THEORY OF NERVOUS REGULATION OF INTRAOCULAR PRESSURE

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Introduction

AMONG THE MOST CHALLENGING AND IMPORTANT FEATURES of intraocular pressure regulation are those associated with nervous mediation. This is especially so in connection with glaucoma, because of the efficacy of adrenergic drugs in controlling both the progressive increase in intraocular pressure and the accompanying deterioration (and ultimate loss) of pressure regulation.

Accordingly, we are led to make a first attempt to formulate a phenomenological theory for describing influences of the sympathetic nervous system on the control of intraocular pressure. The theory is found to be in good agreement with many experimental data, so that it affords a simple conceptual framework for understanding important aspects of aqueous dynamics, including some of the characteristics of early glaucoma.

We attempt to be anatomically and physiologically consistent with respect to essential features of the eye that have been firmly established. Where firm information is not available, however, it is necessary to make certain assumptions. But, since this presentation is intended for the physical scientist and engineer, we shall pass over most of the anatomical and physiological evidence in support of these assumptions, striving merely to render them physically reasonable. A few of these assumptions may not agree with some widely held concepts; however they are amenable to experimental test. For those who may be interested in such aspects, a more complete development may be found in the original work, of which this presentation is a digest.[1]

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[1] R. W. Hart, "Theory of Neural Mediation of Intraocular Dynamics," to be submitted for publication.

Proper regulation of intraocular pressure is essential to normal eye function. Many experimental studies have indicated that the nervous system plays an important role, but how the mediation is accomplished has remained obscure. Here, we develop a phenomenological theory that mimics a number of features characteristic of the living eye. The two essential concepts are (a) both aqueous humor and venous blood compete for space in the aqueous outflow drainage channels so that the aqueous outflow resistance depends on the rate of blood flow, and (b) blood flow, and thereby rate of formation of aqueous humor, is controlled by vasoconstrictors and vasodilators excited by neural elements that respond to tissue deformation. The theory offers unifying concepts formulated mathematically so that they can be confirmed or denied by experiments.

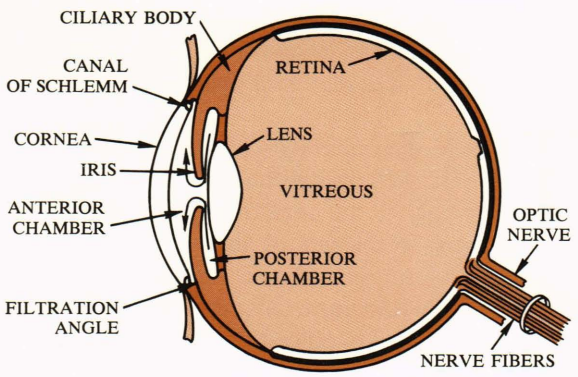

Fig. 1—Schematic representation of the eye, showing locations of structures of primary concern to intraocular pressure regulation. The eye is pressurized by the aqueous humor, which is "pumped" into the eye through ciliary processes in the anterior ciliary body and leaks out through the eye wall in the vicinity of the filtration angle. The flow rate is very slow and the contents of the globe are relatively flaccid but incompressible so that pressure is transmitted uniformly throughout the interior volume (as it would be if the contents of the eye were water).

Background

The gross anatomy of the eye is diagrammed in Fig. 1, which shows the components of major concern to intraocular pressure regulation and their spatial relationship with other eye structures. We shall, of course, have to examine these components in more detail in order to formulate their behavior. Before doing so, however, it will be helpful to review briefly some of the general aspects of the problem.

Functions of Intraocular Pressure—Function of the eye as a sense organ requires the delivery of an image to the retina and this, in turn, requires a dimensionally stable orb as well as optical transparency of the tissues through which light must pass in order to reach the retina. Dimensional stability presents a problem because the eye is made up of very flexible tissues. Transparency presents a problem because the tissues of the light pathway must be nourished, and intimate use of blood for this purpose is precluded because blood is not transparent (ordinarily, a blood vessel can supply nourishment and remove waste from only a very small region, radius $\sim 10^{-2}$cm, in its immediate neighborhood).

Both of these problems are solved by derivation from the blood of a few microliters per minute of a watery fluid, the aqueous humor. This fluid is "pumped" into the eye at a sufficient rate to pressurize it, thereby achieving dimensional stability in much the same way that a tire or a football is made dimensionally stable by pressurization. Further, the aqueous humor contains essential nutrients and bathes the tissues of the light pathway, thereby providing for their nourishment. Finally, the aqueous humor leaks out of the eye through a drainage network, whereupon it flows through episcleral veins to rejoin the blood stream. As the aqueous flows from the eye it carries with it the metabolic wastes from the tissues that it nourishes, thus taking care of the waste disposal problem.

Basic Aspects of Pressure Regulation and Stability—Normally, the pressure within the eye is maintained in the neighborhood of 15 to 20 Torr. Maintenance of a suitable pressure is important. If the pressure is too low, the shape of the globe is variable and the optic image is not stabilized on the retina. On the other hand, if the pressure is too high, the hydraulic head forcing blood into the

eye will be insufficient to nourish tissues such as the retina. (This is believed to account at least in part for the loss of vision associated with glaucoma.)

The basic idea underlying intraocular pressure regulation is well established—the pressure can be steady only if the rate of aqueous outflow is exactly equal to the rate of aqueous formation. If the rate of formation should temporarily exceed the rate of outflow, for example, the fluid accumulates within the eye. Since the contents of the eye are essentially incompressible, the accumulation is accommodated by the stretching of the eye wall to increase the intraocular volume. This stretching is opposed by the elasticity of the eye wall, so that the intraocular pressure rises, representing an increase in the hydraulic head driving the aqueous out of the eye, so that the rate of outflow increases. Thus, the accumulation of fluid and the accompanying increase of pressure would continue until the outflow matches the rate of formation.

