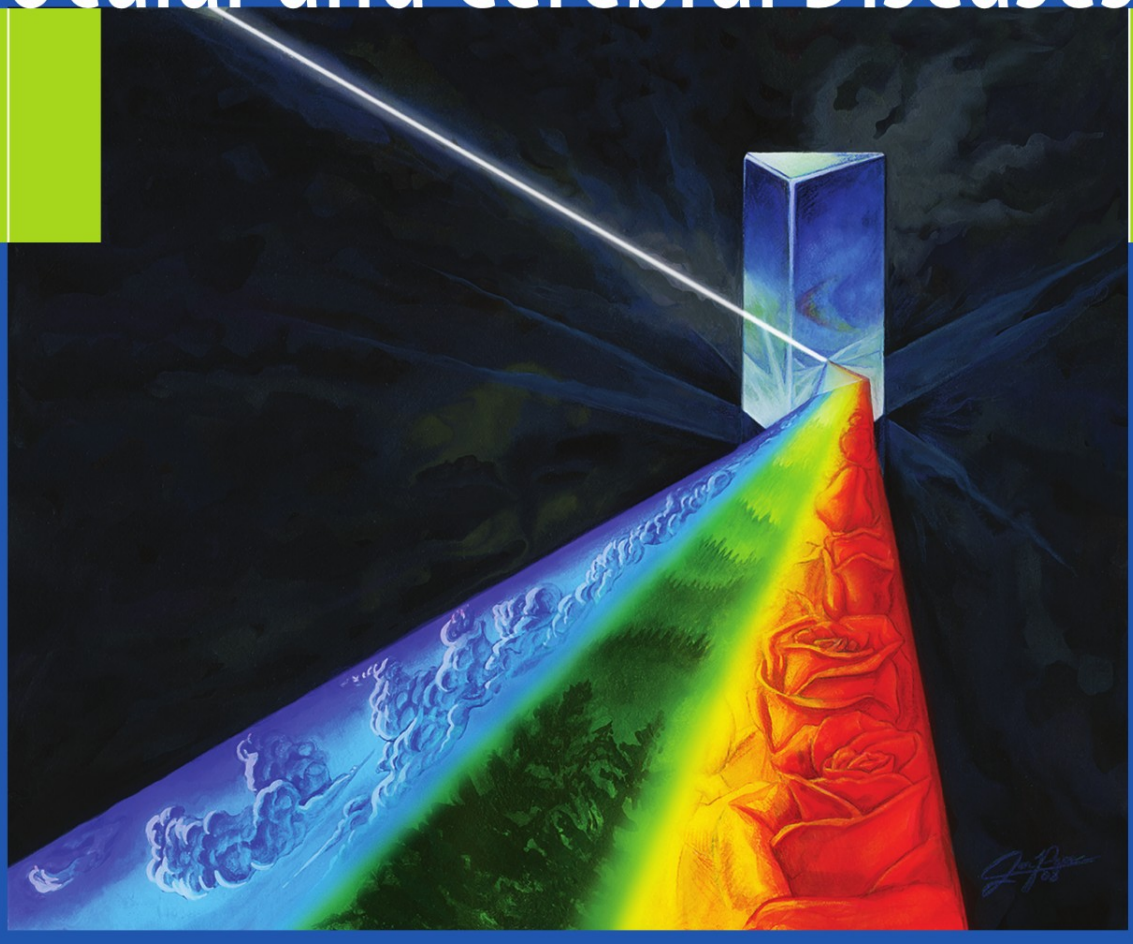
Maurice E. Langham

Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases



A New Perspective

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Dedicated to

Pamela and to our daughters Susan, Jennifer, Christine, and Fiona for bringing me much happiness.

and to

Torsten C.E. Krakau, Emeritus Professor of Experimental Ophthalmology, Lund, Sweden. A true friend who has made outstanding contributions to our understanding of the fundamentals of the ocular circulation and vision and to the clinical applications of this knowledge.

Preface

The research and teaching of Physiology at University College, London, England is renowned and includes the outstanding contributions of the internationally known research workers J.N. Langley, who introduced the term "autonomic nervous system," E.H. Starling, known for his heart–lung preparation, Sir Charles Lovatt Evans, the author of the widely used Textbook of Physiology and Chairman of the Department, and A.V. Hill, the Nobel laureate in Physiology and Medicine. For the duration of the Second World War, the course in honors Physiology at University College was suspended and not restarted until 1947. At that time I was one of a very fortunate group of eight students accepted for the full-time course in honors Physiology. At this time Sir Charles Lovatt Evans was Chairman of the Department of Physiology and his faculty included A.V. Hill, L.E. Bayliss, and the neurophysiologist Bernard Katz. No young student could have wished for more stimulating and superbly organized theoretical and experimental courses.

It was during this time that I first met Hugh Davson and Sir Stewart Duke-Elder, who had a research unit in the Department of Physiology at University College, London. Hugh Davson had recently published with Danielli a major treatise "Permeability of Natural Membranes" (University Press, Cambridge 1945) and had turned his focus to the transfer of solutes across the barriers separating the blood stream from the avascular intraocular and cerebrospinal fluids.

Soon after the end of the Second World War, the Medical Research Council of Great Britain set up a research unit (the Ophthalmologic Research Unit) under the direction of Sir Stewart Duke-Elder, the Oculist to King George VI and Queen Elizabeth II. This research unit began its work in the Department of Physiology at University College under the direction of Hugh Davson, and 2 years later the unit moved to the new Institute of Ophthalmology in Judd St., London. It was in Davson's laboratory at University College, London that I started my career in physiological research on the eye.

Acknowledgments

I am grateful to Hugh Davson and Sir William Stewart Duke-Elder for introducing me to the field of Ocular Physiology with its fascination and its challenges. My early years in research were helped greatly by the influence of Ernst Barany, Professor of Pharmacology in the University of Uppsala, Sweden, with whom I spent many happy research hours. I then spent 18 months as a research fellow at Harvard University and worked in the research laboratories of Professor David Cogan. In 1959, I was appointed Director of Ocular Research at The Hopkins University Medical School and Hospital in Baltimore, USA. During my 32 years at the Wilmer Institute, I had the good fortune to work with numerous research fellows from countries around the world who contributed greatly to the success of our basic research programs. Twenty of these fellows subsequently became Chairmen in Departments of Ophthalmology. In 1969, a collaborative research program was initiated with members of the Applied Physics Laboratory, a school of the University. Robert Hart, a senior investigator at the Applied Physics laboratory and an outstanding research worker, undertook with his two colleagues, David Silver and Richard Farrell, superb collaborative investigations of the fundamental questions of the transparency of the cornea and the fluid dynamics of the eye, and my research assistants, Theresa Kramer Rhonda Grebe and Karen Palewicz, gave invaluable support. Over many years I have had the good fortune to interact and collaborate from afar with Torsten Krakau, Professor Emeritus of Ocular Research in the University of Lund, Sweden. His outstanding contribution and understanding of the problems of ophthalmology and his ingenuity in development of new techniques to solve the outstanding problems have made him a leader in both experimental and clinical ophthalmic research. I am also indebted to Peter Schilder and Tom Preziosi, neurologists at the Johns Hopkins Hospital, for their contribution to the understanding of the blood flow changes associated with the onset and progression of stroke.

Introduction

There are not many, if any, anatomic organs in which structure and shape count so much as in the human eye. This visual system, fashioned in the absence of light over 9 months of gestation, is, from the moment of birth, ready to receive visual images, and transmit them to the actively developing brain, where the perception of a three-dimensional world is perceived and analyzed. The symmetry of the eyes with their complex light-sensitive retinas moving in unison enables them to and transmit images to the visual cortex for interpretation and storage.

The maintenance of the structure and physiology of this sensory organ requires an arterial blood flow bringing oxygen and glucose, the principal metabolic substrates. In turn, these substrates provide the energy essential to maintain the activity of the photoreceptors and the tissues on which the optical properties and the tensile stability of the eye depend. The photoreceptors with their extremely high sensitivity to light (respond to less than ten photons) are energized by aerobic glycolytic metabolism and are supplied with nutrients principally from blood flowing through the narrow vascular choroidal network lying between the retina and the sclera. A much smaller blood flow through the retinal arteries spreads outward from the optic disc to cover the retinal surface and supply oxygen and nutrients to the bipolar and the ganglion cell layers. The inner segments of the visual cell contain high densities of mitochondria with their relatively high oxygen requirements. These needs of the mitochondria are facilitated by their closeness to the retinal epithelium and to the choroidal lobules with their relatively high arterial blood flow.

The neurons connecting the retinal photoreceptors to the brain form an intricate spatial pattern. The retinal neurons with approximately 137 million individual seeing elements form the visual field. The neurons from these seeing elements condense to a little over one million fibers, which pass through the optic nerve to connect with the appropriate nerve cells in the visual cortex. The retinal neurons form a spatial pattern in which the visual image is the sum of the responses of very small, discrete areas of the retina.

This discrete separation of visual responses allows the spatial differential light sensitivity of the visual field to be mapped

and provides a means to identify changes in visual sensitivity associated with the onset of ocular disease. Similarly, this spatial pattern allows the effects of experimentally induced changes in blood flow to very small retinal areas to be identified quantitatively; in this respect, one simple technique for modulating the blood flow is by inducing a change in either the intraocular pressure (IOP) or the ophthalmic arterial pressure.

In addition to the specific metabolic needs of the internal structures of the eye, the blood flow has to maintain a dimensionally stable orb and a flexible but rigid sclera and cornea. The structural rigidity of this envelope is essential for optical transparency and for the transmission of clear images to the photoreceptors. The rigidity of the walls is governed by the outward force of the IOP, which is balanced by the tensile strength of the sclera and cornea. In turn, the level of the steady state IOP is dependent on a dynamic balance between the continuous secretion of aqueous humor across the ciliary processes into the posterior chamber and the resistance to outflow of aqueous humor through the trabecular meshwork, the circumferential canal of Schlemm, the vessels of the intrascleral plexus, and into the episcleral veins and the large veins feeding the heart.

The major proportion of the total blood flow (approximately 90%) flows through the choroid leaving only a small proportion of the total flow to the retina vessels. The arterial inflow is predominantly pulsatile in character and each pulse is in synchrony with the beat of the heart. The stability of the IOP and the constancy of the ocular blood flow are facilitated by regulatory systems involving neural, vascular, and metabolic processes. The capacities of these compensatory mechanisms are limited and when exceeded cause localized and more general ischemia and visual loss.

It is well known that the blood flow to the eye exceeds substantially the metabolic requirements of the intraocular tissues. However, the availability of oxygen and metabolic substrates to the avascular tissues of the eye is limited by the relatively long pathways for the diffusion of oxygen and carbon dioxide between the blood stream and the metabolically active cells.

The supply of oxygen to the many thousands of fibers comprising the optic nerve is dependent on a complex three-dimensional capillary network. Each bundle of nerve fibers is surrounded by a network of capillaries that supply oxygen and carry away the end products of metabolism. The patency of this complex spatial complex network is finely tuned between the pressures within the capillaries and the pressure in the interstitial fluid. The forces maintaining this dynamic transmural balance are little understood but their importance to the maintenance of vision is well established.

Interests in the physiology and in the clinical aspects of the ophthalmic arterial pressure are relatively recent developments. The blood flow to the eye, supplied from the ophthalmic artery, is dependent on the ophthalmic arterial pressure, the IOP, and the venous pressure. In turn, the ophthalmic arterial pressure is determined by the central cardiac pressure, the cerebral vascular resistance, and the ocular vascular resistance. With advancing age, the ophthalmic arterial pressure is commonly impaired by stenosis of the internal carotid artery proximal to the eye and by increased cerebral vascular resistance. Stenosis of the arteries to the eye may give rise to stroke and neurological deficit. The stenosis commonly affects the symmetry of the IOP and the pulse amplitude in pairs of eyes, and thereby recognition of asymmetry in these parameters provides sensitive and simple noninvasive approaches to the early diagnosis of internal carotid occlusive disease and the stroke suspect.

Stroke is the third leading cause of death in the USA, just behind in prevalence to heart disease and cancer. It is a disease especially feared because 75% of those suffering from stroke do not die, but survive with variable, frequently disabling degrees of neurological deficit. More than half of the patients who suffer fatal stroke have partial to complete stenosis of one or both internal carotid arteries. The pressure in the ophthalmic artery provides a very sensitive indicator of the severity of the stenosis. The ophthalmic arterial pressure in man is substantially less than the pressure feeding the brain, and consequently its value compared with the central arterial pressure provides an objective means for evaluating the degree of arterial stenosis proximal to the ophthalmic artery, and the magnitude of changes in the flow resistance in the brain.

The value of physiological research lies in its potential to facilitate practical medical and therapeutic applications. In this respect, it is the impairment of integrative physiology of organs that marks the onset of the diseases of the body. It is the purpose of physiological research to understand the mechanisms by which the function of the healthy body works. In this way, early recognition of the impairment of function becomes possible and opens the way for early detection of disease and the application of therapy.

Treatises aimed at bringing together progress in the physiology of the eye are few compared with the many texts on the clinical and surgical aspects of ophthalmology. Major contributions to our understanding of the physiology of the eye and brain include Davson,[1,2] Adler,[3] Duke-Elder,[4] and Nesterov et al.[5]

The purpose of the present book is to bring together, in a coherent manner, new knowledge gained from research over the past 50 years on the physiology of the intraocular pressure, ocular blood flow, and the relation of these fundamental parameters to early diagnosis and therapy of vascular diseases of the eye and brain.

It will be evident to the reader that the presentation is influenced significantly by the author's own research. My justification is that by good fortune I have spent many years with superb collaboration helping solve outstanding problems of ocular physiology. This knowledge has increased understanding of the parameters underlying the onset of ischemia and the loss of autoregulation associated with common ocular disease and thereby led to new perspectives in diagnosis and therapy. This knowledge has led to questioning of present concepts.

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Contents

About the Author

Maurice E. Langham has served as Research Associate, The Ophthalmological Research Unit of The Medical Research Council, the United Kingdom 1947–1959; Research Fellow, Harvard University Medical School, 1955–1956; and Associate Director of the Ophthalmological Research Unit, The Medical Research Council, The United Kingdom 1957–1959. He served as Director of Research, The Wilmer Ophthalmological Institute, The Johns Hopkins University Medical School and Hospital, from 1959 to 1991, and Senior Research Investigator, The Applied Physics Laboratory, at The Johns Hopkins University from 1970 to 1991.

Section 1

Invasive Studies of the Parameters Regulating Ocular Physiology and Vision

This section deals with the invasive techniques used to measure the parameters that are fundamental to understanding the physiology and regulation of the intraocular pressure (IOP), aqueous humor dynamics, and ocular blood flow. These include the steady state IOP, the IOP pulse, the formation of the aqueous humor, the pulsatile and total ocular blood flows, the pressure/volume relation, and autoregulation of the choroidal blood flow. In extension of these subjects, the morphology and hydrodynamics of the chamber angle, the sympathetic innervation of the ocular tissues, and the actions of the adrenergic transmitter on ocular blood flow and autoregulation are presented.

1

"In Vivo" Manometric Studies of the Steady State Intraocular Pressure and the Intraocular Pressure Pulse in Animals and Man

Soon after Hermann von Helmholtz, Professor of Physiology in the University of Heidelberg in 1851, introduced the ophthalmoscope, one of his colleagues (Donders 1818–1889, **Fig. 1.1**) observed the flow of blood in the retinal arteries to pulsate and to have abnormal pulsations in diseased eyes. This observation of Donders would appear to be prophetic, for experimental studies in recent years have confirmed that the intraocular pressure (IOP) pulse in eyes of healthy subjects differs qualitatively and quantitatively from that in most, if not all, diseased eyes.

These qualitative observations of Donders had to wait a half century before manometric recordings on the eyes of curarized cats by Wessely confirmed the form of the IOP and its relation to the cardiac pulse.[1] Another further 50 years were to pass before manometric recordings on the eyes of anesthetized and conscious rabbits revealed the quantitative form of the IOP wave, its symmetry in pairs of eyes, and its response to increased IOP.[2]

These studies led to the application of similar manometric procedures on the eyes of anesthetized and conscious humans in which the pulsatile character of the IOP was recorded using highly sensitive pressure transducers (**Figs. 1.2** and **1.3**). Subsequently, a noninvasive tonometric technology was developed that gave analog recordings of the IOP and its pulse with accuracy equal to the manometric measurements.[3,4] Finally, the limitation of tonometric procedures to record the pulsatile nature of the IOP was eliminated with the development of a computerized pneumatic tonometer that recorded digitized IOP readings at a rate of 500 s^{-1}.[5] With this technology, the detailed form of the IOP pulse and trains of pulses could be recorded, stored on floppy discs, analyzed, and printed out.

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FIGURE 1.1. Donders (1818–1889): Daguerreotype taken in ca. 1862

The development in the 1950s of highly precise pressure transducers with minimal volume displacement (approximately 0.4 µl per 100-mmHg pressure) provided, for the first time, a means to objectively measure and record continuously the IOP and its pulsatile character. The manometric procedure comprised cannulation of the anterior chamber using a fine-grade needle connected by tubing to a highly sensitive pressure transducer and recording the analog output of the transducer on a moving heat-sensitive paper. An IOP recording using this procedure in a conscious healthy adult subject is shown in **Fig. 1.2**. The recording dramatically illustrates that the IOP is not a single constant value but has a dynamic wave form, which is in synchrony with the cardiac pulse. The amplitude of a healthy adult subject ranges from 2 to 4 mmHg. Superimposed on the fundamental IOP wave are slower waves induced by respiration and modulations of vasomotor tone. The arterial pulsatile flow from the ophthalmic artery enters the retinal and choroidal networks and flows through the capillary networks and drains into the veins, by which time the flow has completely lost its pulsatility (**Figs. 1.4** and **1.5**).

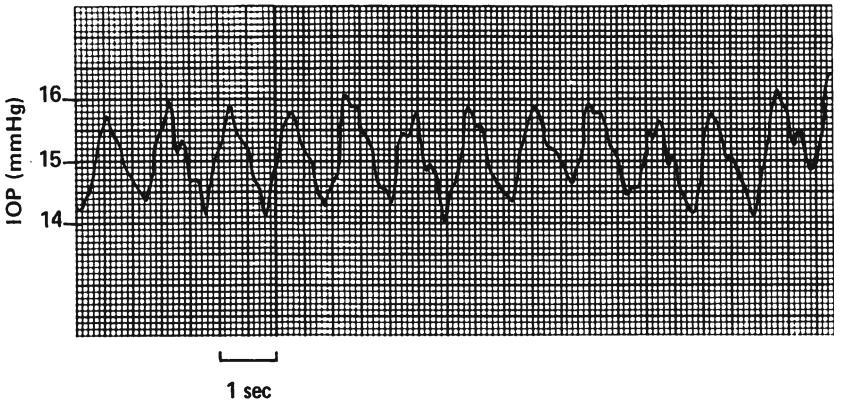

FIGURE 1.2. The IOP recorded from the anterior chamber of a conscious adult healthy human subject after topical application of anesthetic. The slight irregularity of the recordings was due to the need to hold the needle connected to the anterior chamber manually

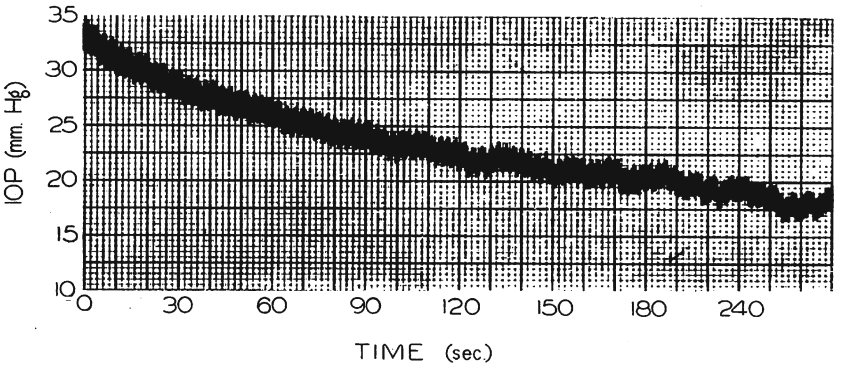

FIGURE 1.3. A typical manometric IOP recording from the anterior chamber of a healthy adult subject. The steady state IOP was 16 mmHg. The IOP had been raised to 35 mmHg at time 0 s by transient connection of the anterior chamber to a saline reservoir

Confirmation of the pulsatile flows in the retinal and choroidal circulations and the nonpulsatile form of the blood flow in the vortex veins has been achieved in Doppler sonographic recordings of the ophthalmic and the posterior ciliary arteries.[6–8]

The form of the IOP wave in the eye of a conscious adult human subject is shown in **Fig. 1.2**. The ascending portion of the IOP pulse wave increases proportionately with time and the maximal amplitude is reached in approximately one-half (0.4–0.5 s) of the total duration of the wave (approximately 1.0 s). The IOP of the individual wave then decreases exponentially until the next inflow of a bolus of blood starts a new pressure wave; during this declining

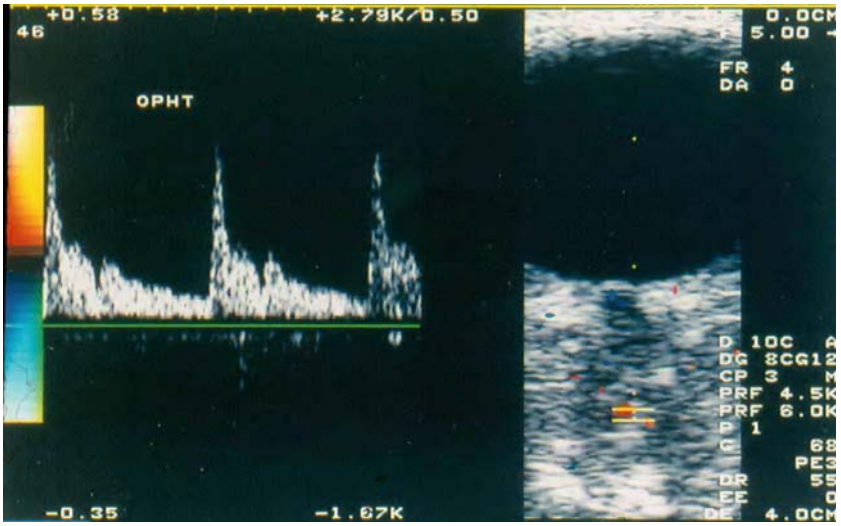

FIGURE 1.4. A Doppler waveform spectrum of the blood flow in the ophthalmic artery in a normal eye of a healthy adult subject. On the left is a recording of the blood velocities over two cardiac pulses. On the right is the outline of the eye and indicates the area of the ophthalmic artery at which the recording was taken

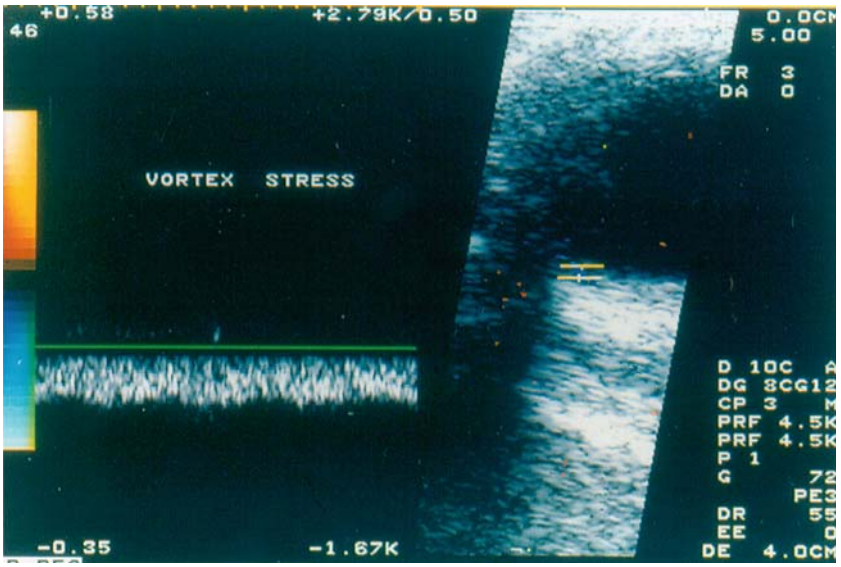

FIGURE 1.5. The Doppler waveform recorded from the vortex vein in a healthy eye of an adult subject. The left side shows the nonpulsatile blood flow and the right figure indicates the site of the vortex vein at which the recording was made

phase, the cardiac dichrotic notch may frequently be discerned. In manometric recordings in eyes of humans, the IOP, the form of the IOP pulse, and its amplitudes have been shown to remain essentially unchanged over extended periods (more than 30 min). This stability of the IOP over a sustained period contrasts with the reported instability of IOP in conscious human subjects measured at minute intervals with the Goldmann tonometer. Decreases of 2–4-mmHg IOP have been reported to occur with repeated readings every 60 s for 4 min using the Goldmann tonometer.[9,10]

It appears that this instability results from the response to the transient overshoot of the IOP induced during application of the tonometer to the cornea. This instability is not experienced with the Langham pneumatic tonometer, which does not have the transient overshoot (see Sect. 2).

The stability of the IOP, the constancy of the pulse wave and the pulse amplitude, and the equality of these parameters in pairs of eyes are lost in diseased eyes, and the comparison of IOPs in pairs of eyes is valuable in facilitating early detection of the impairment of the physiological status.

In healthy eyes a transient artificially induced disturbance of the steady state IOP is followed by a rapid recovery. Examples of this time-dependent IOP decay curve to the steady state IOP in an anesthetized human and cat are shown in **Figs. 1.3** and **1.6** . In these two examples, the IOPs were increased by connection of the anterior chamber to a reservoir of physiological saline set at a pressure of approximately 35 mmHg. In **Fig. 1.3** the time course of the recovery of the steady state IOP of 16 mmHg in a human eye is shown; the IOP decreased as a simple exponential of time with a time constant of 0.32 min^{-1} ($T_{0.5}$ of 2.2 min). **Figure 1.6** shows a similar study of the time course of the IOP decay curve in an anesthetized cat with a steady state IOP of 20 mmHg; the IOP decay constant was 0.61 min^{-1}.

The abnormally high rate of IOP recovery in the cat is associated with the relatively high rate of aqueous humor formation and outflow facility in this species. **Figure 1.6** also shows the time course of the IOP recovery after the IOP was decreased below the steady state value of 20 mmHg; the time constant of the IOP recovery is similar to that of the IOP pressure decay curve. It is to be noted that the pulse rate in individual eyes is identical to the heart rate.

The amplitudes of the IOP wave in pairs of healthy eyes are identical in both animals and humans. In a typical series of eyes of healthy anaesthetized rabbits the average minimal IOP of ten pulse waves recorded manometrically in pairs of cannulated eyes was 20.3 ± 0.3 mmHg (left eyes), and 20.3 ± 0.3 mmHg agrees with the noninvasive tonometric IOP made with the Goldmann applanation tonometer in anesthetized rabbits. In making this comparison, it is to be noted that readings of the IOP using the Goldmann tonometer are taken as

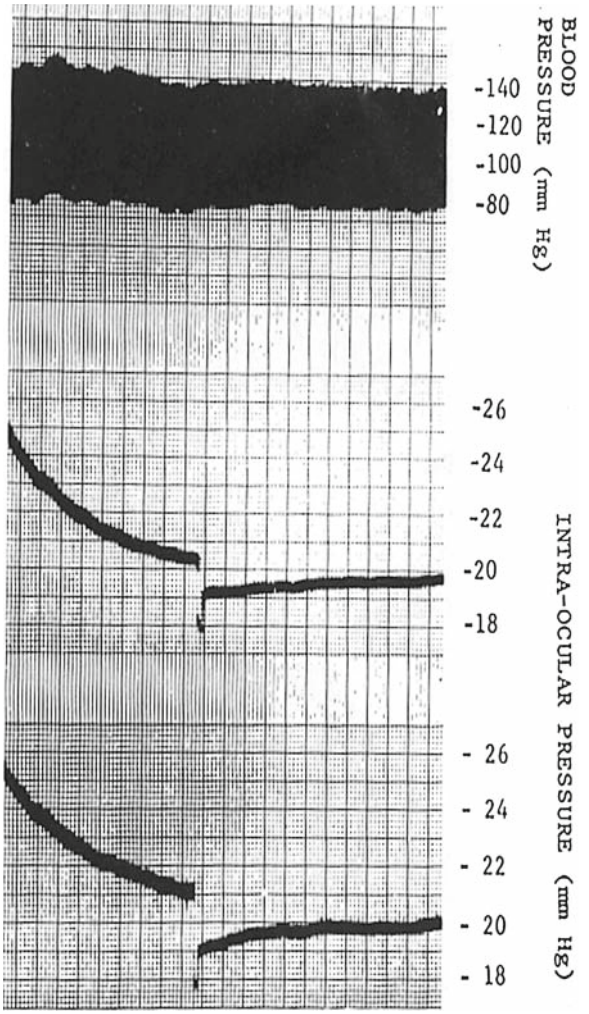

FIGURE 1.6. Manometric recordings in an anesthetized cat of the femoral blood pressure and the IOPs in pairs of eyes. The records show the convergence of the pressure decay curves after setting the IOPs above and then below the equilibrium pressure, respectively. The steady state IOPs were 20 mmHg. Each *large square* on the abscissa represents 1 min

the point at which the two half circles of the prism just meet, which corresponds to the minimal IOP of the pressure wave.

The amplitude of the IOP pulse is influenced substantially by the level of the IOP. In manometric studies on anaesthetized healthy animal and human eyes, the pulse amplitude has been shown to increase with the IOP, increasing to 50–60 mmHg and then decreasing with the further rise of the IOP and becoming 0 (**Fig 1.7**). As the IOP reaches the point of 0 pulse amplitude there is a rapid loss of vision from the periphery inward followed by complete blindness;

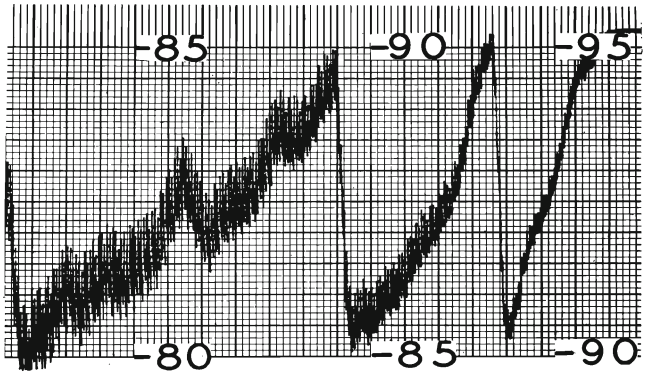

FIGURE 1.7. The effect of increased pressure on the IOP pulse recorded in vivo as the IOP approached the ophthalmic arterial systolic pressure in an anesthetized rabbit. The IOP was increased steadily by the infusion into the anterior chamber of physiological saline at a rate of 100 µl min^{-1}. It will be noted that the pulse amplitude decreased sharply at approximately 88 mmHg. In the same rabbit, the mean ophthalmic arterial systolic pressure measured manometrically was 89 mmHg. One large square on the abscissa represents 1 s

vision rapidly returns when the IOP is reduced by 5–10 mmHg. In this respect it is to be noted that the nonpulsatile component of ocular blood flow, which is approximately 15–20% of the total flow in the undisturbed eye, falls to 0 with increased IOP and reaches 0 at an IOP equal to the diastolic ocular arterial blood pressure. In healthy eyes, the complete loss of the pulse amplitude always causes immediate loss of vision.

2

The Rate of Formation of the Aqueous Humor

The mean steady state intraocular pressure (IOP) is set by equilibrium between the rate of formation of the aqueous humor and the resistance to the outflow of the aqueous humor through the trabecular meshwork and the intrascleral drainage channels. In the undisturbed eye, the relation between the inflow and outflow of the aqueous humor may be described mathematically by the equation $F = C(P - P_v)$, where F is the rate of formation of the aqueous humor in $\mu l\ min^{-1}$, C is the outflow facility (the reciprocal of the outflow resistance and expressed as $\mu l\ min^{-1}\ mmHg^{-1}$), P is the IOP in mmHg, and P_v is the pressure in mmHg in the veins exterior to the eye.

In the undisturbed eye, F, the rate of formation of the aqueous humor, may be calculated from an analysis of the time courses of the concentrations of freely diffusible fluorescein in the anterior chamber and in the blood stream, following a single intravenous injection of the fluorescent dye fluorescein. The unbound fluorescein diffuses from the bloodstream across the ciliary processes into the posterior chamber and then flows into the anterior chamber through the pupillary space. The mixing of the dye in the anterior chamber and the time courses of accumulation and decay of the fluorescent dye may be recorded by a sensitive photocell attached to the microscope of a slit lamp set at a fixed angle (approximately 60°) to the incident light beam. Because of the slow mixing of the fluorescein in the posterior and the anterior chambers, a significant concentration gradient between the back and front of the anterior chamber occurs in the first period (approximately 20 min), and it must be taken into account in the mathematical evaluation of the turnover rate of the fluorescein and the evaluation of the rate of formation of the aqueous humor.[11] The time courses of the concentrations of freely diffusible fluorescein in the blood stream and in the aqueous humor (**Fig. 2.1**) are used to evaluate the turnover rate of the fluorescein and thereby give the rate of flow of the aqueous humor.

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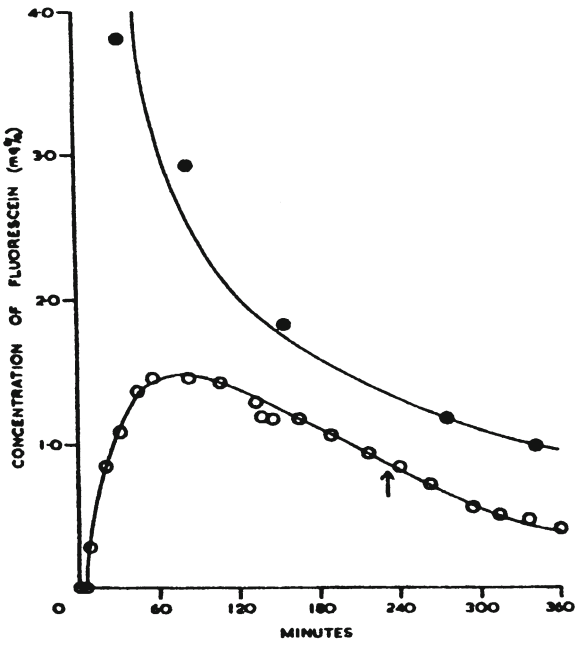

FIGURE 2.1. The time courses of the concentrations of freely diffusible fluorescein in the blood (*filled circles*) and in the aqueous humor of the anterior chamber following a single intravenous injection of 1 ml of an aqueous solution of 5% of sodium fluorescein in a conscious rabbit (From Hart and Langham).[11,12]

The mean values of the IOP, the rate of aqueous humor formation, and the outflow facility in conscious animals and man are summarized in Table 2.1. In healthy subjects the mean rate of flow of the aqueous humor is 2.1 µl min^{-1}. Note that cats (Table 2.1) have a substantially higher rate of aqueous humor formation than rabbits, primates, and man. This table also includes two individual results on patients with open angle glaucoma.

A manometric direct objective procedure to measure the rate of formation of the aqueous humor and the effect of pressure on the rate of aqueous humor formation was described by Langham.[13] In anesthetized rabbits and cats, the outflow channels were blocked by an injection of mineral oil into the drainage angle of the anterior chamber, leaving the main volume of aqueous humor in the anterior chamber intact. The blockage led the IOP to increase at a rate determined by the rate of aqueous humor formation (**Fig. 2.2**). The analysis of the time course of this IOP increase was used to calculate the rate of aqueous humor formation. In addition, the method was modified in order to record the rate of formation of the aqueous humor at constant IOP by using a micropipette kept horizontally and connected to the anterior chamber. At the end of

Table 2.1. The average IOP, rate of formation of the aqueous humor (measured by photofluorometry), and the outflow facility in rabbits, cats, monkeys, and man, and in two patients with open angle glaucoma.

Species	IOP (mmHg)	Formation ($\mu l\ min^{-1}$)	Venous P (mmHg)	Outflow Facility ($\mu l\ min^{-1}\ mmHg^{-1}$)
Rabbit	20	2.5	8	0.28
Cat	20	10.0	8	0.76
Monkey	17	2.0	8	0.21
Man	16	2.1	8	0.26
Open angle glaucoma	40	1.8	8	0.05
Open angle glaucoma	27	1.8	8	0.09

The results have been taken from published studies of the author with the exception of *F*, for normal man, which is taken from the published photofluorometric studies of Goldmann[14] and Bloom et al.[15] The photofluorometric measurements on the two glaucoma patients were made by Langham and Wybar[16] by the technique shown in Fig. 2.1. P_v – the venous pressure of 8 mmHg is taken from the studies of Perkins[17] and Goldmann.[18] The relatively high rate of aqueous humor formation in cats reflects the relative large volume of aqueous humor in this animal (approximately 800 µl) compared with the smaller volumes (approximately 200 µl) in rabbits dogs, primates, and man. Results of similar studies on two subjects with open angle glaucoma are included in this table to show that, in eyes with increased IOP, there may be little abnormality in the rate of aqueous humor formation but a major change in the outflow resistance

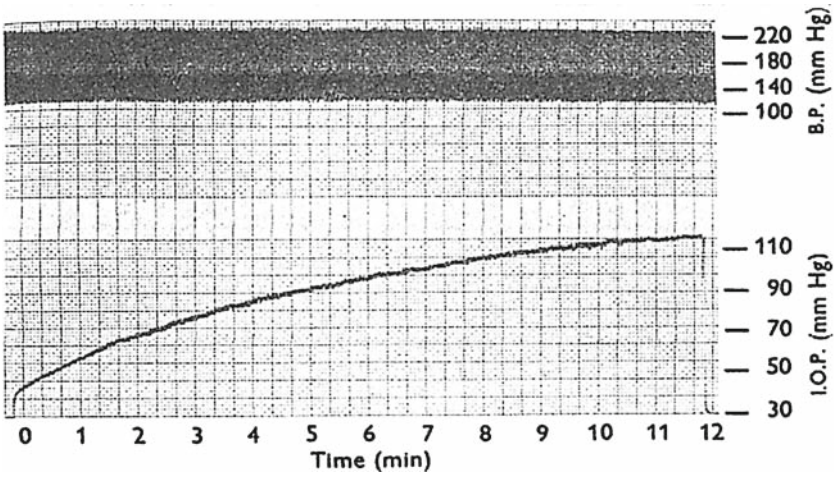

FIGURE 2.2. Manometric recordings of the femoral arterial blood pressure (upper recording) and the IOP in a cat anesthetized with urethane after blockage of the outflow vessels with liquid mineral oil (From Langham.[13] Reprinted from the *Journal of Physiology.* Used with permission from Blackwell.)

each study, closure of the outflow channels in the experimental eyes was confirmed by the absence of an IOP decline when the pressure was artificially increased in the dead eye. Using this micropipette procedure, the average rate of formation of the aqueous humor in anesthetized rabbits at an IOP of 20 mmHg was 2.2 μl min^{-1} and at an IOP of 50 mmHg was 1.1 μl min^{-1}. The finding that the overall rate of formation of the aqueous humor decreases with increased IOP and becomes 0 at an IOP at which blood flow into the eye ceases illustrates the critical role played by blood flow and the pressure gradient acting across the ciliary processes in the formation of the aqueous humor.[13]

Using the same objective measurement of the rate of formation of the aqueous humor, the response to a substantial decrease in the ocular perfusion pressure on the rate of aqueous humor formation has been examined following unilateral ligation of the common carotid artery. Ligation of the common carotid artery caused an immediate decrease of approximately 20% in the rate of aqueous humor formation with the IOP maintained at 20 mmHg. The corresponding ophthalmic arterial pressures were approximately 45 and 78 mmHg on the operated and control sides, respectively. In similar studies, electrical stimulation of the preganglionic cervical sympathetic nerve at 4 V and a frequency of 4 Hz caused an immediate decrease of approximately 40% in the rate of formation of the aqueous humor.

3

The Steady State Intraocular Pressure/Flow Relations in Dead and Living Animal and Human Eyes

The steady state intraocular pressures (IOPs) of healthy animal eyes have a diurnal variation of approximately 2–3 mmHg.[19] A similar small diurnal variation of the IOP and of the aqueous humor dynamics of healthy humans has been documented[20] and has been shown to remain essentially unchanged throughout life.[21] In the age range of 10–20 to 60–80 years, the average IOP in healthy eyes increases by no more than 1.5 mmHg.[21] This stability of the IOP is remarkable in that the ocular volume of approximately 2,000 µl requires an increase of 10 µl, less than 1%, to increase the IOP by 10 mmHg. Moreover, this stability is sustained despite a continuous formation of aqueous humor into the eye of approximately 130 µl h^{-1} in man and approximately 720 µl h^{-1} in cats.

The level of the IOP depends on a dynamic balance between the rate of formation of the aqueous humor, the outflow resistance, and the venous pressure in the recipient veins, external to the eye. Should one of these parameters alter, the IOP undergoes a proportionate change unless compensatory actions occur in either one or both of the remaining parameters.

The relation between the steady state IOP, the inflow of aqueous humor, and the outflow resistance has been clarified by analysis of the response of the steady state IOP and aqueous humor dynamics to experimentally induced incremental changes in inflow. In the eyes of rabbits, cats, and primates, immediately after death the IOP decreases and stabilizes at an IOP of 6–8 mmHg. At this pressure the outflow vessels collapse and no further loss of aqueous humor occurs. With a positive inflow of fluid (e.g., with an infusion of physiological saline phosphate at a constant rate into the anterior chamber), the intrascleral channels begin to open and become fully patent at an IOP of approximately 15 mmHg (**Fig. 3.1**). With the outflow channels fully patent the steady state IOP of the dead rabbit

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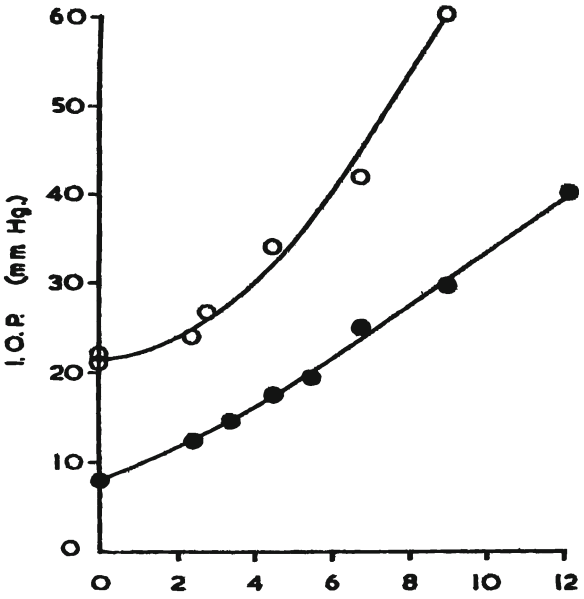

FIGURE 3.1. The steady state IOP/flow relations in living and dead eyes of a rabbit. The abscissa represents the rates of the infusion of physiologic saline that produced a series of steady state IOPs in mmHg (the ordinate) of the living (*open circles*) and dead eyes (*filled circles*) of the same rabbit; the infusions on the dead eye were made in situ immediately after death induced by intravenous injection of sodium phenobarbital. The abscissa shows the added rates of infusion of physiological saline in µl min^{-1}. The rate of flow of the aqueous humor in the normal eye of the rabbit is approximately 2 µl min^{-1} (From Langham.[2] Reprinted from the *British Journal of Ophthalmology*. Used with permission from BMJ Publishing.)

eye increases linearly with the rate of inflow (**Fig. 3.1**), i.e., the slope of the IOP/inflow relation remains essentially unchanged over the IOP range of 15–60 mmHg. This slope expressed as the outflow facility (the reciprocal of the outflow resistance) has a value of approximately 1.2 µl min^{-1} $mmHg^{-1}$.

