minutenvolumen und Widerstand der Kammerwasserströmung des Menschen. Docum. Ophth., V-VI: 278–356, 1951.
79. Goldmann, H.: Outflow of the intraocular fluid. Coun. Internat. Org. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
80. Grant, W. M.: Miotic and antiglaucoma activity of tetraethyl pyrophosphate in human eyes. A.M.A. Arch. Ophth., 39: 579–586, 1948.
81. Grant, W. M.: Additional experiences with tetraethyl pyrophosphate in treatment of glaucoma. A.M.A. Arch. Ophth., 44: 362–364, 1950.
82. Grant, W. M.: Tonographic method for measuring the facility and rate of aqueous flow in human eyes. A.M.A. Arch. Ophth., 44: 204–214, 1950.
83. Grant, W. M.: Clinical measurements of aqueous outflow. A.M.A. Arch. Ophth., 46: 113–131, 1951.
84. Grant, W. M.: Clinical tonography. Tr. Am. Acad. Ophth., 1951, pp. 774–781.
85. Grant, W. M.: Tonography. In: Modern trends in ophthalmology, ed. by Sorsby, A., vol. 3. Butterworth & Co., London 1955.
86. Grant, W. M.: Unpublished data.
87. Grant, W. M. and Trotter, R. R.: Diamox (acetazoleamide) in the treatment of glaucoma. A.M.A. Arch. Ophth., 51: 735–739, 1954.
88. Grant, W. M. and Trotter, R. R.: Outflow of intraocular fluid (clinical aspects). Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications Ltd., Oxford. To be published in 1955.
89. Grant, W. M. and Trotter, R. R.: Tonographic measurements in enucleated eyes. A.M.A. Arch. Ophth., 53: 191-200, 1955.
90. Grant, W. M. and Trotter, R. R.: Factors responsible for resistance to outflow of intraocular fluid. Internat. Congress of Ophthalmology, New York, 1954, in press.
91. Greaves, D. P. and Perkins, E. S.: Aqueous veins in rabbits. Brit. J. Ophth., 35: 119–124, 1951.
92. Greaves, D. P. and Perkins, E. S.: Influence of the sympathetic nervous system on the intraocular pressure and vascular circulation of the eye. Brit. J. Ophth., 36: 258–264, 1952.
93. Greaves, D. P. and Perkins, E. S.: Influence of the third cranial nerve on intraocular pressure. Brit. J. Ophth., 37: 54–57, 1953.
94. Gualdi, G.: L'azione della jaluronidasi sul tono endoculare e sul diametro pupillare. Rass. ital. ottal., 19: 405–423, 1950.
95. Guerry, D.: The use of the Sanborn electromanometer in the study of pharmacological effects upon the intraocular pressure. Tr. Am. Ophth. Soc., 49: 525–555, 1951.
96. Gutton, J. S.: Pharmaco-dynamics of the intraocular muscles. A.M.A. Arch. Ophth., 24: 555–560, 1940.
97. Haas, J. S. and Scheie, H. G.: Peripheral iridectomy in narrow angle glaucoma. Tr. Am. Acad. Ophth., 56: 589–595, 1952.
98. Hakim, S. A. E.: Argemone oil, sanguinarine and epidemic-dropsy glaucoma. Brit. J. Ophth., 38: 193–215, 1954.
99. Hamburger, C.: Das stärkste Mioticum. Ztschr. Augenh., 60: 109–110, 1926.
100. Hara, K.: Influence of epinephrine and acetylcholine on the pulsation curve of intraocular tension. Acta Soc. Ophth. Jap., 56: 883–890, 1952.

101. HEATH, P.: Use of phenylephrine hydrochloride (neo-synephrine hydrochloride) in ophthalmology. A.M.A. Arch. Ophth., 41: 172–177, 1949.
102. HENDERSON, E. E. AND STARLING, E. H.: The factors which determine the production of intraocular fluid. Proc. Roy. Soc. London, s.B, 77: 294–310, 1905–6.
103. HERTEL, E.: Experimental investigation of the dependence of the intraocular pressure on the composition of the blood. Arch. Ophth., 88: 197–229, 1914.
104. HODGSON, T. H.: Studies on the aqueous humor in normal and glaucomatous eyes. Tr. Ophth. Soc. U. Kingdom, 58, Part I: 87–97, 1938.