The basic mathematical formulation is equally well established. If we denote the volume of the aqueous humor by v_a and the aqueous formation and outflow rates by F and Q, respectively, then the equation expressing conservation of volume is

$$-\frac{dv_a}{dt} = (Q-F). \qquad (1a)$$

Since the volume of aqueous within the eye is difficult to measure, it is usually convenient to multiply through by $\frac{dP}{dv_a}$, a positive, experimentally determined quantity that measures the (pressure dependent) extensibility of the eye; (P denotes the intraocular pressure). Then Eq. (1a) transforms to

$$\frac{dP}{dt} = -\frac{dP}{dv_a}(Q-F). \qquad (1b)$$

Equation (1b) shows that the pressure can be steady only if the right-hand side is zero, i.e., at a pressure $P \rightarrow \hat{P}$ for which the outflow rate ($Q \rightarrow \hat{Q}$) equals the formation rate ($F \rightarrow \hat{F}$). It also shows that the pressure is not necessarily stable at that value, for stability requires that the pressure tends to decay back to $\hat{P}$ if perturbed. Thus, $Q - F$ must be positive for pressures slightly greater than $\hat{P}$ and negative for pressures slightly less than $\hat{P}$.

The rate at which the pressure decays to normal after a perturbation provides a quantitative indication of stability that finds wide clinical use. In fact, the progressive pressure elevation that is characteristic of glaucoma is typically accompanied by a progressive decrease in and eventual loss of stability. Accordingly, the onset of instability with increasing intraocular pressure is one of the features that we shall expect to illuminate by the theoretical analysis.

Outflow Facility—To begin to probe more deeply into the implications of instability, consider the relationship between aqueous outflow and intraocular pressure. We recall that the rate of flow through a resistive fluid circuit is equal to the pressure head divided by the resistance. Thus, the aqueous outflow (Q) may be written as

$$Q = C_o\ (P - P_v), \qquad (1c)$$

where C_o, the reciprocal of the outflow resistance, is called the outflow facility and

P_v, the pressure in the veins exterior to the eye is in the range of $\sim$ 6 to 10 Torr, and supposed to be sensibly independent of the aqueous flow rate.

Substitution of the above expression for the outflow rate in Eq. (1b) yields

$$\frac{dP}{dt} = -\left(\frac{dP}{dv_a}\right)\{C_o\ (P - P_v) - F\}. \qquad (1d)$$

The pressure $\hat{P}$ at which the bracketed term is zero is the nominal intraocular pressure. Equation (1d) shows that an elevated intraocular pressure will occur if the outflow facility is abnormally low and/or the formation rate is abnormally high.

Anatomical and physiological studies suggest that both the rate of outflow and the rate of formation vary with pressure, but neither pressure dependence has been established—the experimental difficulties are perhaps self-evident, because the anatomy is such that neither the rate of outflow nor the rate of formation is accessible for direct measurement.* Their difference is readily determined, however, (as will be discussed shortly), and its behavior provides one important basis for quantitative comparison with experiment.

Pressure Dependence of ($Q - F$)—Equation (1d) shows that the pressure decay with time

* The literature contains many data purporting to represent outflow facility and formation rate, but does not do so precisely because both are conventionally derived from (Q—F) measurements on the assumption that the outflow facility and the rate of formation are not pressure dependent.

following an initial perturbation would be exponential if $\frac{dP}{dv_a}$, C_o, and F were independent of pressure. Actually, they are not, but the pressure decay for normal living eyes is approximately exponential anyway (cf., e.g., Langham and Eisenlohr[2]), the pressure dependence of the several variables being such that the right-hand side of Eq. (1d) is nearly a straight-line function of pressure over a rather wide range. (The mean exponential decay constant for rabbit eyes is $\sim$ 0.48 min^{-1}; that for normal human eyes is somewhat smaller, and depends on age.) Thus, another important feature that we must look for in the theory is the pressure dependence of $Q - F$.

This pressure dependence has been determined both by perturbing the pressure and recording its subsequent decay, and directly by infusing fluid into the eye at known rates and recording the resulting intraocular pressure. Figure 2 displays the nature of the experimental results, $Q - F$ being denoted by I, the (steady-state) infusion rate. (The considerable dispersion associated with the perturbation method is due primarily to dispersion in the available $\frac{dP}{dv_a}$ data; this source of uncertainty is absent in the steady-state infusion technique.)

Analysis

As the preceding discussion indicates, the core of the pressure control problem lies in the rate of aqueous outflow and the rate of aqueous formation. Here, we prepare the way for the introduction of nervous mediation by analyzing the outflow and formation structures. This leads to a representation of the behavior in the absence of nervous system intervention.

Aqueous Outflow in the Enucleated Eye—Before examining the outflow structure itself, we can gain some useful insight into its nature by considering the pressure flow behavior of the enucleated eye as shown in Fig. 2. The figure reveals a rather different pressure flow relationship than the linear one that characterizes more familiar fluid circuits. In the low-pressure domain, it shows that a substantial ($\sim$ 7 Torr) threshold pressure is required to sustain flow, and at higher pressures there is some curvature suggestive of partial constriction of the outflow channels due to stretching of the eye wall. (Such a threshold pressure is characteristic of flow through biological tissues that have a tendency to collapse; it is familiar in treatments of the blood circulatory system where it is referred to as the critical closing pressure.)

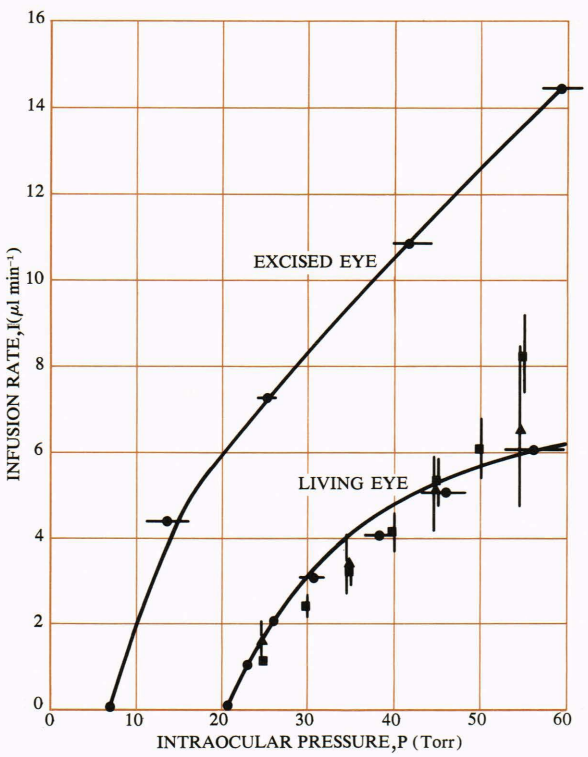

Fig. 2—Mean pressure flow relationship for living and dead rabbit eyes. Aqueous dynamics is studied by infusing fluid into the eye at known rates and recording the resulting pressures within the eye. The circles are steady-state infusion rate data of Langham,[3] 26 eyes. Other points are determined from the pressure decay constant (Langham,[4] 38 eyes), using rigidity data from Eisenlohr and Langham,[5] 12 eyes, and from Viernstein and Cowan,[6] 7 eyes. The curve is calculated from the theory, as discussed in the text.