The dead eye of the rabbit requires an infusion of 7–8 µl min^{-1} to sustain an IOP of 20 mmHg (**Fig. 3.1**). The steady state IOP then increases proportionately with additional inflow over the IOP range of 15–60 mmHg. With higher IOPs, the resistance to the outflow of fluid increases due to increased scleral tension compressing the intrascleral drainage channels. The mean IOP in the undisturbed eyes of living rabbits is 20 mmHg and is maintained by an average flow of aqueous humor of 2.1 µl min^{-1} (see Table 5.1).

This rate of flow is approximately 25% of the infusion of 7–8 µl min^{-1} needed to maintain an IOP of 20 mmHg in the dead rabbit eye. This difference in flow of 5–6 µl min^{-1} (at an IOP of 20 mmHg) between dead and living eyes is due to the absence of blood in the intrascleral channels of dead eyes. Thus, the flow resistance of the

intrascleral vessels of living eyes, where the flows of blood and aqueous humor compete for the same channels, is substantial, and comprises a major proportion of the total outflow resistance of the living animal and human eyes. This convergence of the flows of aqueous humor and blood in the intrascleral plexus leads to three distinct patterns of flow: first are veins full of blood, second are veins full of aqueous humor (the so-called aqueous veins), and third are veins that have clearly defined, side by side, linear flows of blood and aqueous humor (see Fig. 8.1). These three functional distinct types of channels have been identified in rabbits, cats, monkeys, and man. Qualitative changes in the patterns of flow in individual veins have been observed and documented following the topical application of drugs and by neuronal stimulation including an increase in the filling of the veins with aqueous humor following electrical stimulation of the preganglionic cervical sympathetic nerve.[22]

The major difference between the IOP/inflow relations in living and dead eyes of rabbits is shown in a typical example in **Fig. 3.1**. The IOP/flow relation in the living eye is nonlinear with a minimal slope in the initial part of the curve. For example, an incremental inflow equal to the flow in the undisturbed eye, namely 2–3 μl min^{-1}, causes the IOP to increase less than 2–3 mmHg (20–23 mm Hg) whereas the same infusion of 2–3 μl min^{-1} at an IOP of 30 mmHg causes the IOP to increase by approximately 8 mmHg (i.e., from 30 to 38 mmHg). It is evident that the tendency for the IOP to be affected by moderate increases (up to100%) of the normal rate of flow is minimal in the undisturbed eye. This tendency for the IOP to remain constant in the face of increased inflow is consistent with autoregulation of the IOP.

The dead and living eyes of humans have similar qualitative and quantitative IOP/flow relations to those of dead and living rabbits, respectively. Pressure decay curves on dead human eyes *in situ* within 2 h of death show the intrascleral outflow channels to close completely when the IOP falls to 6–8 mmHg; *parri passu*, the outflow channels open and become fully perfused when the IOP reaches approximately 15 mmHg. Similar to the findings in animal eyes, the trabecular meshwork plays little, if any, part in this pressure-dependent closure of the outflow channels as trabeculotomy (opening of the meshwork) leaves intact the closure pressure of 7–8 mmHg.

In in situ eyes of recently dead humans (within 3–12 h of death), an inflow of approximately 6 μl min^{-1} was needed to maintain an IOP of 16 mmHg compared with the rate of formation of aqueous humor of approximately 2 μl min^{-1} in eyes of healthy adults.

Confirmation that the trabecular meshwork plays a minor role in the total outflow resistance in healthy human eyes has been found in manometric measurements of the outflow resistance prior to and following opening of the trabecular meshwork (**Fig. 3.2**). By contrast, a substantial decrease of outflow resistance occurred after

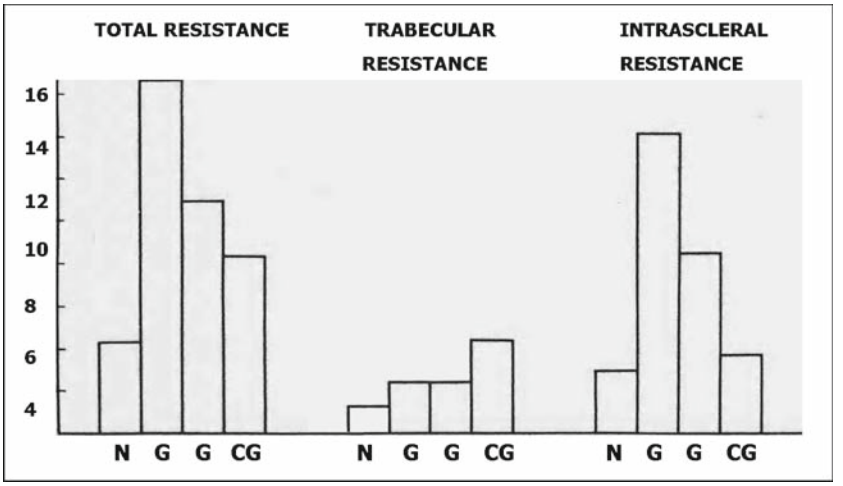

FIGURE 3.2. The outflow resistances in the trabecular meshwork and the intrascleral plexus in human eyes. *N* is the mean value for eight normal eyes, G represents two open angle glaucoma eyes, and CG is a congenital glaucomatous eye (From Fenstermacher et al.[23] Reprinted from *The Ocular and Cerebrospinal Fluids, Proceedings of a Fogarty International Center Symposium, Bethesda, MD, May 3–6, 1976*. Used with permission from Elsevier/Academic.)

trabeculotomy in the eyes of young subjects and patients with congenital glaucoma. The results summarized in **Fig. 3.2** revealed that, in living human eyes, the flow resistance of the intrascleral channels was more than twice that of the trabecular meshwork, and in cases of open angle glaucoma, the intrascleral resistance was three to five times that in the trabecular meshwork. Only in the cases of congenital glaucoma was the intrascleral resistance less than between the anterior chamber and Schlemm's canal.

4

Homeostasis, Autoregulation, and Relative Ischemia

The vascular circulatory network of the human body is a complex dynamic fluid system in which a series of metabolic and neurogenic mechanisms act in unison to keep within narrow limits the physiologic milieu. In this system, perhaps the most dominant controlled variable is the central blood pressure. A series of control mechanisms act to keep the contributing physiological variables at an optimal level, and the overriding control feedback is within the brain. The science of these control mechanisms is the field of cybernetics.

The sensor mechanism is one arm of the autoregulation, which responds to a change in the controlled variable. In the general circulation, the central blood pressure sensor arm includes the baroreceptors and the chemoreceptors strategically placed in the walls of certain arteries. The baroreceptors signal a pressure error by the number of nerve pulses sent by its afferent nerves to the vasomotor and the cardiac centers in the brain. Similar neuronal trains of impulses are sent to the vasomotor centers from sensors (chemoreceptors), which respond to abnormal chemistry in the interstitial tissues including the concentrations of oxygen and carbon dioxide.

The autoregulatory effector arm of homeostasis is the means by which the "error" is rectified. It acts to produce a change in the controlled variable in the direction to reduce the error. This effector arm may act relatively directly or indirectly on the controlled variable. The recovery motion toward homeostasis is called "negative feedback," in that it acts on the controlled variable directed in the opposite direction. By contrast, positive feedback increases the deviation (error) and leads to greater instability. In the systemic vascular system the effector arm is almost always negative feedback. Only in disease is there positive feedback and this leads to instability. One example of instability in the eye is the increased instability and abnormal values of the intraocular pressure (IOP) in open-angle glaucoma.

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In the general circulation, the feedback system frequently operates through the sympathetic innervation of resistance vessels and with the participation of circulating epinephrine. The nature and the mechanism of the negative feedback often remain difficult to identify unless the system becomes impaired. The sensitivity of the feedback system is measured in "gain" and in terms of the response to unit change in the controlled variable. For example, a feedback mechanism acts to maintain the blood pressure constant in resting conditions. However, in exercise the blood pressure increases and the error signal rises. By contrast, other physiological systems possess so great a gain that the error signal is difficult to detect. For example, the respiratory center is exquisitely sensitive to the partial tension of carbon dioxide in the blood. Vasomotor responses to pCO_2 tension are also seen in the hyperemia of muscle. Further, the oxygen tension in blood and tissues modulates the response of the heart and the lobes of the lungs during respiration.

In the eye, the level of the IOP, the amplitude and form of the IOP pulse, and the symmetry of these parameters in pairs of eyes are controlled variables that are modulated by the autoregulation of the steady state IOP and ocular blood flow. The vascular tissues of the eye are densely innervated by adrenergic neurons and they provide potentially powerful effector mechanisms for modulating the IOP and the ocular pulsatile and non pulsatile blood flows (PBFs).

The level of the IOP is determined by a balance between the rate of formation of the aqueous humor, the outflow resistance, and the recipient venous pressure. Both the formation of the aqueous humor and the resistance to outflow of the aqueous humor are strongly influenced by adrenergic neural activity, and this system plays a critical role in the autoregulation of the IOP and the ocular blood flow (see later).

The rapid recoveries of the IOP following artificially induced increased or decreased IOP are examples of the rapid autoregulation (see Figs. 1.3 and 1.6). A different but slower example of autoregulation is seen in the ocular response to a fall in the ocular perfusion pressure such as that occurs following experimentally induced ligation of the common carotid artery in animals and following moderate to severe stenosis of the internal carotid artery in man. In manometric studies on anesthetized rabbits and cats, the immediate response to a unilateral ligation of the common carotid artery is a substantial decrease in the IOP from an initial mean steady state IOP of 20 mmHg to an IOP of approximately 15 mmHg and a decrease of approximately 25% in the amplitude of the IOP pulse. The immediate fall in IOP is due partly to blood volume changes and is followed rapidly by a secondary increase in the steady state IOP to a value 3 mmHg below that in the contralateral eyes. In a series of six rabbits 1 h after surgery, the steady state IOP had decreased from an initial mean of 20.2 ± 0.8 to 16.1 ± 1.1 mmHg.

The steady state IOP in the affected eyes returns fully to normal within 12–36-h, and is identical to the values prior to surgery.

This complete recovery of the IOP occurs despite the continued substantial decrease of the ophthalmic arterial pressure, which persists for many weeks. For example, in eight rabbits unilateral ligation of the common carotid artery caused an immediate mean decrease of 45 ± 2.6 mmHg in the ophthalmic arterial systolic pressure on the operated side from an initial mean of 110 ± 1.3 mmHg. At 28 days, the mean ophthalmic arterial pressures in pairs of eyes remained at 52 ± 3.5 (3) and 108 ± 2.3 mmHg (3) in the operated and nonoperated sides, respectively.

Typical IOP/PBF relations of pairs of eyes of rabbits under urethane anesthesia at 1 and 24 h following unilateral ligation of the common carotid artery are shown in **Fig. 4.1**. Prior to surgery the IOP/infusion rate relations were identical in pairs of eyes, and unilateral common carotid ligation induced a marked change in the slope of the IOP/infusion rate relation. This difference in slopes of the IOP/flow relations in pairs of eyes remained essentially unchanged in the ensuing 28 days. However, despite this change in the IOP/infusion relation, there was nearly complete recovery of the IOP accompanied by a substantial improvement in the rate of pulsatile ocular blood flow (**Fig. 4.2**). A typical result of the IOP/PBF relations in pairs of eyes of a conscious rabbit prior to and 24 h after a unilateral ligation of the common carotid artery is shown in **Fig. 4.1**.

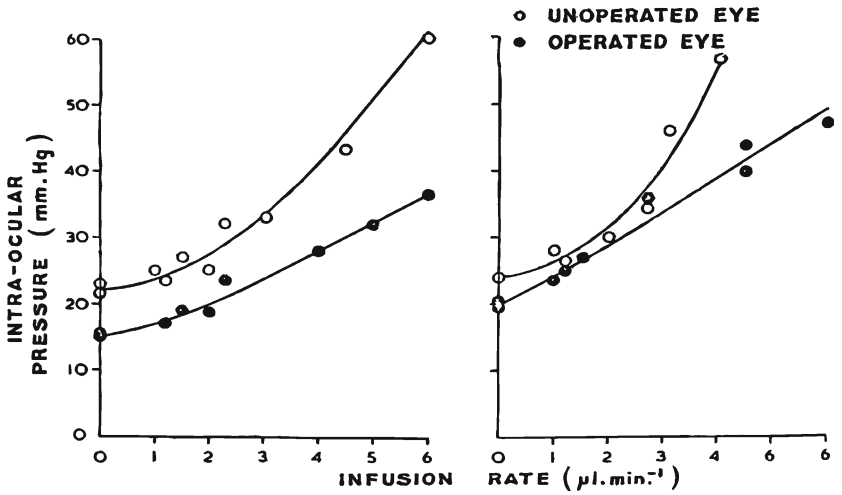

FIGURE 4.1. The relation between the steady state IOP and the rates of infusion of physiological saline in the eyes of living anesthetized rabbits following a unilateral ligation of the common carotid artery. The result on the left was made 1 h after the ligation and that on the right was made on a second anesthetized rabbit 24 h following unilateral ligation of the common carotid artery. The *filled circles* are results on the operated sides and the *open circles* were taken on the contralateral normal eyes (From Langham.[2] Reprinted from the *British Journal of Ophthalmology*. Used with permission from BMJ Publishing.)

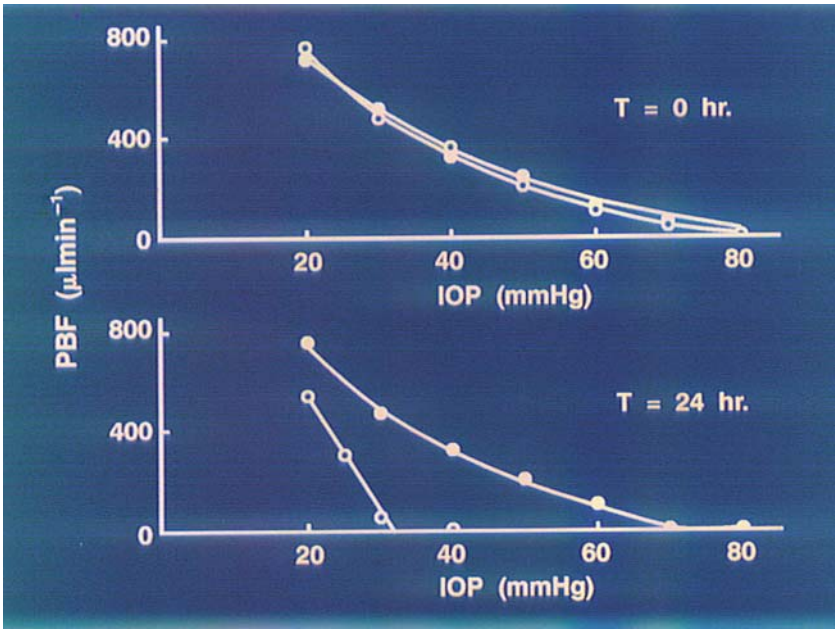

FIGURE 4.2. The effect of unilateral ligation of the common carotid artery on the IOP and ocular pulsatile blood flow (PBF) in a conscious rabbit. The upper figure shows the rates of PBF in pairs of eyes in the conscious rabbit prior to surgery. The lower figure shows the rates of PBF in the eye on the operated side (*open circles*) and in the control eye (*filled circles*) 24 h following surgery of the same conscious rabbit

Prior to surgery, the IOP/PBF relations were identical in pairs of eyes and the pulsatile rates of blood flow were 734 and 750 µl min^{-1}, respectively. Immediately after unilateral ligation of the common carotid artery, the PBF fell to a mean of 350 ± 12 (6) µl min^{-1} but at 24 h had recovered to a mean of 623 ± 9 µl min^{-1}, a recovery (autoregulation) of approximately 300 µl min^{-1}. In the same rabbits, the IOP on the operated sides at 24 h had recovered to slightly below that on the control side. The relatively small decrease of the blood flow in the eye on the operated side at 24 h contrasted with a mean decrease of 35 mmHg in the ocular perfusion pressure. The slope of the IOP/pulsatile flow relations on the operated sides (**Fig. 4.2**) had increased significantly, reflecting a decrease in ocular vascular resistance.

A relatively small decrease of PBF (approximately 20%) at 24 h in the eye after unilateral ligation of the common carotid artery is in agreement with numerous studies on rabbits confirming a decrease of approximately 20% in the total rate of ocular blood flow to the eye and to the ciliary processes. In direct measurements of ocular blood flow in the vortex veins Nakamura and Bron[24] and Linner[25] reported a decrease of approximately 20% in ocular blood flow following unilateral ligation of the common carotid artery in

anesthetized rabbits. Also, analysis of the transfer of ascorbic acid across the ciliary processes showed the total rate of blood flow to the ciliary processes to be decreased by approximately 20% following unilateral ligation of the common carotid artery.[25]

Finally, analysis of the rate of aqueous humor formation based on the rate of transfer of radioactive sodium from the blood to the aqueous humor and the transfer of fluorescein from the blood to the aqueous humor showed a reduction of approximately 20% in the rate of aqueous humor formation following unilateral ligation of the common carotid artery in rabbits.[26–29]

In man, the effect of unilateral loss of blood flow to the eye occurs with moderate to severe stenosis of the internal carotid artery. A typical example is summarized in **Fig. 4.3**. The ophthalmic arterial pressure in the affected eye is approximately 30 mmHg below that in the control eye, yet the IOPs in pairs of eyes are approximately equal. The PBFs in the undisturbed eyes were 740 and 674 μl min^{-1}, respectively. Following successful surgical endarterectomy, the IOP/pulse amplitude (PA) relations became identical and the ophthalmic arterial pressure in the affected eye recovered completely.

In summary, experimental and clinical observations provide convincing evidence that in eyes of healthy animals and man in which the ophthalmic arterial pressure and ocular blood flow have been substantially reduced, autoregulation of choroidal blood flow acts to minimize a decrease of the IOP and to minimize loss of ocular pulsatile and total blood flows.

A very important consequence of autoregulation is that oxygen loss is substantially minimized. For example, the oxygen tension in the ocular fluids in normal rabbits following unilateral ligation of the common carotid artery changes very little despite the large fall (approximately 50%) in the ophthalmic arterial pressure.[30] Consequently the risk of visual loss due to loss of oxygen to the mitochondria of the visual cells is minimized.

The maintenance of a normal oxygen tension in the internal fluids of the eye by the autoregulation helps to maintain the aerobic metabolism essential to the photoreceptors and vision. In healthy adult humans, the oxyhemoglobin level in arterial blood sustains an oxygen tension of approximately 100 mmHg in the retina close to the lobules of the choroid. This tension decreases to nearly 0 in the middle layers of the retina.[31]

Consequently, in healthy eyes the oxygen tension and the rate of diffusion of oxygen from the choroidal vessels provide little, if any, oxygen reserve to the inner segments of the retina. Fortunately, there is a substantial diffusion of oxygen into the aqueous humor, which flows backward from the posterior chamber to the retinal surface and the vitreous humor. In healthy animals and man, the pO_2 tension in the aqueous and vitreous humors has mean values of approximately 40 mmHg and remains essentially unchanged following unilateral ligation of the common carotid artery.[30]

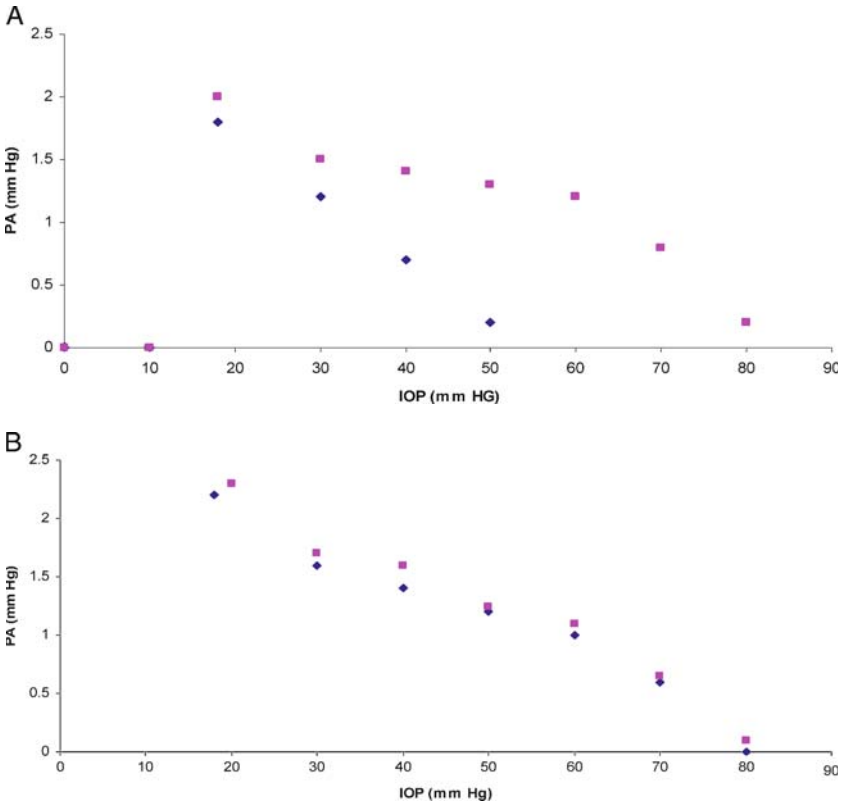

FIGURE 4.3. The IOP/ pulse amplitude (PA) relations in the eyes of a patient with a severe unilateral stenosis (75%) of the internal carotid artery. The *squares* and *diamonds* are measurements on the unaffected and affected eyes, respectively. (**a**) shows observations made prior to surgery and (**b**) shows results taken 2 months after endarterectomy on the side with the stenosis

The continuous and stable diffusion of oxygen to the surface of the retina from the posterior chamber is sufficient to sustain the aerobic metabolism of the ganglion cell layer and minimizes the possibility of a relative ischemia. Thus, while the retinal blood flow of fully oxygenated normal red cells has sufficient oxygen to support only 25–30% of the aerobic metabolism of the retina,[32] an impairment of the retinal blood flow would increase risk to the ganglion cell layer. However, it is evident that this is unlikely due to the autoregulation of the choroidal blood flow, which maintains nearly constant the pO_2 in the aqueous and vitreous humors.

The optic nerve head contains a dense anastomatic plexus of small vessels supplied mainly from the choroid but also from retinal vessels.[33] It is not therefore unexpected that the choroidal blood flow induces autoregulation in the optic disk. In this respect, little, if any, change in blood flow in the optic disk was found when the perfusion pressure was decreased by an increased IOP or decreased ophthalmic arterial pressure.[34]

The efficiency of the system maintaining constant the physiological function of the ganglion cell layer is evident in observations that the pressure-dependent differential light sensitivity in humans remains stable when the IOP is increased to 50–60 mmHg, and also remains stable when the ophthalmic arterial pressure and the ocular perfusion pressures are decreased by more than 50% in man.[35,36] In this respect there are the results of numerous investigations that have been interpreted as supporting the view that the retinal arterial network has efficient autoregulation.[37,38] However, these conclusions may have to be modified as these investigators assumed that the choroidal blood flow was not autoregulated as claimed by Alm and Bill.[39]

In the systemic vascular circulation, autoregulation acts via the efferent sympathetic nervous system by modulation of the peripheral resistance. The dense network of adrenergic neurons innervating the vessels of the choroid and the knowledge that both increased sympathetic nerve activity and cervical sympathetic denervation have substantial effects on ocular blood flow and on aqueous humor dynamics indicates that similar mechanisms most probably act in the eye.

In both animals and man, cervical sympathetic ganglion denervation induces a substantial decrease in IOP, changes the IOP/flow relation, and increases the rate of ocular blood flow.[26,40,41] In anesthetized rabbits, cervical preganglionic sympathotomy induces a linear IOP/flow relation similar to that found in eyes of dead animals. In addition, the preganglionic sympathotomy causes the close symmetry of the IOPs and the pulse forms in pairs of eyes to be lost (**Fig. 4.4**).

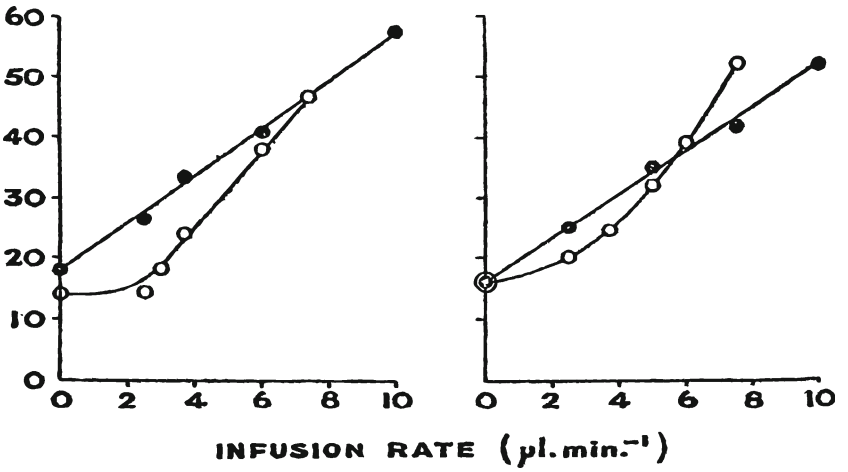

FIGURE 4.4. The effect of unilateral preganglionic cervical sympathotomy. The measurements were made on the operated eyes control (*open circles*) and the experimental eyes (*filled circles*) 24 h after section of the nerve. The ordinate represents the IOP in mmHg (From Langham and Taylor.[40] Reprinted from *Journal of Physiology, London*. Used with permission from Blackwell.)

The response to increased sympathetic nerve activity has been documented in animals given electrical stimulation of the preganglionic cervical sympathetic nerve. Stimulation causes a decrease of the steady state IOP, a decrease in the rates of total ocular blood flow, and a decrease in the rate of aqueous humor formation.[42] In man, the adrenergic nerve transmitter norepinephrine applied topically to the eye is known to decrease the steady state IOP and to decrease the rate of aqueous humor formation.

In summary, adrenergic innervation of the ocular vessels provides an efficient effector mechanism for autoregulation of the IOP and ocular blood flow.

5

The Pressure/Volume Relation in Eyes of Dead and Living Animal and Human Eyes

The steady state intraocular pressure (IOP) in animal and human eyes is dependent on a continuous inflow of a few microliters (approximately 2 µl min^{-1}) of aqueous humor. This fluid brings oxygen and nutrients to the intraocular tissues and carries away the products of metabolism through the drainage channels, located in the angle of the anterior chamber into the episcleral venous plexus, and then rejoins the main venous blood flowing back to the heart.

Volumetric changes in the eye induced by the IOP pulse are small compared with the total volume of the eye and cannot be measured directly. However, even small changes in volume cause significant change in IOP, which can be measured with accuracy. Thus, the key to evaluation of volume changes, aqueous humor dynamics, and ocular blood flow is the relation between volume and pressure. This relation of changes in volume and pressure was termed, rather inappropriately, the coefficient of ocular rigidity – inappropriate because it is not the total volume of the eye that is measured but is the volume needed to change the IOP by a given amount. Further, it is not rigidity of the eye that is being measured.

The coefficient of ocular rigidity, i.e., the relation between changes in ocular volume and IOP for dead human eyes, was used extensively in the calibration of the Schiotz indentation tonometer and applied later to the evaluation of the tonographic coefficient of the outflow facility.[43]

In a theoretical approach to the relation between changes in volume and pressure, Friedenwald made the assumption that the proportional increase of the IOP varied directly with the proportional increase in volume of the eye as expressed in the relation

$$dP/P = k\, dV/V, \tag{5.1}$$

where dP is the change in IOP, dV is the change in volume of the eye, and k is a constant.[44] Since dV is very small compared with V,

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the total volume of the eye, Friedenwald considered the total volume to be a constant. Consequently, k/V is also a constant, which Friedenwald called the coefficient of ocular rigidity. The earlier equation (5.1) then takes the form $dP/P = K\,dV$, and integration of this equation yields the expression $K = (\ln P_2 - \ln P_1)/dV$, where P_1 is the initial IOP, and P_2 is the modified IOP, expressed in terms of a natural logarithm. Rather than using natural logarithms, K, the Friedenwald coefficient of ocular rigidity, has been expressed in terms of common logarithms. This use of common rather than natural logs simply changes the value of K ($\log P = \ln P/2.303$).

Subsequent experimental studies revealed that Friedenwald's coefficient of ocular rigidity was not constant, but changed with IOP in both dead and living human eyes. In the period 1958–1962, three groups of investigators, one group in Oslo, Norway, a group in Liege, Belgium, and one in Baltimore, USA, published results of manometric studies of the relation between changes in IOP and ocular volume in dead and living human eyes.[45–47] The studies included measurements "in situ" within 2–4 h of death, prior to and immediately after enucleation. In these manometric studies, the anterior chamber was cannulated and connected to a highly sensitive pressure transducer and the IOP was recorded continuously as the ocular volume was increased either by an instantaneous inflow of physiological saline or by steady rates of infusion (**Figs. 5.1** and **5.2**). The results, defining the relations between changes in IOP and volume, revealed a substantial difference between dead and living human eyes.

The results on dead eyes measured by these techniques were similar to those of Friedenwald, giving a similar coefficient of the scleral rigidity of 0.0215. However, Friedenwald[50] argued that this relation would also hold for living eyes but subsequent studies showed this not to be true for it failed to take into account changes in blood volume induced by increased IOP (**Figs. 5.1** and **5.2**).[50]

Subsequently Silver and Geyer[51] made a detailed analysis of the published data from the aforementioned three groups of investigators and proposed a new pressure–volume relation for living human eyes.[51] Their results led to a mathematical relation:

$$\Delta V = V\,(C + C_0 \ln P + C_1 P), \tag{5.2}$$

where V is the volume of the eye, P is the IOP, and ΔV is the increment of volume over an arbitrary reference volume. Since the volume change between two IOPs is generally of interest, the arbitrary reference volume cancels out of the calculation. They confirmed that, for the IOP range of 10–60 mmHg based on 182 data points from 21 living human eyes, the pressure/volume relation derived from all the current available data on living human eyes gave a substantially larger volume increment for a given increment of pressure than Friedenwald's equation based on cadaver eyes. The mean curve of the pressure/volume relation for living human eyes shown in **Fig. 5.3** includes the scatter of ±2 and 3 standard deviations around the mean.

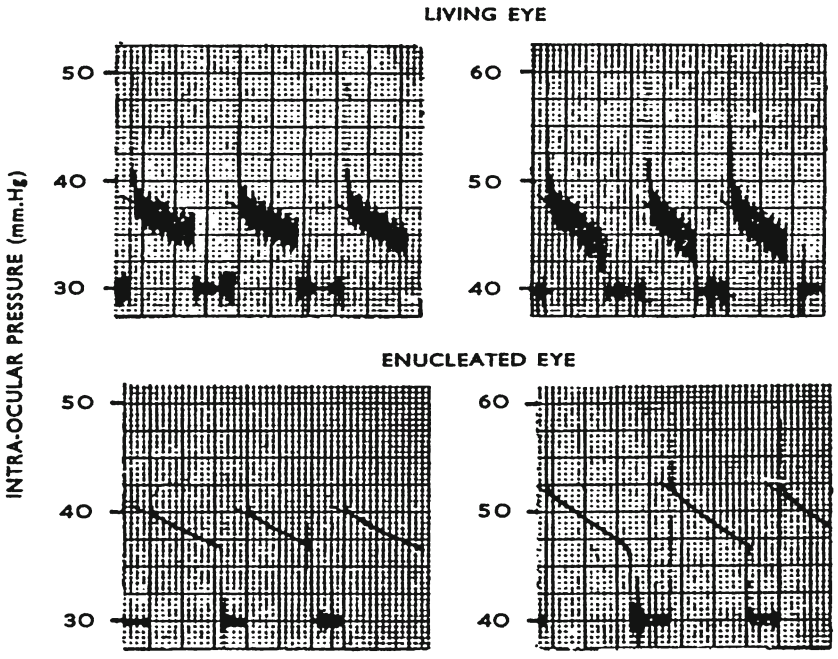

FIGURE 5.1. Typical recordings of the IOP in an anesthetized living human eye and in the same eye after enucleation to rapid infusions of physiological saline. The volumes infused to the living and dead eyes were identical. Note that that the IOP responses in the enucleated eye exceeded those in the living eye at corresponding initial IOPs (From Eisenlohr and Langham.[48] Reprinted from *Investigative Ophthalmology and Visual Science*. Used with permission from the Association for Research in Vision and Ophthalmology.)

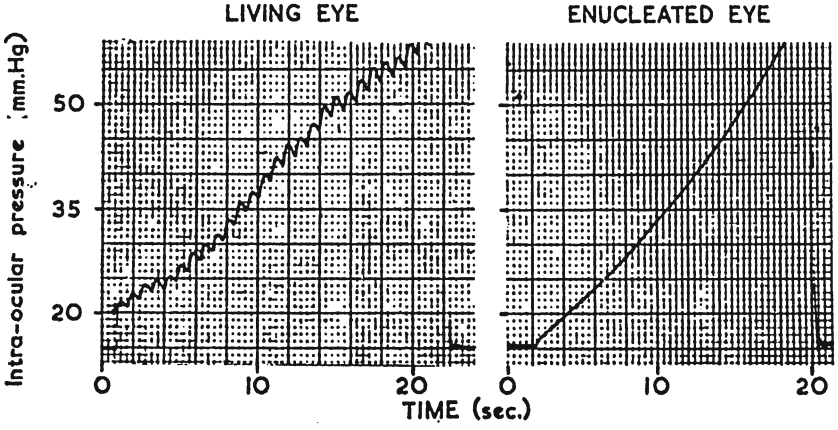

FIGURE 5.2. IOP recordings from the same living (*left figure*) and enucleated human eye (*figure on the right*) during the infusion of 197 µl min^{-1}. Note the difference between the shapes of the two curves indicative of the difference in the pressure/volume relation between living and dead eyes (From Langham and Eisenlohr.[49] Reprinted from *Investigative Ophthalmology and Visual Science*. Used with permission from the Association for Research in Vision and Ophthalmology.)

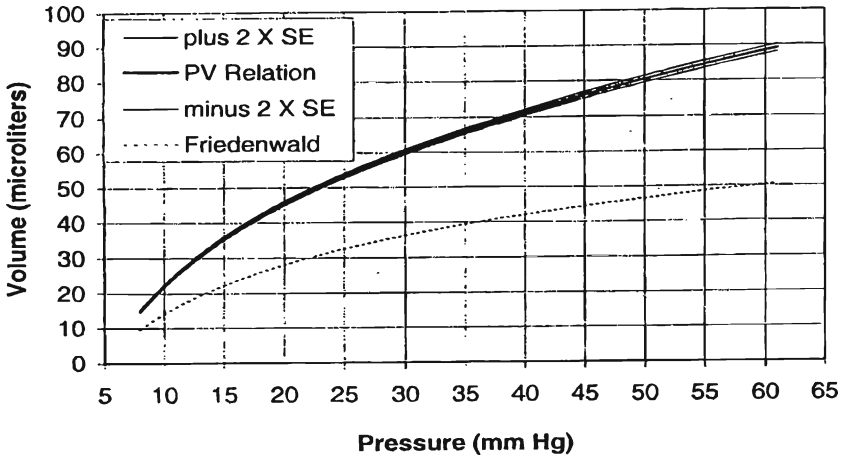

FIGURE 5.3. The mean IOP/volume relation for human eyes of average volume (*upper curve*) taken from the paper of Silver and Geyer.[51] The curve was based on data taken from 21 living human eyes reported by Prijot,[45] Ytteborg,[46] and Eisenlohr et al.[47] The lower curve is that of Friedenwald[50]

Table 5.1. The mean coefficients of outflow facility in six healthy eyes and six eyes of glaucomatous patients.

Series	Normal eyes (N)	Glaucoma eyes (GL)	N–GL
1	0.30 ± 0.11 (6)	0.15 ± 0.11 (6)	0.15 ± 0.12 (6)
2	0.35 ± 0.13 (6)	0.16 ± 0.12 (6)	0.19 ± 0.12 (6)

The studies were made using a standard Schiotz tonometer with a 5.5-g weight for 4 min. The results in Series 1 were evaluated using the Friedenwald coefficient of scleral rigidity of 0.215; the results in Series 2 were evaluated using the pressure/volume relation of living human eyes (scleral coefficient of 0.125)

The Friedenwald coefficient of ocular rigidity has been, and still is, widely used in the calculation of the coefficient of the outflow resistance in the diagnosis and therapy of ocular disease by the method of tonography. The error in evaluation of the coefficient of outflow facility using Friedenwald rigidity coefficient rather than the true coefficient for living eyes is significant, but fortunately the errors have not prevented its value in diagnosis and therapy of open angle glaucoma.[43] However, the use of the true values of the IOP/volume relation in the evaluation of the coefficient of outflow facility by the method of tonography rather than using the erroneous Friedenwald coefficient of ocular rigidity substantially increases the sensitivity of the technique to differentiate between normal and abnormal eyes. Table 5.1 summarizes typical coefficients of outflow resistance in a small series of normal and glaucomatous eyes using the coefficients of scleral rigidity of dead (the Friedenwald coefficient of ocular rigidity) and of living eyes.

6

The Ocular Perfusion Pressure and Its Influence on the Intraocular Pressure Pulse

The general principle of hemodynamics is expressed in the simple law $F = \Delta P/R$ where the flow F depends on the driving force ΔP, which is the "pressure drop" down the circulatory network (i.e., from artery to vein), and R is the resistance to flow for the particular route of blood flow (i.e., of the vessels of the particular vascular bed). This resistance depends on the geometry of the vessels (their length and diameter), as well as the nature of the fluid driven through, specifically viscosity. It follows that control of the distribution of blood through a specific network can be modulated by (a) the driving pressure ΔP, and (b) the resistance, R, to flow in each vascular bed.

In addition to the perfusion pressure that drives fluids through the vessels there are elastic elements (elastin and collagen) in the vessel walls that act to maintain a steady tension and equilibrium between the blood pressure and the interstitial pressure; the elastic tension is effected by smooth muscle cells, usually arranged circumferentially in the vessel wall. The function of the vascular smooth muscle is to produce active tension by contraction and thereby modulate the internal pressure within the vessel. The precapillary arterioles are the major sites of this active vasomotor control and provide the main sites for modulation of the total vascular resistance.

The possibility of a complete closure of a vessel arises when the vasomotor tone decreases and results in a critical transmural balance with the pressure within the vessel in equilibrium with the interstitial pressure. In this condition, an increase in the interstitial pressure or a decrease in the internal pressure may lead to complete closure of the vessel; in the eye, the interstitial pressure is the intraocular pressure (IOP). This phenomenon of spontaneous closure is of considerable physiological importance in the eye because the eye is a closed system and increased IOP, such as found in glaucomatous eyes, increases substantially the possibility of vessel

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closure and subsequent hemorrhage. This phenomenon may account for the prevalence of local hemorrhages in the optic nerve head in the early stage of open angle glaucoma[52] and may explain the observations that the relatively small decrease of the IOP associated with the action of ocular hypotensive drugs may be sufficient to sustain blood flow in the small vessels of the optic disk.

The arterial pressure creating the driving force to the flow of blood through the body is pulsatile and changes continuously with cardiac contraction and relaxation, and by respiration and vasomotor tone. Depending on the flow resistance and geometry of the vessels in an individual organ, there will be a variation in the percentages of the total flow that is pulsatile and nonpulsatile, respectively. With the start of each heartbeat, the velocity of the forward flow in the aorta increases rapidly to a maximal value and then decreases to 0 and may even fall to a negative value (reversed flow) following closure of the aortic valve. The mean pressure of the pressure wave is defined as that pressure that would maintain a constant blood flow. This mean value approximates closely to the value of the *diastolic pressure* + (*systolic pressure* – *diastolic pressure*)/3. On this basis, the central arterial systolic and diastolic pressures of 120/80 mmHg, respectively, yield a mean arterial pressure of 93 mmHg.

The pressure in an artery may be measured manometrically using a needle connected to a highly sensitive low-volume differential pressure transducer, which is inserted into an artery against the flow of the blood. The cannula causes a block of the artery and cessation of the blood flow; the pressure measured in this way differs from that recorded when the cannula goes with the flow of blood. An alternative method is to apply a compression force against the artery and record the pressure needed to completely stop flow (the systolic pressure) and record the lower pressure that just allows complete blood flow (the diastolic pressure). This technique is widely used for the indirect measurement of the brachial arterial pressure.

The ophthalmic arterial pressure has been measured objectively using manometric techniques in the living eyes of anesthetized animals and humans. The procedure involves simultaneous recording of the IOP and the pulse wave from the anterior chamber as the IOP is increased until the pulse amplitude becomes 0. In anesthetized rabbits, the pulse reaches 0 amplitude at an IOP of approximately 90 mmHg, compared with the femoral arterial blood pressure of 105/80 mmHg. In similar studies on anesthetized rabbits, the ophthalmic arterial pressure has been recorded via a cannula inserted into the median ear artery to the level of the ophthalmic artery. In these conditions, the pulse amplitude recorded manually from the anterior chamber reached 0 at an IOP within 10 mmHg of the ophthalmic systolic arterial pressure.