105. HODGSON, T. H. AND MACDONALD, R. K.: Slit-lamp studies on the flow of the aqueous humor. Brit. J. Ophth., 38: 266–272, 1954.
106. HOFMANN, H.: Nor-Adrenalin in der Augenheilkunde. Klin. Monatsbl. Augenh., 124: 63–76, 1954.
107. HUBER, A.: Zur Pharmakologie der Blut-Kammerwasserschranke. Ophthalmologica, 114: 217–227, 1947.
108. HUGGERT, A.: The use of privine as a pressure reducing medium in iridocyclitis glaucomatosa. Acta ophth. 28: 393–408, 1950.
109. KINSEY, V. E.: Dehydroascorbic acid—ascorbic acid in the aqueous humor of rabbits. Am. J. Ophth., 33: 257–268, 1950.
110. KINSEY, V. E.: A unified concept of aqueous humor dynamics and the maintenance of intraocular pressure. A.M.A. Arch. Ophth., 44: 215–235, 1950.
111. KINSEY, V. E.: Chemical composition and osmotic pressure of the aqueous humor and plasma of the rabbit. J. Gen. Physiol., 34: 389–402, 1951.
112. KINSEY, V. E.: Comparative chemistry of aqueous humor in posterior and anterior chambers of rabbit eyes. A.M.A. Arch. Ophth., 50: 401–417, 1953.
113. KINSEY, V. E. AND GRANT, W. M.: The mechanism of aqueous humor formation inferred from chemical studies on blood-aqueous humor dynamics. J. Gen. Physiol., 26: 131–149, 1942.
114. KINSEY, V. E. AND GRANT, W. M.: The secretion-diffusion theory of intraocular fluid dynamics. Brit. J. Ophth. 28: 355–361, 1944.
115. KINSEY, V. E., GRANT, W. M. AND COGAN, D. G.: Water movement and the eye. A.M.A. Arch. Ophth., 27: 242–252, 1942.
116. KINSEY, V. E., PALM, E. AND CAVANAUGH, G. A.: Mechanism of posterior and anterior aqueous humor formation. Internat. Congress of Ophthalmology, New York, 1954, in press.
117. KOCHMANN, M. AND ROWER, P.: Experimental investigation of pathologic fluid exchange in the eye. Arch. Ophth., 88: 528–533, 1914.
118. KRONFELD, P. C.: Gonioscopic correlates of responsiveness to miotics. A.M.A. Arch. Ophth., 32: 447–448, 1944.
119. KRONFELD, P. C.: Provocative tests. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications, Oxford. To be published in 1955.
120. KRONFELD, P. C., MCGARRY, H. I. AND SMITH, H. I.: Gonioscopic studies on the canal of Schlemm. Am. J. Ophth., 25: 1163–1173, 1942.
121. LANGHAM, M.: The nature and origin of the aqueous humor. Internat. Congress of Ophthalmology, New York, 1954, in press.
122. LANGHAM, M. AND WYBAR, K. C.: Fluorophotometric apparatus for the objective determination of fluorescence in the anterior chamber of the living eye. Brit. J. Ophth., 38: 52–57, 1954.
123. LANGLEY, D. AND MACDONALD, R. K.: Clinical method of observing changes in the rate of flow of aqueous humour in the human eye. I. Normal eyes. Brit. J. Ophth., 36: 432–437, 1952.
124. LEOPOLD, I. AND COMROE, J.: Use of diisopropyl fluorophosphate (DFP) in treatment of glaucoma. A.M.A. Arch. Ophth., 35: 1–16, 1946.
125. LEYDHECKER, W.: The water drinking test. Brit. J. Ophth., 34: 457–479, 1950.
126. LEYDHECKER, W.: Mydriatica und primäres Glaukom. Ber. deutsch. ophth. Gesellsch., 57: 199–203, 1951.
127. LEYDHECKER, W.: Glaukombehandlung mit Vasculat. Klin. Monatsbl. Augenh., 121: 513–524, 1952.
128. LEYDHECKER, W.: Eine neue Belastungsprobe zur Diagnose des Glaukoms. Klin. Monatsbl. Augenh., 123: 568–577, 1953.
129. LEYDHECKER, W.: Die Wirkung von Homatropin auf die Tension des gesunden und des glaucomkranken Auges. Arch. Ophth. (von Graefes), 155: 387–396, 1954.