[2] M. E. Langham and J. E. Eisenlohr, "A Manometric Study of the Rate of Fall of the Intraocular Pressure in the Living and Dead Eyes of Human Subjects," *Invest. Ophthal.* **2**, 1963, 72–82.

[3] M. E. Langham, "Influence of the Intraocular Pressure on the Formation of the Aqueous Humor and the Outflow Resistance in the Living Eye," *British Journal of Ophthal.* **43**, 1959, 705–732.

[4] M. E. Langham, "Manometric, Pressure-cup and Tonographic Procedures in the Evaluation of Intraocular Dynamics," *Proc. Glaucoma Symposium*, (Tutzing Castle, 1966), 126–150, Karger Pub. Co., Basel and New York, 1967.

[5] J. E. Eisenlohr and M. E. Langham, "The Relationship between Pressure and Volume Changes in Living and Dead Rabbit Eyes," *Invest. Ophthal.* **1**, 1962, 63–77.

[6] L. Viernstein and M. Cowan, "Static and Dynamic Measurements of the Pressure-Volume Relationship in Living and Dead Rabbit Eyes," *Exptl. Eye Research* **8**, 1969, 183–192.

General Nature of the Outflow Structure—The significant resistance to flow of aqueous is associated with a complex network of many outflow vessels contained in the eye wall in the vicinity of the so-called "filtration angle," cf. Fig. 1. The intricacy of the network can be appreciated qualitatively by recognizing that its resistance to flow is about equivalent to that of a single straight pipe 10μ in diameter passing through the eye wall. Its structure is discussed in detail elsewhere (cf. Duke-Elder and Wybar,[7] and Ruskell[8]) and will be discussed here only briefly.

In general, the outflow network is comprised of an inner network and an outer network joined in man, e.g., by the relatively wide ($\sim 10^2\mu$) canal of Schlemm, cf. Fig. 3. On the upstream side of the division is a meshwork of channels that provides access to the anterior chamber. The outer network provides access to the episcleral veins and also to the intrascleral venous plexus which receives blood from the anterior venous plexus of the ciliary body. Thus, both aqueous humor and blood must compete for channels in the outer drainage network so that the outflow resistance will depend on the blood flow through the anterior venous plexus.

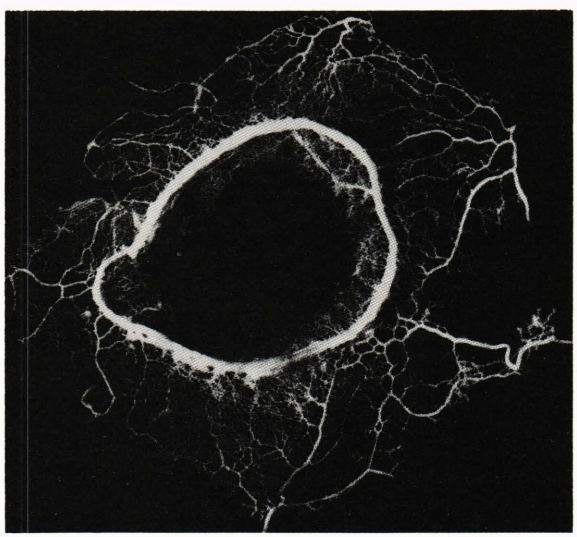

Fig. 3—Photograph of a neoprene cast of the canal of Schlemm and associated vessels (Norman Ashton). Aqueous humor filters from the anterior chamber into the canal, and is subsequently carried through the eye wall by the outer network of vessels, where it rejoins the venous blood system. The outer network also communicates with the venous system within the eye so that both aqueous and blood compete for drainage in this network.

Schematic Representation of the Outflow Network—In the present theory, the outflow network of the eye is highly idealized, to be schematized by Fig. 4. (For definiteness, the terminology of the figure is that appropriate to the human eye.) Aqueous humor enters Schlemm's canal after passing through the inner (trabecular) meshwork whose equivalent flow resistance is denoted by R_T. It leaves the canal through numerous collector channels and their associated networks, only one being depicted. Most of the collector channels branch and rebranch, the shunting branches $\{r_k\}$ being drained by relatively large drainage veins having negligible resistance. Thus, the individual resistances of the figure represent numerous shunting channels by single equivalent resistances. Blood enters the network from the anterior ciliary venous plexus and competes with aqueous for space in the channels. The fraction of the network occupied by either fluid is determined by local equality of pressure where they meet.

Mathematical Representation of the Outer Network—We turn our attention first to the aqueous side. Consider the network downstream of Schlemm's canal. Let M_k denote the volumetric flow rate through R_k so that the pressure difference between the k-th and k-1st junctions is (in the differential approximation)

$$\frac{dP_k}{dk} = -M_k R_k \qquad (2a)$$

and the difference between the feeder flow rates into the two junctions is (in the differential approximation)

$$\frac{dM_k}{dk} = -\frac{(P_k - P_v)}{r_k} \quad , \qquad (2b)$$

where P_v is the external venous pressure.

In general, the resistances are expected to vary with locus in the network, R_k first increasing (and r_k decreasing) toward the right in the diverging part of the network near Schlemm's canal, and ultimately decreasing again in the converging area that communicates closely with the intrascleral venous plexus. In the absence of further information on this matter, we adopt the simplest plausible assumption, namely that $R_k r_k$ can be regarded as an independent of k, i.e., as a constant whose value, denoted by $(c_*)^{-2}$, characterizes the

[7] S. Duke-Elder and K. Wybar, *System of Ophthalmology, Vol. II, Anatomy of the Visual System,* Mosby Co., St. Louis, 1961.