In similar studies on anesthetized humans, the anterior chamber was cannulated and the IOP and the pulse wave were recorded

simultaneously as the IOP was steadily increased until the pulse amplitude fell to 0. This occurred at an IOP of approximately 80 mmHg compared with a brachial arterial blood pressure of 130/85 mmHg.[47] An important observation from these studies is that the ophthalmic arterial pressure in humans, but not in rabbits and cats, is significantly less than the central blood pressure. These observations confirm the prior manometric studies on humans by Niesel and Ismiridis,[53] and the measurements of the retinal artery systolic and diastolic pressures by ophthalmodynamometry.[54]

The relatively low ophthalmic arterial pressure compared with the central arterial pressure appears to be unique to man and reflects the large size of the brain compared with the eye. In this respect, the blood flow to the human brain exceeds by approximately 70 times the blood flow to the eye.

The response of the ophthalmic arterial pressure to change in the central arterial blood pressure has been analyzed in anesthetized rabbits and cats. Experimentally induced unilateral occlusion of the common carotid artery causes a small increase in the central arterial blood pressure and a substantial decrease of the ophthalmic arterial pressure on the ligated side. In a series of six rabbits the ophthalmic arterial systolic pressures on the ligated and nonligated sides were 46 ± 3 and 93 ± 4 mmHg, respectively, and the mean difference in pairs of eyes was 47 ± 3 mmHg.

The sensitivity of the ophthalmic arterial pressure in humans to the cerebral vascular resistance (CVR) was first demonstrated in objective manometric measurements by Neisel.[55] Niesel employed the nitrous oxide method of Kety and Schmidt to measure the CVR and compared the effect of experimentally induced increased CVR on the ophthalmic arterial systolic pressure.[56] This method is based on the principle of tissue clearance of rapidly diffusing inert isotopes such as Na_{21}, Xe_{133}, and K_{85}. These elements pass so rapidly from tissue to blood that their elimination is, in most situations, limited only by the rate of blood flow. In 53 patients, increased CVR was found to induce a proportionate increase in the ophthalmic arterial pressure (**Fig. 6.1**).

A decrease in the CVR is found in humans treated systemically with carbonic anhydrase inhibitors such as acetazoleamide. The carbonic anhydrase inhibitors increase the pCO_2, which induces cerebral vasodilatation (decreased vascular resistance). The drug also causes vascular dilatation and decreased vascular resistance in the eye but the flow increase in the brain dominates the ocular response and causes a preferential flow ("steal") of blood to the brain.[57]

Because the ophthalmic arterial pressure in humans is substantially lower than the arterial pressure feeding the brain, it is affected both by changes in the CVR of the brain and the vascular resistance in the internal carotid artery. An increase of the CVR causes the ophthalmic arterial pressure to rise proportionately above its normal value while a decrease of the CVR causes the

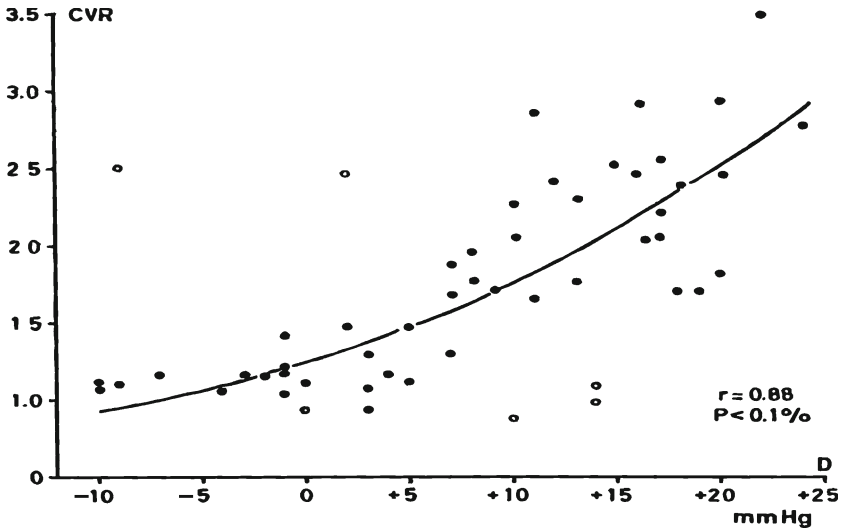

FIGURE 6.1. The relationship between the cerebral vascular resistance (CVR) determined by the Kety–Schmidt method[56] and the pressure deviation (mmHg) of the ophthalmic arterial pressure from normal in a series of 53 patients (From Weigelin and Lobstein.[54] Reprinted from *Ophthalmodynamometry* – Publisher: Hafner.)

ophthalmic arterial pressure to decrease. The effect of modulations of the CVR on the ophthalmic arterial pressure may be substantial; a twofold increase of CVR increases the ophthalmic arterial pressure by approximately 18 mmHg and the mean ocular perfusion pressure to increase from its normal of 50 mmHg to approximately 70 mmHg (see Chap. 18).

7

Direct and Indirect Measurements of Ocular Blood Flow in Anesthetized and Conscious Animals and Humans

Direct measurements of the total rate of ocular blood flow have been made almost exclusively on anesthetized animals. One of the first attempts was made by Kaneka on anesthetized cats, in which the blood flowing from a cut vortex vein was collected and weighed.[58] This flow was then multiplied by 4 to account for the four vortex veins draining blood from the eye. His results indicated a blood flow of approximately 1,300 µl min^{-1}. Similar measurements made on the vortex veins of anesthetized rabbits by several groups of investigators (Meesman and Fischer[59] and Sondermann[60]) gave total ocular blood flow rates of 1,200–2,000 µl min^{-1}. Later, Nakamura and Goulstine, using a flow recorder connected by a cannula inserted into a vortex vein in rabbits anesthetized with urethane, reported a total flow in four vortex veins of 800–900 ml min^{-1}.[61] These investigators observed that the flow decreased with increased intraocular pressure (IOP) and reached 0 at an IOP of approximately 80 mmHg (compared with a femoral arterial blood pressure of 120/80 mmHg). From a limited series of measurements of blood flow at different IOPs, they concluded that blood flow decreased linearly with IOP.

There have been numerous indirect methods used to measure the rate of total ocular blood flow. These include the entrapment of radioactive microspheres in the small vessels of tissues, thermography (in which the rate of heat dissipation is measured), and tissue clearance techniques using compounds that diffuse rapidly such as radioactive krypton and nitrous oxide.[62,63] One comprehensive series of studies was made by Bill using the radioactive labeled microsphere technique.[64] The microspheres had well-defined diameters (15 ± 5 µm), labeled with Sr_{85} and were injected into the left cardiac ventricle of anesthetized animals. The microspheres become evenly mixed in the arterial blood and then become trapped within the capillary beds. A reference sample of blood is taken from one of the major arteries and at the same time the eye is enucleated and

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the specific tissue isolated and analyzed. Under these conditions the radioactivity of the sample is proportional to the blood flow through the tissue. Using this procedure, Bill reported that the total blood flow in the rabbit eyes was approximately 2,000 μl min^{-1}.[65]

This value was higher than the direct volumetric measurements of blood flow in the vortex veins by prior investigators. In a subsequent study on conscious rabbits, he exteriorized the common carotid artery on one side and then injected the microspheres into the circulation of conscious animals the following day.[66] Under these conditions, Bill reported the total ocular blood flow in conscious rabbits to be approximately 1,300 μl min^{-1}, a value closer to that reported in the majority of prior published studies.[67]

The total blood flow may be considered to have pulsatile and nonpulsatile components, and simultaneous measurements of the pulsatile and total blood flows have been made in rabbit and human eyes. In the studies on animals, the blood flow in the vortex vein of anesthetized rabbits was measured at a constant IOP, at the same time as the IOP pulse was recorded manometrically. In six rabbits, the total mean ocular blood flow at an IOP of 20 mmHg was 800 ± 25 μl min^{-1} and the mean pulsatile blood flow was 656 ± 24 μl min^{-1}. The mean rate of pulsatile blood flow in conscious rabbits with a mean IOP of 20 mmHg based on the analysis of the IOP pulse and frequency is approximately 720 μl min^{-1}. The pulsatile component in these studies was made from the analysis of the IOP pulse using the technique described by Silver et al.[68,69]

An alternative experimental approach to the measurement of the total rate of blood flow in conscious adult humans has been made, based on the diameter of the ophthalmic artery and the velocity of the blood flowing through the artery. In these conditions $F = AV$ where F is the flow in μl min^{-1}, A is the cross-sectional area of the ophthalmic artery in mm^2, and V is the velocity in mm s^{-1}. The diameter of the human artery was measured in eyes that had been enucleated with a relatively long segment of intact ophthalmic artery. The internal diameter of the artery was made at a point just prior of the junction of the ophthalmic artery with the posterior ciliary arteries. A tapered glass rod was gently pushed into the artery at a pressure of 80–90 mmHg until it fit snugly at the predetermined point. The rod was cut at this position and the diameter of the cut end was measured. The velocity of blood flow in the ophthalmic artery of normal subjects was taken as the mean value from published sonographic measurements, namely 300 mm s^{-1}.[6] In a series of eight human eyes, the total ocular blood flow ranged from 900–1,050 μl min^{-1} with a mean of 927 ± 21 μl min^{-1}. The average rate of ocular pulsatile blood flow in healthy eyes of adult subjects based on the analysis of the IOP pulse is 740 μl min^{-1}.[70] On this basis, the total ocular blood flow in humans, approximately 900–1,000 μl min^{-1}, comprises pulsatile and nonpulsatile components of approximately 80 and 20%, respectively.

The total blood flow includes the uveal-choroidal and the retinal vascular networks. Published data indicates that the retinal flow is 10–15% of the total flow, leaving the major flow to be choroidal. The blood flow in the retina of healthy adult subjects has been reported to range from 33 ± 9.6 (Riva et al.[71]) to 80 μl min^{-1} (Feke et al.[32]), measured by laser Doppler velocimetry (Feke and Riva[72]).

The relatively small retinal blood flow has only sufficient oxygen to support 20–25% of the aerobic metabolism of the retina,[32] based on the blood flow of 50 μl min^{-1} of fully oxygenated normal red cells. It is this inability of the retinal blood flow to sustain fully the aerobic metabolism of the retina that underlines the importance of the choroidal blood flow to provide and sustain the remaining 75–80% of the oxygen needs of the retinal cells **(Fig. 7.1**).

Mitochondria, densely packed in the inner segments of the photoreceptors, are responsible for the majority of the oxygen uptake of the retina, and these photoreceptors lie in close proximity to the vascular lobules of the choroid. The high oxygen uptake of the

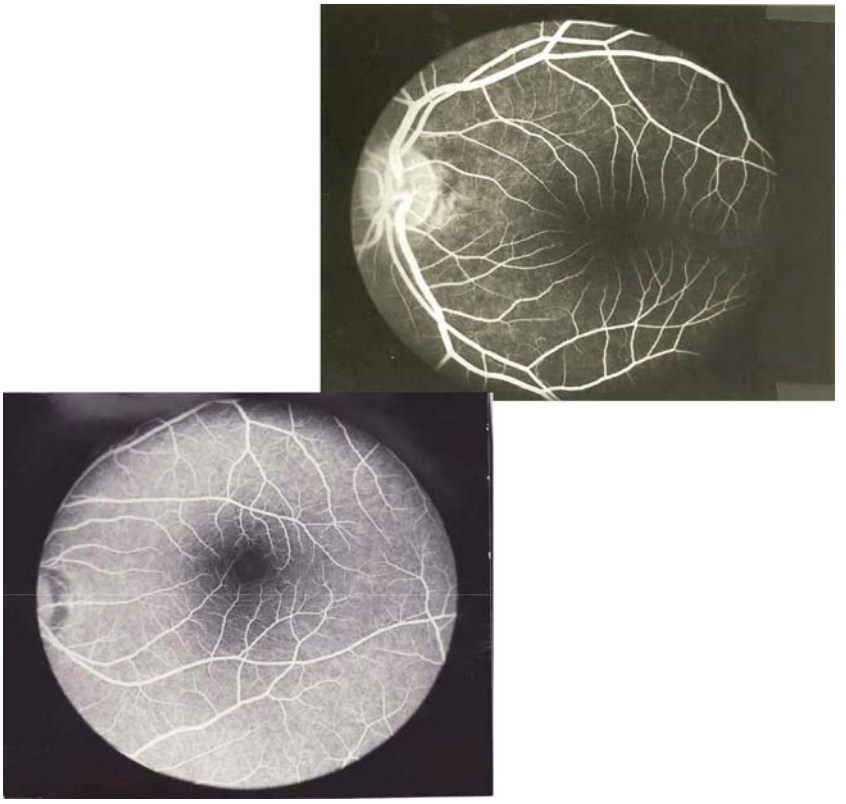

FIGURE 7.1. The retinal blood vessels. The optic nerve (*left*) shows the emerging retinal arteries, which form the network of vessels supplying the underlying dense capillary network feeding the ganglion nerve fibers. The dark avascular area in the middle is the fovea. It is this network of retinal vessels that carry 10–15% of the total ocular blood flow

photoreceptors results in a very steep slope of the oxygen tension profile across the retina, from a tension of approximately 80 mmHg at the inner segments of the photoreceptors close to the lobules of the choroid, to an oxygen tension of only 2–10 mmHg in the middle and inner layers.[31,73,74] It follows from the relatively low retinal blood flow of 50 μl min^{-1} in human eyes that not only are the oxygen needs of the retina dependent on sufficient blood flow of the choroid, but also this supply will be endangered when the blood flow from the internal carotid artery is compromised.

Examples of the significant decrease of choroidal blood flow include the loss of perfusion pressure to the eye due to stenosis of the internal carotid artery, increased flow resistance in the vessels of the eye, and a decreased oxygen tension of the arterial blood. In these events, a major increase of oxygen supply to the retina from an increased retinal blood flow may be ruled out in view of its relatively low rate of blood flow in the retina of healthy eyes. This means that an increased blood flow, when needed, must be sought in the ability of the choroid to increase its rate of blood flow to maintain and sustain the optimal oxygen tension.

Studies on subjects with moderate to severe stenosis of the internal carotid artery show that the increase in total ocular blood flow associated with vascular autoregulation is in the order of 300–500 μl min^{-1}.[75] This blood flow increment is many times greater than the total retinal blood flow in normal eyes.

While the oxygen needs of the retina must always be dependent primarily on the oxygen capacity and tension in the arterial blood flowing through the choroid, there is evidence that transient increases in retinal blood flow, consistent with autoregulation, occur. Thus, isotope entrapment studies have indicated that autoregulation occurs in response to experimentally induced circulatory changes including elevated IOP.[39] In addition, the blood flow in retinal arteries has been claimed to increase during dark adaptation to hypercapnia and to hypoxia.[32,76,77] These modulations of flow are immediate and their importance may well lie in their ability to supply transient demands of the photoreceptors.

Based on the evidence that the oxygen needs of the retina require the total oxygen contained in a blood flow of 150–200 μl min^{-1}, it is evident that the normal total ocular blood flow of approximately 900 μl min^{-1} provides a large reserve to offset abnormally low ophthalmic arterial pressure, such as that occurs in patients with moderate to severe stenosis of the internal carotid artery.[75] Fortunately, the autoregulation of blood flow to the choroid, in the order of 400 μl min^{-1}, is more than sufficient to supply the aerobic metabolic needs of the retina, sustain vision, and have minimal effect on the steady state IOP. The survival of a normal differential threshold of visual sensitivity under these conditions has been confirmed in observations that the time-dependent visual threshold

remains intact in pairs of eyes of patients with a unilateral moderate to severe stenosis of the internal carotid arteries.[78]

The blood flow to the anterior optic disk is an extremely small percentage of the total blood flow. Nevertheless, its role in maintaining the oxygen needs of the nerve fibers is critical. Bundles of nerve fibers of widely differing diameters are enmeshed in a network of capillaries. Evidence based on the pressure- and time-dependent visual threshold suggests that the spatial distribution of blood flow through these vessels varies with changes in IOP.[35]

In healthy eyes, there is a minimal perfusion pressure and a minimal rate of ocular blood flow, at which the rate of ocular blood flow becomes insufficient to maintain a normal visual threshold. The level of the critical perfusion pressure essential to maintain the oxygen needs of the retina and vision in normal eyes would appear to be in the order of 25 mmHg, based on observations on a subject with a severe bilateral stenosis of one internal carotid artery and with complete occlusion in one internal carotid artery (**Fig. 7.2**). At the time of the initial ocular examination of this subject, the brachial blood pressure was 160/98 mmHg and the ophthalmic arterial pressures

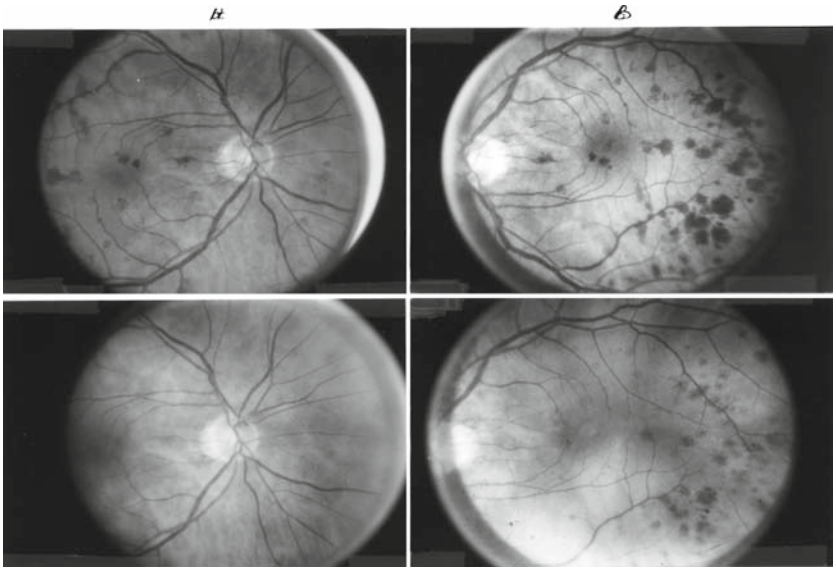

FIGURE 7.2. Retinal hemorrhages induced by severe bilateral stenoses of both internal carotid arteries in a male subject of 63 years. The upper photos show the left (**a**) and right (**b**) eyes prior to endarterectomy and the lower photos show the same eyes 6 weeks after unilateral endarterectomy on the side with the less severe stenosis (left eye) based on arteriography. The ophthalmic arterial pressures were 45 mmHg (left eye) and 34 mmHg (right eye) prior to surgery and 65 mmHg (left eye) and 55 mmHg (right eye) 6 weeks after surgery. The ocular pulsatile blood flows were 340 ml min^{-1} (left eye) and 245 ml min^{-1} (right eye) prior to surgery and 630 ml min^{-1} (left eye) and 560 ml min^{-1} (right eye) 6 weeks after surgery

were 44 mmHg (right eye) and 45 mmHg (left eye); the IOPs were 10 mmHg (right eye) and 15 mmHg (left eye) and the ocular pulsatile blood flows were 280 μl min^{-1} (right eye) and 350 μl min^{-1} (left eye), compared with 740 μl min^{-1} the mean of normal eyes.

Both retinas of this subject had numerous hemorrhages and vision was impaired in both eyes (Fig. 7.2). The patient underwent endarterectomy on the left internal carotid artery, and the ophthalmic arterial pressures increased to 55 and 65 mmHg in the two eyes, and the pulse amplitudes increased to 1.8 mmHg. Six months following unilateral endarterectomy, all the hemorrhages had almost, if not completely, resolved.

8

The Morphology and Hydrodynamics of the Chamber Angle Draining the Aqueous Humor

The resistance to outflow of aqueous humor has long been recognized to be localized in the trabecular meshwork and in the approximately 20 small channels that originate in the outer wall of Schlemm's canal and pass through the wall of the eye to merge with the episcleral veins at the "chamber angle." Thus, the drainage pathway of the aqueous humor flow forms a series of two communicating networks: an inner trabecular meshwork of small channels, which feed into the canal of Schlemm, and an intrascleral plexus, which drains aqueous humor from the canal of Schlemm. In all species, the aqueous humor leaves the intrascleral plexus and drains toward the heart via the episcleral, the anterior ciliary, and the ophthalmic veins.

Aqueous humor drainage through the trabecular meshwork appears to account for essentially the entire bulk outflow in man. The channels (veins) of the intrascleral plexus may be divided into three functional components dependent on whether they are filled with blood, aqueous humor, or a mixture of blood and aqueous humor. The last component includes veins in which a laminar separation of blood and aqueous humor may be visible to the eye. Veins containing aqueous humor only (the aqueous veins) have been identified in animal species whether or not they possess a canal of Schlemm.

In principle, the in vivo outflow resistance may be regarded as having a mechanical component derived from the small caliber of the flow channels, and a vascular component derived from the flows of blood and aqueous humor through the intrascleral plexus. Additional factors in the flow resistance in the plexus are the different viscosities of blood and aqueous humor (blood is 1.8 times the viscosity of aqueous humor), and the fact that the space available for aqueous outflow depends on the extent to which the plexus is filled with blood.

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A widely held, current view is that the outflow resistance is essentially mechanical, resulting from the morphologic properties of the trabecular meshwork and in particular, the sheet of endothelial cells lining the inner wall of Schlemm's canal.[79] This view was based on evidence that the pressure in the aqueous veins appeared to be significantly lower than the intraocular pressure (IOP).[17,18] The experimental approach of these investigators was based on the assumption that when an aqueous vein was occluded by the application of pressure, the occluding pressure would reflect the pressure in the canal of Schlemm if there was no branching. In 28 normal eyes of conscious human subjects, Linner reported that the average IOP was 15.7 ± 0.42 mmHg, the average pressure that occluded an aqueous vein was 11.9 ± 0.24 mmHg, and the average pressure to occlude an epicsleral vein was 10.99 ± 0.27 mmHg.[80] On the assumption of no branching therefore, only 20% of the outflow resistance would lie between Schlemm's canal and the recipient external veins. A similar result was found by Goldman.[18] However, the assumption of no branching was not borne out by anatomical studies, and consequently the magnitude of the intrascleral resistance was underestimated.[81,82]

An alternative approach to the assessment of the relative contribution of the trabecular and intrascleral components to the total outflow resistance in living eyes has been to measure directly the pressure in the canal of Schlemm. The experimental procedure was found to be difficult and meaningful results have been questioned.[83–85] The results from the different groups of investigators were generally similar and indicated that approximately 75% of the outflow resistance lies distal to Schlemm's canal. However, this evidence was not supported by measurements of the pressure in the canal of Schlemm and the finding that the pressure fell to 0 when the canal was opened to the exterior.

In dead eyes, there is compelling evidence that the trabecular meshwork is the main site of outflow resistance. The outflow resistance in dead human eyes has been quantitatively analyzed from measurements of the relation between the steady state IOP and experimentally induced infusions of saline phosphate into the anterior chamber. At death, the IOP falls spontaneously to approximately 8 mmHg, at which point the outflow vessels close (the critical closure pressure). When the anterior chamber of the dead human eye is perfused with physiological saline within 2 h of death, the outflow channels begin to open and become fully patent at an IOP of 15–16 mmHg. Then, the IOP increases directly with the perfusion rate up to an IOP of approximately 60 mmHg; this means that the outflow resistance remains constant over the IOP pressure range of 15–60 mmHg. At higher perfusion pressures, the outflow resistance increases substantially due to the deformation pressure on the vessels within the sclera by abnormally high IOP.

The flow resistance proximal and distal to the trabecular meshwork in the dead human eye has been differentiated by surgically

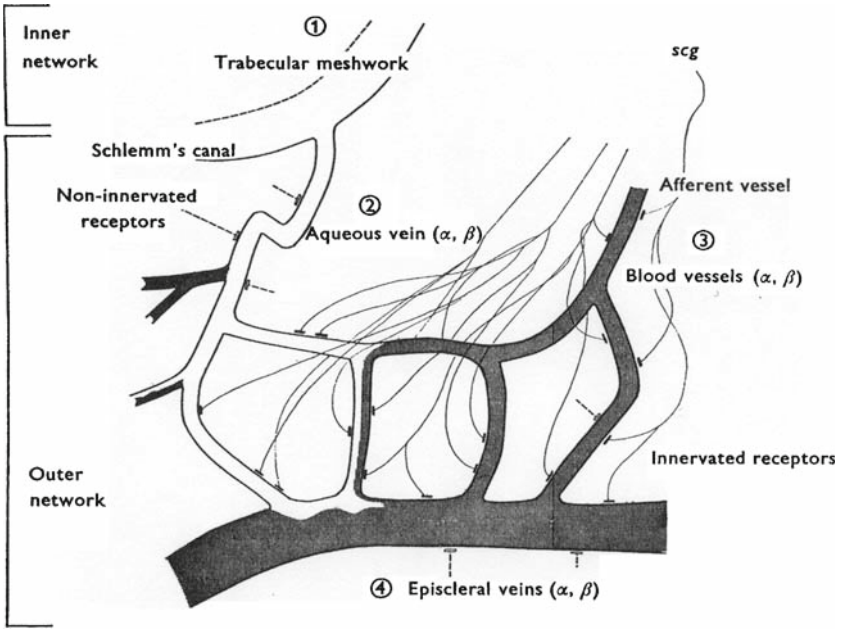

Figure 8.1. The anatomical components of the inner and outer networks of the channels draining the aqueous humor from the human eye. The inner network includes the trabecular meshwork and the layer of endothelial cells lining the inner wall of Schlemm's canal. There is no innervation of the inner network (1). The outer network comprises the intrascleral vessels filled with aqueous humor (2), blood (3), or a mixture of blood and aqueous humor (4). Postganglionic adrenergic neurons from the superior cervical ganglia (scg) innervate the vessels of the outer network but it would appear that the aqueous veins are sparsely innervated compared with the blood-filled vessels. The adrenergic receptors include both α and β types (From Langham and Palewicz.[87] Reprinted from the *Journal of Physiology (London)*. Used with permission from Blackwell.)

opening the trabecular meshwork. Following trabeculotomy on dead eyes, the critical closure pressure remains unchanged, namely at an IOP of approximately 8 mmHg, whereas the total outflow resistance decreases by 50–70%. A similar result has been found in the eyes of freshly killed rabbits treated with the enzyme hyaluronidase, which acts to decrease the flow resistance across the trabecular meshwork.[86] Thus, in the dead eye, the flow resistances in the intrascleral plexus and the episcaleral veins are relatively low (**Fig. 8.1**).

The distribution of the outflow resistance proximally and distal to Schlemm's canal in living human eyes differs greatly from that in dead eyes. The steady state IOP/flow relations before and after enucleation, followed by trabeculectomy, revealed the flow resistance distal to the canal of Schlemm to be approximately four times that across the trabecular meshwork. This major proportion of the total outflow resistance is due to the filling of the channels with blood, for in the absence of blood, the resistance is negligible (see **Fig. 6.1**).

9

The Sympathetic Nerve Innervation of the Eye and the Actions of the Adrenergic Neuron Transmitter Norepinephrine on Intraocular Pressure and Ocular Blood Flow

The efferent sympathetic nerves passing from the vasomotor center in the brain form a major efferent pathway for the autoregulation of the intraocular pressure (IOP) and the ocular blood flow. The sympathetic nerve relays from the spinal roots to the eye via the cervical and stellate ganglia. Passing into the eye, the fibers innervate the vessels, and lobules of the choroid, the epithelial layers of the ciliary processes and the intra and episcleral plexuses, where the aqueous humor flows to rejoin the venous circulation. Fluorescent histochemical studies show that the neurons make syncitial-like processes enveloping individual vessels. In addition to the innervation of the vessels of the eye, sympathetic nerves are also found in the anterior layers of the epithelium of the avascular cornea.[88]

The capacity of the sympathetic nerve activity to control and regulate the IOP is seen qualitatively and quantitatively in the actions of denervation, electrical stimulation, and in the actions of the adrenergic transmitter norepinephrine on the rate of formation of the aqueous humor, on the chemical composition of the aqueous humor, and on the resistance to outflow of the aqueous humor through the intrascleral venous plexus. The responses to electrical stimulation of the sympathetic nerve are mediated by the release of the adrenergic transmitter norepinephrine from presynaptic sites, which then interact with adjacent adrenergic smooth muscle receptors. A dense sympathetic nerve innervation of the ciliary processes and a less dense innervation of the intrascleral vessels draining the aqueous humor

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have been identified by fluorescent histochemical studies.[88] These studies show the sympathetic nerve innervation to pass through the trabecular meshwork but not to innervate it. The main concentration of adrenergic fibers in the area of drainage of the aqueous humor forms a moderately dense syncitial meshwork surrounding the vessels of the intrascleral meshwork and the episcleral veins.

The response of the IOP and aqueous humor dynamics to adrenergic denervation differs qualitatively and quantitatively, depending on whether the denervation is made pre or postganglionic. Cervical preganglionic denervation leaves intact the postganglionic neurons and its pharmacologic integrity. In the final neuron and terminal synapse, the concentration of the transmitter norepinephrine remains intact following preganglionic sympathectomy, and the ability of the nerve to release the transmitter by electrical stimulation of the postganglionic fiber and mediate rapid reuptake of the transmitter to the nerve remains unchanged. Furthermore, the ocular responses to electrical stimulation of the postganglionic neurons remain identical to the responses in the intact innervated eye.

Cervical postganglionic sympathotomy results in degeneration of the postganglionic neurons. Consequently, there is a complete loss of the transmitter norepinephrine at the nerve–muscle junction. In addition, the degeneration of the postganglionic neuron causes a loss of the reuptake mechanism of the norepinephrine. It is the reuptake of the transmitter norepinephrine into the neuron that determines the duration of the response to the adrenergic transmitter. In the absence of the postganglionic neuron (sympathotomy), the response to norepinephrine increases in magnitude and in duration and is termed adrenergic supersensitivity.

Cervical preganglionic sympathectomy has several actions on the eye. It causes an immediate and persistent meiosis of the pupil, a small and relatively short change in the IOP, and a significant increase in the pulse amplitude. In addition it causes an increase of approximately 20% in the blood flow to the ciliary processes.[25,26] This increased blood flow to the ciliary processes is associated with increased secretion of ascorbic acid into the aqueous humor and a small increase in oxygen tension.[25,26,30] The denervation also increases the protein concentration in the aqueous humor signifying increased permeability of the blood aqueous barrier; this increased permeability persists for at least several weeks.

Although cervical preganglionic sympathectomy has no significant immediate or persistent effect on the IOP, it does induce a marked change in the IOP/flow relation (**Fig. 9.1**) and a substantial decrease in the ocular vascular resistance. The denervation causes the IOP/flow relation to be approximately linear, and to differ from normal eyes in the absence of the low slope of the IOP/flow relation close to the steady state IOP (see Fig. 7.2). This abnormal IOP/flow relation persists for at least several months and may indeed be permanent.

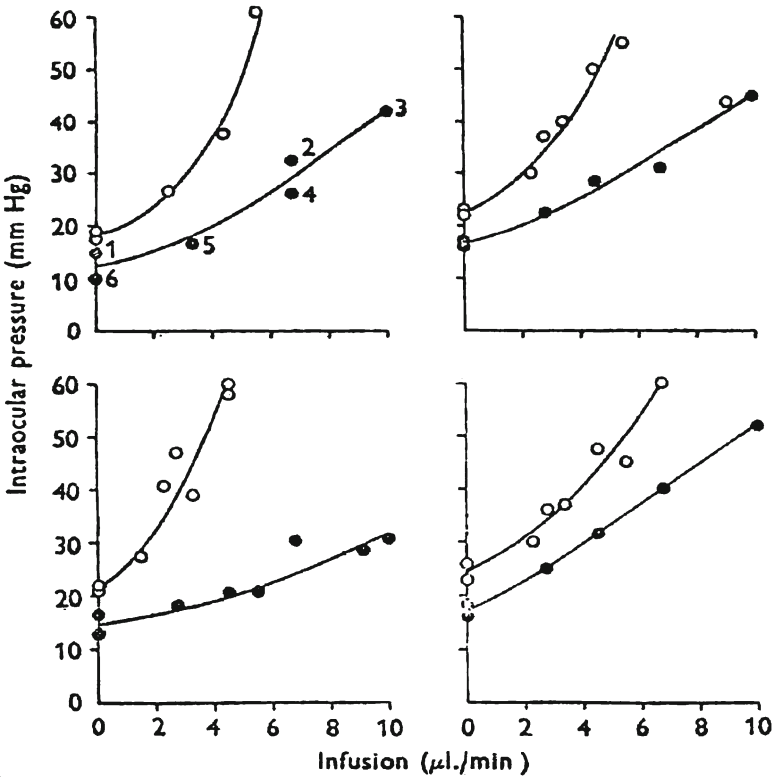

FIGURE 9.1. The effect of superior cervical ganglionectomy on the response of the IOP to the infusions of physiological saline (pH 7.4) into the anterior chamber. Each of the four graphs gives the results on pairs of eyes at 24 h after denervation: the denervated eyes (*filled circles*) and the control eyes (*open circles*). The numbers printed on the first graph reflect the order of the infusions (From Langham and Taylor.[41] Reprinted from the *Journal of Physiology*. Used with permission from BMJ Publishing.)

These findings have major physiological importance in that changes in blood flow and in the IOP/flow relation result from the loss of the neural connection of the efferent sympathetic nerves that leave the brain to innervate the ocular tissues. This neuronal activity modulates the normal steady state circulations and is a fundamental physiologic property of the undisturbed eye. Thus, the ocular circulation of the intact undisturbed eye is dependent on efferent sympathetic nerve activity emanating from centers in the brain and innervating the vessels of the eye. This is in keeping with the concept of a continuous sympathetic tone that acts on the pupil, the IOP, the pulse amplitude, the composition of the aqueous humor, and the IOP/flow relation.

Complete excision of the cervical sympathetic ganglion provides further evidence of the major physiological role of efferent sympathetic nerve activity in the autoregulation of the steady state IOP,

the control of aqueous humor dynamics, and ocular blood flow. Excision of the cervical ganglion causes an immediate decrease in the steady state IOP, which slowly recovers to normal over a period of several weeks. For example, the mean IOP of eight rabbits 24 h following surgical cervical ganglionectomy fell to a mean of 16.1 ± 0.64 mmHg compared with 22.0 ± 0.65 mmHg in the control eyes. In subsequent days, the IOP in the denervated eyes slowly recovered to normal and at 14 days the IOPs in pairs of eyes were equal.

The cervical ganglionectomy leads to degeneration of the postganglionic neurons and to the release of the adrenergic transmitter norepinephrine stored in the terminal neuron. The initial fall in the IOP (not seen following cervical preganglionectomy) is associated with an accumulation of norepinephrine in the aqueous humor, confirmed by chemical analysis of samples of aqueous humor. The released norepinephrine flows into the drainage channels where it acts on the noninnervated adrenergic receptors, causing changes in the outflow facility. The specificity of this effect on the outflow facility by norepinephrine has been confirmed by the ability of the adrenergic antagonist phenoxybenzamine applied topically to block the norepinephrine effect on the IOP and the outflow facility in adrenergic denervated eyes.

The rate of aqueous humor formation following excision of the ganglion has been measured from the time courses of the concentrations of diffusible fluorescein in the anterior chamber and blood after an intravenous injection of the dye (see Fig. 2.1). The mean turnover rate of the aqueous humor in the control and denervated eyes of conscious rabbits 24 h after cervical ganglionectomy was found to be identical, namely 0.117 ± 0.0012 and 0.116 ± 0.0013 min^{-1}, respectively.[40]

Consequently, in view of the decreased steady state IOP in the denervated eyes, there must have been an increased outflow facility. This conclusion has been confirmed in measurements of the outflow facility based on the change in IOP (ΔIOP) induced by two separately experimentally induced rates of inflow of physiological saline (ΔF).[89] This result is consistent with the measured IOP/flow relations in the innervated and denervated eyes (**Fig. 9.1**).

Following cervical sympathotomy (postganglionic denervation), and with the absence of the mechanism for reuptake of norepinephrine, the ocular responses, including dilatation of the pupil and the decrease of IOP to the transmitter, are substantially increased (typically by two to three log units) both in degree and in duration. This phenomenon is supersensitivity, and in the eye it is seen in the increased pupillary dilatation and in the increased IOP response induced by norepinephrine and related adrenergic agonists.

The absence of an immediate effect of cervical ganglionectomy on the rate of aqueous humor, despite an immediate effect on the outflow facility (within the first 24 h after denervation), may be ascribed to the absence of an accumulation of norepinephrine in

the area of the ciliary processes. Thus, norepinephrine, released from degenerating neurons in the epithelial layers of the ciliary processes and from adrenergic neurons in the iris, is readily washed away into the bloodstream rather than accumulating in the aqueous humor and the drainage channels.

The development of adrenergic supersensitivity is rapid and remains for many years. Following denervation, the decrease of the IOP and the rate of formation of the aqueous humor become two to three log units more sensitive to the topical application of norepinephrine.[90] In addition, this denervation supersensitivity increases the responses of the outflow facility and the rate of blood flow to norepinephrine by two to three log units.

The effects of pre and postcervical sympathectomy in the human eye appear to be similar to those in animals. Surgical denervation of the stellate ganglion has been observed to increase the pupillary and the IOP responses to norepinephrine applied topically by two to three log units. Furthermore, spontaneous sympathetic denervation (Horner's syndrome) in man has been found to maintain supersensitivity to norepinephrine, and to epinephrine, for many years. Like in animals, patients with a cervical preganglionic denervation do not develop adrenergic supersensitivity, while those patients with postganglionic lesions do. In the latter situation, the decrease of IOP and the increase of the outflow facility induced by the applications of either norepinephrine or epinephrine have been observed to persist for more than 20 years. The lack of adrenergic supersensitivity following the preganglionic lesion, and the marked supersensitivity following the postganglionic lesion in man, have been used to facilitate the differential diagnosis of Horner's syndrome.[91]

The ocular response to increased sympathetic nerve activity has been evaluated in detail in manometric studies of the response to electrical stimulation of the sympathetic nerve.[42] While the physiologic rate of stimulus is less than 1 Hz, the maximal response to applied electrical stimulation occurs with a stimulation of 4 Hz and 4 V. Using these guidelines, 2 min of electrical stimulation at 4 Hz caused a decrease of IOP in rabbits from an initial mean of 18.8 ± 0.2 to 10.5 ± 0.6 mmHg.[42] Higher rates of stimulation failed to increase this response significantly. The dose-response curves for pupil dilatation and decreased IOP to electrical stimulation are identical.

The electrical stimulation at 4 V and frequency of 1–4 Hz cause an immediate decrease of approximately 50% in the pulse amplitude and a vasoconstriction that is reflected in a decrease of ocular blood volume. Analysis of the pulse wave indicates a decrease of approximately 50% in the rate of pulsatile ocular blood flow. This change in rate of blood flow has been found to be associated with a decrease of approximately 50% in the rate of blood flow to the ciliary processes based on the ascorbic acid clearance technique. The rate of turnover of fluorescein in the anterior chamber after an intravenous injection of the dye showed the electrical stimulation to reduce the rate of

formation of the aqueous humor by 30–50%.[42] These responses of the IOP and ocular blood flow to short trains of electrical stimulation are fully reversible, and cessation of the stimulus results in an immediate return of the pupil diameter to normal and a rapid full recovery of the IOP and the pulse amplitude. To differentiate the steady state responses of these parameters to electrical stimulation and from the changes induced by vasoconstriction, it is necessary to continue the stimulation for sufficient time (30 min) to ensure a new steady state.

A typical recording of the prolonged electrical stimulation of the preganglionic sympathetic nerve on the IOP and on the IOP decay curves is shown in **Fig. 9.2**. Following 30 min of electrical stimulation, the IOP in the experimental eyes was approximately 15 mmHg compared with 20 mmHg in the eyes on the nonstimulated side. The pulse amplitude values were approximately 50% of normal and there was a corresponding decrease in the rate of ocular pulsatile blood flow.

One unexpected finding was that cessation of the electrical stimulation (for 30 min) failed to cause a rapid recovery of the IOP as had been observed after a short period of stimulation, and it took 60–90 min for the IOP to fully recover. In addition, the prolonged stimulation was associated with a decrease in the outflow facility. This was in contradiction to the observations that the release of the adrenergic transmitter caused an increased outflow resistance.

The possibility arose that electrical stimulation through the release of the transmitter norepinephrine could induce either an increase or a decrease of the outflow facility, depending on the duration of the stimulation. This was confirmed in several ways and revealed the complex nature of the responses of the outflow channels to the adrenergic agonists.[42] First, the biphasic nature of the response to the transmitter could be duplicated by repeated topical administrations of norepinephrine to eyes of both animals and man.

A single dose of 50 μl of 1.0% physiological solution of norepinephrine ascorbate (10 μg) applied topically to the eyes of conscious rabbits, cats, and monkeys caused a monophasic decrease of the IOP associated with an increased facility of outflow. The IOPs in the treated eyes were still below the initial level at 24 h. At this time, the application of a further drop of the solution of norepinephrine caused the IOP to increase substantially and decrease the coefficient of outflow facility within 1–2 h. After this time, the IOP slowly fell below that of the contralateral eye and remained low for a further 24 h; at 48 h the outflow facility in the treated eye exceeded that in the contralateral eyes. At 48 h a further single application of the norepinephrine solution was applied and again the IOP increased within the first hour and then fell below the initial IOP; contrary to the biphasic IOP response, the time course of the pupil response at 48 h was identical to that on the first day. At 72 h, the IOP was again significantly lower than in the control eyes. The application was repeated on the following 3 days, and each time the IOP increased during the first hour and then began to fall. The raised IOP was

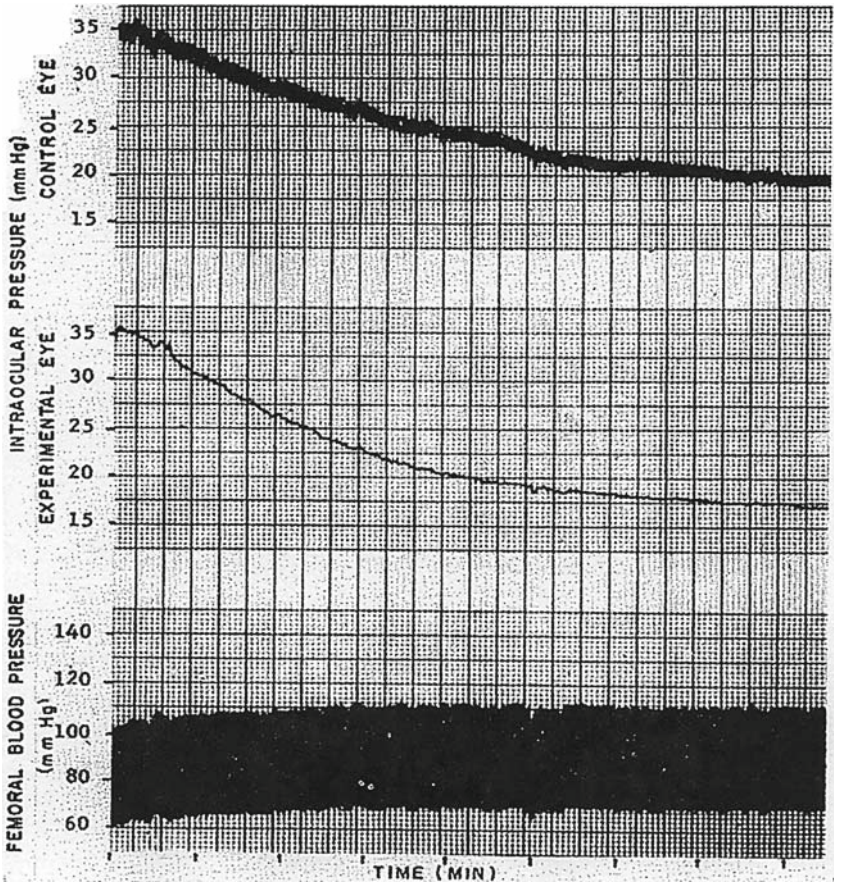

FIGURE 9.2. Unilateral electrical stimulation of the cervical preganglionic nerve in an anesthetized rabbit at 4 V and frequency 4 Hz for 25 min before manometric cannulation and recording of the IOP decay curves in both eyes. At this time the IOPs were 20 and 15 mmHg in the control and experimental eyes, respectively. The IOPs were then raised to 35 mmHg in both eyes by connection to a reservoir of physiological saline (approximately 20 μl) set at 35 mmHg and recorded as they returned to their steady state. Note the lower pulse amplitude in the eye on the stimulated side. Analysis of the pressure decay curves indicated the absence of an increased facility of outflow (From Langham and Rosenthal.[42] Reprinted from the *American Journal of Physiology*. Used with permission from The American Physiological Society.)

associated with a decrease in the outflow facility. Second, the intravenous administration of the adrenergic receptor antagonist phenoxybenzamine blocked the pupil, the biphasic IOP, and the outflow facility responses to norepinephrine applied topically.