130. LEYDHECKER, W.: Die Priscolprobe bei Glaukom. Klin. Monatsbl. Augenh., 125: 57–61, 1954.
131. LEYDHECKER, W.: Experiences with provocative tests in glaucoma. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications, Oxford. To be published in 1955.
132. LINKE, A.: Untersuchungen über den Einfluss des Sympathikus auf die Permeabilität der Augengefässe. Arch. Augenh., 104: 264–323, 1931.
133. LINN, J. G. JR. AND TOMARELLI, R. C.: An evaluation of the various anticholinesterase agents. Am. J. Ophth., 35, part II: 46–53, 1952.
134. LINNER, E.: Measurement of the pressure in Schlemm's canal and in the anterior chamber of the human eye. Experientia, 5: 541–542, 1949.
135. LINNER, E.: The episcleral venous pressure during tonography. Internat. Congress of Ophthalmology, New York, 1954, in press.
136. LINNER, E., RICKENBACH, C. AND WERNER, H.: Comparative measurements of pressure in aqueous veins and conjunctival veins using different methods. Acta ophth., 28: 469–479, 1950.
137. LJUŠTINA-IVANČIĆ, V.: Tetra-Aethyl-Ammonium in der Therapie des Glaucoms. Ophthalmologica, 126: 378–387, 1953.

138. Löhlein, H.: Beeinflussung von episkleralem Venendruck und Abflussdruck des Kammerwassers im gesunden und glaukomkranken Auge. Ber. deutsch. ophth. Gesellsch., 56: 146-151, 1950.
139. Löhlein, H. and Weigelin, E.: Abflussdruck des Kammerwassers im normalen und glaukomatösen Auge. Ber. deutsch. ophth. Gesellsch., 55: 170-174, 1949.
140. Miller, S. J. H.: Stellate ganglion block in glaucoma. Brit. J. Ophth., 37: 70-76, 1953.
141. 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.
142. Mullen, C. R. and Leopold, I. H.: Adrenergic blocking agents in treatment of glaucoma. A.M.A. Arch. Ophth., 46: 549-552, 1951.
143. Müller, L.: Hypophyse und Auge. Klin. Monatsbl. Augenh., 74: 709-712, 1926.
144. Nash, C. B. and Woodbury, R. A.: Influence of atropine on intraocular pressure in dogs. Am. J. Physiol., 176: 65-66, 1954.
145. Newell, F. W., Ridgway, W. L. and Zeller, R. W.: The treatment of glaucoma with dibenamine. Am. J. Ophth., 34: 527-536, 1951.
146. Obal, A.: Gelbkörperhormon-Anwendung zur Glaukomtherapie. Klin. Monatsbl. Augenh., 117: 201-203, 1950.
147. O'Brien, C. S. and Swan, K. C.: Doryl in the treatment of glaucoma simplex. Tr. Am. Ophth. Soc., 39: 175-193, 1941.
147a. Ophthalmic pathology; An atlas and textbook. Saunders, Philadelphia 1953, pp. 289-308.
148. Owens, E. U. and Woods, A. C.: The use of furmethide in comparison with pilocarpine and eserine for the treatment of glaucoma. Am. J. Ophth., 30: 995-996, 1947.
149. Pereyra, L.: First clinical investigations on the action of dihydroergotamine (DHE 45) in ophthalmology. Gior. ital. oftal., 1: 165-171, 1948. (As abstracted in Am. J. Ophth., 32: 159, 1948.)
150. Persichetti, C.: Sull'efficacia della diidroergotamina (D.H.E. 45) nell'emicrania oftalmica e nel glaucoma. Boll. ocul., 29: 234-250, 1950.
151. Peters, A.: Das Glaukom. Springer, Berlin 1930.
152. Planten, J. T. and Hoffenbrouwers, R.: Experiments on intraocular hyaluronidase administration. Ophthalmologica, 127: 117-121, 1954.
153. Posner, A.: The effect of certain hydrogenated alkaloids of ergot on glaucoma. Am. J. Ophth., 33: 1551-1554, 1950.
154. Post, L. T.: Laevo-glaukosan and epinephrine bitartrate in the treatment of glaucoma. A.M.A. Arch. Ophth., 11: 187-193, 1934.
155. Posthumas, R. G.: The use and possibilities of progesterone in the treatment of glaucoma. Ophthalmologica, 124: 17-18, 1952.