[8] G. Ruskell, "Aqueous Drainage Paths in Rabbit," *Archives of Ophthal.* **66**, 1961, 861–870.

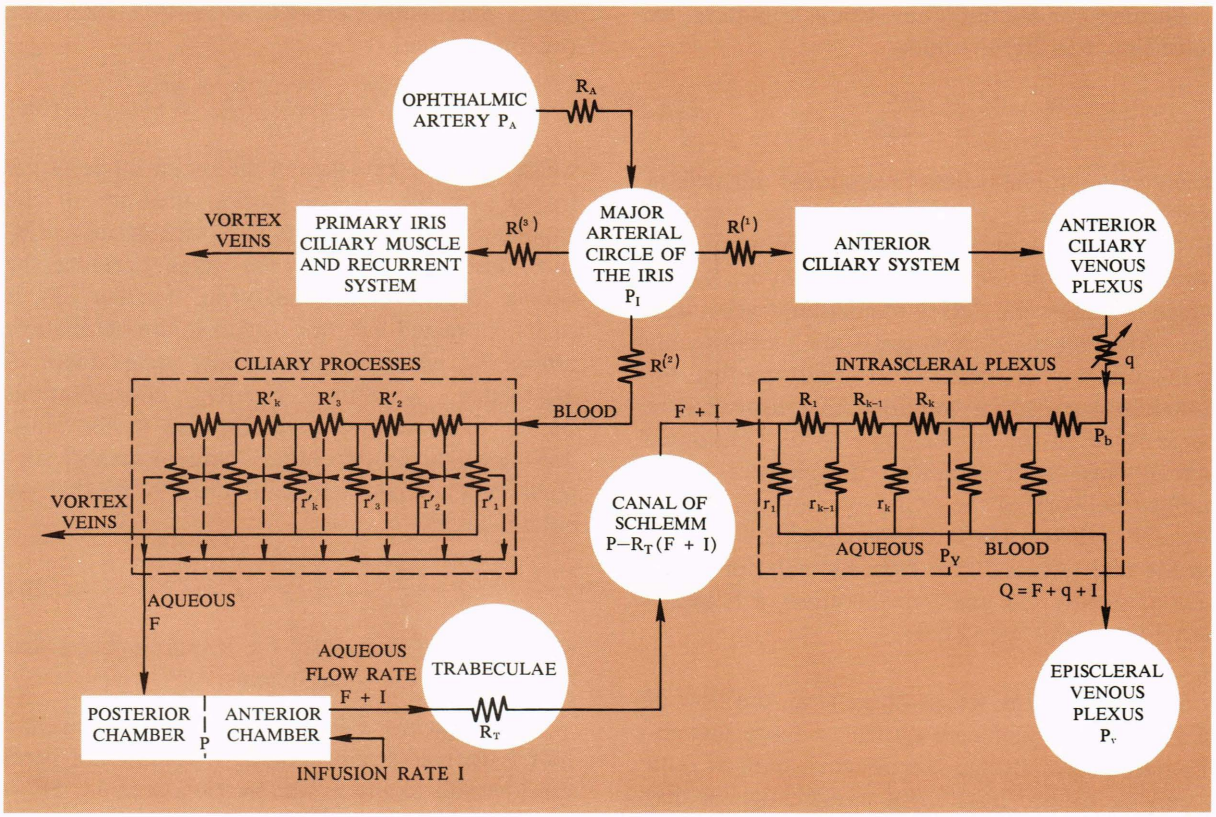

Fig. 4—Schematic diagram of blood and aqueous flow paths.

network. With this assumption, integration of the differential equations is straightforward (after defining a new independent variable

$$z = \frac{1}{c_*}\int_0^k \frac{dk'}{r_k'}\ ).$$

For the excised eye, where blood is absent, aqueous is assumed to penetrate into the network to the point where the pressure becomes equal to the critical closing pressure, P_c. The solution is then straightforward, and yields good agreement with experimental infusion rate data for eyes whose infusion rate asymptote passes through the origin. However, many human eyes, as well as the rabbit eye of Fig. 2, show a slightly different behavior, and to achieve fully satisfactory agreement between theory and experiment it is necessary to recognize that the outflow channels may be deformed somewhat as the eye wall becomes stretched. Thus, it is expected that c_* will vary somewhat with pressure and that, for small deformations, this variation can be expressed as a linear function of the strain in the eye wall. Regarding the eye wall as a spherical shell, the strain is expressed by the fractional volume change. For rabbit eyes, on which we shall focus attention in this study, this change is approximately proportional to the logarithm of the intraocular pressure over a rather wide range, so that we write

$$c_* = c_*^{(o)}\left(1 - \epsilon \ln \frac{P - P_v}{P_*}\right), \qquad (2c)$$

where ϵ is a (small) number that introduces the strain effect, and P_* is a "reference pressure" that nondimensionalizes the argument of the logarithm (the venous pressure P_v is zero for the dead eye but not for the living eye). We find agreement between theory and experiment when Eqs. (2a, 2b) are evaluated using Eq. (2c) for c_*, with $\epsilon = \frac{1}{4}$, $P_* = 21$ Torr, as the smooth curve of Fig. 2b illustrates.†

† The assignment of parameters for this figure corresponds to assuming that half of the nominal outflow resistance of the totally perfused network resides in the trabeculae. This is somewhat arbitrary since definitive experimental data are lacking, for rabbit, and since equally good agreement between theory and experiment can be achieved on the assumption of a smaller fraction, as found for certain monkeys.[9]

Turning our attention now to the living eye, we solve Eqs. (2a,2b) to obtain

$$P - P_v = \frac{Q}{c} + \frac{\eta\, c\, q}{c_* \sinh Z} \quad , \qquad (2d)$$

where q is the blood flow through the intrascleral plexus, η, ~ 1.8, is the ratio of the viscosity of blood to that of aqueous, and c is a constant whose value is determined by c_* and by R_T and Z, which measures the degree of communication with the ciliary plexus. (Equation (2d) pertains only if the pressure is sufficient to totally perfuse the intrascleral plexus, a condition that turns out to be satisfied in the applications to be considered here.) This result completes the analysis of the outflow network of the living eye, and portrays a variable aqueous outflow resistance that depends on the rate of blood flow from the anterior ciliary venous plexus. To proceed, therefore, it is necessary to treat this blood flow.