The biphasic response of the IOP and the outflow facility to norepinephrine and epinephrine applied topically is not restricted to rabbits, cats, and primates, but it also occurs in man. Figure 9.3 shows the response of repeated topical applications of a standard commercial preparation of 1% epinephrine borate to a healthy adult

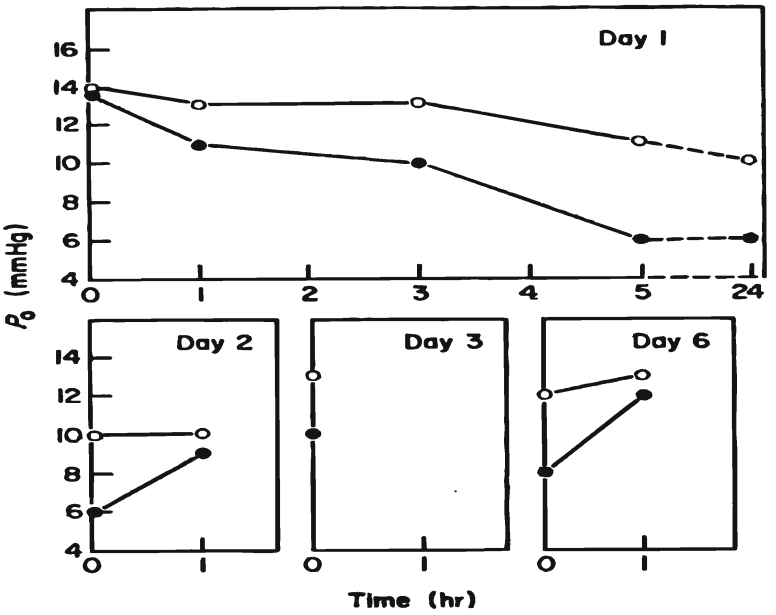

FIGURE 9.3. The biphasic IOP response in man to epinephrine. Day 1 shows the initial part of the time course of the IOP response to 50 µl of a 1% solution of epinephrine borate (Alcon Lab) applied topically to the treated (*filled circles*) and untreated eyes (*open circles*), respectively. After 24 h the IOP in the treated eye was low compared with that in the untreated eye. A second application of the norepinephrine was made at 24 h and the IOP increased to approximately the IOP in the untreated eye. At 48 h, the IOP in the treated eye was again less than in the untreated eye. Single applications were repeated at days 4, 5, and 6. At day 6, the application again caused an initial substantial increase of the IOP (Langham[23] In Fenstermacher et al.[23] *The Ocular and Cerebrospinal Fluids, Proceedings of a Fogarty International Center Symposium, Bethesda, MD, May 3–6, 1976*. Used with permission from Elsevier.)

subject.[92] The epinephrine caused a steady fall of IOP in the treated eye and a lesser fall in the untreated eye; a small pupil dilatation was observed lasting approximately 2 h. At 24 h, the topical application of norepinephrine was repeated and the IOP increased in the treated eye in the first 1–2 h and then fell. At 48 h, the IOP in the treated eye was still low compared to that in the untreated eye. Single topical applications of the solution of norepinephrine were repeated at 72, 96, and 112 h, and each time there was an initial period of increased IOP. Measurements of the coefficient of outflow facility on the first day during the period of ocular hypotension showed the decreased IOP to be associated with increased outflow facility. By contrast, the initial increase of IOP after administration of the norepinephrine was associated with a decreased coefficient of outflow facility compared with the untreated eye.

The cause of the biphasic changes in IOP and in the outflow facility to the adrenergic agonists, norepinephrine and epinephrine, lies

in the confluence of blood and aqueous humor flowing through the vessels of the intrascleral plexus and the spatial distribution of the adrenergic fibers, which primarily innervate these blood vessels. The part played by the trabecular meshwork in the biphasic change must be minimal for its adrenergic innervation is either minimal or absent. The high viscosity of the blood compared to that of the aqueous humor makes these changes more dramatic.

The time courses of the pupil dilatation, IOP change, and vasoconstriction in the outflow channels are shown diagrammatically in **Fig. 9.4**. The pupil and IOP responses are those seen after the unilateral topical administration of a solution of 1% norepinephrine at times 0, 5, and 24 h. The final column represents the working model of the vasoconstrictor response in the intra and episcleral channels.

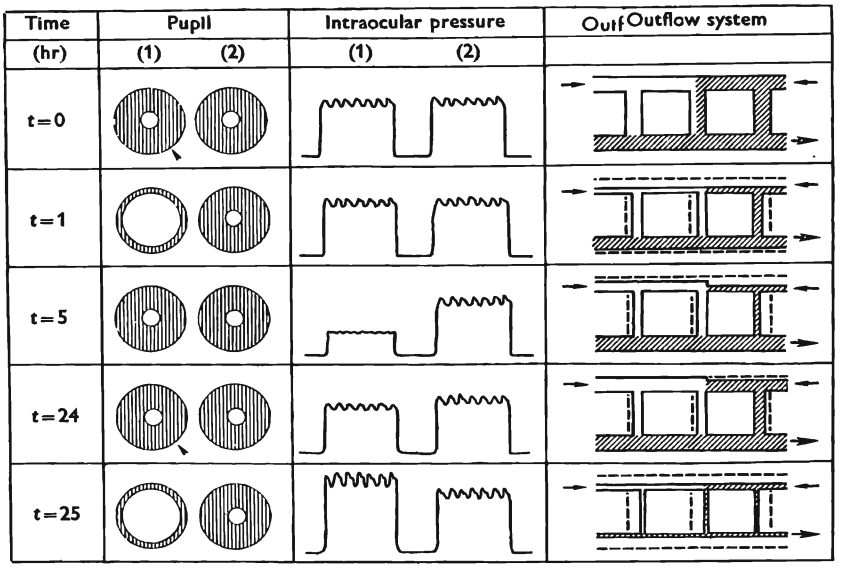

FIGURE 9.4. A diagrammatic representation of the pupillary, IOP, and vasoconstrictor responses to norepinephrine applied unilaterally (eye 1) at 1, 5, and 24 h to conscious rabbits. The outflow system column shows the inflow of aqueous humor (*top left arrow*) and blood (*top right arrow*) into the intrascleral plexus, and the outflow of mixed blood (*top right arrow*) into the intrascleral plexus, and the outflow of mixed blood and aqueous humor into the episcleral system (*lower arrow*). The *continuous and dashed lines* represent the normal and vasoconstrictor responses at the three proposed sites in the outflow system. At t = 1 h, pupil dilatation is maximal but the IOP remains essentially unchanged. At t = 5 h, the pupil has recovered but the IOP is now decreased. Because of the vasoconstriction of the intrascleral blood vessels the resistance to aqueous outflow is decreased. At t = 24 h, the diminished level of norepinephrine led again to lower IOP, the absence of pupil dilatation, and decreased outflow resistance. A second application of drug was performed at 24 h, and 1-h later the pupil had fully dilated and the increased vasoconstriction caused the IOP to increase due to more general vasoconstriction (From Langham and Palewicz.[87] Reprinted from the *Journal of Physiology, London*. Used with permission from Blackwell.)

10

Manometric Studies on the Intraocular Pressure and Vascular Circulation in Ophthalmic Disease

Congenital Glaucoma

This clinical condition provides a dramatic example of the absence of a normal outflow system and the effects on intraocular pressure (IOP), the outflow facility, and the effect of high IOP on the cornea. The clinical signs of congenital glaucoma include thickening, edema, clouding, and increased diameter of the cornea. The corneal edema and swelling precludes use of indentation and Goldmann tonometers to measure the IOP. Under these conditions, cannulation of the anterior chamber using a manometric technique provides a direct way to evaluate the IOP and to investigate the possibility of surgical therapy.

A needle with a double-cutting edge connected to a bottle of sterile saline set at approximately 40–50 mmHg and connected to a sterilized pressure transducer is inserted from the area of the corneal scleral junction and directed toward the middle of the anterior chamber. The steady state IOP is determined by a short recording of the IOP (**Fig. 10.1**). The steady state IOP in this patient was 40 mmHg, the pulse amplitude was 2.2 mmHg, and the corresponding rate of pulsatile blood flow was 365 µl min^{-1}. An attempt was then made to open up the trabecular meshwork with the cutting edge of the recording needle; the needle was then brought into contact with the trabecular meshwork and a cut of approximately 10° was made into the Schlemm's canal. In this patient success was immediate and the IOP started to fall (see **Fig. 10.1**) with a new state IOP of 17 mmHg. In this patient it required only a very small opening through the meshwork to achieve a normal outflow and IOP. Full recovery ensued, and a normal IOP and transparency of the cornea were confirmed at 1 year.

This clinical case gave a good example of the abnormal drainage of aqueous humor resulting in an abnormally high IOP from a

M.E. Langham, *Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases: A New Perspective*, DOI: 10.1007/978-0-387-09716-9_10,

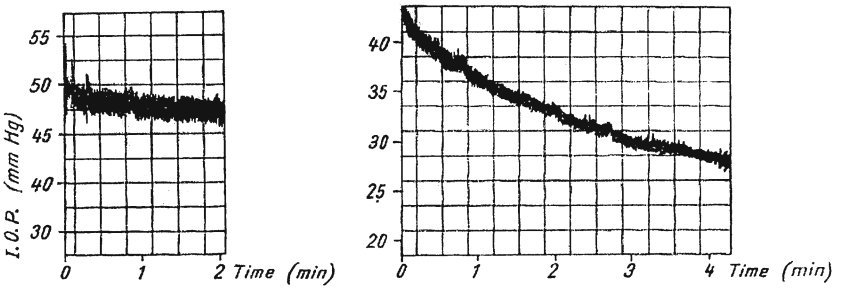

Figure 10.1. The IOP in a child of 2 months with congenital glaucoma and the results of surgery. The first recording shows the IOP approaching its steady state of 45 mmHg. The second recording shows the IOP decay curve approaching the new steady state of 17 mmHg after a limited section (approximately 10°) of the occluded angle using the sharpened cannulating needle (From Langham.[21] Reprinted from *Glaucoma, Tutzing Symposium*. Used with permission from Basel-Karger.)

mechanically induced high resistance in the trabecular meshwork, while the flow resistance distal to the canal of Schlemm remained essentially normal.

This patient formed one of a series of four similar cases on children of less than 2 years of age with congenital glaucoma. In one case, the IOP was 35 mmHg, but attempts to cut open the trabecular meshwork failed despite making a penetrating cut exceeding 180°. It was concluded that the abnormal outflow was due to the absence of a normal trabecular meshwork and Schlemm's canal, and the possible absence of a normal intrascleral drainage system. In the remaining two cases, the initial IOPs were 26 and 30 mmHg, respectively, and the operations were successful in normalizing the IOP with several cuts into the trabecular meshwork, each of approximately 20°.

Normal Adult Eyes

An opportunity to examine the flow resistance in the trabecular meshwork in normal eyes was found in living eyes of several young adults who had developed small melanomas in the choroid. In a typical case on a male of 22 years, the IOPs in the affected and unaffected eyes were 18 and 18 mmHg, respectively, measured by Goldman applanation tonometry, and the corresponding outflow facilities measured by conventional indentation topography were 0.22 and 0 23 μl min^{-1} mmHg, respectively. On the basis of the symmetry of the results, it was concluded that the IOPs and the aqueous humor dynamics in the pairs of eyes were normal.

The affected eye was enucleated and measurements of the IOP decay curves were made immediately. Analysis of the pressure

decay curve in the enucleated eye indicated an outflow facility of 0.4 μl min^{-1} mmHg. The trabecular meshwork was then opened with the cutting edge of the recording needle and the IOP decay curve was recorded. The new outflow facility following the trabeculectomy was 0.3 μl min^{-1} mmHg. The results confirmed the marked increase in the outflow facility following enucleation and the major resistance to outflow to be distal to Schlemm's canal in the living eye.

Similar results were recorded on two further enucleated eyes, and in both cases the major site of the outflow resistance was distal to Schlemm's canal.

Adult Open Angle Glaucoma

A manometric investigation was made on a patient who had been treated for open angle glaucoma for many years and then examined within 3 h of death (in the morgue). Glaucomatous field loss had been present in both eyes for more than 20 years and the patient had been treated with increasing concentrations of pilocarpine and epinephrine for many years. The IOP recordings over the years ranged from 23 to 29 mmHg in both eyes and the outflow facilities measured by conventional tonography were approximately 0.10–0.13 μl min^{-1} mmHg in the two eyes. Perfusion studies were made on one of the eyes in situ. The outflow facility based on analysis of the pressure decay curve from an IOP of 35 mmHg was 0.3 μl min^{-1} mmHg and, after opening the trabecular meshwork, increased to 0.4 μl min^{-1} mmHg. Thus, in this glaucomatous eye, the abnormally high outflow resistance was distal to Schlemm's canal and not in the area of the trabecular meshwork.

Section 1
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Section 2

Noninvasive Studies on the IOP, PA, and Blood Flow Autoregulation in Healthy and Diseased Eyes

This section deals with the noninvasive methods for measurements of the steady state IOP and the amplitude and form of the IOP pulse, from a consideration of the accuracy and limitation of Goldmann applanation tonometer for measurement of the steady state IOP, to a detailed presentation of the theory, accuracy, and applications of the Langham pneumatic tonometer with its ability to measure both the steady state IOP and the amplitude and form of its pulsations. The relation between the IOP and the pulse amplitude (PA) in healthy eyes and the marked changes in this relation in diseased eyes are presented. The measurement of the ocular blood flow autoregulation leads to the discussion of the onset of ischemia and the loss of autoregulation in the onset and progression of the ocular vascular diseases. This is followed by detailed presentation of the action of therapeutic drugs on ocular blood flow and autoregulation.

11

Indirect Measurements of the Intraocular Pressure and the Intraocular Pressure Pulse

Deformation of the eyeball by an externally applied force provides the basis for the indirect measurements of the intraocular pressure. According to the nature and extent of the deformation, these systems, termed tonometers, are divided into two groups: indentation and applanation. The former included the first accurate instrument that was developed by Hjalmar August Schiøtz (1850–1927) – the first Professor of Ophthalmology in Oslo, Norway. Schiøtz spent many years perfecting his instrument and even built each instrument in his own workshop and certified each one produced. His tonometer had a geometrically defined plunger that produced an indentation of the cornea. The extent of the indentation was inversely related to the IOP and the reading was transmitted mechanically to a scale. The weight of the probe increased the IOP and, as a consequence, the evaluation of the IOP of the undisturbed eye required a special table for relating the IOP caused by the indentation to the true IOP of the undisturbed eye.

The first applanation tonometers were based on the Imbert-Fick law, which states that the pressure in a sphere filled with fluid and surrounded by an infinitely thin and flexible membrane is equal to the applied pressure that just flattens the membrane.[1,2] One of the first tonometers using this principle was proposed by Maklahov in 1884 using the simple approximate relation $F = A/P$ where F is the applied force in gram weight of the probe, A is the area of applanation in mm^2, and P is the IOP in mmHg. The Maklahov tonometer comprised a cylinder flared out at both ends with one end tapered as a flat glass plate and the other end forming a cup in which known weights may be placed.[2] The end flat plate was moistened with a solution of glycerin containing a brown dye. After resting the probe on the cornea for one second, the probe was removed and pressed down on a piece of paper, leaving a brown circular stain, and the diameter of the stain was measured. The true IOP was then

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evaluated from the diameter of the stain using an appropriate calibration table.

The Maklahov tonometer is still widely used in a number of countries including Russia. The increased accuracy of the Maklahov tonometer over the Schiotz tonometer was due to providing a mechanism to minimize disturbance of the IOP. Thus, the area of the applanation induced by the Maklahov tonometer could be made optimal by having an appropriate weight on the probe to minimize the indentation effect of the probe. In this respect, accurate measurements of the IOP depend on avoiding disturbing the curvature of inner surface of the corneal endothelium.

In 1947, Goldmann (**Fig. 11.1**) improved the ability of applanation tonometers to measure the IOP of the undisturbed eye. He described an applanation instrument in which the force needed to create a defined area of corneal flattening was measured. He concluded from experimental studies on enucleated human eyes that the ideal area of applanation should be approximately 10 mm^2 and calculated that this area kept the volume of indentation of the cornea to be approximately 0.4 µl. A torsion balance operated manually produced the force required to create this area of applanation. The instrument was

FIGURE 11.1. Hans Goldmann 1900–1980 – Professor of Ophthalmology, Berne University, Switzerland (Reprinted with permission from Jon Parr.)

attached to a slit lamp, and a split prism illuminated from the arm of the slit lamp provided the means of defining the area of applanation. The edges of the two rings of the split prism were accurately defined by making the image fluoresce with a topical application of a drop of fluorescein and using a blue filter on the incident beam of the slit lamp. The reading of the IOP with the Goldmann tonometer required the alignment of the two half circles manually. In achieving this endpoint, the operator adjusts the torsion control forward and backward, causing transient variations in the area of applanation and, as a consequence, transient abnormal increases of the IOP. It is this overshoot that probably accounts for the time-dependent instability of the IOP observed in measurements of the IOP repeated at minute intervals using the Goldmann tonometer.[4,5]

The reproducibility of IOP measurements in humans using the Goldmann tonometer has been evaluated from duplicate measurements on individual subject's eyes with two specially standardized instruments provided from the International Center for tonometer standardization in Berlin, Germany. The evaluation was undertaken by three ophthalmic specialists with many years of experience using Goldman tonometers (**Fig. 11.2**). The results show that the reproducibility is good with a scatter of IOP readings around the equality line of 45° of approximately ± 2 mmHg.

The widespread use of the Haag Streit slit lamp, and the ease of making IOP measurements with the Goldmann tonometer, led to it being accepted as the hallmark of tonometers and the international standard for measurement of the IOP for all tonometers.

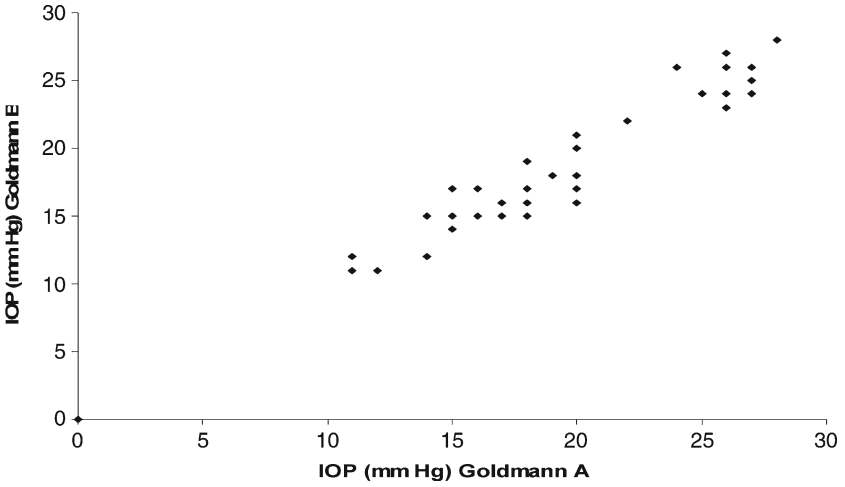

FIGURE 11.2. Comparison of IOP measurements on individual eyes in a series of 26 normal and ocular hypertensive subjects, measured with two standardized Goldmann applanation tonometers attached to Haag Streit slit lamps. An IOP measurement was made twice on each eye and the average reading was taken. The patient then moved to the second slit lamp and the readings were repeated. The test on each patient was completed within 6 min (previously unpublished studies of Kreiglstein, Weigelin, and Langham)

12

The Effect of Posture and Corneal Thickness on the Measurement of the Intraocular Pressure

A major difference in the clinical uses of Schiøtz and Goldmann tonometers is the Schiøtz tonometer, which was designed for use on supine patients while the Goldmann tonometer was designed for use on seated subjects. Consequently, the question arose whether measurements of intraocular pressure (IOP) on individual subjects with the two systems agreed. It rapidly became clear that this was not so, and led to intense efforts to make the two systems conform.[6] This problem was further complicated by recognition that IOP of the undisturbed eye increases when the subject was supine. Despite knowledge of the substantial effect of posture on the central blood pressure, the assumption was made that the postural response on the IOP did not exceed 1 mmHg, based on the measured increment in pressure in the episcleral veins when lying down.[7,8] Confirmation of this conclusion and the consequent agreement of the two systems for the measurement of the IOP was accepted by the Committee for Tonometer Standardization.[9–12]

However, paired measurements using the Goldmann and the Schiøtz tonometers on the same subjects by investigators continued to show a significant disagreement. For example, in a series of 45 normal and 45 glaucomatous eyes, the mean difference in IOPs measured with the Goldmann and Schiøtz tonometers was 3.12 ± 1.98 mmHg.[6]

The difficulty in bringing conformity to the two tonometers was aggravated by the pulsatile nature of the IOP. The plunger of the Schiøtz tonometer induces an indentation of the cornea, which is measured by a needle moving across a curved scale in proportion to the magnitude of the indentation. This needle moves to and fro with the pulsations of the IOP and the final reading is taken as the mean of the IOP readings associated with the fluctuations. In this respect, the excursion of the needle represents approximately 2–4 mmHg in healthy subjects.

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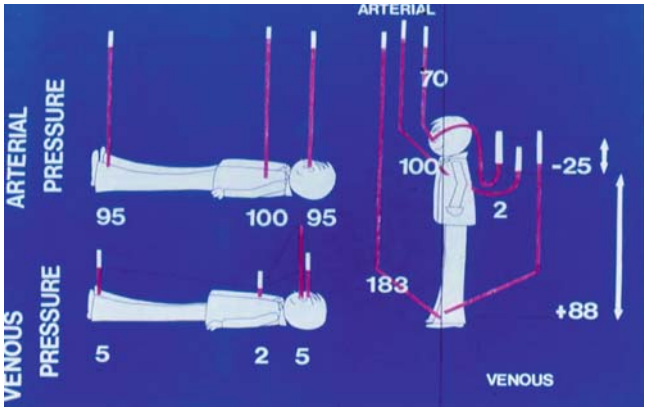

FIGURE 12.1. The influence of posture on the arterial and venous blood pressures below and above the heart

The procedure for recording the IOP reading with the Goldmann tonometer differs from that of the Schiøtz tonometer in that the operator seeks the applied pressure at which the two half circles of the applanation prism are just in alignment.[13] This reading corresponds to the minimal point of the IOP pulse wave and is not the average of the minimal and maximal values of the IOP pulse. In Goldmann tonometry, fluctuation of the rings due to the pulsation of the IOP may be observed, but the system provides no way for measurements of either the maximal IOP of the IOP wave, or the magnitude of the pulse amplitude.

The assumption that the postural effect on IOP is small and not greater than 1–2 mmHg for both healthy and diseased eyes was seriously questioned by several investigators and shown to be erroneous based on measurements using modified Goldmann applanation tonometers that could be used in both supine and seated positions.[14–16] The results of these studies revealed the postural effect to vary from a mean of 2.5 mmHg in normal eyes to much higher values in glaucomatous eyes (**Fig. 12.1**).

More recently, using the Langham pneumatic objective recording tonometer (see later) that may be used on both supine and seated subjects, a mean IOP postural increase of 2.5 ± 0.2 mmHg (supine – seated) was reported in the eyes of 77 healthy adult subjects, and a mean postural response of 3.5 ± 2.8 mmHg (supine – seated) in the eyes of 45 glaucoma patients (**Fig. 12.2**). A similar abnormal postural response on the IOP was found in patients with low-tension glaucoma (**Fig. 12.3**).

The parameters that determine the postural effects on systemic blood pressure and IOP are gravity and vascular autoregulation. On standing, the eye and the brain are above the level of the heart and, because the vascular resistance in the cervical arteries and the brain is relatively low, the arterial pressures feeding the eye and the

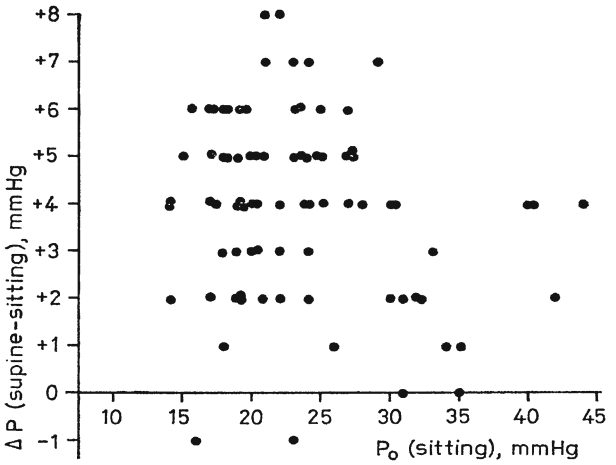

FIGURE 12.2. The response of the IOP to posture in eyes of 45 glaucoma patients. The abscissa is the IOP measured in the seated position. The ordinate shows the change in IOP in individual eyes when the subject changed from the seated to the supine positions (From Kreiglstein and Langham.[17] Reprinted from *Ophthalmologica*. Used with permission from S. Karger AG, Basel.)

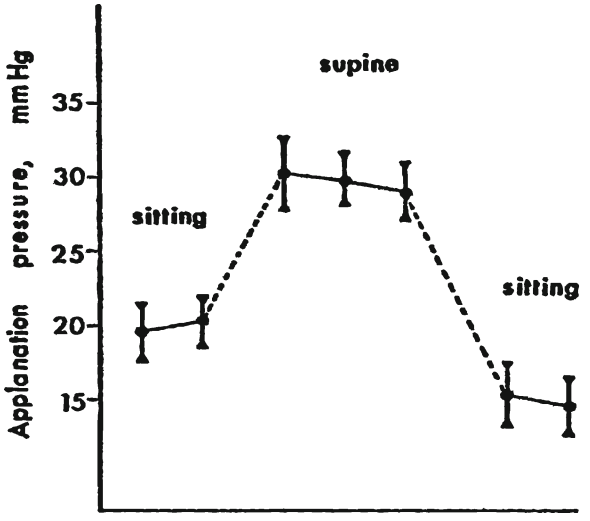

FIGURE 12.3. The postural response on the IOPs in six patients with low-tension glaucoma. The interval between readings in each position was, on the average, 7 min (From Kreiglstein and Langham.[17] Reprinted from *Ophthalmologica*. Used with permission from S. Karger AG, Basel.)

brain are exposed to the full hydrostatic action of gravity, namely a pressure change of approximately 35–40 mmHg. The brain is an open system, and the hydrostatic effects on the arterial and venous pressures are equal, and consequently the cerebral perfusion is

affected only by the change in the cervical arterial response to posture. By contrast, the eye is a closed system, and the venous pressure within the eye must always exceed the IOP, albeit if only by a small amount, to maintain a continuous flow of blood through the eye.

The eye is a unique system in respect that the increase in hydrostatic pressure while lying supine would substantially modify the ocular perfusion pressure and the steady state IOP, unless compensatory physiological mechanisms acted to minimize the postural effect. In the systemic vascular circulation these compensatory mechanisms are located in the cervical arteries. An increase of blood pressure in the internal carotid artery due to lying down activates vascular reflexes, including the baroreceptor sensory nerve located in the carotid sinus at the bifurcation of the internal and common carotid arteries. The sensory receptors connect by afferent nerves to neural centers in the medulla, which send inhibitory efferent pulses via the vagus nerve to the heart, to decrease cardiac ejection and peripheral resistance. In normal healthy subjects, this autoregulation of the arterial circulation from the carotid receptors reduces the anticipated postural increase of 35–40 mmHg in the ophthalmic arterial pressure to 10–12 mmHg. Should the baroreceptors be impaired, such as that occurs when the cervical sympathetic nerve is denervated or modulated by hypotensive drugs, the fall in arterial pressure on standing may be sufficient to cause syncope and induce a major change in the ocular perfusion pressure with transient visual loss.

The physiological significance of the compensatory vascular reflexes is seen in the relatively small effect of posture on the IOP in healthy subjects, namely, a mean of 2.4 mmHg (supine minus seated values). This limited effect of posture on the IOP in healthy subjects contrasts with the abnormally high effect of posture on the IOP in patients with certain ocular diseases including open angle glaucoma. The cause of this abnormally large impairment of the postural response on the IOP in clinical disease remains to be clarified but suggests that the autoregulation in the cervical arterial circulation is impaired. The postural effect is not a transient volumetric response but is a change in the steady state IOP and consequently has to be associated with change in either or both the rate of formation of the aqueous humor and the outflow resistance in the drainage channels.

The Effect of Corneal Thickness on Tonometric Measurement of the IOP

Goldmann recognized that the thickness of the cornea would influence the readings made with his tonometer and advised that the accuracy was confined to corneas of normal thickness (i.e., 540 μm). In 1961, Goldmann and Schmidt reported that the error was 7

mmHg in measurements of IOP in rabbit eyes having a mean corneal thickness 100 μm thinner than normal human corneas in man (namely a true IOP of 20 mmHg gave a Goldmann IOP reading of 13 mmHg).[18] Errors of this magnitude were confirmed in manometric studies on human eyes about to undergo cataract surgery by Ehlers et al.[19] These investigators found a strong correlation between corneal thickness and the disparity between the actual IOP and the Goldmann reading. Analysis of the corneal thickness revealed that thin corneas gave an underestimate of the IOP and thick corneas gave an overestimate of the IOP. Ehlers calculated that a cornea of 460-μm thickness yielded an underestimate of the IOP of 5.2 mmHg; namely, an IOP reading of 14.8 mmHg was really 20.0 mmHg.

The importance of corneal thickness in the measurement of the IOP has been underlined by subjects who have undergone LASIK corneal refractive surgery. In this procedure, the refractive character of the cornea is modified by a reshaping, which causes a substantial decrease (average approximately 100 μm) in corneal thickness, from the normal mean thickness of 540 μm in healthy eyes, to a mean of approximately 440 mm. On the basis of the observations of Goldmann, this thinning of the cornea would mean an underestimate of approximately 4–6 mmHg in IOP. This potential error of Goldman applanation IOP in measurement of abnormally thin corneas has been confirmed in patients who underwent LASIK refractive surgery. Langham and O'Brien, using the Langham pneumatic tonometer that is essentially unaffected by changes in corneal thickness (see later), studied ten subjects prior to LASIK surgery and reported the mean IOP measured by the Goldmann and the Langham tonometers to agree well (16.7 ± 1.2 and 16.2 ± 0.9 mmHg, respectively); the mean difference between the IOP readings made with the two tonometers in individual eyes was 0.5 ± 0.3 mmHg. In the same patients, 3–58 weeks after LASIK refractive surgery, the mean IOPs were 13.1 ± 1.5 mmHg in the operated eyes and 16.9 ± 1.4 mmHg in the unoperated eyes, measured by the Goldmann and Langham tonometers, respectively; the difference of the IOPs measured with the two tonometers in individual eyes was 3.8 ± 0.4 mmHg (Langham – Goldmann). Thus, the IOP measured with the Langham tonometer showed LASIK refractive surgery to have no significant effect on the IOP whereas the Goldmann readings indicated that surgery induced a substantial decrease of IOP. The mean corneal thickness in these patients was 535 ± 10 and 425 ± 23 μm prior to and following surgery, respectively.[20]

13

The Langham Pneumatic Analogue and Digitized Tonometers

The manometric studies of the intraocular pressure (IOP) in animals and humans presented in Sect. 1 provided detailed descriptions of the dynamic character of the IOP, which oscillates from a minimum to a maximum with each beat of the heart. In particular, the manometric recordings of the IOP show the steady state IOP, which is determined by the balance between the rate of formation and the resistance to the outflow of the aqueous humor, and the pulsatile nature of the IOP, which is generated by the flow of blood into the eye. Because more than 85–90% of the total ocular blood flow is confined to the choroidal network of vessels, the form and amplitude of the pulse reflects predominantly the blood flow to the choroid.

Historically, it is of interest to note that after the development of the ophthalmoscope by Herman von Helmholtz (1821–1894), it was his colleague, Donders, using the new ophthalmoscope in 1852, who observed that the retinal pulse was abnormal in ocular disease. Unfortunately, the absence of an appropriate clinical analytical technique to record the IOP pulse for many years prevented further evaluation and analysis of this fundamental physiological parameter.

An instrument to make continuous accurate recordings of the IOP and its pulsatile form was achieved by Langham and colleagues with the development of a continuous recording tonometer based on pneumatic principles. This pneumatic tonometer enabled the steady state IOP and the form of the pulsatile character of the IOP to be recorded with the same accuracy as a manometric recording (**Fig. 13.1**). In this example, a comparison is shown of a direct manometric recording of the IOP from a needle inserted into the anterior chamber of an anesthetized rabbit, with the indirect recording made with the Langham tonometer in contact with the corneal surface. In this experiment, the IOP was increased to approximately 40 mmHg by connection of the anterior chamber to a saline reservoir

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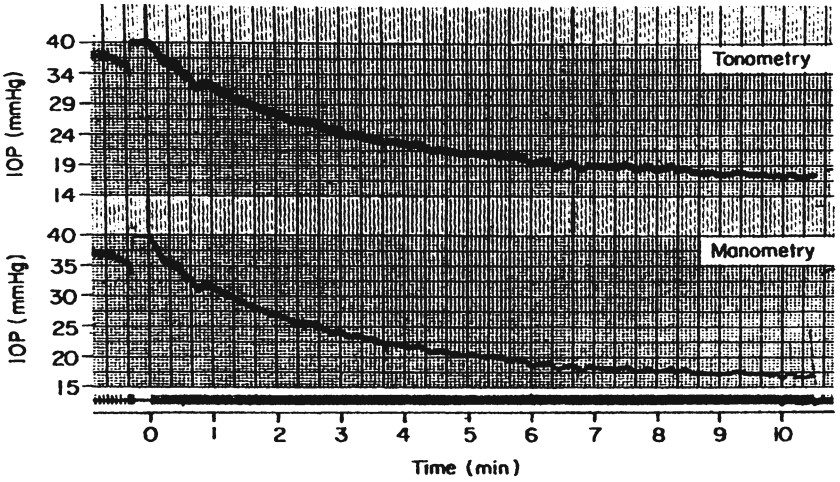


FIGURE 13.1. Comparison of IOP measurements made with the Langham tonometer (*top record*) resting on the corneal surface, and by a manometric recording from the anterior chamber (*lower record*) in an anesthetized rabbit. The IOP was increased initially by connection of the anterior chamber to a saline reservoir set at approximately 40 mmHg (From Langham et al.[29] Reprinted from *Acta Ophthalmologica Supplement.* Used with permission from Blackwell.)

and the IOP was allowed to fall spontaneously to its steady state. It will be noted that the recording by the tonometer reflected with accuracy the mean IOP and the oscillations of the pulse around the mean IOP.

The Langham pneumatic tonometer differs from both the Schiøtz and the Goldmann tonometers in that it is based on a balance of forces between the IOP acting on the cornea, and the pressure exerted against the cornea by a stream of air flowing at a constant rate from a relatively high-pressure source. This flow of air impinges on a membrane, which makes applanation contact with the cornea over an area similar to that made by the Goldmann prism. A standardized disposable sterile silastic membrane covers the tip of the probe. The backpressure in the plenum of the sensor is recorded by a highly accurate pressure transducer, and the electrical output is collected on the screen of a personal computer using the appropriate software.

The IOP in the first version of the Langham tonometer was recorded using an analogue pressure recording system with a rigid probe that was applied to the eye manually. On contact with the cornea, the pressure in the plenum of the sensor increases very rapidly and, at the point of equilibrium with the IOP, a break in the recorded pressure occurs; this break was analogous to an "oil drum effect."[20]

In applying the fixed tip probe to the eye it was observed that the IOP pulse could be recorded for several minutes by maintaining the

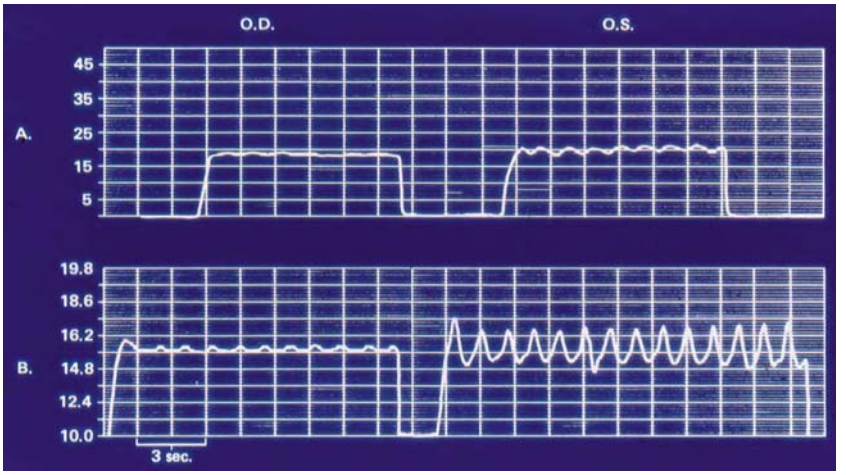
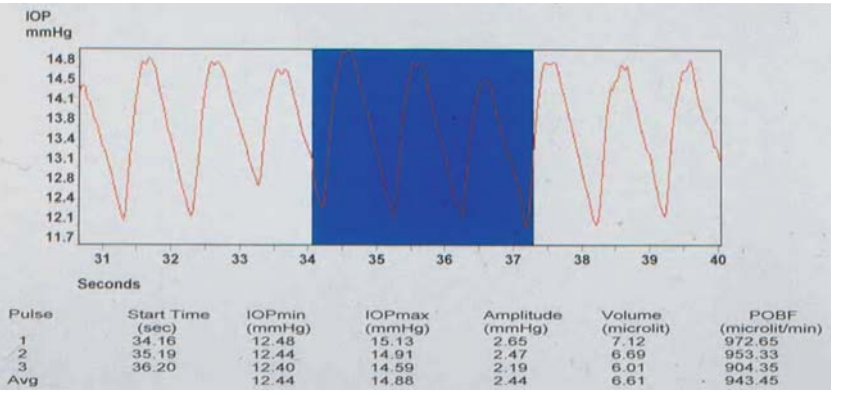


FIGURE 13.2. The IOPs in pairs of eyes of an adult subject with no apparent ocular pathology. These are analog recordings using the Langham tonometer and show the steady state IOPs to be equal in pairs of eyes but the pulse amplitudes to differ substantially. The lower recordings were taken on the same eyes at a higher magnification. In subsequent tests, this difference in pulse amplitudes was found to be due to a partial stenosis of the internal carotid artery on the right side. The ordinates represent the IOP (mmHg)

probe in contact with the cornea. This observation led to a subsequent instrument with a "floating" tip to facilitate the recording of the IOP pulse. This early instrument used analogue measurements of the IOP, but in a subsequent model the pressure measurements were digitized to allow recordings of the IOP pulse at 500 s^{-1}. The capacity of the first digitized recording tonometer allowed a total of 60,000 measurements to be recorded over a period of 120 s.

The independence of the steady state IOP reading from the dynamic pulsation of the IOP is illustrated in typical results on pairs of eyes of an individual subject (**Fig. 13.2**). The subject had no apparent ocular pathology and the steady state IOPs in the two eyes were normal and equal. However, the amplitudes of the IOP pulses differed substantially, namely 0.5 and 1.4 mmHg, in the right and left eyes, respectively. On further examination, using Doppler technology and carotid arteriography, the subject was found to have a unilateral moderate stenosis of the right internal carotid artery.

A representative digitized recording of the IOP in a normal adult human using the current floating tip probe is shown in **Fig. 13.3**. This recording shows a 9-s train of IOP pulses taken from a total recording of 60 s. The pattern of the IOP and the pulses remained essentially unchanged over this period. Each pulse had a sharp peak and the amplitudes were of the order of 2–3 mmHg. A modulation of the amplitudes of the pulses in this subject corresponded in frequency with the respiratory rate. (These slower modulations of the IOP have frequently been recorded in manometric studies on cats.[22,23])



Pulse	Start Time (sec)	IOPmin (mmHg)	IOPmax (mmHg)	Amplitude (mmHg)	Volume (microlit)	POBF (microlit/min)
1	34.16	12.48	15.13	2.65	7.12	972.65
2	35.19	12.44	14.91	2.47	6.69	953.33
3	36.20	12.40	14.59	2.19	6.01	904.35
Avg		12.44	14.88	2.44	6.61	943.45

FIGURE 13.3. A typical IOP recording on the right eye of a healthy adult subject (age 34 years) with no history of ocular or systemic disease; the record was taken with the subject seated. The systemic brachial blood pressure was 130/85 mmHg. The analyses in the table refer to the three highlighted pulses. The mean IOP and the rate of ocular pulsatile blood flow were 12.1 (minimal value) and 943 μl min^{-1}, respectively

The electronic output of the pressure transducer is analyzed by an appropriate software program to allow graphical representation of the pulses to be shown on a computer screen. The ordinate of the pulse amplitude is programmed to a scale that is defined by the lowest and highest IOP readings on the screen. The time scale (the abscissa) is set to a predetermined time period.