156. Prijot, E. and Weekers, R.: Mesure de la résistance à l'écoulement de l'humeur aqueuse au moyen du tonomètre électronique. Part IV. Mode d'action de la pilocarpine dans le glaucome chronique non inflammatoire. Ophthalmologica, 124: 12-14, 1952.
157. Radnot, M.: Effect of testosterone (androgen) preparation on pressure. Ophthalmologica, 114: 168-171, 1947.
158. Rickenbach, K. and Werner, H.: Scheinbarer Abflussdruck, Tension und Druck in Kammerwasservenen. Ophthalmologica, 120: 22-27, 1950.
159. Robertson, J. D.: Formation and exit of the intraocular fluids. Brit. J. Ophth., 21: 401-447, 1937.
160. Robertson, J. D.: The aqueous humour; A secretion. Tr. Ophth. Soc. U. Kingdom, 49: 611-681, 1939.
161. Roepke, R. R. and Hetherington, W. A.: Osmotic relation between aqueous humour and blood plasma. Am. J. Physiol., 130: 340-345, 1940.
162. Roetth, A. de, Jr.: Relation of tonography to phasic variations of intraocular pressure. A.M.A. Arch. Ophth. 51: 740-749, 1954.
163. Roetth, A. de, Jr.: Effect of changes in osmotic pressure of blood on aqueous humor dynamics. A.M.A. Arch. Ophth., 52: 571-582, 1954.
164. Ross, E. J.: Circulation of the aqueous humour and the experimental determination of its rate of flow. Brit. J. Ophth., 36: 41-51, 1952.
165. Rycroft, B. W. and Romanes, G. J.: Preliminary report on the use of methonium compounds and general anesthesia in ophthalmic surgery. Brit. J. Ophth., 36: 29-39, 1952.
166. Sallmann, L. von and Dillon, B.: The effect of di-isopropyl fluorophosphate on the capillaries of the anterior segment of the eye in rabbits. Am. J. Ophth., 30: 1244-1262, 1947.
167. Sallmann, L. von, Meyers, M. P. and Pilat, B.: Studies of the effect of noradrenaline and adrenaline on the eye. Am. J. Ophth., 36, Part II: 91-102, 1953.
168. Samojloff, J.: Einige Untersuchungen über die Wirkung des Pituitrins auf den Augendruck. Klin. Monatsbl. Augenh., 78: 55-61, 1927.
169. Scheie, H. G.: Primary glaucoma III: The treatment of primary glaucoma by medical means. Tr. Am. Acad. Ophth., 1949, pp. 186-212.
170. Schmidt, K.: Blutmengenschwankungen bei Anwendung von Bariumchlorid und Suprarenin und Versuch einer absoluten Blutmengenbestimmung im Kaninchenauge. Arch. Augenh., 104: 427-440, 1931.
171. Seidel, E.: Weitere experimentelle Untersuchungen über die Quelle und den Verlauf der intraokularen Saftströmung. XX. Mitteilung über die Messung des Blutdruckes in dem episcleralen Venengeflecht, den vorderen Ciliar- und den Wirbelvenen normaler Augen. Arch. Ophth. (von Graefes), 112: 252-259, 1923.
172. Seidel, E.: Weitere experimentelle Untersuchungen über die Quelle und den Verlauf der intraokularen Saftströmung. XXII. Über die Messung des Blutdruckes in den vorderen Ciliararterien des menschlichen Auges. Arch. Ophth. (von Graefes), 114: 157-162, 1924.

173. Sondermann, R.: Experimentelle Untersuchungen über die Durchblutungsgrösse des Auges bei normalem und abnormalem Drucke. Arch. Augenh., 105: 698-703, 1932.
174. Snydacker, D., Deutsch, W. E. and Bayard, W. L.: Various anesthetic agents used in retrobulbar injections (a comparative study). A.M.A. Arch. Ophth., 51: 473-480, 1954.
175. Swan, K. C. and Hart, W. M.: A comparative study of the effects of mecholyl, doryl, eserine, pilocarpine, atropine and epinephrine on the blood-aqueous barrier. Am. J. Ophth., 23: 1311-1319, 1940.
176. Szasz, A.: Die medikamentöse Beeinflussung der reaktiven Hypertonie. Arch. Augenh., 104: 155-166, 1931.
177. Szasz, A.: Die medikamentöse Beeinflussung des Eiweissgehaltes des Kammerwassers. Arch. Augenh., 104: 167-176, 1931.