The Blood Flow Rate—In general, the flow of blood presents problems similar to those just encountered in analyzing the aqueous outflow, and it may be treated by a slight modification of that analysis, as becomes apparent by inspection of Fig. 4. There, it is evident that the major arterial circle of the iris (so-called in spite of the fact that it actually lies in the anterior ciliary body rather than in the iris), the small artery resistance $R^{(1)}$ and the collapsible capillary channels of the anterior venous plexus play roles analogous to the anterior chamber, the resistance of the trabeculae (R_T), and the intrascleral plexus, respectively. Thus, since there is only one fluid involved in the present case, the general analysis is similar to that for aqueous outflow in the dead eye, with new boundary conditions.

In view of the present lack of information regarding the network parameters, we elect to make certain approximations whose justifications derive from elementary physiological considerations regarding capillary beds. In general, capillary networks are only fractionally perfused, the normal flow being insufficient to maintain a pressure greater than the critical closing pressure throughout. Thus, such a network tends to function as a constant pressure-drop circuit element, new channels opening as the flow rate is increased so that the pressure drop across the bed cannot greatly exceed the critical closing pressure so long as the bed is not totally perfused. It follows, therefore, (cf. Fig. 4) that

$$q \approx \frac{P_I - (P + P_t + P'_c)}{R^{(1)}} \quad , \qquad (3a)$$

where P_I is the pressure in the major circle of the iris, P'_c is the critical closing pressure of the capillary vessels, and P_t is the (transmural) pressure necessary to keep the veins draining the venous plexus from collapsing. Further, P_I is easily expressed in terms of that in the ophthalmic artery P_A, which is substantially independent of intraocular pressure. Finally, considerations similar to those above pertain also to the blood flow through the two other "compartments" supplied by the major circle of the iris, so that we obtain, finally,

$$q \approx \frac{\theta}{R_A}\,[P_A - P_t - P'_c - P] \quad , \qquad (3b)$$

where θ is the fraction of the iris circle blood that flows through the ciliary plexus.

The Aqueous Formation Rate—Aqueous humor is derived from blood by a complex of processes whose nature is not well understood. However, we are concerned here only with the pressure dependence of the formation rate, and this may be readily approximated.

In general, the major constituents of aqueous humor pass from the blood stream through the thin-walled (and therefore relatively permeable) capillary vessels of the ciliary processes. It follows that the analysis of aqueous formation may be divided into two parts, one concerned essentially with determining the number of perfused channels and the other concerned with transport through the walls of these channels.

Transfer of fluid through the membraneous walls depends in part on the transmural pressure (hydrostatically driven flow), in part on the difference between internal and external species concentrations (diffusion), and in part on metabolically activated (species selective) transport. In general, species-dependent processes are not sensitive to pressure and to the extent that the transmural pressure approximates the critical closing pressure, it may be regarded as independent of the intraocular pressure. In this approximation, therefore, the pressure dependence of the rate of aqueous formation is determined largely by the rate of blood flow through the bed.

Insufficient information is available regarding the ultrastructure of the capillary bed to permit calculation of the perfused wall area as a function of blood throughput. However, to the extent that the perfused channels of the network can be regarded as equivalent, the permeable wall area of the perfused channels is proportional to the number of perfused channels and thus to the blood throughput. In this approximation, therefore, the rate of formation of aqueous is expressed by

$$F = Bq \quad , \qquad (4)$$

where q is given by Eq. (3b), and B is a dimensionless constant. This result, and its synthesis with the previous outflow network analysis, leads to a description of the pressure-flow behavior in the absence of nervous control. This description is in accord with data of several experimental studies, as discussed in Ref. 1, but we shall pass over these features because our present interest centers on neural control.

Neural Control—Nature's nervous feedback mechanisms generally involve a balance between two opposing influences, so that we are motivated to look for such competition in neural control of intraocular pressure. Unfortunately, the relevant neural pathways have not as yet been established, so that we must assume them.

Some clues are available, however. The effects of adrenergic drugs introduced through the cornea into the anterior chamber suggest that an essential portion of the neural network is accessible to the aqueous humor. Histological studies reveal a network with bare axonal endings associated with the trabeculae and since the endings are undifferentiated, it is presumed that they respond to "squeezing" when the tissue surrounding them is deformed. These would be sensitive to a pressure gradient and thus to the product of flow rate and trabecular resistance. Other neurons have been found in the eye wall, and these are likely to respond to strain in the eye wall. Thus, we are led to assume two competing feedback loops, one deriving its excitation from QR_T, and the other deriving its excitation from eye-wall strain, ln $(P - P_v)$.

Next, we consider how these two feedback signals might be expected to influence the outflow resistance and the rate of aqueous formation. Since histological studies of the outflow region do not reveal a network of differentiated endings that would appear to be capable of changing the outflow resistance by changing the dimensions of the outflow channels, we must look elsewhere for the effector elements. Neural control of ciliary muscle tension has commonly been supposed to be an important factor because it would deform the flow spaces in the trabecular meshwork (which has been described as the tendon of insertion of the ciliary muscle). However, in the light of recent evidence that only a small fraction of the aqueous outflow resistance resides there, that mechanism now seems to offer little capability for effective pressure control. Rather, the weight of the evidence, as discussed in Ref. 1 and elsewhere, points toward vasomotor function as a prime neural control mechanism.

Since both outflow resistance and rate of aqueous formation are influenced by blood flow, and since nervous regulation of blood flow is general elsewhere in the body, the vascular bed of the eye is a likely site. It is well supplied with adrenergic nerves having differentiated endings. Many of these must be associated with control of iris diameter and other functions, but others have long been supposed to be implicated in the control of intraocular pressure. We build on this supposition by postulating a specific mechanism.

The simplest successful scheme that we have envisaged for regulation of intraocular pressure is by vasomotor control of R_A, the resistance of the arterial supply to the major circle of the iris. Control of this resistance not only affects the rate of formation directly by modifying the blood flow through the ciliary processes, but also affects the outflow resistance indirectly because of the competition between blood and aqueous in the drainage channels. For simplicity, the arterial conductance is assumed to be modified linearly by vasoconstriction excited by the tissue strain sensors and by vasodilatation excited by the QR_T sensors. For the purposes of the present study, we shall make one further simplifying assumption, namely that the neural control system is highly sensitive (loop gains $> > 1$).