Continuous recordings of the IOP for 20 min in normal subjects showed no significant change in IOP. This stability of the IOP is similar to that recorded in manometric IOP measurements but contrasts with the instability reported in repeated IOP readings using the Goldmann tonometer.[24–26]

The apparent difference in the stability and reproducibility of the IOP readings in the Goldmann and Langham tonometers is due to the instantaneous equilibration (within milliseconds of contact with the cornea) between the pneumatic pressure and the IOP (without an overshoot); this extremely rapid equilibration minimizes the apparent tonographic effects observed with the Goldmann tonometer due to transient overshoot of the IOP when defining subjectively the alignment of the two half prisms.

The IOP pulse occurs in synchrony with the heartbeat and has a form, in healthy eyes, which is qualitatively similar to the central cardiac pulse. The initial ascending phase of the pulse is linear and reaches a sharp inversion maximal pressure within approximately 40% of the pulse width. The pulse amplitude then decreases as a simple exponential of time until the following bolus of blood starts to flow into the eye. A dichrotic notch caused by the closure of the aortic valve may frequently be discerned in the initial part of the descending phase of the pulse.

The IOP wave reflects the inflow of blood into the arteries of the retina and choroid eye and their subsequent flows through the

vascular networks, and final drainage into the vortex veins and to the large veins flowing back to the heart. The amplitude of the inflowing arterial pulse decreases as the blood flows from the main arteries and into the arterioles and capillaries; the pulse is lost completely by the time the blood flow reaches the vortex veins.

The ability of the Langham tonometer to be applied to the eye independent of the body position simplifies evaluation of the postural response on IOP (**Figs. 13.4** and **13.5**). However, it is necessary to make a correction of 1.5 mmHg when using the probe vertically on the eye of supine subjects to account for the weight of the sensor of the probe resting on the eye, a mean increase of 1.5 mmHg.

The basic components of the Langham tonometer comprise a pump that generates a constant gas flow through the probe. This gas flow is controlled by software that maintains a constant pressure in the air pump at 500 mmHg; the air passes through high flow resistance tubing at the point of entry into the plenum of the sensor. This high resistance acts like a waterfall in that a relatively small change of pressure beyond the resistor has negligible effect on the overall rate of gas flow. To allow continuous recording of the IOP, the sensor

FIGURE 13.4. The Langham pneumatic digitized tonometer: The output of the pressure sensor is fed into a personal computer and is analyzed using specifically designed software on a Windows-based program. The number of complete IOP pulses is chosen by highlighting them for immediate analysis (see **Fig. 13.3**) and the results are printed as a hard copy. The Langham tonometer box also has a vacuum system, controlled by the computer, for modifying the IOP. This vacuum system is connected to a scleral suction cup that is applied to the sclera to induce a predetermined IOP. In addition, the cup is used to increase the IOP for measurement of aqueous humor dynamics and the ophthalmic arterial pressure

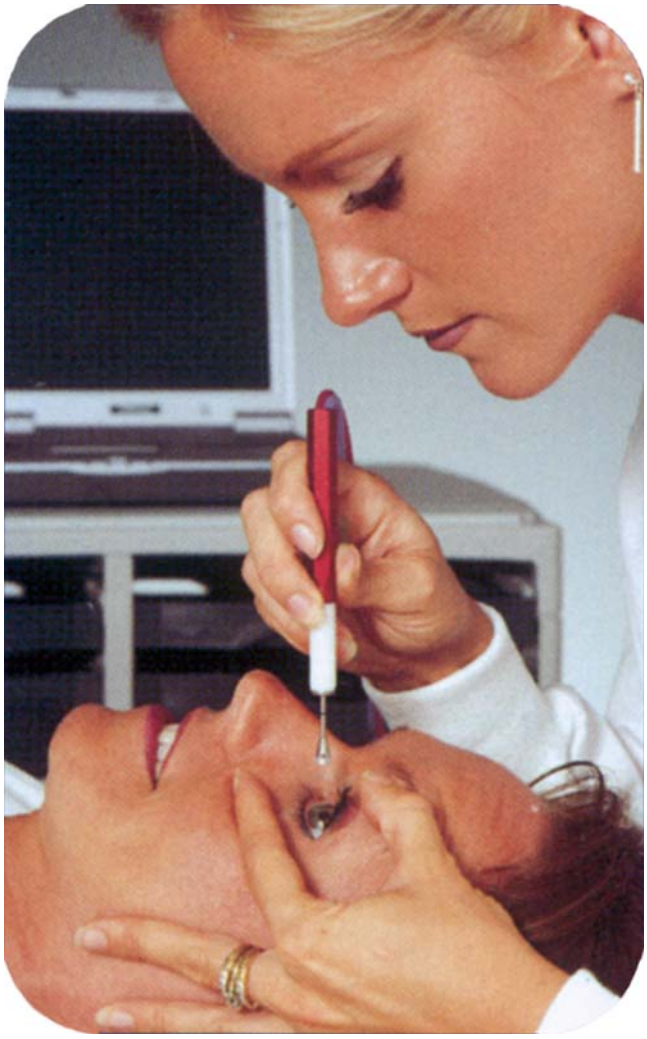


Figure 13.5. The Langham tonometer applied manually on the eye of a supine subject

and membrane are part of a "floating" cylinder that is independent of the plenum and moves freely with negligible resistance.

The tip of the sensor that makes contact with the cornea has the same diameter as that of the Goldmann applanation prism and acts similarly in causing an applanation with minimal flattening of the inside surface of the endothelium. The sensor is fashioned out of a solid stainless steel and the tip is flat and covered by a standard silastic disposable membrane of 5-µm thickness. This membrane covers the exit of the sensor and deflects the gas backward through ports to the atmosphere (nominal pressure of 0 mmHg). The membrane tip is made of medical grade silastic, and the reproducibility of the disposable membranes is facilitated by a production using multichamber molds. Randomly chosen membranes from a large series revealed a variation of less than 2% over a pressure range of 0–100 mmHg.

The gain factor is determined by the design of the probe and the physical characteristic of the gas, the elastic properties of the membrane, and the cornea (see theory later). The offset of the membrane from the orifice determines the pressure generated in the plenum; in this respect, it will be understood that if the membrane is too far from the orifice it will lose sensitivity, whereas if the membrane is too close to the jet, the sensitivity (gain) will be high and cause instability. A gain between 2 and 3 for animal and human eyes gives optimal stability and sensitivity employing the standard silastic standard membrane. In the Langham tonometer, the gain for the human eyes is 2.6–2.7 mmHg.

The Langham system also includes a separate vacuum pump attached by silastic tubing to a scleral cup, which is used to increase the IOP by predetermined amounts. The scleral cup is applied to the eye, and suction is applied in the measurements of aqueous humor dynamics, the effects of IOP on ocular blood flow and on the IOP pulse amplitude, and in measurement of the ophthalmic arterial pressure (see later).

One test of the reproducibility of the Langham tonometer to measure IOP has been to compare IOP readings on individual eyes using two standard Langham systems. In a series of 20 normal subjects, the mean IOPs, using the two randomly chosen tonometers, were 15.7 ± 0.2 and 15.7 ± 0.2 mmHg, and the mean difference in IOPs on individual eyes was 0.1 ± 0.1 mmHg.

In a further study, a comparison was made on pairs of eyes of individual subjects using one tonometer. The results summarized in **Fig. 13.6** indicate an agreement of within 1 mmHg based on the minimal point of the IOP pulse wave. These results reinforce the conclusion that the IOPs in pairs of healthy eyes of normal subjects are essentially identical.

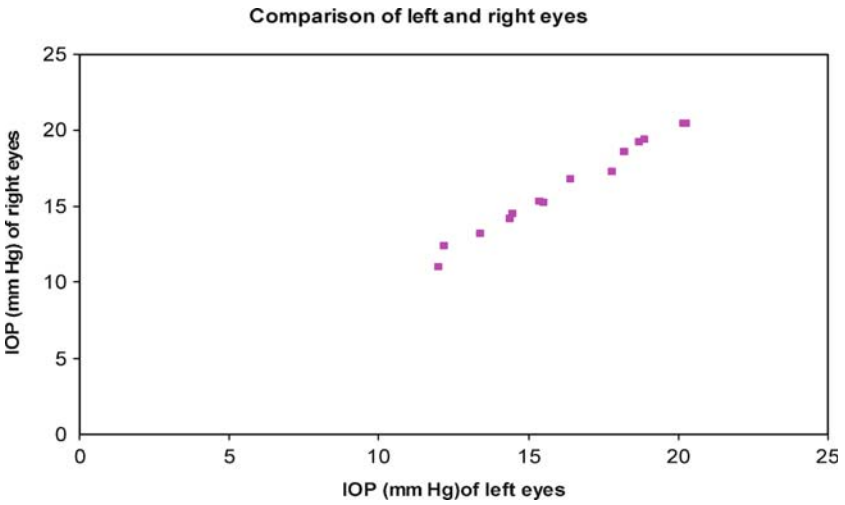


FIGURE 13.6. Comparison of the minimal IOPs (mmHg) in pairs of eyes of adult normal subjects (seated) using the Langham tonometer. The readings are the minimal values of the IOP pulse

14

The Calibration of the Intraocular Pressure and the Intraocular Pressure Pulse using the Langham Pneumatic Tonometer

Calibration of the Steady State IOP

A typical result of the relation between the set intraocular pressure (IOP) in an enucleated human eye and the readout of the Langham pneumatic tonometer is shown in **Fig. 14.1**. This calibration was made under open stopcock conditions, namely the needle was inserted into the anterior chamber and connected to a pressure reservoir at set pressures. In a series of six enucleated human eyes, the relations between IOP and the tonometric readings in individual eyes were linear over the pressure range 0–150 mmHg with a mean gain of 2.55 ± 0.01. The disturbance of the IOP (the indentation effect), when the probe is used horizontally, is less than 1 mmHg. When used vertically, the weight of the sensor increases the indentation effect to 1.5–2 mmHg. This difference is adjusted automatically in the software when the tonometer is applied vertically on the supine patient.

The "day-to-day" accuracy of the Langham tonometer may be checked using a verifier comprising a pressure gauge with a manually operated pump (**Fig. 14.2**). This verifier includes a medical grade silastic standardized membrane of 5-µm thickness, which is locked into position by a plate, leaving a membrane diameter of 12 mm open for application of the probe. The verifier may be used either vertically or horizontally. For pressures from 10 to 100 mmHg, the relation between the set pressure and the read pressure is linear except for a short nonlinearity in the pressure range of 0–12 mmHg, reflecting a change in curvature of the membrane at low pressures.

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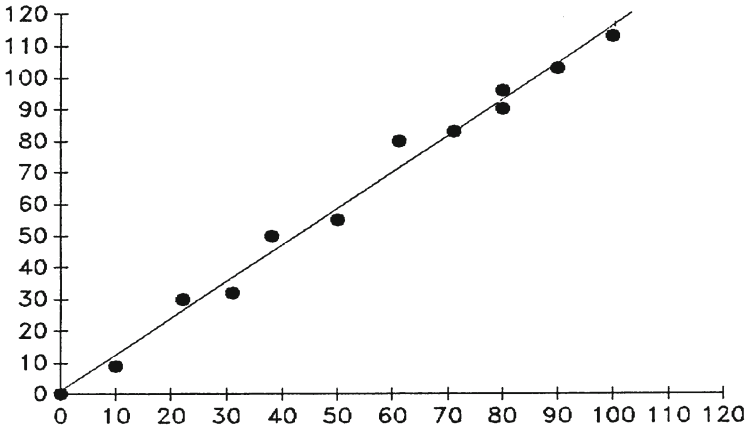


FIGURE 14.1. Manometric study in an enucleated human eye of the relation between the set IOP in mmHg (abscissa) and the tonometer reading in mmHg (ordinate) under open stopcock conditions. The gain factor (the pressure in the plenum to the readout IOP) was set at 2.7 (see theory)

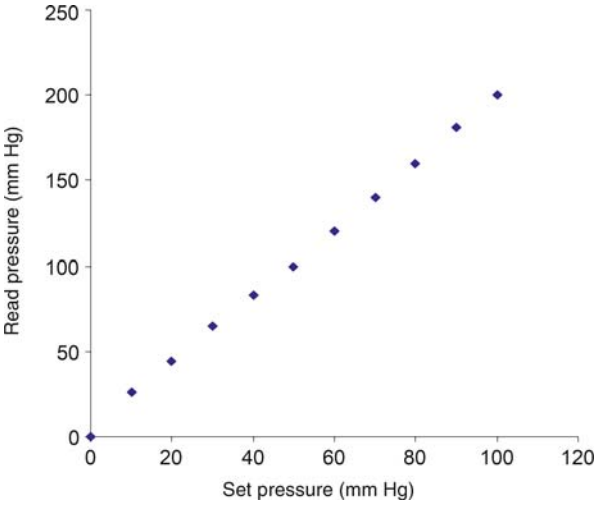
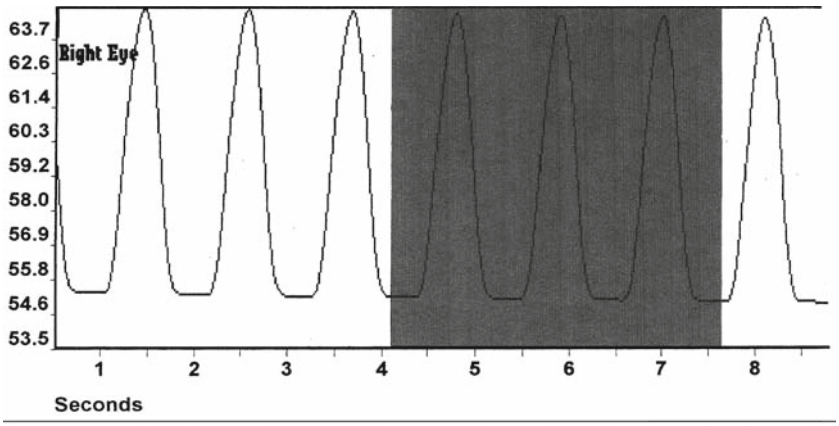


FIGURE 14.2. The relation of the set pressure and the readout pressure using the Langham tonometer on the standard verifier with a 12-mm diameter, 5-μm thick membrane and pressurized by air. It is to be noted that the gain is approximately 2.0

Calibration of the IOP Pulse

The accuracy of the IOP pulse measurements is dependent on the ability of the system to respond to a range of pulses of variable frequencies and amplitudes. The amplitude of the IOP pulse in normal human eyes has a mean of 2–3 mmHg and the frequency of



Pulse	Start Time (sec)	IOPmin (mmHg)	IOPmax (mmHg)	Amplitude (mmHg)
1	4.30	55.13	64.65	9.52
2	5.42	55.09	64.59	9.50
3	6.53	55.05	64.55	9.50
Avg		55.09	64.60	9.51

FIGURE 14.3. A recording of the IOP using the Langham pneumatic probe applied to the corneal surface of an eye of a rabbit. The IOP was set at 55 mmHg and the pulse amplitude was set at 9.6 mmHg with a frequency of 1 Hz using a cyclical pump connected to the anterior chamber

the pulse is identical to that of the cardiac pulse, namely approximately 1 Hz. A range of pulse amplitudes from 0.25 to 10 mmHg and a range of frequencies from 0.5 to 10 Hz were induced in the eyes of rabbits and enucleated human eyes and compared with measurements made on the cornea using the Langham tonometer. The results have shown the system to accurately measure the IOP pulse well above the amplitudes and frequencies seen in healthy and diseased eyes. In these studies the amplitude and frequency of the pulse were produced by a rotary pump connected to the anterior chamber of the eye via a standard-size needle. The pump could be adjusted to give a series of predetermined pulse frequencies and amplitudes. The needle connected to the anterior chamber simultaneously recorded the IOP.

A representative manometric recording of the IOP from the anterior chamber of an enucleated human eye given a pulsatile infusion of physiological saline phosphate (pH 7.4) is shown in **Fig. 14.3**. In this case, the base IOP was set at approximately 55 mmHg; the pulse amplitude was set at 9.5 mmHg and the frequency to approximately 1 Hz. The mean pulse amplitude of 9.5 mmHg measured by the recording tonometer agreed closely with the set amplitude of 9.5 mmHg.

Figure 14.4 shows a similar study in which the pulse amplitude was set at 1.80 mmHg and a frequency of approximately 2 Hz. The mean recorded pulse amplitude of 1.8 mmHg agreed closely with

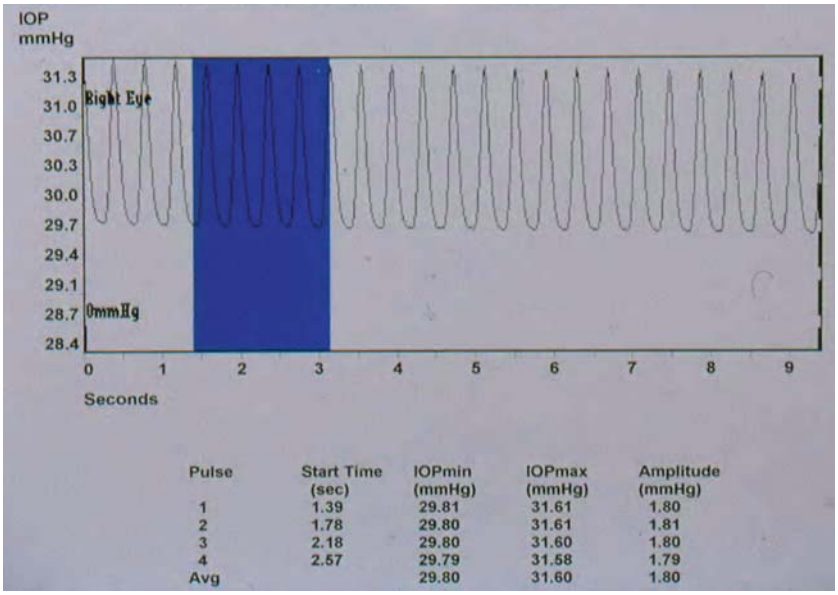


FIGURE 14.4. Recording of the IOP from an enucleated human eye with the Langham probe placed on the cornea and the IOP set at 30 mmHg and the pulse amplitude at 1.8 mmHg and a frequency of approximately 3 Hz

the set amplitude. In a series of similar studies the system was found to measure pulse amplitudes varying from 0.25 to 10 mmHg and frequencies ranging from 0.25 to 10 Hz with accuracies exceeding 95%, respectively.

15

The Theory of the Langham Tonometer

The fundamental physical principles that underlie the Langham probe are summarized in **Fig. 15.1**. The basic concept in the measurement of the intraocular pressure (IOP) is that a gas at an elevated constant pressure P_1 flows through a hollow tube and pushes against a membrane that covers the tip of the probe, causing the membrane to flatten the corneal surface when applied to the eye. The wall of the inner tube ($r = a$) (**Fig. 15.1**) allows the gas to flow through the hollow tube and exit from the region whose outer boundary is the thin wall of the inner tube (at $r = a$); the gas passes through a gap whose height is the distance between the tip of the inner tube and the membrane. As the gas passes through the gap, its pressure drops to a gauge pressure of 0, that is, the actual pressure drops to atmospheric pressure P_o. The height of the gap is determined by the balance of the forces due to the flow of gas through the gap and the opposing force of the IOP that is exerted on the cornea, and the elastic forces of the cornea itself. If the pressure in the tube is sufficiently high, it will deform the cornea (and the covering membrane) and allow gas to escape from the outer cylinder.

The balance of forces across the cornea is given in **Fig. 15.1**. The deflection height is defined to be $w(r)$ and a step-function pressure $P(r)$ to be P_1 for $o \leq r \leq a$, and to be 0 for $r\ ^3 \geq a$. Ignoring the membrane that covers the probe tip, the downward force per unit area (r), created by the pressure of the gas in the probe tip is balanced by the upward force per unit area due to the IOP, P_2, the tension T of the cornea, and the flexural rigidity D of the cornea.

The theory of the dynamic measurements of the IOP pulsations with the pneumatic tonometer has been described in detail in three publications.[27–29] In considering the nature of the pulse, it is evident that the pulse amplitude is a small fraction of the IOP and consequently to be considered as a small perturbation, allowing a linear approximation to be made. The initial consideration of the rigid probe

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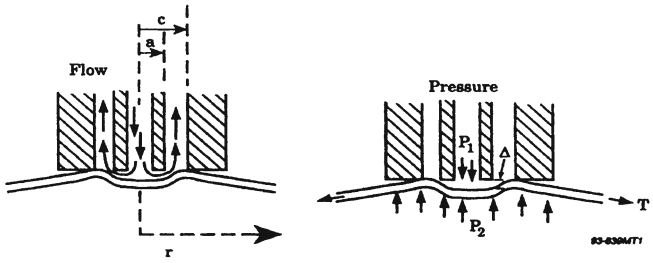

Force Balance Equation

$$p(r) = P_2 - \frac{T}{r}\frac{d}{dr}\left(r\frac{dw(r)}{dr}\right) + \frac{D}{r}\frac{d}{dr}\left\{r\frac{d}{dr}\left[\frac{1}{r}\frac{d}{dr}\left(r\frac{dw(r)}{dr}\right)\right]\right\}$$

where $w(r)$ is the membrane deflection

$p(r) = P_1$ for $0 \le r \le a$, and $= 0$ for $a < r \le c$

T **is the radial tension**

D **is the flexural rigidity**

P_2 **is the intraocular pressure**

P_1 **is the pressure at the probe exit (probe pressure)**

Figure 15.1. Diagram of the physical principles of the Langham pneumatic tonometer (From Silver and Farrell.[27] Reprinted from *Survey of Ophthalmology Supplement.* Used with permission from Elsevier.)

indicated that a floating tip probe that allows continuous recording of the IOP would function similarly to the fixed probe, and this was confirmed for inert membranes and animal and human eyes.[28]

The experimental studies on inert membranes using a fixed plenum volume showed the floating tip tonometer to respond accurately to pulse frequencies up to 100 Hz. In the more normal rates of flow (approximately 5 ml s^{-1}) and plenum volume (approximately 0.2 ml), as used in the Langham tonometer, the upper frequency limit is close to 10 Hz. This frequency limit is one decade higher than the fundamental frequency of the heartbeat and therefore should be sufficient to record the IOP pulse with fidelity. This conclusion has been confirmed in simultaneous manometric and tonometric recordings on humans with a heartbeat of approximately 1 Hz and in rabbits with a heartbeat of approximately 3–4 Hz (see Fig. 13.1).

The magnitude of the pulse amplitude in healthy eyes ranges from 1 to approximately 3 mmHg in seated subjects. The symmetry of the minimal and maximal values of the IOP wave in healthy eyes is extremely close, with the majority of readings agreeing within 1 mmHg. Similarly, the agreement between the IOP pulse amplitudes in pairs of healthy eyes is within 0.15 mmHg.

16

The Intraocular Pressure/Pulse Amplitude Relation in Healthy Animal and Human Eyes

In manometric studies on animal and human eyes (Sect. 1), the intraocular pressure/pulse amplitude (IOP/PA) relation was shown to describe the pulse amplitude changes with increased IOP. This relation is bounded at its maximum by the ophthalmic arterial systolic pressure and at its minimum by the steady state IOP. For normal healthy eyes on seated subjects the lower boundary has a mean of 15–16 mmHg and the upper boundary a mean of 84 mmHg.[30] When the IOP reaches the ophthalmic arterial pressure, the pulse amplitude becomes 0 and vision is rapidly lost (see Sect. 1). This association of the IOP pulsations and vision includes subjects in whom the ophthalmic arterial pressure is substantially reduced by stenosis of the internal carotid artery.

A method for the evaluation of the IOP/PA relation in conscious healthy adult human subjects was described by Langham and To'mey.[30] Using a suction cup of 12-mm diameter applied to the sclera, adjoining the perilimbal area of the cornea, and applying a series of negative pressures to the cup to increase the IOP, a series of recordings of the pulse waveform was performed at each step of increased IOP.

In eyes of healthy subjects of all ages the qualitative form of the IOP/PA relation has the S-shape illustrated in **Fig. 16.1**. The decrease of the PA (approximately 1.0 mmHg) when the IOP was increased modestly (increase of 10–15 mmHg) was followed by a phase (IOP of 30–60 mmHg) in which the PA fell more slowly with unit increase of the IOP . In a final phase of increased IOP, the PA fell to 0 amplitude. This final IOP is the ophthalmic arterial systolic pressure.

The finding that the PA falls with increased IOP in the healthy eyes of conscious subjects was unexpected because under certain anesthesias the IOP/PA relations differ from that in the conscious rabbit as illustrated in a representative result (**Fig. 16.2**). Under barbiturate anesthesia, the PA increases with modest increase of the

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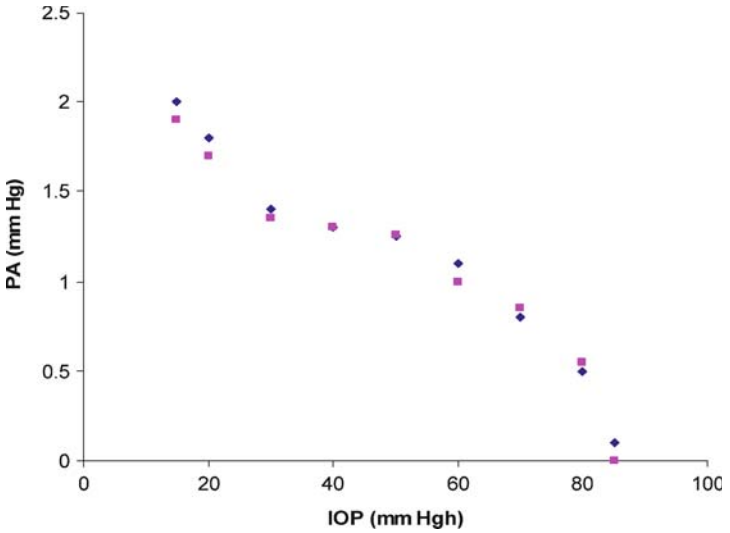


FIGURE 16.1. The IOP/PA relation in pairs of eyes of healthy eyes of an adult subject. The *squares* and *diamonds* are those recorded on the right and left eyes, respectively. The pulse amplitudes fell to 0 at an IOP of 85 mmHg in both eyes, with the corresponding brachial blood pressure of 120/85 mmHg

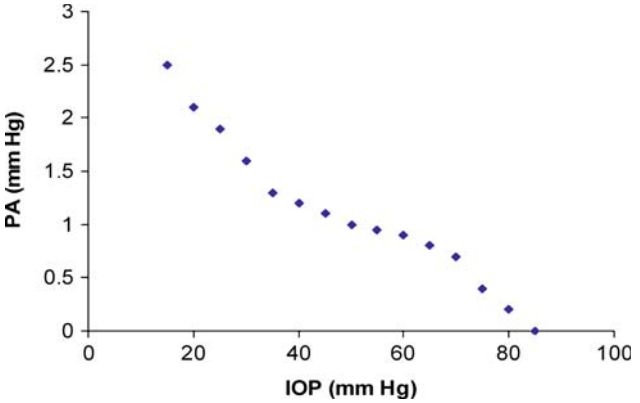


FIGURE 16.2. The mean IOP/PA relation in a group of 12 healthy adult subjects. The results are expressed as the arithmetic mean ± the standard error of the mean where the standard error of the PA at each point was less than 0.1 mmHg

IOP and subsequently begins to decrease with higher IOP until the PA becomes 0 (**Fig. 16.3**).

The physiological significance of the effect of anesthesia on the IOP/PA relation emerges in the analysis of the PA to evaluate the rate of ocular pulsatile blood flow (PBF) using the pressure/volume relation of living animal and human eyes.[31] The relation between the IOP and the PBF in barbiturate anesthetized humans is approximately linear and is consistent with a constant resistance to blood flow with

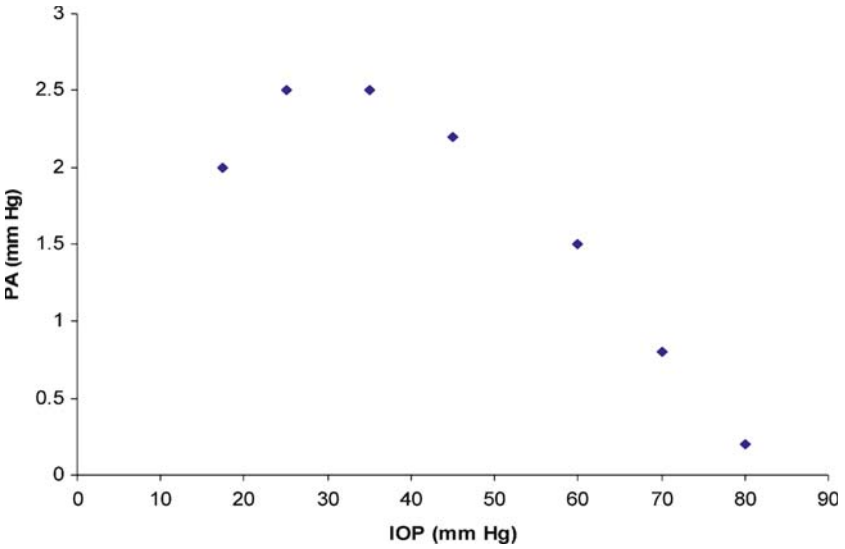


FIGURE 16.3. The IOP/PA relation was measured manometrically in a young healthy subject under sodium pentothal anesthesia

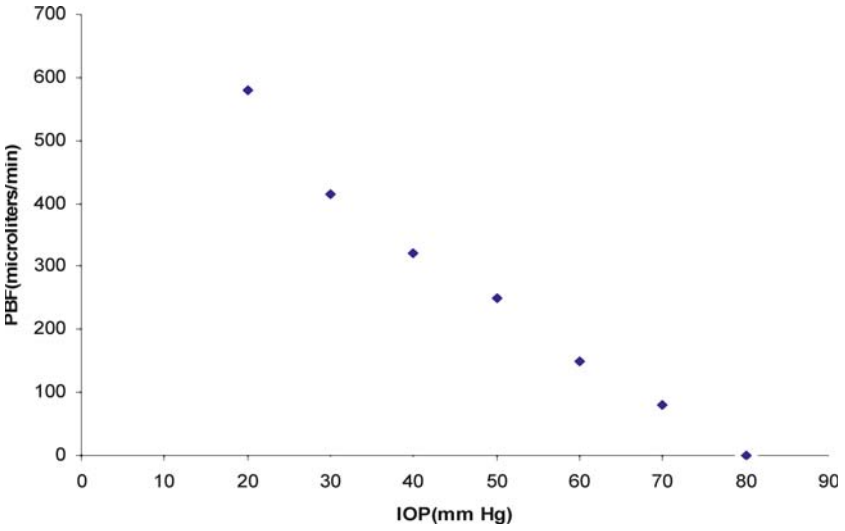


FIGURE 16.4. The IOP/PBF relation in a phenobarbiturate anesthetized adult subject. Note the constancy of the slope of the IOP/PBF relation over the IOP range of 30–80 mmHg; for the IOPs from 20 to 30 mmHg, the relation appears to be slightly nonlinear and consistent with a small degree of autoregulation

little, if any, evidence of autoregulation (**Fig. 16.4**). In conscious adult humans, analysis of the IOP/PA relation yields an IOP/PBF relation, which is nonlinear indicating that the resistance to blood flow changes with the IOP and consistent with an active regulation of ocular blood flow (**Fig. 16.5**).

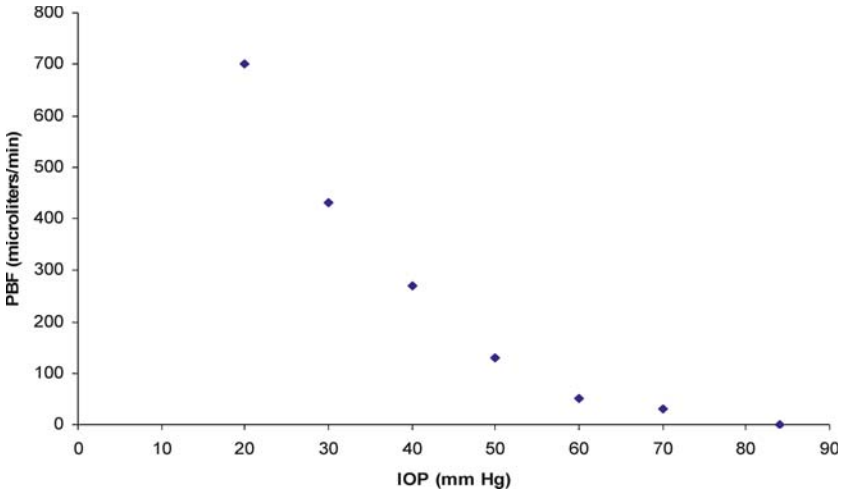


FIGURE 16.5. The IOP/PBF relation in a conscious adult human subject. Note the nonlinearity of the relation and the relatively rapid decrease of the PBF over the IOP range of 20–40 mmHg. This relation is consistent with the presence of an active autoregulation

The linearity of the IOP/PBF relation in barbiturate anesthetized animals and man is consistent with the findings of several investigators, based on direct and indirect measurements of the effect of IOP on the rate of ocular blood flow. Nakamura and Goulstine measured the blood flow through a cannulated vortex vein of anesthetized rabbits and reported the IOP/flow relation to be approximately linear over the IOP range of 40–80 mmHg but to show nonlinearity below an IOP of 40 mmHg.[32] Friedman cannulated the long ciliary arteries of anesthetized cats and evaluated choroidal blood flow from the rate of loss of radioactive Kr_{85} from the ciliary artery and concluded that the choroid had a "mild degree of autoregulation."[33]

A linear relation between ocular blood flow and IOP, and an almost, or complete absence of autoregulation in the choroid of primates anesthetized with sodium pentothal was claimed by Alm and Bill, based on a series of individual measurements of choroidal blood flow at increasing IOP in anesthetized primates.[34] The abnormal IOP/PA and a linear IOP/PBF relations in anesthetized animals and man is in agreement with the IOP/PA relation calculated on the assumption that the IOP/PBF relation is linear and has an ocular pulsatile blood flow of 740 µl min^{-1} (the mean of healthy eyes) with an undisturbed IOP of 15 mmHg (**Fig. 16.6**). In this condition, the IOP/PA relation is qualitatively and quantitatively similar to that in anesthetized humans. Note that in this situation the IOP/PA relation has a convex shape similar to that seen in human subjects under general anesthesia (see **Fig. 16.3**).

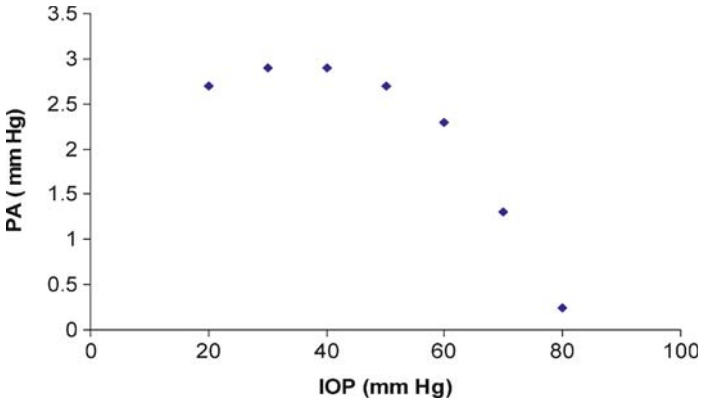


FIGURE 16.6. The IOP/PA relation assuming a linear decrease of ocular pulsatile blood flow (mean 740 µl min^{-1} in the undisturbed eye) to zero flow at the ophthalmic arterial pressure of approximately 85 mmHg. The PA values have been calculated using a coefficient of ocular rigidity of 0.0125, the mean of healthy eyes

The conclusion that pentothal anesthesia modifies the IOP/PA relation and impairs the autoregulation is not surprising, for certain anesthetics have been known for many years to modify significantly peripheral adrenergic neuron activity and specifically to modify the steady state IOP and aqueous humor dynamics in the eye. For example, in four conscious human subjects the mean IOP and the mean pulse amplitudes were 15.5 ± 1.2 and 2.1 ± 0.2 mmHg, respectively, whereas under pentobarbital anesthesia the mean IOP and PA of the same four subjects were 13.7 ± 0.7 and 0.92 ± 0.1 mmHg, respectively. A similar decease in the IOP and PA occurs in rabbits and monkeys under barbiturate anesthesia.

The conclusion that the choroid in man and animals has an active autoregulation of the ocular blood flow with a substantial capacity to minimize changes in IOP and ocular blood flow is in contradiction to reports in recent textbooks and reviews that the choroid has little, if any, blood flow regulation.[35,36] Therefore, it is of importance to review in detail the evidence of the qualitative and the quantitative aspects that provide convincing evidence of the autoregulation and its magnitude.

Two of the most dramatic examples of the ocular blood flow autoregulation have been described in Sect. 1. The first was the response in rabbits to a unilateral ligation of the common carotid (**Fig. 16.7a, b**) and the second was in humans who have suffered a unilateral severe to complete stenosis of the internal carotid followed by surgical endarterectomy (**Figs. 16.8** and **16.9**).

It is evident that autoregulation plays a major effect on the rate of ocular blood flow in man and animals and quantitatively is of the order of several hundred microliters per minute. This capacity of

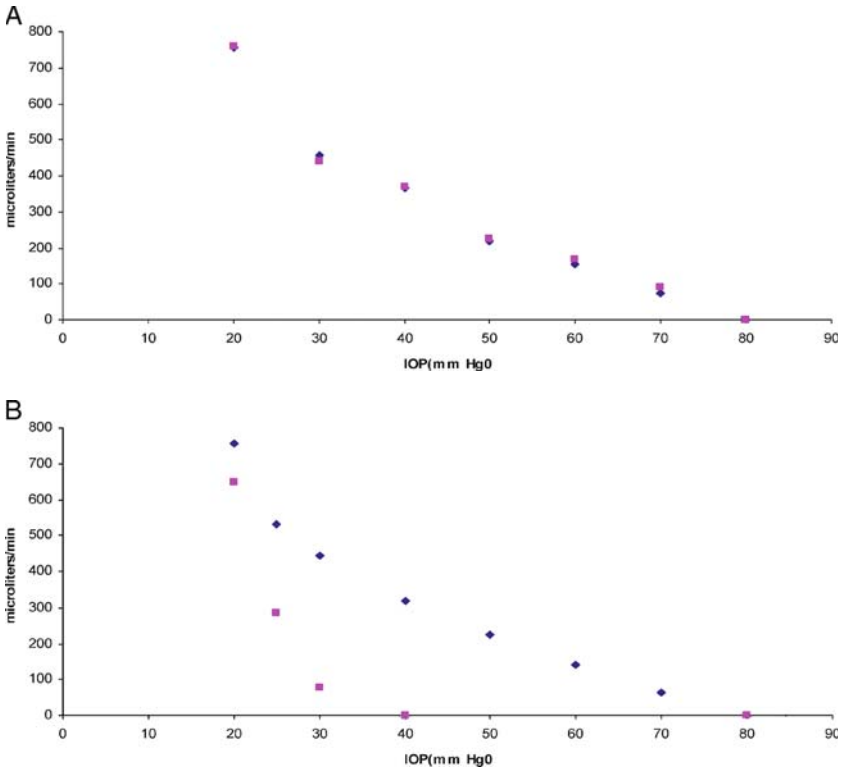


FIGURE 16.7. (**a**) The upper figure is the IOP/PBF relation in pairs of eyes of a conscious rabbit and (**b**) the lower figure shows the IOP/PBF relation 14 days after a unilateral ligation of the common carotid artery. The *diamonds* are values in the eye on the control side and the *squares* are readings taken on the eye on the ligated side. Following removal of the ligation the IOP/PBF curves and the IOP/PA relations recovered to normal and symmetrical in the two eyes

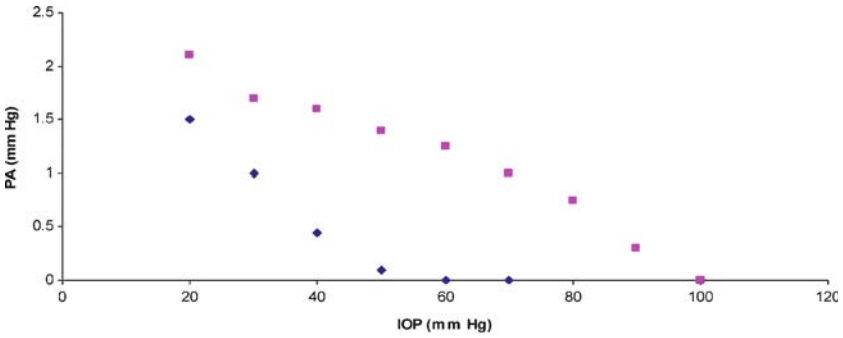


FIGURE 16.8. The IOP/PA recordings in pairs of eyes of a patient with a severe unilateral stenosis of the left internal carotid artery. The *squares* are readings on the eye, which has minimal stenosis of the internal carotid artery and the *diamonds* are from the eye on the side with an internal stenosis of approximately 70% based on arterial angiography. The rates of pulsatile blood flow were 690 and 580 μl min^{-1} and the IOPs were 20 mmHg in the two eyes

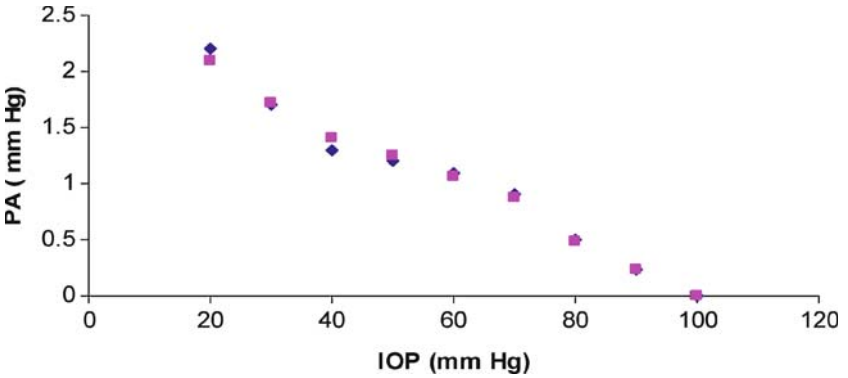


FIGURE 16.9. The IOP/PA curves on pairs of eyes of the patient shown in Fig. 16.8 following successful surgical endarterectomy on the left eye. Prior to surgery the ophthalmic arterial pressure in the left eye was 53 mmHg and angiography revealed a stenosis of approximately 80%. The ophthalmic arterial pressures in pairs of eyes had recovered to approximately 95 mmHg

the autoregulation may appear to be a surprisingly large value but is well within the change in ocular blood flow induced by modulation of adrenergic activity. Electrical stimulation of the preganglionic cervical nerve decreases total and pulsatile ocular blood flow by 50%, namely by 400–500 μl min^{-1}.[37] Further, cervical ganglionectomy increases ocular blood flow by 20–25%, namely 200–250 μl min^{-1}. Thus, adrenergic activity has the capacity to reduce ocular blood flow by 400–500 μl min^{-1} and to increase it by at least 200–250 μl min^{-1}. In addition, there are the compensatory responses of the ocular blood flow induced by localized relative ischemic responses affected by the metabolic changes in the endothelium of the small precapillary arterioles. Thus, the ability to compensate for moderate ocular ischemia and for substantial decrease in ocular perfusion pressure includes neurogenic and metabolic processes that act efficiently and have substantial modulating capacity.