178. Szasz, A.: Die medikamentöse Beeinflussung des Eiweissgehaltes des Kammerwassers. Arch. Augenh., 105: 690-697, 1932.
179. Theobald, G. D.: Schlemm's canal. Its anastomoses and anatomic relations. Tr. Am. Ophth. Soc., 32: 574-595, 1934.
180. Thiel, H. L.: Über Versuche mit einem neuen synthetischen Miotikum "Mintacol" bei Glaukom. Klin. Monatsbl. Augenh., 114: 454-455, 1949.
181. Thiel, R.: Über die Wirkung des Ergotamins (Gynergen) auf den Augendruck. Klin. Wchnschr., 5: 895-899, 1926.
182. Thomassen, T. L.: Experimental investigations into the conditions of tension in normal eyes and in simple glaucoma. Acta ophth., 27: 9-191, 1946.
183. Thomassen, T. L.: On aqueous veins. Acta ophth., 25: 369-376, 1947.
184. Thomassen, T. L.: The venous tension in eyes suffering from simple glaucoma. Acta ophth., 25: 221-235, 1947.
185. Thomassen, T. L.: On the exit of aqueous humor in normal eyes. Acta ophth., 28: 479-487, 1950.
186. Thomassen, T. L., Perkins, E. S. and Dobree, J. H.: Aqueous veins in glaucomatous eyes. Brit. J. Ophth., 34: 221-237, 1950.
187. Thomson, A.: The gross anatomy of the filtration angle of the human eye. Ophthalmoscope, 8: 608-614, 1910.
188. Thorpe, H. E.: Diamox in the treatment of non-leaking flat anterior chamber occurring after cataract extraction and associated with choroidal detachment. Internat. Congress of Ophthalmology, New York, 1954, in press.
189. Tromoso, M. A.: The intrascleral vascular plexus and its relations to the aqueous outflow. Am. J. Ophth., 25: 1153-1162, 1942.
190. Trotter, R. R.: Unpublished data.
191. Tutui, Y.: Über den Einfluss der Blutbeschaffenheit auf das Kammerwasser. Arch. Augenh., 104: 110-154, 1931.
192. Velhagen, K.: Die Grundlagen der okularen Pharmakologie und Toxikologie des Carbaminoylcholin (Lentin, Doryl). Arch. Augenh., 107: 319-334, 1933.
193. Wekkers, R.: The mode of action of medical and surgical methods of reducing the ocular tension. Coun. Internat. Org. Med. Sc. Symp. on Glaucoma, Canada, 1954. Blackwell Scientific Publications, Oxford. To be published in 1955.
194. Wekkers, R. and Delmarcelle, Y.: Pathogenesis of intraocular hypertension in cases of arteriovenous aneurysm. A.M.A. Arch. Ophth., 48: 338-343, 1952.
195. Wekkers, R. and Delmarcelle, Y.: Hypotonie oculaire par réduction du débit de l'humeur aqueuse. Ophthalmologica, 125: 426-437, 1953.
196. Wekkers, R. and Delmarcelle, Y.: Pathogénie et traitement des altérations de la tension oculaire au cours des uvéities. Ann. ocul., 186: 876-887, 1953.
197. Wekkers, R., Heintz, A. and Prijot, E.: Recherches expérimentales sur les fonctions des veines aqueuses. Bull. Soc. Belge Opht., 95: 1-16, 1950.
198. Wekkers, R. and Prijot, E.: Vasoconstriction des veines aqueuses et ophtalmotonus. Ophthalmologica, 121: 264-274, 1951.
199. Wekkers, R. and Prijot, E.: Mesure de la résistance à l'écoulement de l'humeur aqueuse au moyen du tonomètre electronique. Ophthalmologica, 123: 114-122, 1952.
200. Weinstein, P.: Glaucoma. Pathology and therapy. Mosby, St. Louis 1953.
201. Wirth, W.: Zur Pharmakologie der Phosphorsäureester. Diäthyl-p-nitrophenylphosphat ("Mintacol"). Arch. exper. Path. u. Pharmakol., 207: 547-566, 1949.
202. Westrand, P. J.: Carbonic anhydrase in the anterior uvea of the rabbit. Acta physiol. scandinav., 24: 144-148, 1951.
203. Zarrabi, M. Observations on priscol in ophthalmology. Ophthalmologica, 122: 76-80, 1951.