Then, provided that the intraocular pressure is not too close to the arterial pressure or the threshold, the results of the theoretical analysis of the living rabbit eye may then be encapsuled in the form of four equations:

1. The aqueous outflow equation

$$Q = \hat{Q} + \alpha \ln\left(\frac{P - P_v}{\hat{P} - P_v}\right) \quad , \qquad (5a)$$

where α measures the ratio of the constrictor to dilator gains divided by R_T.

2. The formation rate equation

$$F = \frac{(P - P_v)}{\beta} - \frac{Q}{\beta c} \quad , \qquad (5b)$$

where β is a second parameter, proportional to B.

3. The normal formation rate equation

$$\hat{F} = \frac{\hat{c}\,(\hat{P} - P_v)}{1 + \hat{\beta}\,\hat{c}} \quad , \qquad (5c)$$

4. The normal pressure equation

$$\hat{P} - P_v = P_* \exp\left\{\frac{\hat{F} - Q_*}{\alpha}\right\} \quad , \qquad (5d)$$

where P_* and Q_* are the thresholds for excitation of the constrictor and dilator sensors, respectively.

The pressure-flow behavior of the eye as described by these four equations will now be discussed and compared with experiment.

Discussion

Here, we consider the application of the theory primarily to develop a detailed conception of how intraocular pressure is regulated in the normal eye and what may go wrong when pressure regulation deteriorates in the abnormal eye.

First, let us briefly review the basic concepts. We recall that the pressure within the eye assumes a steady value such that the rate at which aqueous humor flows out of the eye equals the rate at which it is formed within the eye. Both the outflow resistance and the rate of formation depend on blood flow; the outflow resistance because both blood and aqueous compete for drainage channels in the intrascleral plexus, the rate of formation because blood flow through the ciliary body determines the wall area of perfused vessels in the capillary bed wherein the aqueous is derived from blood. Finally, the rate of flow of blood through the intrascleral plexus and the ciliary processes are subject to nervous control by vasomotor function whose competitive excitations derive from sensing flow-induced deformation in the trabeculae and strain-induced deformation in the eye wall. Thus we may expect the theory to illuminate the characteristics of the eye that are important to each of these individual factors, and to their cooperative interplay in the regulation of the intraocular pressure.

Several facets will be explored in the following discussion. We begin by considering the dependence of infusion rate on pressure, because this behavior, which has been well studied experimentally, provides a basis for estimating the parameter α of the theory, and because this behavior reflects the ability of the eye to reestablish its normal intraocular pressure subsequent to a perturbation. Then, we shall probe the functioning of the eye more deeply by examining the pressure dependence of the outflow resistance and the pressure in the intrascleral plexus. Subsequently, we shall examine the pressure dependence of the rate of formation to aqueous. These factors will then be considered together to show how pressure instability might develop in glaucomatous eyes. Finally, we shall discuss the relationship between the normal intraocular pressure and the characteristics of the neural circuitry and touch on the effects of adrenergic drugs.

The Dependence of Infusion Rate on Pressure —Inspection of Eqs. (5a,b) reveals that the steady infusion rate, $I = Q - F$, depends on two parameters characterizing the eye (in addition to the parameters of the outflow network which have already been estimated by consideration of the dead eye). One of the new parameters is α, whose determination requires knowledge of the ratio of neural vasoconstrictor-vasodilator sensitivity, and the other (β) requires knowledge of the ratio of normal rate of blood flow through the intrascleral plexus to normal rate of aqueous formation. No information is available as to the sensitivity ratio and the best information as to the blood/aqueous flow ratio is that it is of the order of unity. Thus, we shall assign values to these parameters such that the calculated infusion rate curves agree well with the living eye data points of Fig. 2. For the rabbit eye, Fig. 2 indicates that correspondence between theory (the smooth curve) and experiment is satisfactory for $\alpha = 5.3$ μl/min, with $\beta = 4.3$, which corresponds to the normal outflow being approximately 60% blood and 40% aqueous. Assignment of different but comparable values leads to correspondence between theory and experiment for the human eye when the appropriate strain relationship is used in place of the logarithmic one that characterizes rabbit eye. That α is relatively large (compared with unity) means that the vasoconstrictor branch of the neural feedback loop is more sensitive than the vasodilator branch, and this will turn out to have a number of important consequences.

Outflow Resistance—As noted in the background section, the rates of aqueous formation and outflow are extraordinarily hard to measure individually so that the most reliable experimental studies are concerned with their difference (e.g., the infusion rate as discussed above). In theory, however, we may easily probe much more deeply by studying the outflow and formation rates individually.

Figure 5a illustrates the pressure dependence of the outflow resistance, $(P - P_v)/Q$, of the live rabbit eye, and also shows that of the excised eye for comparison. With respect to the outflow resistance of the excised eye, we recall that its resistance falls as the pressure is increased away from the critical closing pressure ($\sim$ 7 Torr) until the pressure is sufficient to perfuse all of the collapsible channels of the intrascleral plexus, and that it then increases slightly with pressure (for pressures higher than the total perfusion pressure) because the outflow channels are slightly distorted as the eye wall stretches. The outflow resistance of the living eye is shown to be substantially higher than that of the excised eye primarily because the outflow channels of the intrascleral plexus contain blood as well as aqueous. Thus, we see that at the nominal intraocular pressure of 21 Torr, for example, the resistance to aqueous outflow of the intrascleral plexus is more than three times its value for the excised eye. This result is in accord with the findings of Sears[9] for several monkey eyes.

Pressures in the Intrascleral Plexus—Pressure in the intrascleral plexus is difficult to measure and, since the pressure varies from place to place within the plexus, it is also difficult to interpret because it is difficult to specify the location of the probe within the plexus. Generally, however, the pressure at the aqueous input (e.g., for primates, the canal of Schlemm) and the pressure of the blood tend to be somewhat less than and to increase more or less linearly with the intraocular pressure. Figure 5b illustrates the pressure P_b at the blood input to the intrascleral plexus, as calculated for the "typical" eye of Fig. 2. For this hypothetical case, the aqueous pressure at its input to the intrascleral pressure turns out to be substantially equal to P_b, and both pressures increase more or less linearly with intraocular pressure, in general accord with the findings of Sears[9] for the pressure in Schlemm's canal (in monkey) and Macri[10] for "head-on" intrascleral venous pressures (in cat).