17

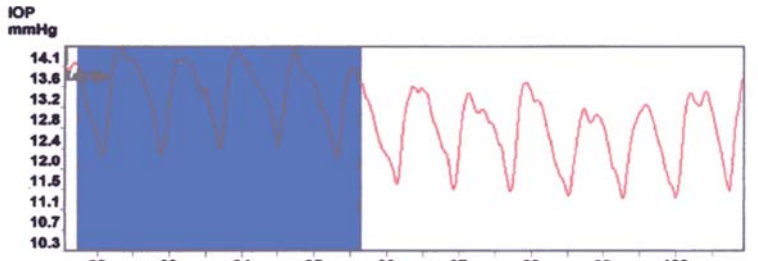
The Intraocular Pressure/Pulse Amplitude Relation and Loss of Autoregulation in Ocular Diseases

The following clinical cases are representative examples of the ocular circulation in individual patients with normal, suspected, or confirmed ocular disease.

Healthy Subject with No Apparent Ocular Pathology

Young healthy adult male subject (22-years old) with healthy optic discs, full central visual fields, and routine time- and pressure-dependent differential threshold light sensitivities: The steady state intraocular pressures (IOPs) were 14 and 15 mmHg in left and right eyes, respectively, measured with the Goldmann tonometer. The mean minimal and maximal of the IOP waves, recorded with the Langham tonometer, were 12.4/14.4 and 12.4/14.4 mmHg in the left and right eyes, respectively. The pulse amplitudes (PAs) were 2.0 mmHg in both eyes and the corresponding pulsatile blood flows were 934 and 925 µl min^{-1}. **Figure 17.1** shows a representative segment of the IOP recording on the left eye of the seated subject. The shaded area indicates the four pulses, which have been analyzed and tabulated below the recording. The recording shows the modulation of the IOP wave with respiration and the presence of a cardiac dichrotic notch. The postural responses in the left and right eyes were 1.5 and 1.5 mmHg, respectively, which are well within the range for healthy eyes. The IOP/PA relations in pairs of eyes of this subject are shown in **Fig. 17.2**. They were identical in pairs of eyes and showed the rapid decline of the PA with modest increased IOP, reflective of active vascular autoregulation.

M.E. Langham, *Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases: A New Perspective*, DOI: 10.1007/978-0-387-09716-9_17,



ulse	Start Time (sec)	IOPmin (mmHg)	IOPmax (mmHg)	Amplitude (mmHg)	Volume (microlit)	POBF (microlit/mi
1	92.04	12.28	14.52	2.24	6.19	966.66
2	92.87	12.25	14.28	2.03	5.67	991.63
3	93.68	12.41	14.49	2.08	5.73	907.93
4	94.49	12.47	14.48	2.01	5.52	872.95
5	95.30	12.22	14.12	1.90	5.34	0.00
vg		12.33	14.38	2.05	5.69	934.79

FIGURE 17.1. The IOP recording on the left eye of a healthy adult subject. The pulses in the shaded area have been analyzed individually and are tabulated below the recording. The mean values of the chosen pulses are shown on the bottom row. Note that the recording of the fifth pulse was incomplete and therefore rejected by the software. Note the break in the descending phase of the pulse waves, which corresponds to the dichrotic notch

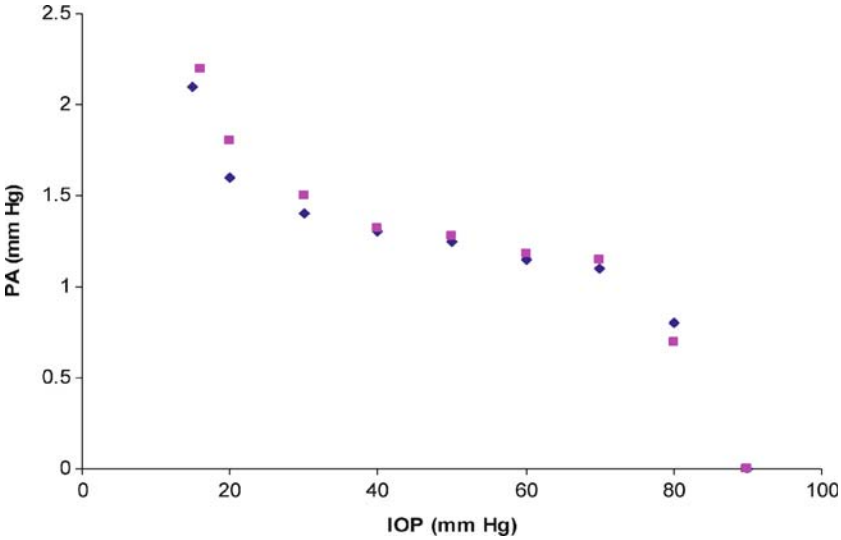


FIGURE 17.2. The IOP/PA relations in eyes of an adult subject with no apparent ocular disease. The OAPs in pairs of eyes were 90 mmHg with corresponding brachial arterial blood pressures of 138/88 mmHg. The pulsatile blood flows in the two eyes were 925 and 937 μl min^{-1}, respectively

Diabetes with No Retinopathy

A male of 34 years diagnosed with diabetes mellitus and insulin dependent for more than 10 years: The patient had no background retinopathy based on fundus photography and fluorescein angiograms.

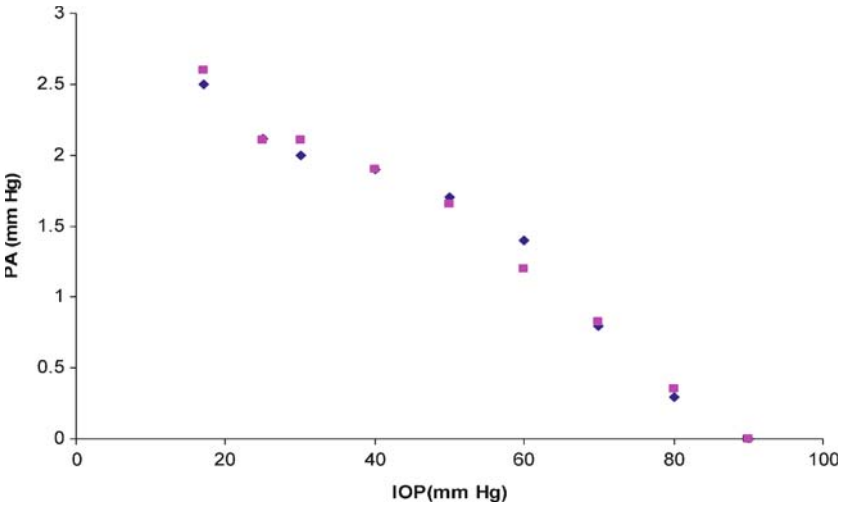


FIGURE 17.3. The IOP/PA relation in a 34-year-old male diagnosed with diabetes mellitus at age 24 years. The patient had been insulin dependent for 10 years but had no detectable retinopathy. The IOPs, PAs, and the pulsatile blood flows (645 and 654 min^{-1}) are well within the range for normal eyes. The IOP/PA relation is just within the normal range

The IOPs were 15 and 16.5 mmHg measured with the Goldmann applanation tonometer and 16.3/18.8 and 17.1/19.5 mmHg, respectively, recorded with the Langham tonometer. The ophthalmic arterial pressures (OAPs) were 85 mmHg in the two eyes and the brachial arterial pressure was 130/85 mmHg.

The IOP/PA curves (**Fig. 17.3**) were borderline normal in that the shape approximated to the S-shape characteristic of healthy eyes. This is of interest in view of the apparent absence of retinopathy, despite the long-term insulin dependency. A similar result was recorded in a male of 52 years with diabetes mellitus on insulin treatment for more than 25 years, who also had no evidence of retinopathy based on retinal photography and fluorescein angiograms.

This finding of normal ocular blood flow and normal IOP/PA curves in two insulin-dependent diabetics with no apparent retinopathy and suffering from diabetes for many years is not readily explained. Both subjects had normal rates of ocular blood flow, normal perfusion pressures, normal IOP/PA relations, and intact vascular autoregulation. The absence of retinopathy and relative ocular ischemia in these two patients is in marked contrast to the findings on diabetics with moderate to severe retinopathy (see later). Pathological changes in the vascular system of patients with diabetes are well recognized and include vascular changes in the kidney and release of the vasoconstrictor molecule angiotensin. In diabetes with background retinopathy, the retinal blood flow has been reported to be normal while Geyer et al. reported that diabetics

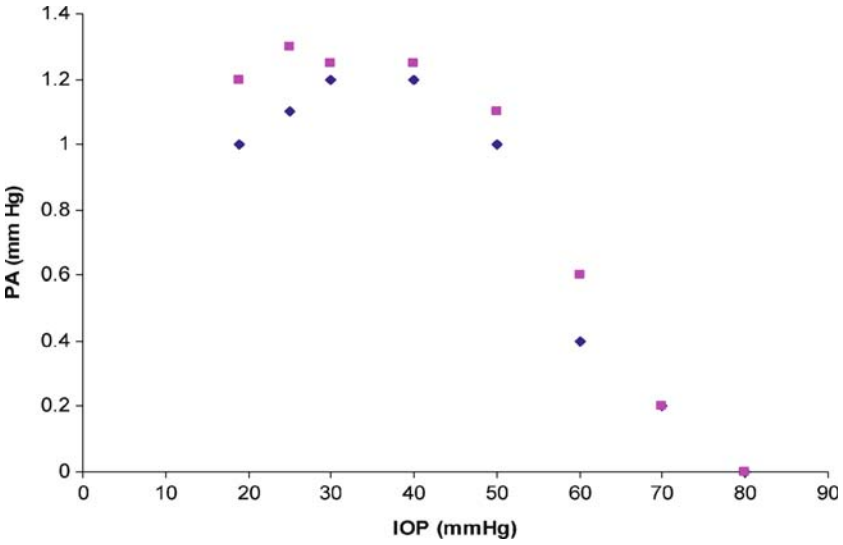


FIGURE 17.4. Diabetes with background retinopathy. The IOP/PA relations in pairs of eyes of a patient with insulin-dependent diabetes and retinopathy in both eyes. Note the asymmetry of the PAs in the undisturbed eyes and the abnormality of the IOP/PA relation, reflecting an absence of autoregulation

with minimal background retinopathy had increased ocular pulsatile blood flow.[38–40]

Diabetes with Background Retinopathy

A female of 45 years with a history of insulin-dependent diabetes for 20 years: Both eyes had background retinopathy, characterized by microlayer infarcts, aneurysms, hemorrhages, exudates, edema, and nerve fiber layer infarcts. The IOPs were 20/21 and 19/20 mmHg in the two eyes and the pulsatile blood flows were 487 and 378 ml min^{-1}.These flow rates are significantly below the range in healthy eyes. The IOP/PA relations in the two eyes shown in **Fig. 17.4** were abnormal and consistent with a complete absence of autoregulation. The OAPs were approximately 75 mmHg and the brachial arterial blood pressure (BrAP) was 145/85 mmHg, giving an OAP/BrAP ratio of 0.51, which is below the range in healthy eyes.

Insulin-Dependent Diabetes with Proliferative Retinopathy

A female patient of 55 years with insulin-dependent diabetes for more than 30 years: The patient had severe retinopathy and areas of epipapillary neovascularization in one eye and epiretinal neovascularization in the second eye (**Fig. 17.5**). The patient had not

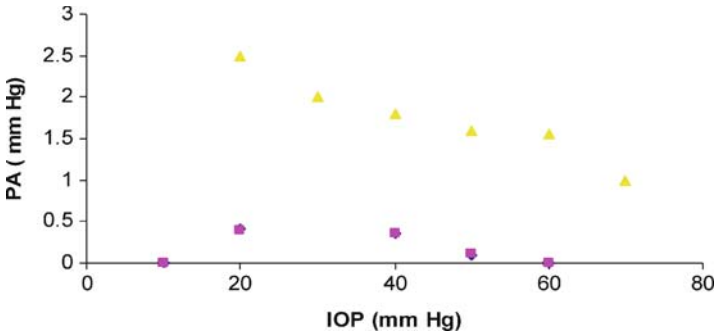


FIGURE 17.5. The IOP/PA relations in two eyes of a patient with insulin-dependent diabetes with severe retinopathy

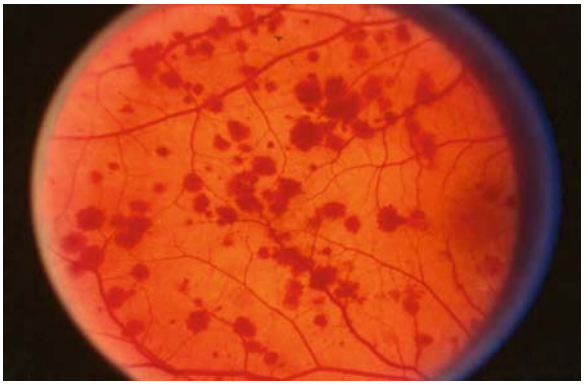


FIGURE 17.6. The retina of the patient with insulin-dependent diabetes with severe retinopathy described earlier

received photocoagulation at the time this study was made. The IOPs were 15.7/16.5 and 16.8/17.6 mmHg (Langham tonometer) and the pulsatile blood flows were 246 and 238 µl min^{-1}, which are well below the range in normal eyes. The OAPs were 55 mmHg in both eyes and the brachial arterial pressure 150 mmHg yielding OAP/BrAP ratios of 0.37, which are well below the mean ratio in healthy subjects (0.67 ± 0.01). The IOP/PA relations in the two eyes were grossly abnormal and the OAPs were very low.

The increased severity of ocular ischemia with progression of the diabetic retinopathy (**Fig. 17.6**) in this patient and the changes of the IOP/PA relation are in keeping with the widely held belief that relative ischemia is implicated in its evolution.[41–46]

Loss of blood flow in diabetes retinopathy may be explained as a result of decreased OAP and/or increased ocular vascular resistance. Both mechanisms appear to be present. The decrease of the OAP without a corresponding decrease in the systemic blood pressure implies increased vascular resistance in vessels exterior to the eye including

the ophthalmic artery. This conclusion is in keeping with the findings of Garner and Ashton on postmortem eyes that the mean diameter of the ophthalmic arteries of patients with proliferative retinopathy was 37% less than in control eyes; their histological studies on the same eyes revealed that the arterial narrowing resulted from atheromatous aggregation.[47] The increased vascular resistance within the diabetic eyes with moderate to severe retinopathy was evident in the abnormally low pulsatile blood flows of 50–75% less than in healthy eyes despite normal ocular perfusion pressures.

Neovascular Age-Related Macular Degeneration

A male of 75 years with age-related macular degeneration with subfoveal neovascularization in both eyes: The optic disc and the retinal vessels appeared to be normal, but in the area just above the fovea there was hyper pigmentation and subretinal fluid. In the left eye there was marked venous dilatation with flame and blot hemorrhages. Drusen were present in both eyes and there was evidence of recurrence of choroidal neovascularization, which had become subfoveal in one eye. The IOPs were 20/20.5 and 21/22.0 mmHg in the right and left eyes, respectively. The PAs and the rates of pulsatile blood flow of 436 and 437 µl min^{-1} in the right and left eyes were below the range in healthy eyes and indicative of a relative ischemia. The shape of the IOP/PA relations are abnormal and consistent with loss of blood flow autoregulation (**Fig. 17.7**).

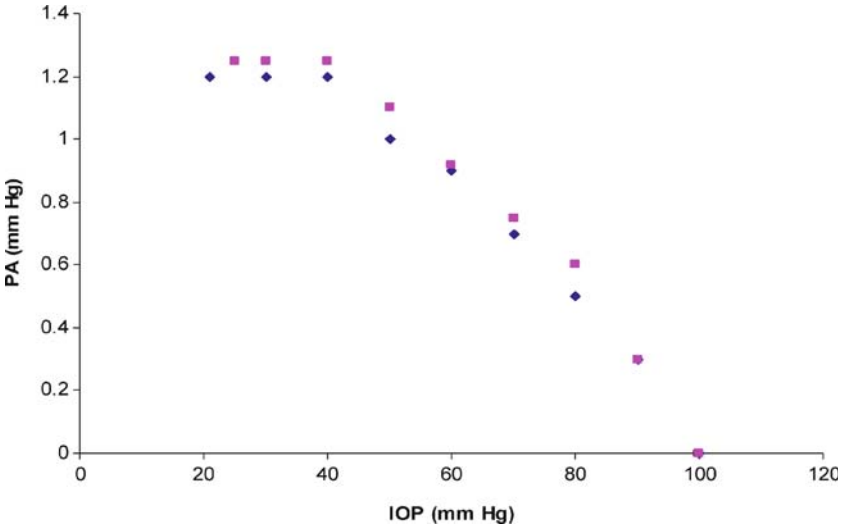


FIGURE 17.7. The IOP/PA relations in eyes of a patient with neovascular age-related macular degeneration. Note that the IOPs were asymmetric and the IOP/PA relations were abnormal and consistent with a loss of autoregulation. The pulsatile blood flows were 436 and 437 µl min^{-1} in the undisturbed eyes and well below normal

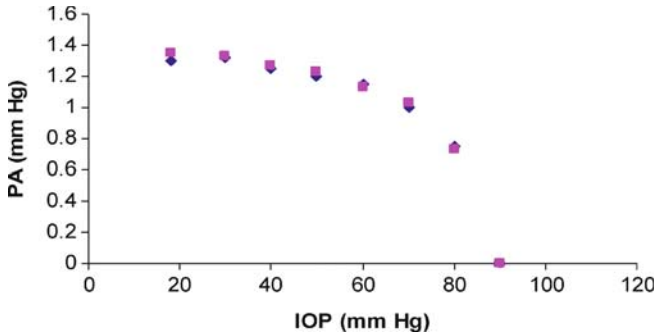


FIGURE 17.8. The IOP/PA relation in an 83-year-old male diagnosed with nonneovascular macular degeneration in both eyes

Nonneovascular Age-Related Macular Degeneration

An 83-year-old male diagnosed with nonneovascular macular degeneration with drusen in both eyes: The IOPs were 14/15.3 and 14/15.4 mmHg and the pulsatile blood flows were 545 and 560 µl min^{-1} (the low end of the normal range), and the OAP in both eyes were 90 mmHg. The brachial arterial blood pressure was 200/100 mmHg. The OAP/BrAP ratios of 0.50 in both eyes were below the range in normal eyes (mean 0.67). The IOP/PA relation was grossly abnormal and indicative of loss of autoregulation (**Fig. 17.8**).

Unilateral Nonvascular Macular Degeneration

Male patient of 57 years followed for 4 years, with a diagnosis of nonneovascular macular degeneration in the left eye: Visual acuity in left and right eyes were 22/100 and 20/20, respectively. The IOP and the PA in the left eye were 15 and 1.0 mmHg, respectively, and 17 and 1.4 mmHg in the right eye, respectively. The pulsatile blood flows were 402 and 462 µl min^{-1} in the left and right eyes. These flow rates are below the range in normal eyes. The brachial arterial pressure was 118/75 mmHg and the OAP/BrAP ratios were 0.54 and 0.65 in the left and right eyes, respectively. The OAP/BrAP ratio in the right eye was within the range in normal eyes, whereas OAP/BrAP in the eye with neo-nonvascular macular degeneration was lower than the range in normal eyes.

The IOP/PA relations in the two eyes of this patient were asymmetric (**Fig. 17.9**). The IOP/PA relation in the apparently healthy eye was normal, whereas the IOP/PA relation in the eye with macular degeneration was abnormal and consistent with a severe loss, or absence of autoregulation. In addition, the OAP in the affected eye was significantly lower than in the contralateral eye. This finding indicates that the vascular resistance in the corresponding internal carotid artery was abnormally high. In this respect, the patient had

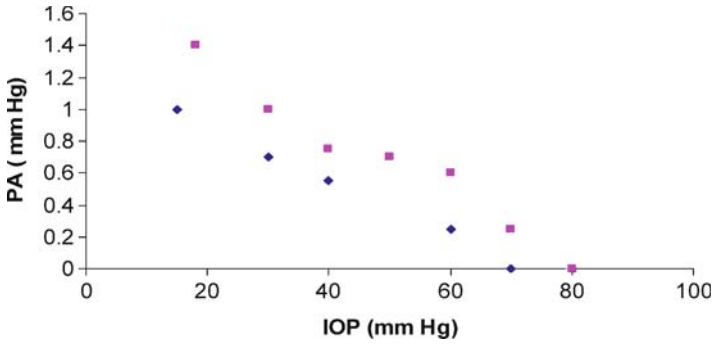


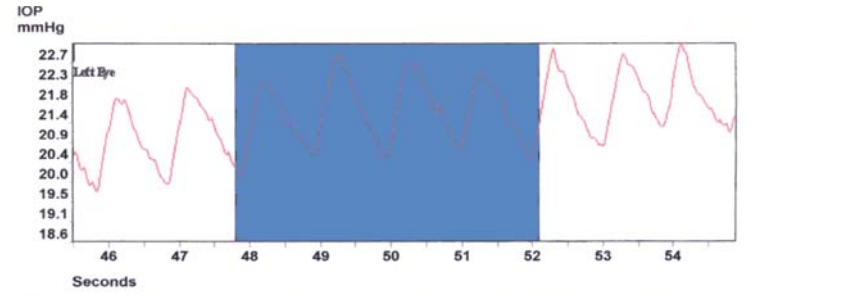
FIGURE 17.9. The IOP/PA relations in a patient with unilateral nonneovascular macular degeneration. The *squares* are recordings on the unaffected eye and the *diamonds* are recordings on the affected eye

an aneurysm in the abdominal aorta that had been treated surgically. These observations support several recent studies indicating that blood flow is abnormally low in the macular and choroid of eyes with both forms of age-related macular degeneration, and more severe in eyes with neovascular macular degeneration.[48] Evidence that the ischemia is present in the macular of patients with nonneovascular macular degeneration was reported by Grunwald et al. who concluded from laser Doppler studies that, in the early stage of the disease, the blood flow in the choroid immediately behind the macula was less than 50% of normal.[49]

Open Angle Glaucoma

A male patient of 55 years with confirmed open angle glaucoma for approximately 23 years, with glaucomatous cupping of both optic cups and central visual field loss. The field loss had always been more pronounced in the left eye. Over this period, the patient had been treated with 2% pilocarpine, 0.5% timolol, and 6 months previously, 0.005% Latanoprost had been added. The IOPs were 23 and 20 mmHg in the left and right eyes, respectively, measured with the Goldmann tonometer and 20/22 mmHg (min/max values) and 18/20 mmHg in the left and right eyes, respectively, measured with the Langham tonometer (seated patient). The rates of pulsatile blood flow were 460 and 390 μl min^{-1} in the right and left eyes and well below the range in healthy eyes (**Fig. 17.10**).

The IOP postural responses were 4 mmHg in both eyes, which are abnormally high and characteristic of patients with open angle glaucoma. The IOP/PA relations recorded on this patient are shown in **Fig. 17.11**. The curves were similar in both eyes and were abnormal. The lack of the S-shape seen in normal eyes is consistent with a loss of the blood flow autoregulation. The OAPs were 100



Pulse	Start Time (sec)	IOPmin (mmHg)	IOPmax (mmHg)	Amplitude (mmHg)	Volume (microlit)	POBF (microlit/min)
1	47.81	20.25	22.23	1.98	3.45	479.97
2	48.84	20.74	22.92	2.18	3.69	507.24
3	49.89	20.57	22.64	2.07	3.54	474.34
4	50.93	20.81	22.48	1.67	2.85	382.66
Avg		20.59	22.57	1.98	3.38	461.05

FIGURE 17.10. A segment of the IOP recording on the right eye (seated) of the patient with open angle glaucoma

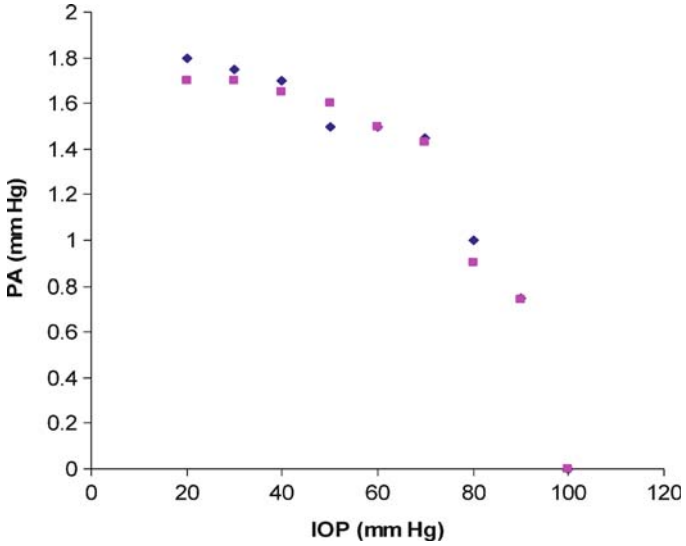


FIGURE 17.11. The IOP/PA relations in the left (*diamonds*) and the right eyes (*squares*) in the patient with open angle glaucoma. Note that the IOP/PA relations are similar in pairs of eyes, but differed from normal in the absence of the initial sharp fall in the PA with increased IOP, indicative of a loss of autoregulation

mmHg in both eyes and the brachial arterial pressure was 160/90 mmHg giving BrAP/OAP ratios of 0.62, which is in the low range of normal eyes.

Low-Tension Open Angle Glaucoma

This was a male patient of 54 years with a confirmed diagnosis of low-tension glaucoma. The IOPs measured with the Goldmann

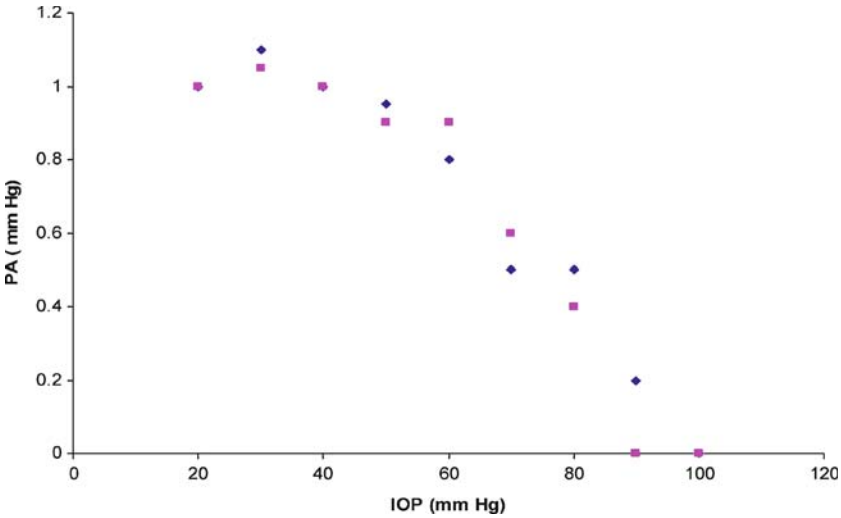


FIGURE 17.12. The IOP/PA relation in pairs of eyes of a patient diagnosed as low-tension glaucoma. The patient had typical moderate glaucomatous field loss in both eyes

applanation tonometer were 18.5 mmHg in both eyes, and 18.5/19.5 mmHg recorded with the Langham tonometer. These IOPs are within the range for healthy eyes; however, the PAs of 0.95 mmHg in both eyes were well below the range in healthy eyes. Similarly, the pulsatile blood flow rates of 328 μl min^{-1} in both eyes were well below the range in healthy eyes. It will be noted that the IOP/PA relations in the eyes of this patient have the convex shape characteristic of eyes with little, if any, autoregulations of the PA and ocular pulsatile blood flow (**Fig. 17.12**).

Open Angle Glaucoma Suspect

A female (age 64 years) referred as glaucoma suspect, based on IOPs of 23–27 mmHg in both eyes measured with the Goldmann tonometer and with asymmetric optic cups – visual fields were not impaired. The patient had an annual eye checkup for the past 5 years, and the Goldmann IOPs of 23–27 mmHg in the two eyes had remained essentially unchanged. Further, the visual fields and the optic disks remained within the normal range over the same period. At the time of the current examination, the IOPs in the right and left eyes (seated subject) recorded with the Langham tonometer were 20/22.3 and 19.5/21.7 mmHg, respectively. The patient had received no glaucoma treatment. The IOPs and the IOP waveform were identical in pairs of eyes, and the IOP postural responses were 1.8 mmHg in both eyes, which is within the normal range. The brachial arterial blood pressure was 160/88 mmHg and the OAPs were 87 mmHg. The threshold central visual fields and the time- and pressure-dependent differential visual thresholds were stable and normal.

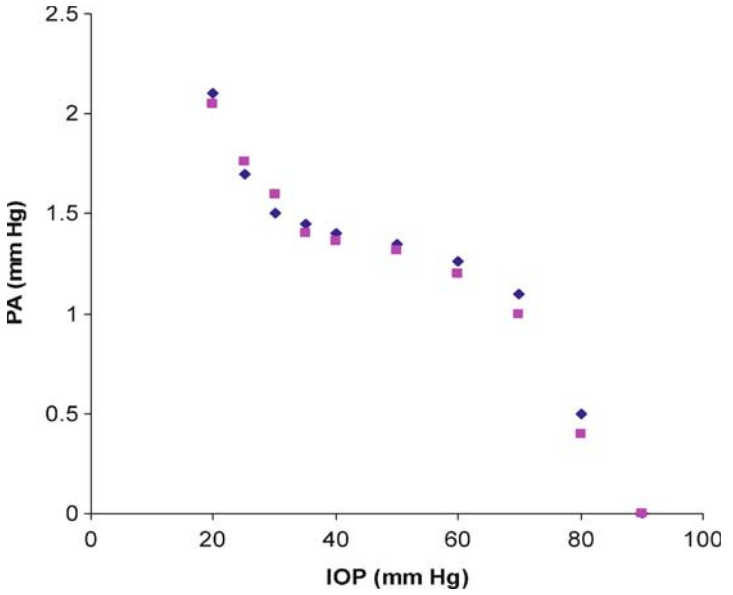


FIGURE 17.13. The IOP/PA relation in pairs of eyes of a female glaucoma suspect of 64 years with a history of abnormally high IOPs over a 5-year period. The optic disks were enlarged but the visual fields were intact and normal. Note the S-shape of the IOP/PA curves, typical of healthy eyes

The IOP/PA relations in pairs of eyes (**Fig. 17.13**) were identical and of normal shape. In this respect, both curves showed the initial decrease in the PA with modest increased IOP, a characteristic of normal healthy eyes. These results are indicative of healthy, ocular hypertensive eyes with intact autoregulation and do not support a diagnosis of open angle glaucoma.

Glaucoma Suspect with Systemic Hypertension

A female subject of 42 years found to have IOPs of 27 mmHg measured with the Goldmann tonometer in both eyes (subject seated) while attending a glaucoma screening program: There was no family history of glaucoma and the high arterial pressure had not been recognized. The postural effects on the IOPs were 2.5 mmHg in both eyes, which is a typical normal response. The outflow facilities were 0.26 and 0.28 μl min^{-1} $mmHg^{-1}$ in the left and right eyes, respectively, which are well within the range of normal eyes. Central visual fields were normal as were the time- and the pressure-dependent differential visual thresholds. The PAs were 2.6 and 2.8 mmHg and the pulsatile blood flows were 556 and 519 μl min^{-1} in the left and right eyes, respectively, and at the low end of the range in normal eyes (**Fig. 17.14**). The brachial blood pressure was 165/105 mmHg and the OAP/BrAP ratios were 0.63 well

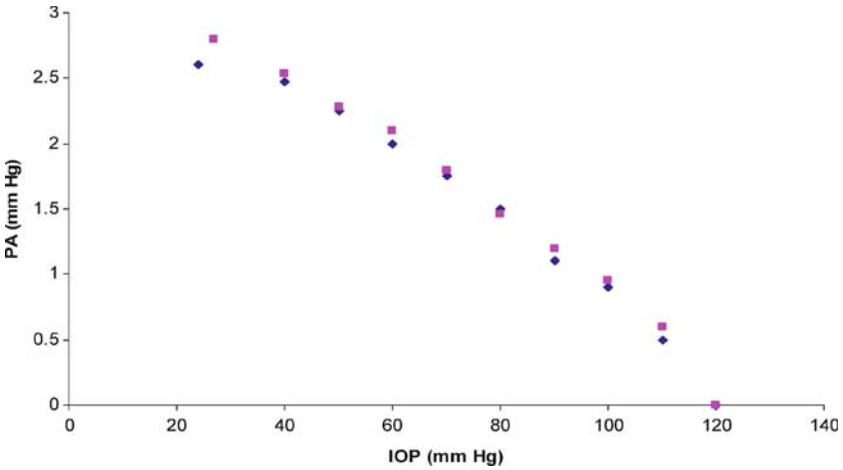


FIGURE 17.14. Glaucoma suspect: The IOP/PA relations in pairs of eyes of a female (42-years old) attending a glaucoma screening program. The curves are abnormal and consistent with little, if any autoregulation. The PAs and the pulsatile blood flows are within the range of normal, but the ophthalmic arterial pressure is abnormally high

within the range in normal subjects. The systemic hypertension and the abnormally high OAP complicate this diagnosis. The observation that the ocular blood flows were on the low side of the normal mean, while the ocular perfusion pressures are abnormally high is consistent with an abnormally high vascular resistance in the brain. In this respect, the relatively high IOP may be explained by the abnormally high ocular perfusion pressure. The normal outflow facilities, normal postural effects on the steady state IOP, and normal visual fields, which remained intact on increasing the IOP higher than 50 mmHg, do not support a diagnosis of open angle glaucoma. This conclusion was confirmed in the observations made 2 years later; the patient was under systemic hypotensive medication, and the IOPs were in the normal range and there continued to be no abnormalities in the visual fields.

Central Retinal Vein Occlusion

A 58-year-old female with a central vein occlusion in the left eye: The patient was on treatment for systemic hypertension. At the time of this examination the brachial blood pressure was 140/80 mmHg. The IOPs were 15 and 20 mmHg in the left and right eyes, respectively, measured with the Goldmann applanation tonometer. The IOPs were 17/18.9 and 22/23.9 mmHg in the left and right eyes, respectively, recorded with the Langham tonometer. The difference in IOP of 5.0 mmHg between the two eyes is abnormal; the PA values were equal in the two eyes and within the range in healthy eyes.

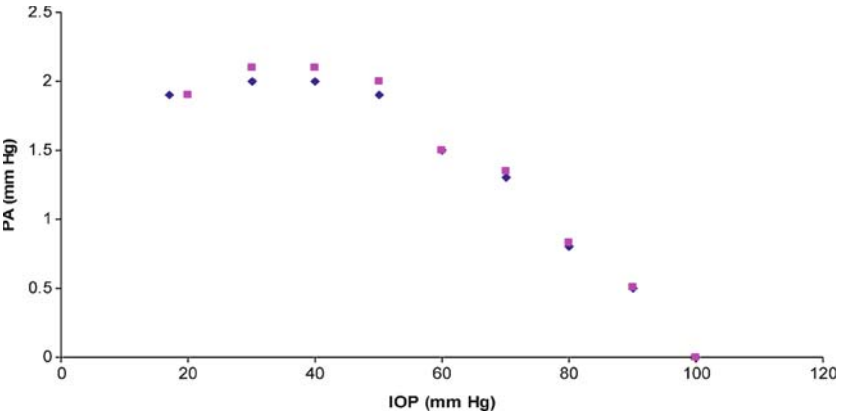


FIGURE 17.15. Patient with a retinal central vein occlusion in the left eye. The left and right eyes are represented by *diamonds* and *squares*, respectively. The IOP/PA relations are abnormal and the rates of pulsatile blood flow are below the range in healthy eyes. The *diamonds* and the *squares* are readings on the left and right eyes, respectively

The rates of pulsatile blood flow were 486 and 541 µl min^{-1} in the left and right eyes, respectively, and below the range in healthy eyes and consequently indicative of relative ischemia. In addition, the IOP/PA relations are abnormal and indicate absence of autoregulation. It is to be noted that the IOP/PA curves are abnormal in both eyes despite the vein occlusion being in only one eye (**Fig. 17.15**).

Chronic Systemic Hypotension

A female patient of 57 years with a history of chronic systemic low blood pressure, with symptoms of dizziness intensified by change of posture: The IOPs were 18 mmHg in both eyes measured with the Goldmann tonometer and 20/21.5 and 20/1.6 mmHg measured with the Langham tonometer (patient seated). The rates of pulsatile blood flow were 455 and 486 µl min^{-1} in the left and right eyes, respectively, and abnormally low compared with the mean of 740 µl min^{-1} in normal eyes. The IOP/PA relations in this patient were abnormal and indicative of an absence of vascular autoregulation. The brachial arterial blood pressure was 100/70 mmHg (patient supine) and the OAPs were approximately 80 mmHg. These IOP/PA relations in both eyes indicate a loss of autoregulation and relative ischemia (**Fig. 17.16**).

Ocular and Systemic Hypertension

A male subject (age 56 years) with a history of repeated abnormally high IOP readings in both eyes of 23–26 mmHg by Goldmann tonometry was referred for ocular vascular evaluation (**Fig. 17.17**).

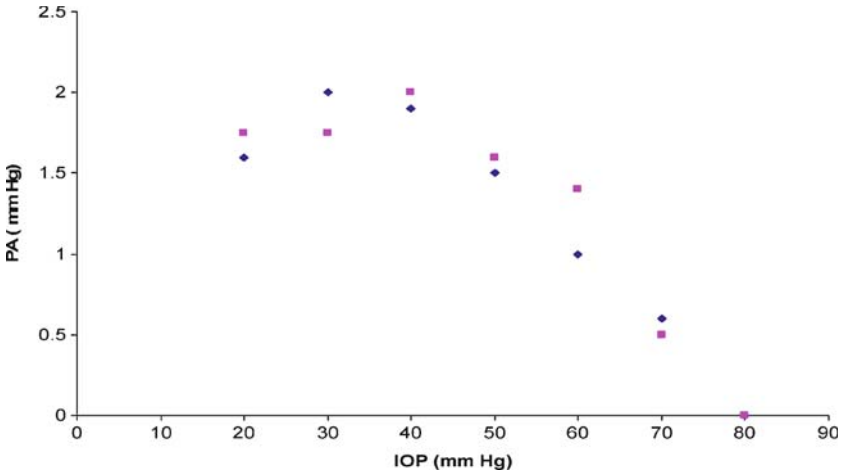


FIGURE 17.16. The IOP/PA relation in a male subject of 57 years with abnormally low systemic blood pressure. The patient had a history of low brachial blood pressure of approximately 90/70 mmHg. The brachial blood pressures lying supine at the time of the test were 110/70 mmHg in both arms. The subject felt chronically dizzy, and especially when changing posture. The rates of pulsatile blood flow in the two eyes were 455 (right eye) and 486 μl min^{-1} (left eye), respectively, which are well below the values in normal eyes

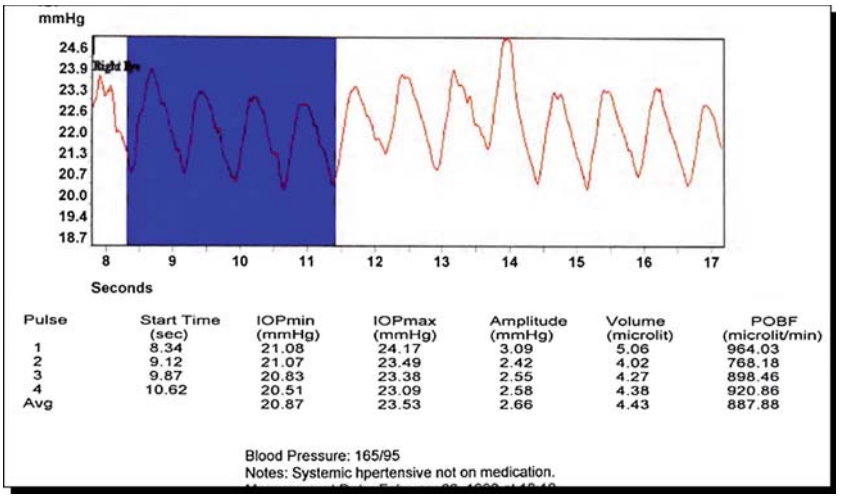


FIGURE 17.17. The recording of the IOP in the patient with systemic hypertension and with antihypertensive medication. The minimal and the maximal IOPs were 20.9/23.5 and 22.5/24.0 mmHg in the right and left eyes, respectively, recorded with the Langham tonometer

The visual fields in both eyes were normal, but the optic disks were asymmetric. At the present examination the brachial blood pressure was 165/95 mmHg, but the patient was not on medication. The IOP postural effect was 2.5 mmHg in both eyes and within the

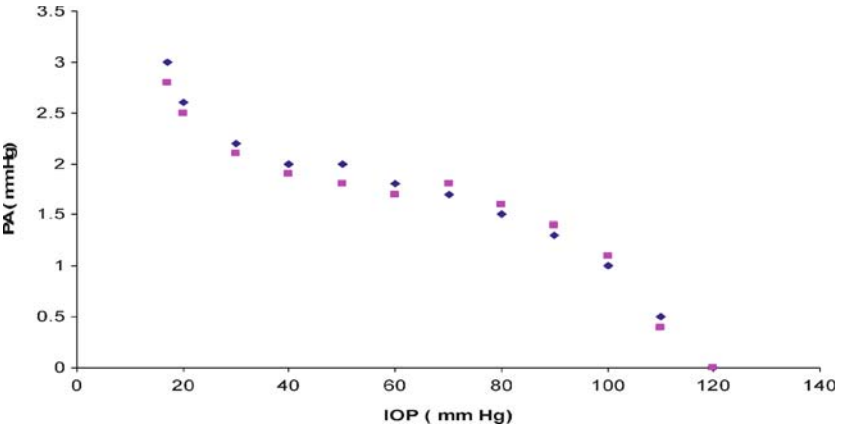


FIGURE 17.18. The IOP/PA relations in pairs of eyes of a subject with systemic hypertension. The left and right brachial blood pressures at the time of the test were 190/100 mmHg. The pulsatile blood flows in the two undisturbed were 944 and 1,009 μl min^{-1}, respectively, which are significantly higher than the mean of normal (740 μl min^{-1}). Note that the shape of the IOP/PA relation is qualitatively normal

range for normal eyes. The PAs in the right and left eyes were 2.6 and 2.8 mmHg, respectively, and consistent with values in healthy eyes. The ocular pulsatile blood flows were 850 (left eye) and 875 μl min^{-1} (right eye), respectively, which are higher than the mean of normal eyes. The time- and pressure-dependent differential visual thresholds were normal in both eyes. The IOP/PA relations in both eyes were similar and showed the S-shape typical of normal eyes (**Fig. 17.18**). These results are consistent with healthy eyes and do not support a diagnosis of open angle glaucoma.

Retinitis Pigmentosa

A white male of 21 years, with visual acuities of 20/16 and 20/25 in the right and left eyes, respectively: The inheritance pattern was simplex. The IOP/PA relations in pairs of eyes differed and both were abnormal and consistent with a substantial loss of autoregulation (**Fig. 17.19**). The rates of pulsatile blood flow in the undisturbed eyes were 710 and 325 μl min^{-1} in the right and left eyes, respectively.

In a series of 13 patients with retinitis pigmentosa, the mean PA and IOP were 1.2 ± 0.6 and 14.1 ± 0.15 mmHg, respectively. The central vision in 11 eyes was very poor and the corresponding visual performances were zero. The 11 eyes had a mean PBF of 265 ± 22 μl min^{-1}, which is well below the mean of 740 μl min^{-1} in normal eyes.

In individual patients, the eye with the lowest pulsatile blood flow had the poorest vision (**Fig. 17.20**). It is of interest that Walsh

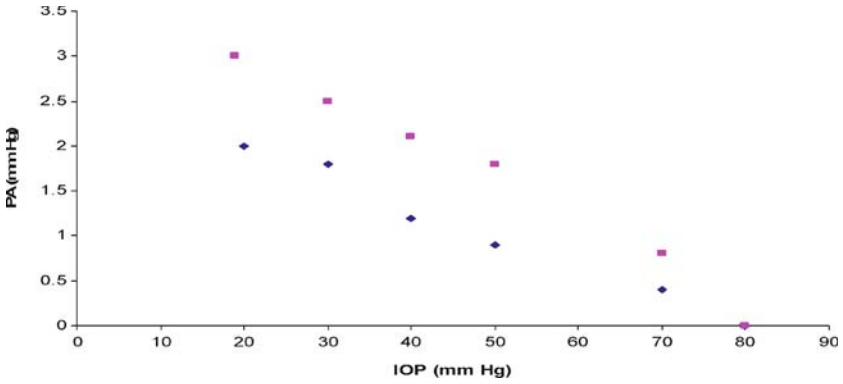


FIGURE 17.19. The IOP/PA relations in pairs of eyes of a male of 21 years with retinitis pigmentosa. The *squares* and the *diamonds* are readings from the left and right eyes, respectively

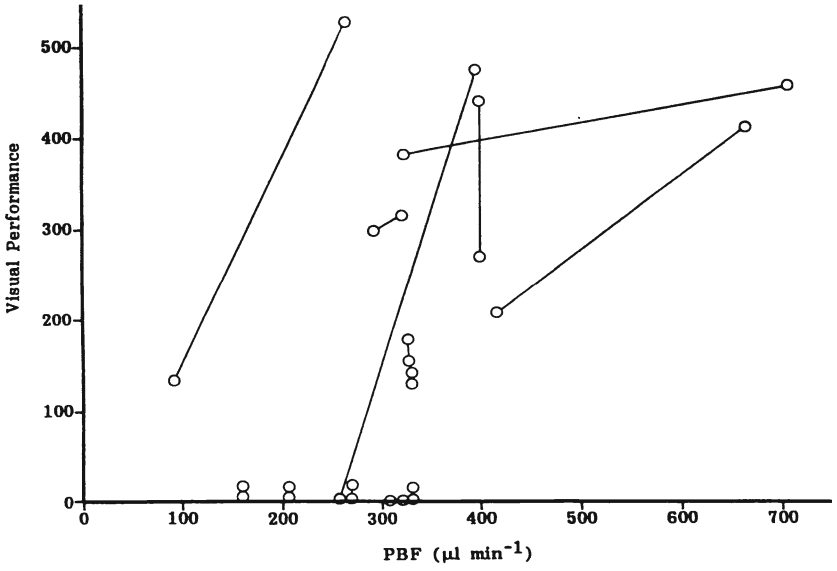


FIGURE 17.20. The relation between the visual performance and ocular pulsatile blood flow in eyes of 11 patients with retinitis pigmentosa. The lines connect the results in pairs of eyes (From Langham and Kramer.[50] Reprinted from *Eye*. Used with permission from Nature Publishing.)

and Sloan reported that the vision of patients with retinitis pigmentosa improved after stellate ganglionectomy, which is known to improve ocular blood flow substantially (see Sect. 1).[51]

Retinal Detachment

Degenerative changes in the periphery of the retina and in the vitreous body are associated with the formation of retinal breaks and the subsequent onset of spontaneous retinal detachment. Ocular hypotension has also been recognized to accompany the detachment. Changes in anterior uveal blood flow are known to cause both a fall in IOP and decrease in the rate of aqueous humor formation, and to be consistent with abnormally low ocular blood flow. Direct measurements of the rate of aqueous humor formation have shown the rates of flow to be below normal and the loss to be worse in the eye with the detachment in cases of unilateral retinal detachment.[52]

In representative recordings in patients with unilateral retinal detachment, the IOP/PA relations were found to be abnormal in both eyes and qualitatively similar to that shown in **Fig. 17.4**. There was little difference in the IOP/PA curves in pairs of eyes except that the eyes with the detachment had lowered IOPs. The observations indicate that the eyes without retinal detachment are also ischemic with loss of vascular autoregulation in both eyes.

18

Autoregulation of the Intraocular Pressure and the Ocular Blood Flow

For the purpose of this discussion, autoregulation is defined to include all processes that operate within the eye to maintain the vascular circulation and the IOP constant in the face of externally and/or internally induced stresses. These include extrinsic mechanisms, such as reflexes involving the central nervous system, variations in central blood pressure, changes in hormone levels, and the concentrations of chemicals in the blood and interstitial fluids. In the systemic circulatory system the physiological parameters that are autoregulated, i.e., the controlled variables include blood flow, the steady state IOP, and the tissue concentrations and tensions of gaseous metabolites including oxygen and carbon dioxide.

The autoregulation of the steady state IOP and of the ocular blood flow are complex processes involving both slow and fast response systems. The slow systems include changes in the vascular resistance in precapillary arterioles and in the capillary network mediated by the endothelial cells lining the vessel walls and muscle cells external to the vessels, including the pericytes. Changes in localized levels of oxygen and carbon dioxide are stimuli to the contractility and autoregulation of the small vessels. The intrinsic slow systems include the response to decrease of the ophthalmic arterial pressure such as that occurs following unilateral ligation of the common carotid artery in animals and moderate to severe stenosis of the internal carotid artery in man.

The slow autoregulation is not dependent on adrenergic innervation of the ocular tissues, for it persists following cervical preganglionic sympathetic denervation. In all probability, it is metabolic in origin and mediated by molecular processes in the endothelium of the small vessels and in the surrounding muscle cells and pericytes. In this respect, it is well established that endothelial cells react rapidly to mechanical stimuli including pulsatility and chemical stimuli, causing either relaxation or constriction of small vessels.

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Molecules that induce vasoconstriction include the potent peptide endothelin, thromboxane, and the prostaglandins (see Kaiser et al.).[53] Vasocative molecules that may be associated with the slow response include nitric oxide and prostacyclin. Major physiological parameters that stimulate endothelial vasomotor activity include the O_2 and CO_2 tensions.

The tissues of the eye have an active aerobic glycolytic metabolism, and a decrease in the pO_2 level increases glycolysis and lactic acid production. A decrease of approximately 20% in ocular blood flow to the ciliary processes from unilateral ligation of the carotid artery results in an immediate fall in the pO_2 in the aqueous humor from an initial value of 40 mmHg to approximately 30 mmHg, but subsequently recovers to normal. This decrease of the oxygen tension, although relatively small, is associated with increased glycolysis and an increased concentration of lactic acid in the aqueous humor of the affected eye.[54,55]

Rapid autoregulation of the ocular blood flow and the steady state IOP is mediated by adrenergic innervation of the resistance precapillary vessels. The sympathetic innervation of the arterioles modulates the rate of ocular blood flow, either by increased or decreased flow resistance; these include vessels supplying blood flow to the ciliary processes, which modulate the rate of formation of the aqueous humor and the outflow resistance in the vessels of the intrascleral plexus (see Sect. 1).

The sympathetic nerves induce rapid autoregulation through modulation of the release of the adrenergic transmitter norepinephrine at adrenergic synapses and stimulation of the α-adrenergic receptors. In addition, there are adrenergic receptors that respond to β adrenergic agonists, which appear to be noninnervated and respond primarily to the mixed α, β adrenergic agonist epinephrine, which circulates throughout the vascular system sustaining vasomotor tone. Stimulation of the β adrenergic receptors induces vasodilatation and decreased flow resistance.

The autonomic centers in the midbrain maintain a constrictor tone on the vessels in the eye equivalent to that induced by an electrical stimulation of approximately 0.5 Hz at 4 V. This basic sympathetic tone is lost when the innervation of the eye is abolished by cervical adrenergic ganglionectomy. The loss of tone results in vasodilatation and increased ocular blood flow of approximately 20% to the ciliary processes, namely, from the mean normal flow of 200 $\mu l\ min^{-1}$ to approximately 240 $\mu l\ min^{-1}$.

The maximal capacity of sympathetic nerve activity to modify the steady state IOP and the ocular blood flow is seen in the responses to electrical stimulation of the nerve. Electrical stimulation causes the blood flow to the ciliary processes to decrease by approximately 50% (by approximately 100 $\mu l\ min^{-1}$) and the steady state IOP to decrease from an initial pressure of 20 mmHg to approximately 15 mmHg, a decrease in the outflow pressure of approximately 50%

(from an initial outflow pressure of approximately 10 mmHg to approximately 5 mmHg in animals). At the same time, there is a decrease of approximately 50% in the rate of the total ocular blood flow, namely from the normal flow rate of approximately 900 µl min^{-1} to approximately 450 µl min^{-1}.[56]

The ability of the sympathetic nerve activity to modify the rate of aqueous humor by changes in the blood flow and pressure is in keeping with knowledge of the mechanism of aqueous humor formation. The aqueous humor is produced by a secretory-pressure-dependent mechanism associated with an active ion transport, which is responsible for 30–40% of the total flow rate (**Fig. 18.1**). A hydrostatic gradient between the blood and the aqueous humor acts on the extracellular pathways into which the solute is secreted.[57]

The modulation and autoregulation of the outflow resistance by sympathetic nerve activity is dependent on modulations of the flow of aqueous humor and blood through the intrascleral veins. These are complex functions involving the differential filling of intrascleral veins with aqueous humor, with blood, or with laminar streams of aqueous humor and blood. In this respect, the flow resistance is affected not only by the fluid composition in the component veins, but also by the degree of constriction and the viscosity of blood flowing through the veins. These outflow vessels are innervated by adrenergic neurons and have the capacity to mediate rapid and slow changes of the steady state IOP, aqueous humor dynamics, and ocular blood flow.

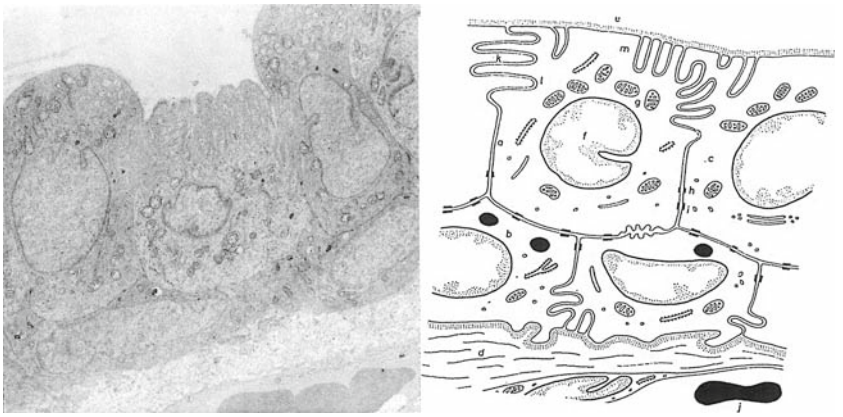

FIGURE 18.1. An electron mictrograph and schematic of the secretory epithelium of the ciliary processes of an adult rabbit. *Note*: Extracellular channels (a), pigmented epithelium (b), the nonpigmented epithelium (c), stromal fluid (d), posterior chamber (e), cell nuclei (f), mitochondria (g), desmosomes (h), zone of partial occlusion (i), red blood cell (j), proposed secretory sites based on ATPase activity (k), lateral infoldings (l), and apical infoldings (m) (×9,000) (From Weinbaum et al.[57] Reprinted from *Experimental Eye Research*. Used with permission from Elsevier Science & Technology Journals.)

The complexity of the adrenergic transmitter actions on the resistance to outflow of aqueous humor is underlined by the ability of the adrenergic transmitter norepinephrine to induce both decreased and increased IOP and the outflow resistance (see Chap. 9).[58,59]

The positive role of the central nervous system in the autoregulation of the IOP and ocular blood flow is confirmed in observations that rapid autoregulation is lost following cervical sympathotomy (see Chap. 9). The sensory afferent pathway by which nerve pulses travel to the control centers in the brain and lead to efferent sympathetic discharge to the eye remains unclear.

There have been many attempts to locate areas within the brain that receive afferent impulses and relay efferent sympathetic impulses to modify the IOP.[60–63] In the most detailed of these studies, the Horsley-Clark stereotactic apparatus was used to locate discrete areas of the brain for subsequent electrical stimulation. In general, changes in IOP induced by stimulation could be ascribed to changes in blood pressure or to change in extraocular muscle tone. The nature of the stimulus (or stimuli) that leads to the modulation of the efferent sympathetic nerve activity causing changes in the IOP and ocular blood flow remains to be clarified.

19

The Evaluation of Ocular Ischemia and the Loss of Autoregulation for the Early Detection of Ocular Vascular Diseases

A relative ischemia and loss of autoregulation of the ocular blood flow appear to be very common characteristics associated with the onset and progression of several ocular diseases including age-related macular degeneration, the retinopathy of diabetes, open angle glaucoma, retinal artery and central vein occlusion, and detachment of the retina. The loss of vascular autoregulation appears to be a consequence of a relative ocular ischemia and reflects a diminished capacity to minimize changes in intraocular pressure (IOP) and ocular blood flow. Based on observations in healthy eyes of subjects who have suffered a stenosis of the internal carotid artery, the maximal capacity of the blood flow autoregulation is found to be of the order of 400–500 µl min^{-1}. This increased blood flow occurs following unilateral occlusion of the internal carotid artery and returns to normal following successful surgical endarterectomy (see Sect. 3).

An abnormally low ocular pulsatile blood flow has been documented in open angle glaucoma,[64,65] low-tension glaucoma,[66] diabetic retinopathy,[46] retinitis pigmentosa,[50] occlusion of the central retinal vein, age-related macular degeneration,[48,67,68] and retinal detachment.[52] In this respect, ocular pulsatile blood flows less than 500 µl min^{-1} compared with the mean ocular pulsatile blood flow of 740 µl min^{-1} in healthy eyes should be considered abnormal and suspect of ocular disease. Further, in studies of pulsatile blood flow and vision in patients with asymmetric disease the ischemia has been found to be more severe in the eyes with visual loss than in the contralateral eyes without visual loss, including open angle glaucoma (e.g., Fontana et al.[69]).

The onset and progression of the ocular ischemia varies between discrete areas of the retinal and choroidal circulations,

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both in time and severity. In the onset of open angle glaucoma and in low-tension glaucoma, evidence of localized severe ischemia is seen in the appearance of splinter-shaped hemorrhages in the anterior segments of the optic nerve, and may precede by years significant structural glaucomatous changes in the disc and retina and in loss of vision.[70–73] These structural changes include a preferential loss of the larger nerve fibers, which are more prone to be affected by the relative ischemia in the entwining capillaries.[74] In diabetic retinopathy and in retinal ischemic disease, choroidal and retinal hemorrhages occur frequently.[41,44,75] In primary detachment of the retina, degenerative changes in the peripheral retina and vitreous, and changes in aqueous humor dynamics precede the detachment and are present in both eyes even though detachment may be present in only one eye.[52] In the avascular cornea, relative anoxia, decreased oxygen uptake, and increased glycolysis cause swelling of the corneal stroma and a breakdown of the perilimbal capillary arcade, with invasion of the cornea by new blood vessels.[76]

One example of a defined domain is seen in the relation between the steady state IOP and the outflow facility in normal eyes and glaucomatous eyes (**Fig. 19.1**). The movement of the healthy to the diseased state is described by a trajectory in which the extent of the movement from the normal to the diseased domain reflects the severity of the condition. In **Fig. 19.1** the onset and progression of

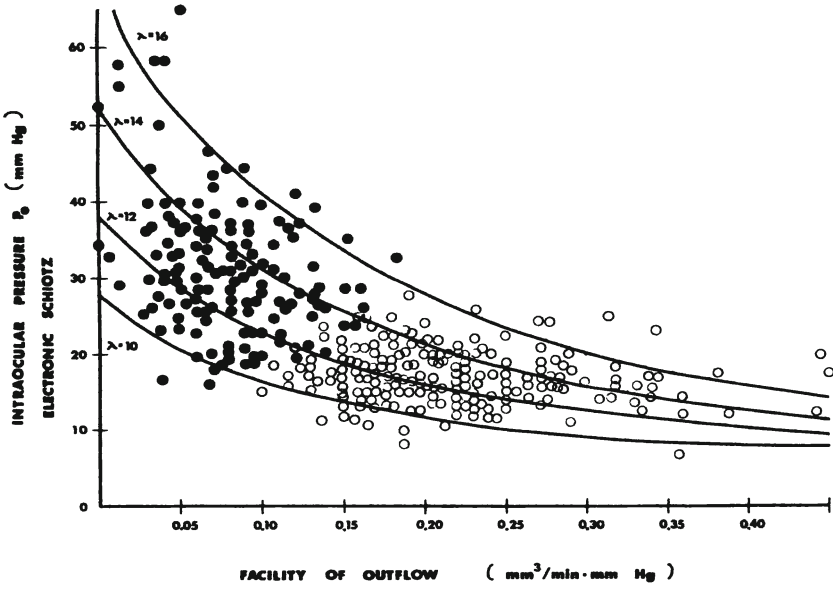

FIGURE 19.1. The domains for normal (*open circles*) and glaucomatous eyes (*filled circles*), and the relationship between IOP and the tonographic outflow facilities. The continuous lines represent the $P_{o,}$ C_T trajectories for different eyes to mixed α, β adrenergic agonists (From Hart and Langham.[77] Reprinted from *Israel Journal of Medical Sciences*. Used with permission from Israel Medical Association.)

open angle glaucoma is seen to be associated with increased IOP and decreased outflow facility. Other examples of domains separating healthy and diseased eyes include the relation between pulsatile blood flow and autoregulation in age-related macular degeneration and in the relation between the pulsatile blood flow and the severity of diabetic retinopathy.

The IOP/PA relation itself has considerable diagnostic capability in providing quantitative data on the degree of ischemia (pulsatile ocular blood flow), the presence of autoregulation, and the extent to which the intraocular pressure/pulse amplitude (IOP/PA) relations are symmetrical in pairs of eyes. Specifically, it is the initial part of the IOP/PA relation that is of particular clinical value, for a rapid fall in the PA with modest increased IOP is characteristic of healthy eyes, whereas the PA tends to remain unchanged or increases with modest increase of the IOP in ischemic eyes. The S-shaped IOP/PA relation has not been found in patients with vascular ocular diseases.[78]

A clinical diagnostic significance of the abnormal IOP/PA relation lies in its presence in the earliest stage of the onset of the disease and well prior to structural damage to the retinal nerve fibers and before loss of vision. One example of the early abnormalities in the IOP/PA relation has been reported with the onset of open angle glaucoma.[64,69] In a retrospective longitudinal study on five subjects, followed for more than 2 years, prior to a clinically confirmed diagnosis of open angle glaucoma, abnormal IOP/PA relations were present in all cases at least 1–3 years before a confirmed clinical diagnosis with demonstrable pathological changes in the optic disc and the retinal fiber layer was made.[64] Further, in patients with a loss of vision more severe in one eye, the ischemia and loss of autoregulation was correspondingly more marked (e.g., see Fig. 17.20). These findings in diseased eyes contrast with the findings on subjects with healthy eyes who have suffered a unilateral moderate to severe stenosis of the internal carotid artery and in whom recovery of the IOP/PA relation and recovery from ischemia occurs with successful surgical endarterectomy.

It is evident that changes in function precede by a substantial period the development of abnormal structure, loss of nerve fibers, and loss of vision. The advantage of defining specific functional changes compared with the identification of the pathological changes in structure, such as in the optic disc and retinal nerve fiber layers lies in the complicating effect of aging on retinal structure. The number of nerve fibers in the optic nerve of the adult human has been reported to be 1,159,000 ± 196,000 based on numerical measurements on 19 eyes.[79] In the same studies, the nerve fiber count was found to decrease at an annual mean rate of approximately 5,426. Fortunately, this loss of nerve fibers with age fails to affect the time- and pressure-dependent visual thresholds over many years in healthy eyes.

20

The Action of Drugs on Ocular Blood Flow and on the Intraocular Pressure/Pulse Amplitude Relation

The presence of relative ocular ischemia and loss of autoregulation in the most common ocular diseases causing visual loss leads to a logical consideration that therapies that increased ocular blood flow would minimize the risk of visual loss. In this respect, the drugs mostly used to modify loss of vision are the ocular hypotensive drugs used widely to reduce the abnormally high IOP in normal and low-tension glaucoma patients.

Sympathetic Denervation of the Eye, Adrenergic Agonists, and Antagonists

In animals including monkeys, excision of the cervical sympathetic ganglion induces an increase of 25% in the ocular blood flow approximately 250 µl min^{-1}, which includes an increase of (approximated) 25% in the rate of blood flow through the ciliary processes. The only report of the clinical use of sympathetic denervation in the therapy of ocular disease is that of Walsh and Sloan on patients with retinitis pigmentosa, and the authors reported favorable clinical responses.[51]

Adrenergic receptor agonists include the specific α adrenergic transmitter norepinephrine, the highly specific β_2 adrenoreceptor agonist salbutamol, and the mixed α, β adrenoceptor agonists epinephrine and isopoproterenol. Norepinephrine applied topically decreases IOP in animals and decreases ocular blood flow; similarly, salbutamol decreases IOP in animals and normal subjects and has been used in the treatment of glaucoma.[80,81] Salbutamol, applied topically to six conscious rabbits, increased pulsatile ocular blood flow from an initial mean of 650 to a mean of 734 µl min^{-1} and increased the pulsatile blood flow (PBF) in individual rabbits by a mean of 84 ± 10 µl min^{-1}. In normal subjects 2% salbutamol applied

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topically increased the ocular pulsatile flow from an initial mean of 720 ± 20 to a mean of 780 ± 13 μl min^{-1} in 6 h.

Adrenergic β Receptor Antagonists

Timolol is an adrenergic β_2 receptor antagonist, which has been widely used as an ocular hypotensive drug in the treatment of glaucoma and the glaucoma suspects.[82] Administered topically, the β_2 receptor antagonists increase peripheral vascular resistance and vasoconstriction extends to ocular vessels as demonstrated by Van Buskirk et al. using an elegant microvascular corrosion casting technique.[83] In rabbits, the ocular hypotensive action of timolol applied topically is associated with a decrease in the rate of formation of the aqueous humor but with little, if any, effect on the outflow resistance.

In view of the ability of timolol to constrict the peripheral vessels, numerous studies have been undertaken to define its action on ocular blood flow. These studies include measurements of retinal and choroidal blood flows in animals,[84,85] in healthy volunteers,[86–88] and in glaucoma patients.[65,89–91] The results from these numerous studies are controversial in that timolol was reported to influence ocular blood flow either positively or negatively; all results were in agreement that the responses were quantitatively small. This modest or negative effect of timolol on ocular blood flow in glaucomatous eyes is supported by observations that the drug applied topically over both short and long terms had no significant effect on the IOP/PA and IOP/PBF relations. In 12 glaucoma patients treated with 0.5% timolol for 12 months, the mean IOP fell from an initial mean of 25 ± 0.6 to a mean of 20 ± 0.7 mmHg and the PBFs decreased from a mean of 532 ± 12 to a mean of 467 ± 18 μl min^{-1}. The IOP/PA relations were measured at the beginning and end of the 12-month period of treatment and in all cases the IOP/PA and the IOP/PBF

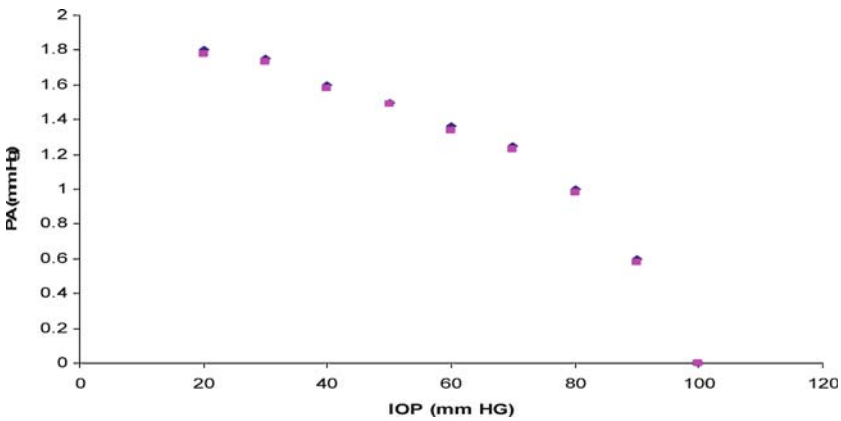

FIGURE 20.1. The IOP/PA relation in the two eyes of a glaucoma patient treated daily with two topical applications of 0.5% timolol for 12 months

relations were abnormal both at the start of treatment and showed no significant improvement at the end of 12 months. **Figure 20.1** shows a representative IOP/PA relation at the 12th month in one of these timolol-treated patients.

The α Adrenoreceptor Antagonists

The drug dapiprazole falls into this class of drugs and has been used widely to reduce pupil dilatation following the use of a mydriatic. In both animals and man, dapiprazole applied topically decreases IOP and increases ocular blood flow (Table 20.1).

The Adrenergic Presynaptic α_2 Agonists

Members of this class of drugs are known to decrease IOP and to increase significantly ocular blood flow in animals and man. They act at peripheral adrenergic presynaptic sites to inhibit norepinephrine release and act in the central nervous system to decrease peripheral adrenergic vasoconstrictor tone. The drug clonidine belongs to this class of drugs and was used widely in Europe as a topical solution to decrease IOP in glaucoma patients. It differs in its action from norepinephrine in causing minimal pupil dilatation at concentrations that induce rapid and maximal IOP decreases. By contrast, norepinephrine applied topically induces decreased IOP, but the response has a delay of 2–3 h, at which time the pupillary response is well past. The α_1 and α_2 adrenoceptor agonists differ in their mechanisms to decrease IOP. The α_2 adrenergic agonists act at presynaptic adrenergic sites and are dependent on an intact adrenergic innervation of the eye. Their function is to mediate a negative feedback modulation of the release of the transmitter norepinephrine. Norepinephrine acts at postsynaptic sites and is not dependent on an intact innervation. Indeed, in the absence of the adrenergic innervation, a supersensitivity of two to three log units develops to norepinephrine.[80]

Table 20.1 The effect of a single topical application of an aqueous solution of 0.5% Dapiprazole (two times a day) on 11 patients with open angle glaucoma.

	IOP (mmHg)			PBF (μl min−1)		
Time (h)	Control	Treated	Treated – control	Control	Treated	Treated – control
0	18.7 ± 0.5	18.4 ± 0.4	−0.3 ± 0.3	627 ± 64	621 ± 64	−6 ± 18
2	17.6 ± 1.6	14.1 ± 0.6	−3.6 ± 0.6	603 ± 65	669 ± 25	66 ± 25
3	18.8 ± 1.0	16.0 ± 0.9	−2.8 ± 0.5	650 ± 80	766 ± 61	116 ± 29
5	19.8 ± 1.3	18.7 ± 1.1	−1.1 ± 1.1	674 ± 74	725 ± 79	51 ± 9
24	19.3 ± 0.4	18.6 ± 0.5	−0.7 ± 0.6	711 ± 73	721 ± 62	11 ± 7

Table 20.2 The effect of a single topical application of 0.065% clonidine to one eye (treated) on the IOP and the pulsatile ocular blood flow in six conscious rabbits.

Time (h)	Control	Treated	Treated – control
0	17.7 ± 0.6	17.5 ± 0.8	−0.2 ± 0.2
1	17.5 ± 0.3	15.3 ± 0.3	−2.2 ± 0.1
3	17.5 ± 0.2	15.1 ± 0.4	−2.4 ± 0.2
5	17.2 ± 0.3	15.5 ± 0.4	−1.7 ± 0.3
24	18.5 ± 0.6	18.0 ± 0.4	−0.6 ± 0.3
	Pulsatile blood flow (μl min−1)		
0	758 ± 67	746 ± 67	−12 ± 7
1	643 ± 15	656 ± 25	12 ± 14
3	772 ± 24	837 ± 29	55 ± 12
5	824 ± 37	894 ± 19	70 ± 30
24	845 ± 40	868 ± 47	23 ± 25

Source: Data from Krieglstein et al.92

Applied topically, clonidine (0.125%) induces a rapid decrease of the IOP accompanied by a significant increase in the rate of PBF, both in animals (Table 20.2) and man. At the same time, sufficient clonidine is absorbed systemically to decrease the arterial blood pressure and the ophthalmic arterial pressure. It has been suggested that this fall of the ophthalmic arterial pressure reduces blood flow to the optic nerve. However, the measurements of ocular PBF, the ophthalmic arterial pressure, and the IOP/PA in individual rabbits indicated that the decrease of the ophthalmic arterial pressure is the consequence of decreased vascular resistance in the eye and not indicative of decreased ocular blood flow due to a decreased ocular perfusion pressure.

Systemically Administered Ocular Hypotensive Drugs

Highly active nontoxic inhibitors of the enzyme carbonic anhydrase (CA) administered either orally or intravenously induce an immediate decrease of the IOP in animals, and normal human and glaucomatous eyes. The most widely used inhibitor acetazoleamide acts by decreasing the rate of formation of the aqueous humor in man by 30–60%.[93]

The carbonic anhydrase inhibitors administered systemically increase the plasma pCO_2 and induce vasodilatation in vessels of both the eye and the brain. Chiou and Chen measured ocular blood flow using radioactively labeled microspheres in ocular hypertensive rabbits treated with acetazoleamide and reported dose-dependent increased rates of blood flow in the retina and choroid.[84] In healthy subjects the administration of acetazolemade either by

mouth or by intravenous injections has been found to increase ocular blood flow by relatively small amounts.[86,94,95]

Topically Applied Carbonic Anhydrase (CA) Inhibitors

Dorzalamide is a CA inhibitor that rapidly penetrates across the cornea and sclera to inhibit the carbonic anhydrase enzyme in the ciliary processes and decrease IOP and the rate of formation of the aqueous humor. It induces vasodilatation in the eye and increases the rate of pulsatile ocular blood flow in glaucoma patients. In a retrospective study, Dorzalamide given topically to 28 glaucoma patients three times daily for 9 months decreased the IOP from a mean of 18 to 15.5 mmHg and increased the rate of ocular PBF from an initial mean of 543 μl min^{-1} to a final mean of 675 μl min^{-1}.[96]

The presence of active autoregulation in healthy eyes and its absence in eyes with ocular disease underlines the likelihood that the responses to a specific drug may differ quantitatively and qualitatively between healthy and diseased eyes. Thus, a full understanding of the ocular blood response to drugs is dependent on knowing the effects on the IOP/PA relation as well as on the effect on the rate of ocular blood flow in the undisturbed eye.

Nonadrenergic Drugs

Historically, the alkaloid pilocarpine in solution applied topically to the eye was, for many years, the primary medical treatment for open angle glaucoma. This compound has an interesting pharmacology in showing a histaminic type of action associated with vasodilatation.[97] Studies in rabbits using the radioactive labeled microsphere technique showed that administration of topically applied pilocarpine had little significant effect on retinal and choroidal blood flows.[98] On the other hand, Mittag et al. reported the PBF to increase significantly in glaucomatous eyes treated topically with a 4% solution of pilocarpine, and that the response was positively correlated with the IOP lowering response.[99]

Prostaglandin Analogs

There are several drugs, including latanoprost, the first in this class of drugs to be introduced for treatment of glaucoma. Pharmacologically, their mode of action is not fully known but they are reported to increase outflow facility and/or uveal–scleral outflow but not to affect the rate of aqueous humor formation. Experimental studies on monkeys, healthy human volunteers, and glaucoma patients, designed to evaluate the effect of latanoprost on ocular blood flow in the retina, choroid, and optic nerve, have given

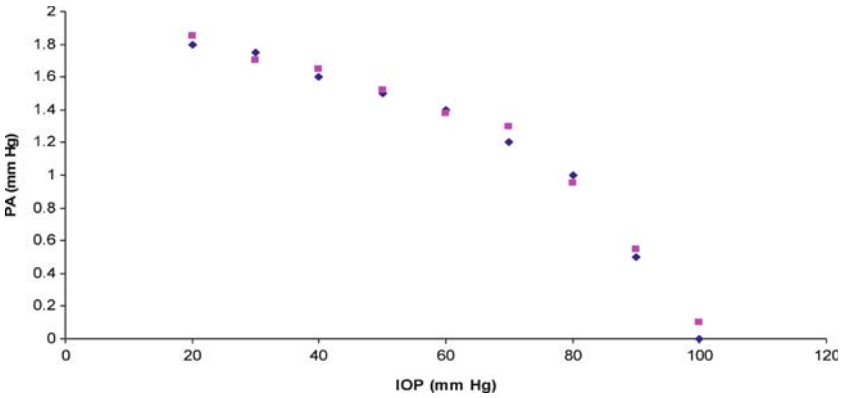

FIGURE 20.2. The IOP/PA relations in pairs of eyes of a patient with open angle glaucoma treated for 6 months with a 0.004% solution of the prostaglandin analog Travatan (travoprost) once daily. Note that the shape of the relation is abnormal and indicative of a loss of autoregulation. The rate of PBFs in both eyes was approximately 550 µl min^{-1}, which is below the range in healthy eyes. The ophthalmic arterial pressures are at the high end of the normal range, which reflects the relatively high brachial arterial pressures of 142/90 mmHg.

equivocal results. Nicolelea et al. reported that latanoprost failed to affect the velocity of the blood flow in retrobulbar vessels.[100] On the other hand, McKibbin and Menage reported that glaucoma patients treated for 3–4 weeks with 0.005% latanoprost daily had an increase in mean pulsatile ocular blood flow from an initial mean value of 656 to 796 µl min^{-1}.[101] Despite the claim that prostaglandin analogs may increase ocular blood flow, it is evident that the increase is insufficient to restore, even partially, the IOP/PA relation to normal in glaucoma patients treated for many weeks with the prostaglandin analog travoprost. In treated eyes, the IOP/PA curves prior to and following treatment remained abnormal and consistent with loss of autoregulation (**Fig. 20.2**).

The Ocular Blood Flow Response to Pentoxyfyline

This compound taken orally decreases the viscosity of blood. Its action on retinal and choroidal blood flow has been studied by Kruger et al. on patients with non-neovascular macular degeneration.[102] Twenty patients received 400 mg of pentoxyfyline orally three times a day, and 20 received placebo for 3 months. Retinal blood flow was assessed by scanning laser Doppler flowmetry, and pulsatile ocular blood flow was assessed by laser interferometric measurement of the fundus pulsation amplitude. The results indicated that the drug induced a significant increase in choroidal blood flow (a mean of 28%) whereas the retinal blood flow remained unchanged.

21

The Confluence and Integration of Therapies Based on Modulation of the Intraocular Pressure and Ocular Blood Flow

The efficiency of the autoregulation of the intraocular pressure (IOP) and blood flow to maintain vision in healthy eyes is reflected in the stability of the time- and the pressure-dependent differential visual thresholds and in the stability of the time-dependent visual threshold when the IOP is experimentally increased to more than 50 mmHg (**Fig. 21.1)**.[103]

In undisturbed, healthy eyes, the time-dependent differential visual thresholds at all retinal points are extremely stable. By contrast, in glaucomatous eyes, at some, if not at all, retinal points, the time-dependent differential visual thresholds are unstable and fluctuate (**Fig. 21.2**). Moreover, if the IOP is increased by 15–20 mmHg the differential light sensitivity decreases sharply at some retinal points but remains stable in other points **(Fig. 21.3)**.

It is evident that in the onset and progression of glaucoma there is are slow declines in the stability of the visual threshold and in retinal sensitivity and that the rate of progression of this pathology differs considerably from point to point in the retina. Thus, at the time of the initial clinical diagnosis of the disease there still remain nearly, if not completely, normal functioning retinal points coexisting with neighboring affected areas. Consequently, the aim of therapy is not only to minimize further damage in the affected points but more importantly, protect those retinal areas that continue to function normally. In this respect there is good reason to belive that the optimal therapy to achieve both aims would not be the same.

For many years a primary use of drugs applied to the eye has been to reduce the IOP of patients with open angle glaucoma. This has been associated with a major effort from pharmaceutical companies to develop more active ocular hypotensive compounds.

The therapeutic action of ocular hypotensive drugs to reduce the rate of loss of vision in patients with open angle glaucoma is of special physiological and pharmaceutical interest in that open angle

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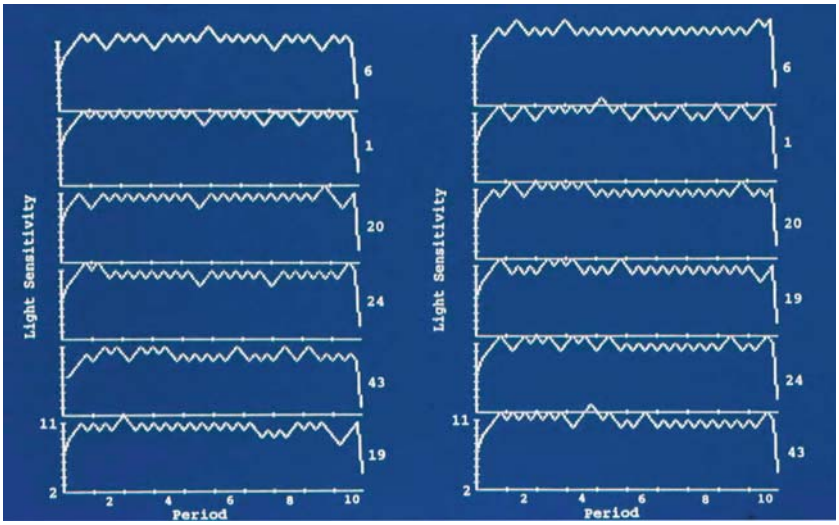

FIGURE 21.1. A representative recording of the time-dependent light sensitivities in pairs of eyes of a healthy adult subject. The numbers on the right side indicate the discrete points in the central visual field tested; it will be noted that the same areas were evaluated in each eye. The mean linear regression equations of the curves in the two eyes were $y = 11.0 \pm 0.06$ (6) and $y = 11.0 \pm 0.04$ (6) (Results from Krakau et al.[103] Data from *Investigative Ophthalmology and Visual Science.* Used with permission from the Association for Research in Vision and Ophthalmology.).

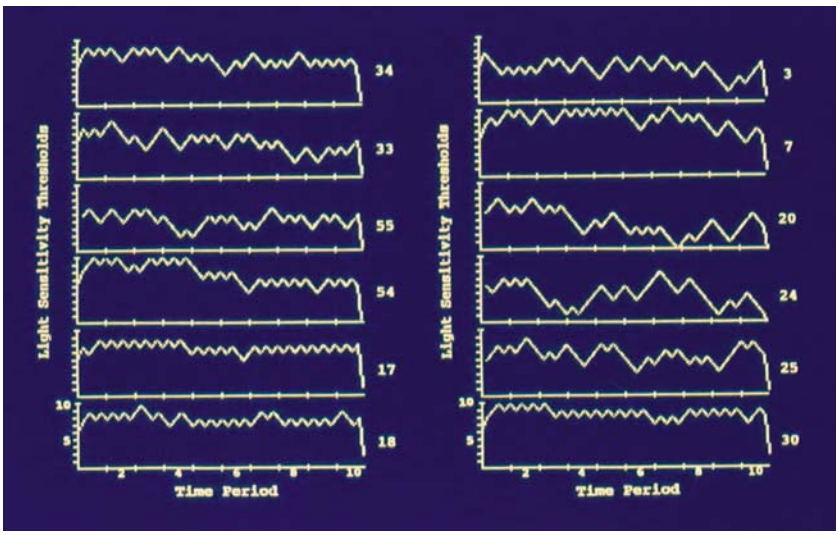

FIGURE 21.2. Typical recordings of the time-dependent differential light sensitivities in glaucomatous eyes of two patients. The measurements were made at six retinal points. Both patients were on treatment with 0.5% timolol twice daily.