Rate of Formation of Aqueous Humor—In the absence of nervous mediation, the rate of formation of aqueous humor would decrease with increasing intraocular pressure as a result of the decreased pressure head available for forcing blood through the ciliary processes. In the presence of nervous mediation, however, the result is quite different. Figure 5c shows the rate of formation vs. pressure as calculated for the typical eye of Fig. 2. It is evident that neural feedback succeeds in keeping the rate of formation nearly independent of pressure over a substantial pressure range in the neighborhood of the normal pressure of 21 Torr. However, recalling that the amount of vasodilatory feedback is proportional to the trabecular resistance, it becomes evident

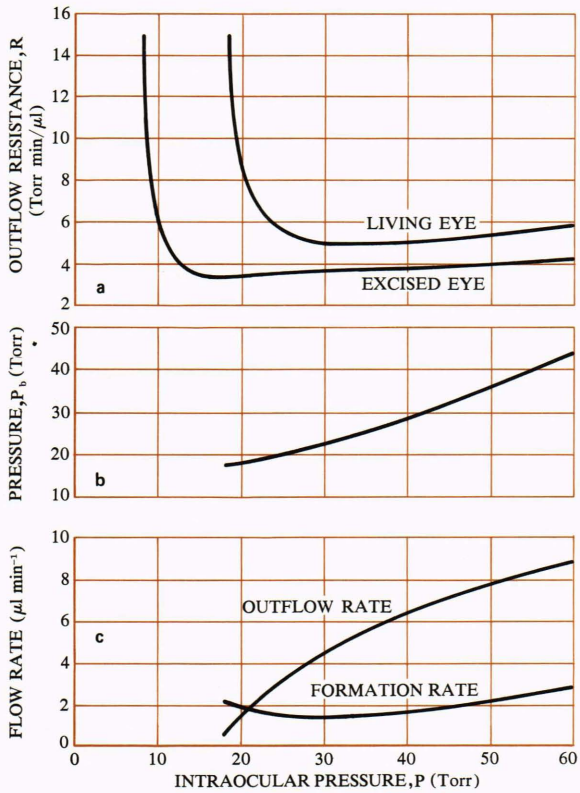

Fig. 5—The calculated pressure dependence of outflow resistance, blood pressure in the outflow network, and rate of aqueous outflow and formation.

[9] M. Sears, "Pressure in the Canal of Schlemm and its Relation to the Site of Resistance to Outflow of Aqueous Humor in the Eyes of Ethiopian Green Monkeys," *Invest. Ophthal.* **5**, 1966, 610–623.

[10] F. Macri, "Further Studies on the Relationship of Intrascleral Venous Pressure and Eye Pressure," *Archives of Ophthal.* **69**, 1963, 622-625.

that the pressure dependence of the formation rate will be sensitive to the value of this resistance. This leads us to investigate the question of stability and how it depends on outflow resistance.

Instability—As mentioned in the background discussion, the nominal intraocular pressure is the pressure P at which the rates of aqueous formation and outflow are equal, but that the intraocular pressure cannot be stable at that value unless

$$\left.\frac{d}{dP}(Q - F)\right|_{\hat{P} = P} > 0 \quad .$$

Thus, instability will result if the formation rate increases sufficiently rapidly with pressure. To explore the potential causes of instability, we formulate the stability criterion explicitly with the aid of Eqs. (5a,b), which lead to

$$\hat{P} - P_v < \alpha\left(\beta + \frac{1}{c}\right) \quad . \qquad (6)$$

(For simplicity, we here ignore the distensibility of the outflow channels by setting $\epsilon = 0$.)

This equation shows that instability will ensue as a result of elevated intraocular pressure, a result which is familiar from the behavior of glaucomatous eyes. Further, however, it shows characteristics of the eye that are important to stability. Among these, we select for illustrative purposes the trabecular resistance because pathology has suggested that it may be abnormally high in glaucomatous eyes.‡ Figure 6 illustrates the pressure dependences of outflow Q and rate of formation F for a hypothetical eye like that of Fig. 2 except that the trabecular resistance has been increased by a factor of 4. It shows that with this elevated outflow resistance, vasodilatation dominates over vasoconstriction to the extent that the eye would be marginally stable if its nominal intraocular pressure were as high as 23 Torr and definitely unstable at $\hat{P}$ = 40 Torr. Moreover, the theory reveals (cf. Eq. (6)) that the deleterious effect of high outflow resistance would be countered by adrenergic drugs which raised the sensitivity of the vasoconstrictor neural feedback loop (relative to that of the vasodilatation loop) and/or which lowered the nominal intraocular pressure.

The Nominal Intraocular Pressure—So far, nominal intraocular pressure $\hat{P}$ has been regarded

‡ Recall that α is inversely proportional to R_T.

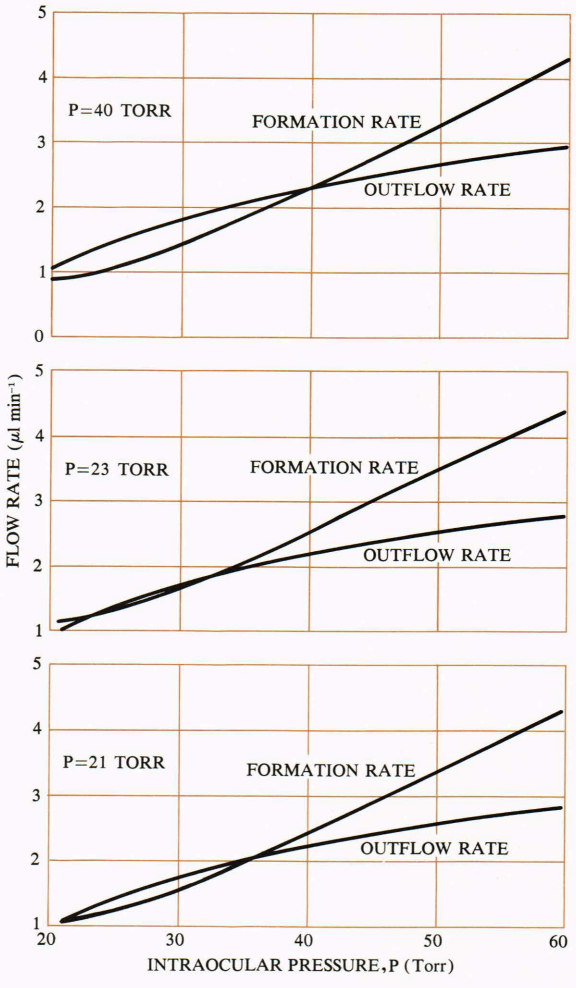

Fig. 6—Development of pressure instability with increasing pressure for a model eye with outflow channels four times the trabecular resistance of the standard eye.

as given, but we now consider how it is determined. For this purpose, we note that the nominal formation rate $\hat{F}$ may be eliminated from Eqs. (5c,d) to yield a transcendental expression for $\hat{P}$ in terms of the neural thresholds P_*, Q_* (and parameters discussed prevously). It is immediately apparent that the pressure is involved only in the combination $\hat{P} - P_v$ so that a change in P_v will be accompanied by an equal change in $\hat{P}$, in agreement with the findings of Bárány[11] who raised the venous pressure in monkey by enclosing their trunks in a pressure suit. Other important features determining the intraocular pressure may be

11 E. Bárány, "Topical Epinephrine Effects on True Outflow Resistance and Pseudo Facility in Vervet Monkeys Studied by the New Anterior Chamber Perfusion Technique," *Invest. Ophthal.* **7**, 1968, 88-104.

deduced by inspection of Eq. (5d). For this purpose, we note that the exponent is rather small compared with unity for values of $\hat{F}$ and α that characterize the "typical" eye of Fig. 2. Thus, the normal intraocular pressure tends to be regulated at a value somewhat higher than but close to $P_v + P_*$, regardless of the precise magnitudes of the outflow resistance or the gains of the neural feedback loops. Since P_* is the threshold pressure at which the strain sensors begin to respond, it is presumed to be a rather general property of neurons and the tissues in which they are imbedded. Thus, the neural feedback achieves a nominal intraocular pressure which is insensitive both to the outflow resistance and to the other parameters of the neural network—provided only that it is sufficiently sensitive that the high loop gain approximation applies, and that the vasoconstrictor loop is somewhat more sensitive than the vasodilatory loop, so that the exponent of Eq. (5d) is small. It is also evident, however, (recalling the dependence of α on R_T), that if the trabecular resistance becomes greatly elevated, the exponent of Eq. (5d) is increased so that the insensitivity to outflow resistance tends to be lost. In any event, the intraocular pressure would be lowered by drugs which may sensitize the vasoconstrictor feedback, lowering P_* and increasing α.

Adrenergic Drugs—The effects of drugs that modify the response of adrenergic nerves are highly complex and neither well documented nor well understood and we shall only touch on the matter briefly.

Figure 7 shows the effect on the infusion rate curve and nominal intraocular pressure of topical application of epinephrine to the eye of rabbit. It is evident that the nominal intraocular pressure has been lowered by the drug, and the increased steepness of the infusion rate curve indicates increased stability. Both of these effects are to be expected from an adrenergic drug which enhances neural activity (such as epinephrine is known to do), provided that it does not oversensitize the vasodilatory sensitivity relative to the vasoconstrictor sensitivity. The smooth curve of Fig. 7, calculated from Eqs. (5a,b), (with $\hat{c} = \frac{1}{3}$ μl/Torr min, $R_T = 1.5$ Torr min/μl, B = 1.75; and $\alpha = 6.7$ μl/min for the control eye and 5.8 μl/min for the treated eye) show that the theory is in good accord with experiment. Thus it appears to provide a useful conceptual framework for developing a better understanding of the influences of drugs used in the treatment and control of glaucoma.

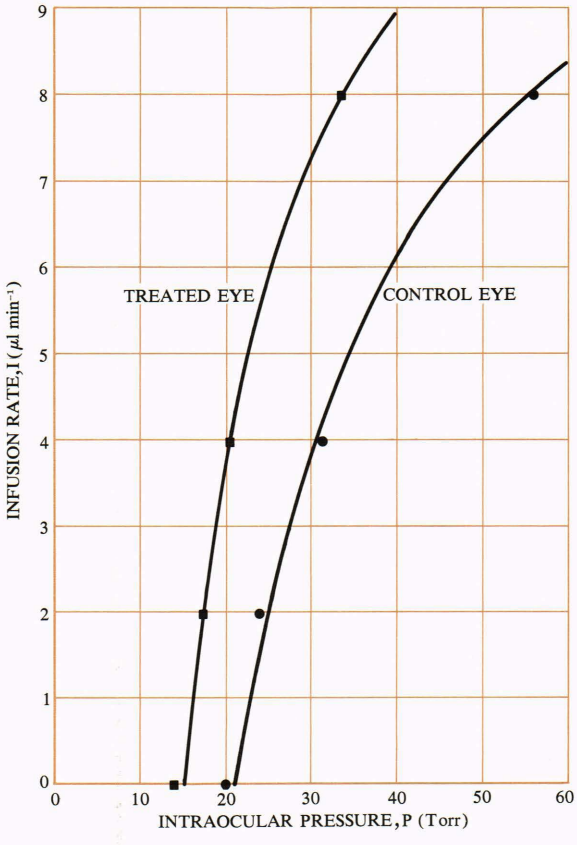

Fig. 7—Effect of epinephrine on the pressure-flow behavior of a living rabbit eye, the circles denoting the control eye and the squares denoting the treated eye, Eakins.[12] The curves are calculated from the theory. Epinephrine has caused the nominal intraocular pressure to fall to about 15 Torr and increased the steepness of the infusion curve. The theory interprets these effects primarily in terms of a reduction in the neural response threshold.

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[12] K. Eakins, "The Effect of Intravitreous Injections of Norepinephrine, Epinephrine and Isoproterenol on the Intraocular Pressure and Aqueous Humor Dynamics of Rabbit Eyes," *J. Pharm. and Exptl. Therapy* **140**, 1963, 79–84.