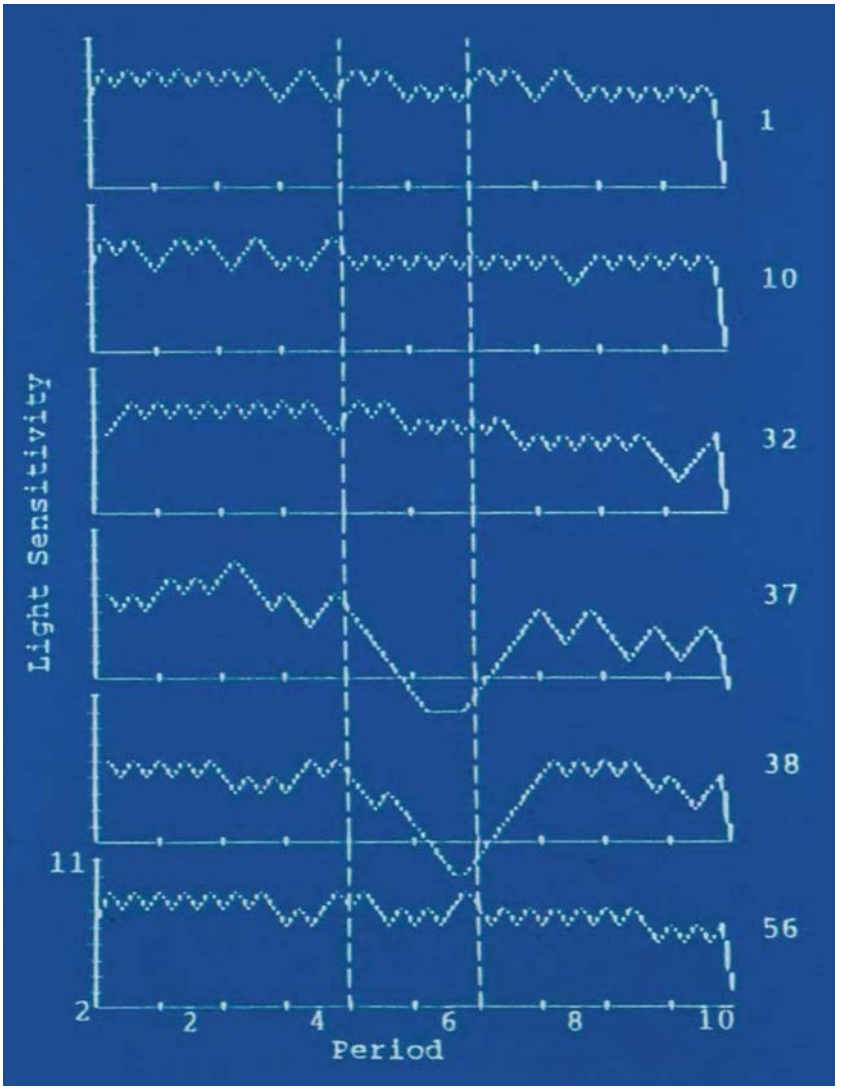

FIGURE 21.3. The effect of experimentally induced increased IOP on the time-dependent differential light sensitivity threshold at individual retinal points in the central visual field in a patient with open angle glaucoma. The *dotted lines* indicate the time period in which the IOP was increased from 20 to 50 mmHg. It will be noted that some retinal points remained unaffected by the increased IOP while other points (e.g., 37 and 38) showed a marked loss of retinal sensitivity during the period of increased IOP (From Krakau et al.[103] Reprinted from *Investigative Ophthalmology and Visual Science.* Used with permission from the Association for Research in Vision and Ophthalmology.).

glaucoma is not a disease associated with high IOPs and the ability of commenly used ocular hypotensive drugs to reduce IOP is no more than a mean of 5–7 mmHg.

The most probable explanation for this modest decrease of the IOP to reduce the rate of visual loss lies in the critical function of the

transmural pressure that acts to sustain optimal blood flow in the small vessels that wrap around the nerve bundles in the optic nerve. The transmural pressure (internal pressure minus the interstitial pressure) is the pressure difference across the wall of each blood vessel. In the arteries entering the eye, the internal pressure is pulsatile and oscillates between the diastolic and systolic ophthalmic arterial pressure (57–84 mmHg) associated with each bolus of blood entering the eye; the interstitial pressure is the dynamic IOP (15–17.5 mmHg). Pulsatility in the small vessels may also play an important role in the balance between vasodilatation and vasoconstriction and in the autoregulation.[104] The transmural pressure decreases rapidly as the arterial blood flows through the choroidal and retinal arteriolar networks, and by the time the blood has passed through the capillary beds into the vortex veins, the pulsatility of the blood flow has been lost completely and the transmural pressure has fallen to approximately 2 mmHg.

With increased ischemia and loss of autoregulation in ocular vascular diseases, including open angle glaucoma, the risk of collapse of the small vessels increases. When the pressure within the vessels falls to a critical value (the critical closure pressure), the resultant force acting inward across the vessel walls (the IOP) may cause the vessel to collapse and blood flow to cease. With closure of the vessel the oxygen tension decreases and the pCO_2 tension increases, leading to metabolic changes in the capillary endothelium with vasodilatation and recovery of the blood flow. This oscillation of vessel closure and loss of blood flow in discrete capillary networks is consistent with the fluctuation of the differential light threshold seen in ischemic eyes (see **Fig. 21.2**). Pulsatility in the small vessels may also play an important role in the balance between vasodilatation and vasoconstriction and the critical closure pressure.[104]

It follows that one important aim of therapy is to maintain the transmural pressure in all the small vessels at levels to give adequate blood flow and thereby minimize visual loss. In healthy eyes, blood flow autoregulation acts to maintain this optimal transmural pressure through modulation of the flow resistance. On the basis of knowledge that the transmural pressure is in the order of a few mmHg in the small vessels surrounding the nerve bundles, it requires only a small decrease of pressure in the interstitial fluid (i.e., the IOP) to increase the transmural pressure and keep the vessels open and maintain blood flow. Although this IOP response is relatively small, it could be sufficient in the therapy of the ocular hypertension of glaucoma to maintain the transmural pressure at a level that sustains patency of the vessels.

In open angle glaucoma, the mean decrease of the IOP in glaucoma patients treated with ocular hypotensive agents is in the order of 3–4 mmHg in the majority of published clinical trials. Although this IOP response is relatively small, it may be sufficient in most cases to maintain the transmural pressure at a level that sustains patency of the vessels.

The choice of an ocular hypotensive drug that increases ocular blood flow, and at the same time decreases the IOP, is a logical approach to attain a maximal therapeutic response and protection of vision. Not all the ocular hypotensive drugs used clinically to treat open angle glaucoma increase ocular blood flow and indeed some, like the adrenergic b adrenergic antagonists, are known to decrease blood flow in systemic and ocular vessels. In addition, there are other ocular hypotensive drugs that have little, if any, positive effect on ocular blood flow, such as the prostaglandin analogs.

In addition to the relative ischemia and decreased vascular resistance from stenosis of the internal carotid artery, there is the alternative possibility of increased vascular resistance from structural changes within the eye. In the common ocular diseases, including open angle glaucoma, the ophthalmic arterial pressure and the ophthalmic arterial perfusion pressures tend to be higher than in normal eyes and to suffer from systemic hypertension. The physiological consequence of this relatively high flow resistance and high IOP is to increase the risk of the transmural pressure falling below the critical closure pressure, and induce vessel closure and impairment of vision. The same abnormally high vascular resistance is present in low-tension glaucoma.

22

Longitudinal Therapeutic Studies

The clinical importance of therapy based on the dual actions of intraocular pressure (IOP) reduction and increased ocular blood flow has been documented in longitudinal therapeutic studies on individual patients with open angle glaucoma.[64] In this study, five glaucoma suspects were followed for 2 years, prior to being diagnosed as open angle glaucoma patients, and treated with 0.5% solution of timolol applied topically twice daily for 3 years. The treatment was changed to topical applications of 0.05% clonidine for 3 years (**Fig. 22.1**). The mean IOP in the 2-year period prior to treatment was 24.0 ± 0.5 mmHg; the mean rate of pulsatile blood flow was 541 ± 24 ml min^{-1}, and the visual performance of the central 30° of the visual field was 652 ± 22. There was a small area of relative scotoma in an eye of one patient, and the time-dependent stability of the differential visual threshold was unstable in all patients. The IOP response to timolol and clonidine was very similar. At the end of 3 years of treatment with timolol, the mean IOP had fallen to 20.8 ± 0.6 mmHg. At the end of the ensuing 3 years of treatment with topical applications of 0.25% clonidine twice daily, the mean IOP was 20.0 ± 1.0 mmHg. The rate of pulsatile blood flow over the 3 years of treatment with timolol decreased from the initial mean of 541 ± 24 to 365 ± 23 µl min^{-1} with a mean decrease of 177 ± 33 µl min^{-1} in individual patients. In addition the number of patients with areas of relative scotoma increased from 1 to 3. The decrease of pulsatile blood flow in the timolol-treated group was associated with a decrease in the visual performance of the central field from a mean of 652 ± 22 to a mean of 533 ± 20, with a mean decrease in individual eyes of 116 ± 2.

At the end of the 3-year treatment with 0.5% timolol, the treatment was changed to topical applications of 0.25% clonidine (twice a day) for 3 years. The mean IOP response during this period did not differ from the response to timolol with a

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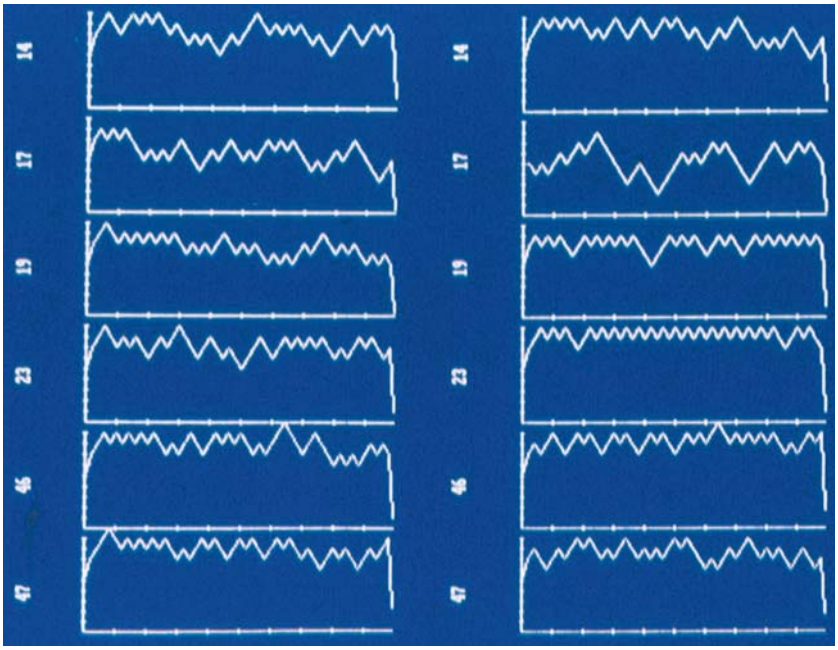

FIGURE 22.1. Representative recordings of the time-dependent differential light sensitivity in the eye of a glaucoma patient treated for 3 years (left recording) with 0.5% timolol (twice daily) followed by 2 years with 0.25% clonidine (twice daily) (right recording).

mean IOP of 20.0 ± 1.0 (12) mmHg, but the pulsatile blood flow increased to a mean of 485 ± 30 (8) µl min^{-1} from the initial value of 365 ± 230 µl min^{-1}. The increase in ocular blood flow induced by the 0.25% clonidine was associated with a small increase in the visual performance to a mean of 554 ± 30 (5) and was associated with an increased stability of the time-dependent differential light sensitivity increased (**Fig. 22.1**).

The results of this longitudinal therapeutic study point to the value of monitoring the rate of ocular blood flow and to the potential value of increased ocular blood flow to induce the optimal means of minimizing visual loss. Further evidence of the therapeutic potential of increased ocular blood flow on ischemia and vision is seen in the report that the increased ocular blood flow induced by cervical sympathetic denervation in man (Horner's Syndrome) may act to abort the onset and progression of open angle glaucoma.[105] These investigators described a male patient of 57 years with unilateral Horner's syndrome (left eye) and unilateral open angle glaucoma (right eye), with a family history of open angle glaucoma. The Horner's syndrome in the left eye had probably been present since birth. Gonioscopy revealed a normal fundus in the uninnervated left eye and marked optic atrophy with a wide, deep optic cup and nasal displacement of vessels in the innervated right eye.

The visual field was normal field in the left eye and a marked superior nasal field loss in the right eye. The patient was under treatment with topical pilocarpine (4% twice daily) and epinephrine (2% twice daily) in both eyes. Prior to the present study, IOPs of 34 mmHg in the right eye and 24 mmHg in the left eye prior to treatment had been reported using Schiotz tonometry. The IOPs measured with the Goldmann tonometer were 15 and 17 mmHg in the left and right eyes, respectively. The tonographic coefficients of outflow facility were 0.30 µl min^{-1} $mmHg^{-1}$ in the left eye and 0.13 ml min^{-1} $mmHg^{-1}$ in the right eye. These values are consistent with a diagnosis of open angle glaucoma in the right eye. Over the ensuing 5-year period vision remained normal in the left eye but worsened further in the right eye. Adrenergic supersensitivity in the denervated eye of this patient was confirmed by the application of 50 µl of a 1.0% solution of norepinephrine bitartrate to both eyes. Maximal dilatation of the pupil in the denervated eye was reached in 20 min whereas there was no pupil response in the innervated eye. From the IOP and the pulse amplitude (PA) measured using a Schiotz tonometer, the PAs were approximately 2.4 and 1.6 mmHg in the innervated and noninnervated eyes, respectively, and the corresponding rates of ocular pulsatile blood flows were approximately 657 µl min^{-1} in the uninnervated eye and 484 µl min^{-1} (abnormally low) in the innervated eye.

The observation that, in this patient, adrenergic ganglionectomy appeared to protect against the development of open angle glaucoma is in keeping with the studies of Reilly and Moyer at the Mayo Clinic, that of 180 patients with Horner's Syndrome, not one had open angle glaucoma.[106] The findings are also consistent with the report of Walsh and Sloan that increased ocular blood flow induced by cervical stellectomy in patients with retinitis pigmentosa had favorable effect on progression of the disease.[51]

The need to increase ocular blood flow, as well as to decrease IOP in the relative ocular ischemia of open angle glaucoma, supports the belief that abnormally high IOP is not the single cause of visual loss in this disease and that impairments of ocular blood flow and autoregulation are of equal or greater concern.[73,107–109]

An Approach to Diagnostic Screening of Ocular and Cerebral Vascular Diseases

The valid question arises whether the present technologies are applicable to populations in underdeveloped areas of the world. The impairment of the physiology that underlies the onset of the ocular vascular diseases is reflected in the basic circulatory parameters and especially in the IOP/PA relation. This relation provides four independent diagnostic parameters, namely, the steady state IOP, the PA, the shape of the IOP/PA relation, and the ophthalmic

arterial pressure. The IOP/PA relation is one, if not only the first, parameter to undergo clearly defined changes with the onset of the major blinding diseases and may be measured objectively and rapidly by presently available technologies. A loss of autoregulation is reflected in the initial part of the IOP/PA curve and requires only two observations for an early detection, namely, the IOP and PA in the undisturbed eye and the IOP and PA at an increased IOP of 10 mmHg (induced by finger pressure or by scleral suction cup). In healthy eyes, the PA falls substantially when the IOP is modestly raised (see **Fig. 17.2**). By contrast, the onset of the main blinding diseases is characterized by the PA remaining either unchanged or increased when the IOP is modestly increased (see Chap. 17). The technology for this diagnosis is provided by the pneumatic tonometer connected to an elementary laptop computer for analysis of the data.

The identification of ischemia in the brain may use the same pneumatic instrumentation with recording of a simplified version of the IOP/PA relation. Abnormalities in the IOP/PA relation associated with pathologic values of the ophthalmic arterial pressure, including the abnormally high values associated with Alzheimer's disease and the stroke suspect, require two measurements, namely, the PA in the undisturbed eye and repeated at an IOP at 50% of the brachial arterial pressure.[64]

Section 2
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Section 3

Ophthalmodynamometry, the Ophthalmic Arterial Pressure and the Effect of Increased Vascular Resistance Proximal and Distal to the Ophthalmic Artery on Ocular Blood Flow, the IOP/PA Relation and Vision

The classical method of ophthalmodynamometry and the subsequent use of the IOP/PA relation to determine the ophthalmic arterial pressure are described. The manner by which the new method provides a simple and accurate means for evaluation of the blood flow regulation and its loss in ocular and cerebral vascular diseases are presented. The effect of increasing stenosis of the internal carotid artery on the IOP/PA relation and on the ophthalmic arterial pressure is presented, and the importance of choroidal blood flow autoregulation to minimize changes in IOP and ocular blood flow in subjects with internal carotid stenosis is discussed. The modulation of the IOP/PA relation and the ophthalmic arterial pressure induced by changes in cerebral vascular resistance is discussed including the substantial loss of cerebral blood flow in Alzheimer's disease. The significance of the ocular perfusion pressure on the stability and the time- and pressure-dependent differential visual threshold is presented.

23

The Ophthalmic Arterial Pressure, the Intraocular Pressure/Pulse Amplitude Curve, and Their Relations to the Ocular and Cerebral Circulations

The blood supply of the eye is derived almost completely from the internal carotid arteries, which carry more than half of the blood flow to the brain. The internal carotid arteries are branches of the common carotid arteries and penetrate the base of the skull through the carotid canals. They enter the cranium between layers of the *dura mater* and ascend along the posterior aspect of the *sellica turcica* to enter the cavernous sinus. Here, the arteries double back to form the upper portion of the siphon. The internal carotid artery is the only artery in the body within a venous plexus and a rupture here may produce an arterial venous fistula (carotid cavernous fistula) with large effects on the both the intraocular pressure (IOP) and on the amplitude of the IOP pulse (pulse amplitudes of 15 mmHg have been recorded in patients with this fistula).

The ophthalmic artery arises from the anterior portion of the carotid siphon and passes with the optic nerve through the optic foramen into the orbital cavity; there it branches to supply the retina, the choroid, and other orbital tissues and also anatomizes with branches of the external carotid artery. Because the internal carotid artery ascends from the common carotid artery and the aorta without branches, other than the ophthalmic artery, the ophthalmic artery reflects closely the pressure in the carotid artery at the point at which it joins the internal carotid artery (**Fig. 23.1**). In turn, the maximal pressure in the carotid artery approximates closely to the central cardiac pressure. The vascular resistance in the carotid arteries in healthy subjects is extremely low, resulting in the arterial blood pressure feeding the brain to approximate closely the central cardiac pressure.

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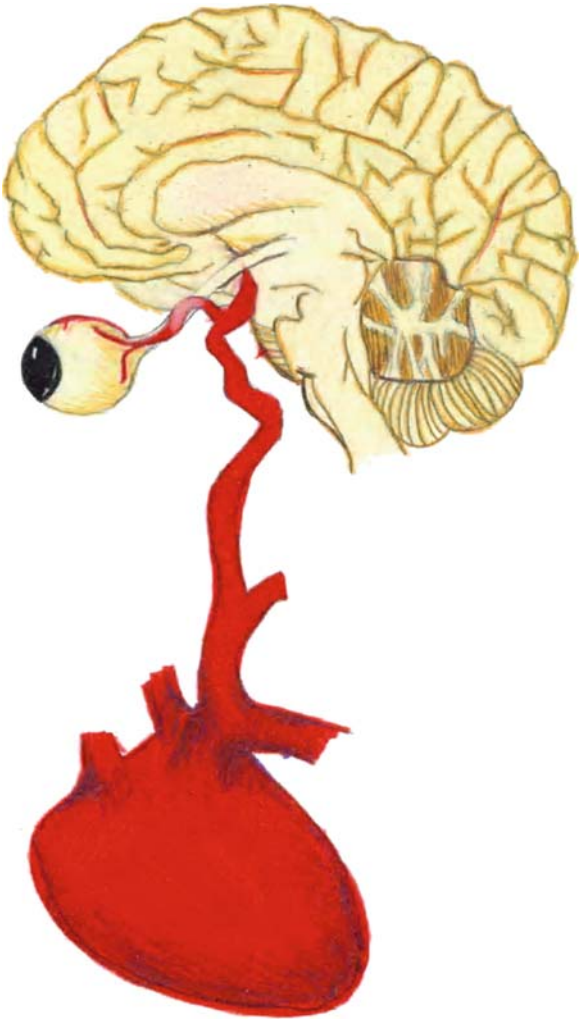

FIGURE 23.1. Diagrammatic view of the principle parameters determining blood flow to the eye. In the supine position the mean blood pressure in the carotid arteries is 120/80 mmHg. The mean systolic and diastolic ophthalmic arterial pressures are 84/54 mmHg, respectively, and the total ocular blood flow is 900–1,000 µl min^{-1}. Note the comparatively small size of the eye compared with that of the brain in man.

The demands of the human brain for a high blood flow and maximal oxygen tension are fulfilled by the relatively low cerebral vascular resistance compared with that of the eye. This results in a preferential flow to the brain with the arterial pressure feeding the eye being substantially less than the cerebral arterial pressure. As a consequence of this difference in perfusion pressures, abnormally high vascular resistance in the brain leads to a proportionate increase of the ophthalmic arterial pressure; *parri passu*, vascular

resistances in the brain below normal such as that induced by increased pCO_2 lead to a lowered ophthalmic arterial pressure.

The ophthalmic arterial pressure has been measured objectively using manometric techniques in living eyes of anesthetized animals and man[1]. In urethane anesthetized rabbits, the femoral arterial pressure is close or equal to the central cardiac pressure, and the ophthalmic arterial pressure may be monitored from a cannula inserted in the median ear artery to a level of the ophthalmic artery. Under these conditions, increasing the IOP in one eye from a physiological saline reservoir connected by a cannula to the anterior chamber causes the pulse amplitude to increase with increased IOP until the IOP reaches approximately 60 mmHg and then begins to decrease and becomes 0 as the IOP equals the ophthalmic arterial pressure. In rabbits, the ophthalmic arterial pressure is approximately the same as the femoral arterial and the central arterial pressure. This approximate equality of the ophthalmic and the central blood pressures in animals differs from the substantial difference in the same pressures (approximately 40 mmHg) in man.

This equality between the ophthalmic arterial pressure and the central arterial pressure in anesthetized rabbits and cats is also seen when the ophthalmic arterial pressure is lowered by unilateral ligation of the common carotid artery. The surgery causes the ophthalmic arterial pressure to fall by approximately 50 mmHg to a mean of approximately 54 mmHg, with a similar decrease in the median ear arterial pressure namely from 110 to approximately 55 mmHg. On the contralateral side, with an intact common carotid artery the pulse amplitude remains normal and decreases to 0 at an IOP of approximately 110 mmHg.

Manometric studies on anesthetized man in which the IOP was increased steadily using a physiological saline reservoir connected by a cannula to the anterior chamber showed the pulse amplitude to increase with increased IOP to approximately 50 mmHg and then to fall steadily to 0 at an IOP of approximately 80 mmHg, compared with the brachial systolic pressure of 120 mmHg, i.e., at an IOP of 40 mmHg less than the brachial arterial blood pressure.[1]

24

Ophthalmodynamometry

In 1854, Albrecht von Graefe observed that finger compression of the eye induced an arterial pulsation at the optic disc, a phenomenon that he noted occurred spontaneously in the ocular hypertension associated with open angle glaucoma.[2] In the ensuing 60 years, many attempts were made to relate the intraocular pressure (IOP) at which the retinal arterial pulsations changed in vascular diseases of the carotid arterial system and of the eye. In 1917, Baillart described the first quantitative method to measure the ophthalmic diastolic and systolic ophthalmic arterial pressures.[3] He used an ophthalmoscope to observe the pulsation of the central retinal artery as the IOP was increased using a spring plunger pressed against either the eyelid or the sclera. At an IOP approximating to the ophthalmic diastolic pressure, he observed a transient complete collapse of the central retinal artery and a distinct and sharp pulsation of the artery. With the application of further pressure, an IOP was reached at which the pulsation disappeared completely with sustained collapse of the central retinal artery. This pressure was considered to be the systolic retinal arterial pressure. He reported that in normal subjects the average readings of the diastolic and systolic pressures in the ophthalmic artery were 47 and 78 mmHg, respectively.

Baillart also made the important observation that the retinal diastolic and systolic pressures varied with the systemic blood pressure and reported the relation of the central retinal pressure to the brachial blood pressure in diastole to be 45:100 and in systole to be 54:100; these ratios imply diastolic and systolic pressures of 36 and 65 mmHg in a normal subject with brachial arterial pressures of 120/80 mmHg. Thus, he established for the first time a substantial difference between the ophthalmic and the central arterial blood pressures in man, which was confirmed in the later manometric studies of Langham et al.[1]

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Baillart's technique of ophthalmodynamometry was further refined by Weigelin and Muller in Bonn, Germany, and by Lobstein and Nordmann in Strasburg, France.[4,5] These investigators described an improved clinical method of ophthalmodynamometry, and a more accurate IOP calibration of the relation between the applied force of the spring plunger used to increase the IOP, and the IOP. Their procedure and calibration tables are still widely used. Weigelin and Lobstein confirmed prior observations that the central retinal arterial pressure varied with the level of the central arterial blood pressure.[6] In normal healthy subjects with a brachial arterial pressure of 120/80 mmHg, they reported the diastolic and systolic ophthalmic pressures to be 60 and 90 mmHg, respectively. These values were higher than those reported by Baillart (see earlier).

Weigelin and Lobstein also expressed their results in terms of the mean of the diastolic and systolic ophthalmic arterial perfusion pressures that would maintain a constant minute volume of flow equal to that resulting from the variable pressure of the pulsation of the arterial inflow. This mean arterial pressure was calculated as the diastolic pressure plus 0.42 of the pulse pressure. On this basis, a normal healthy subject with an IOP of 16 mmHg and diastolic and systolic ophthalmic arterial pressures of 60 and 95 mmHg would be exposed to a mean ophthalmic arterial pressure of 65 mmHg.

Confirmation of the relation between the central blood pressure and the ophthalmodynametric measurement of the ophthalmic arterial pressure was reported by Lobstein et al.[7] In a series of

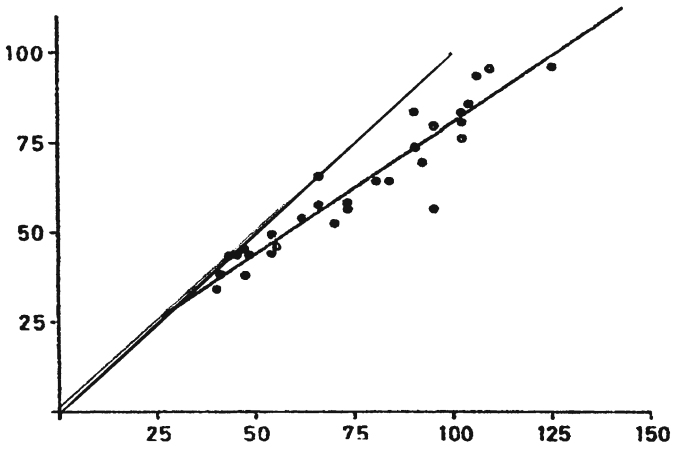

Figure 24.1. The relation between the mean blood pressure measured manometrically in the internal carotid artery (abscissa in mmHg) in anesthetized humans, and the corresponding mean ophthalmic arterial pressure (the ordinate in mmHg) measured by opthalmodynamometry. From Lobstein et al.[7] Reprinted with permission. The mean ophthalmic arterial pressures were calculated as diastolic reading plus 0.42 of the pulse pressure. The conversion table was used to calculate the ophthalmic arterial pressures (From Weigelin and Lobstein.[6]).

patients, the internal and the common carotid arterial pressures were measured manometrically and compared with the central retinal arterial pressure measured with the indirect procedure of opthalmodynamometry, before and after a therapeutic ligation of the common carotid artery. Their results, summarized in **Fig. 24.1**, show the approximate linear relation between the intracarotid pressure and the mean ophthalmic arterial pressure.

25

Autoregulation of the Intraocular Pressure and Blood Flow in the Human Eye

Evidence of intraocular pressure (IOP) and vascular autoregulation in the human eye has been found, as in animals, in the ocular responses to decreased ophthalmic arterial pressure. In this respect, partial or complete unilateral and bilateral stenoses of the internal carotid arteries occur in more than 50% of patients who suffer from stroke. Indeed, internal carotid arterial disease resulting in neurological deficit is one of the most common and serious diseases of man in the Western world. A representative example of an individual with unilateral stenosis of the internal carotid artery with a normal visual threshold and no apparent ocular deficit is shown in **Fig. 25.1**. Arterial angiography on this patient revealed a unilateral stenosis of the internal carotid artery of approximately 75%. The ophthalmic arterial systolic pressures on the affected and normal sides were approximately 60 and 100 mmHg, respectively. Despite this difference of the ophthalmic arterial pressures between pairs of eyes, the IOPs were 18 and 20 mmHg and the rates of pulsatile blood flows were 719 and 614 µl min^{-1}, respectively. If there had been no autoregulation and the vascular resistance constant, the pulsatile blood flow in the affected eye would have been approximately 390 µl min^{-1} compared with the observed flow of 614 µl min^{-1}.

The patient described in **Fig. 25.1** underwent surgical endarterectomy and at 3 weeks the IOP/PA curve on the operated eye had recovered and was identical to that in the eye with the patent artery. The pulsatile blood flows in the unaffected and affected eyes following endarterectomy were 678 and 674 µl min^{-1}, respectively.

The equality of the IOPs in the eyes of this patient with unilateral stenosis of the internal carotid artery, despite the substantial fall in the ocular perfusion, is closely similar to the findings in rabbits after unilateral ligation of the common carotid artery (see Sect. 1). Thus, the ability of physiological mechanisms in the eye to minimize

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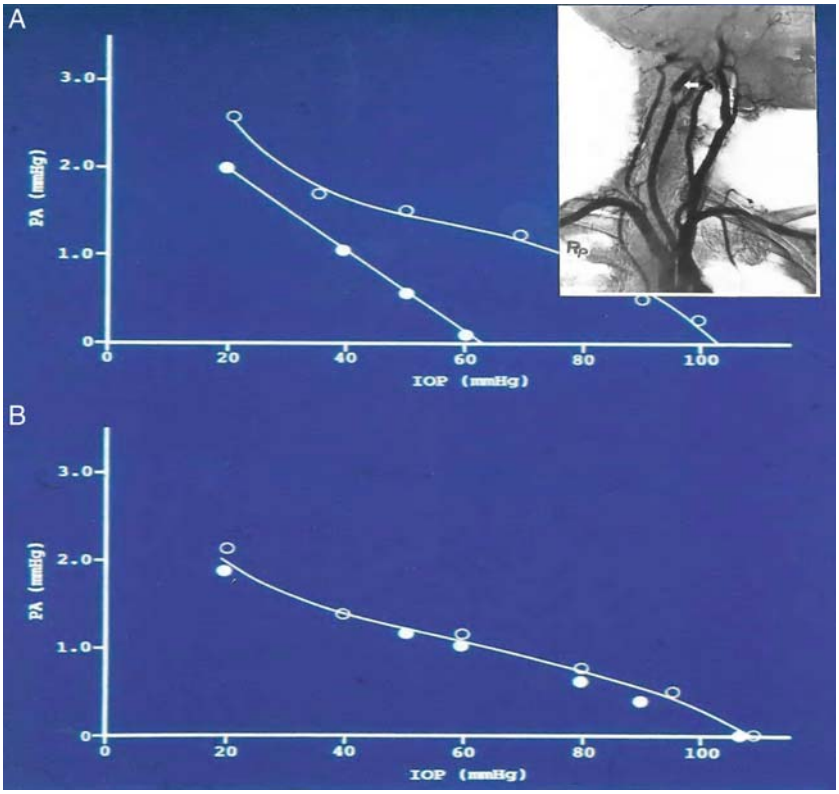

FIGURE 25.1. The IOP/pulse amplitude (PA) relations in the eyes of a patient with a severe unilateral stenosis (75%) of the internal carotid artery. The *open* and *closed circles* are the results on the unaffected and affected eyes, respectively. The upper figure (**a**) shows the observations made prior to surgery and the lower figure (**b**) shows the results taken 3 weeks after endarterectomy on the side with the stenosis of the internal carotid artery. Note that the IOP/PA relation prior to surgery in the affected eye differed significantly from the healthy contralateral eye but the IOPs in the two eyes were the same. The pulsatile blood flows prior to surgery were 719 and 614 μl min^{-1} in the normal and affected eyes, respectively (From Schilder. Ocular blood flow changes with increased vascular resistance external and internal to the eye. *Acta. Ophthalmol*. 1989;67:19–23. Reprinted with permission from Elsevier.).

changes in the steady state IOP and ocular blood flow, i.e., autoregulation of the IOP and ocular pulsatile blood flow, is present in the healthy eyes of humans as well as in animals.

In summary, by the late 1950s it was evident that increased vascular resistance in the internal artery proximal to the ophthalmic artery causes a proportionate decrease of the ophthalmic arterial pressure and that increased vascular resistance, either in the internal carotid artery proximal to the ophthalmic artery or distal to the ophthalmic artery including the brain, causes a proportionate increase of the ophthalmic arterial pressure.

26

Objective Measurement of the Diastolic and Systolic Ophthalmic Arterial Pressures

In 1978, Langham and To'mey described measurements of the intraocular pressure/pulse amplitude (IOP/PA) relation to evaluate the systolic ophthalmic arterial pressure.[9] Their procedure was made on eyes of conscious subjects, either seated or lying supine, using the Langham tonometer to record the IOP and its pulse amplitude in the undisturbed eye, and then repeating the recordings after inducing stepwise increments of the IOP (**Fig. 26.1**). The IOP was increased by application of suction to a plastic cup of diameter 10 mm placed a few millimeters temporal to the limbus of the anesthetized cornea. During the procedure the patient observed a fixation light approximately 6 ft above the face and reported when a change in vision occurred. In healthy eyes, the light remained essentially unchanged as the IOP was increased from the initial IOP of approximately 15 mmHg to more than 60 mmHg. Then, with further increased suction an IOP was reached at which the pulse amplitude decreased rapidly to 0 over a span of approximately 5 mmHg. At this IOP there was a fading of vision from the periphery inward. A complete loss of vision occurred at a mean IOP of 80–85 mmHg in healthy adults. The pulse and vision reappeared when the IOP was reduced by a few mmHg. On the basis of observations on many normal and disclosed eyes a complete loss of vision occurs simultaneously with the complete loss of pulsatility.

A typical plot of the pulse amplitudes in pairs of undisturbed eyes and at increased IOP is shown in **Fig. 26.2**. The upper limit of the IOP/PA relation is the IOP at which the PA is of 0 amplitude, blood flow through the eye ceases, and vision is lost. This is, by definition, the ophthalmic arterial systolic pressure. In a group of 40 adult healthy subjects with no apparent ocular abnormalities the mean ophthalmic arterial systolic pressure was 82 ± 1.2 (40) mmHg and the corresponding mean brachial systolic pressure was 126 ± 2.1 (40) mmHg.

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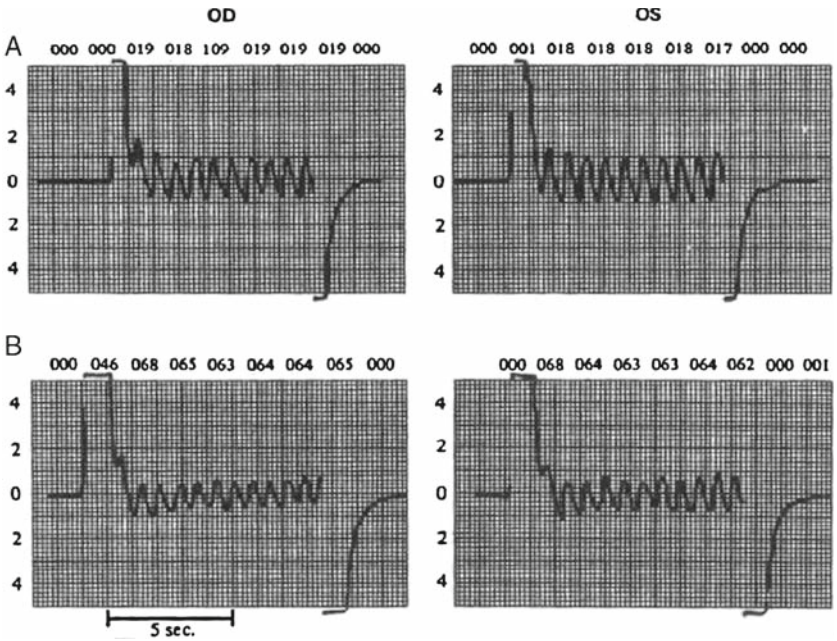

FIGURE 26.1. The IOPs and pulses in pairs of eyes of a healthy adult subject with no ocular pathology. The upper recordings are on the undisturbed eyes and the lower recordings are at IOPs of approximately 65 mmHg. The IOPs sampled at 2-s intervals are printed above each record. These were analog recordings using the Langham pneumatic tonometer.

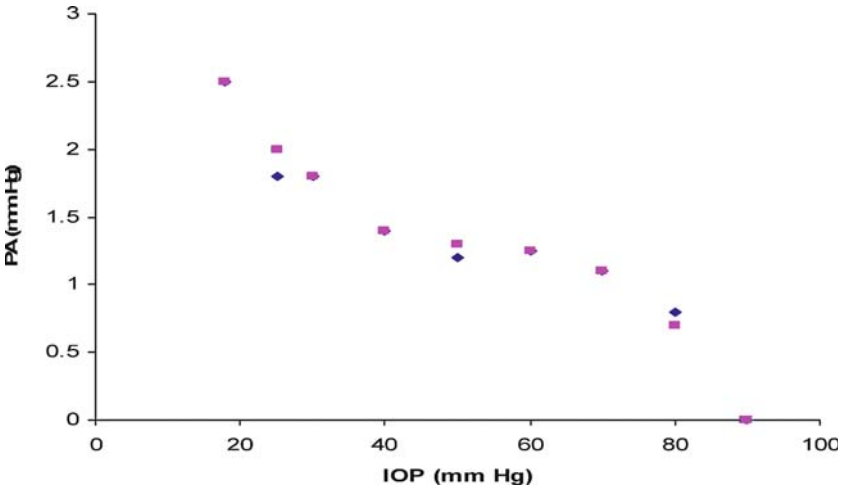

FIGURE 26.2. The evaluation of the ophthalmic arterial systolic pressure from the IOP/PA relation in eyes of a healthy conscious adult subject lying supine. The IOPs in the undisturbed eyes were 17.5 and 18.0 mmHg. The IOP readings are the mean of the IOP of the minimal and maximal IOP of each pulse.

In similar studies the central retinal diastolic pressure was measured by observing the central retinal artery and recording the IOP at which the retinal pulse increased substantially. The mean central retinal diastolic arterial pressure was 54.5 ± 1.6 mmHg. This value is approximately 5 mmHg less than that recorded by Weigelin and Lobstein but agrees with the reports of Galin et al.[6–8]

The gravitational hydrostatic pressure acting between the heart and the eye when standing is approximately 40 mmHg (see Fig. 12.1). In healthy subjects this change in pressure on lying down is compensated in the central blood pressure by an efficient autoregulation. This autoregulation involves the sensory receptors (the baroreceptors) of the carotid sinus and the chemoreceptors of the carotid body, and is associated with a change of the heart rate and of the peripheral resistance. In healthy subjects, the change from the seated to the supine position is associated with an increase of the IOP of approximately 1.5 mmHg and an increase of approximately 8 mmHg in the ophthalmic arterial pressure.

27

The Ophthalmic Arterial Pressure in Healthy Subjects

The ophthalmic arterial pressures (OAPs) in a group of ten healthy adult subjects lying down, and with no apparent ocular abnormalities, are summarized in Table 27.1. The values were symmetrical in pairs of eyes. It is to be noted that the OAP is substantially less than the brachial arterial systolic blood pressure. The mean ocular perfusion pressure based on the difference between the mean OAP (84 mmHg) and a mean intraocular pressure (IOP) (15 mmHg) is approximately 70 mmHg. Alternatively, it has been conventional to calculate the mean perfusion pressure based on the diastolic pressure of 58 mmHg plus 0.42 of the pulse pressure, namely 0.42(84 – 58) mmHg, less the mean IOP (15 mmHg), i.e., 54 mmHg.

It will be noted that there is a significant scatter in the absolute values of the OAP between individual subjects due to variation in the arterial blood pressure. For this reason, the ratio of the OAP to the systolic arterial pressure is widely used (see Table 2.1), namely the mean OAP/BrAP is 0.67 ± 0.02.[9]

Studies on groups of male and female adults indicate that the results do not differ significantly (Table 27.2). Similarly, in healthy subjects, age has little effect on the absolute values of the OAP and little effect on the OAP/BrAP ratios (Table 27.3). This stability extends to the IOP, the PA, and to the rate of ocular pulsatile blood flow.

The procedure of Langham and To'mey to evaluate the OAP differs from the classical ophthalmodynamometry in which observations are made on the retinal artery and performed on seated patients.

In the technique of Langham and To'mey, it is the retinal pulse that is observed in measurements of the retinal diastolic and systolic pressures. Because the blood flow and its pulsatile component in the choroid comprise 85–90% of the total ocular blood flow, the technique of Langham and To'mey deals almost exclusively with the pressure and the pulsatile blood flow in the choroid.[9]

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Table 27.1. The IOP, PA, OAP, POBF, and BrAP in a series of ten healthy adults with no apparent ocular pathology.

Stenosis (%)	**0**	**0**	**0**
IOP (mmHg)	17.7 ± 2.0	17.7 ± 2.0	0 ± 0.1
PA (mmHg)	2.51 ± 0.1	2.51 ± 0.9	0.0 ± 0.1
OAP (mmHg)	83.3 ± 6.7	83.4 ± 8.0	1.0 ± 2.7
POBF (μl min^{-1})	745 ± 75	740 ± 32	5.0 ± 7.7
OAP/BrAP	0.67 ± 0.1	0.67 ± 0.05	0.2 ± 0.04
BrAP (mmHg)	123 ± 6.7/78 ± 1.6		

Tests were made on supine subjects and the mean age was 34 years

Table 27.2. The age, IOP, PA, and the systolic and brachial arterial blood pressures in groups of young male and female healthy subjects.

	Males (10)	**Females (10)**
Age (years)	27.3 ± 5.2	23.4 ± 3.3
P_o (sitting)	16.4 ± 0.9	16.8 ± 0.8
Pulse amplitude	2.1 ± 0.2	2.2 ± 0.2
P_o (supine)	19.6 ± 0.8	19.3 ± 0.9
Pulse amplitude	2.3 ± 0.2	2.6 ± 0.2
Sys. Oph. Art. Pr.	81.5 ± 2.1	82.5 ± 1.8
Diast. Br. Art. Pr.	80.7 ± 3.0	72.2 ± 3.0
Sys. Br. Art. Pr.	125.0 ± 4.2	121.0 ± 2.4
Mean Br. Art. Pr.	95.5 ± 3.4	89.6 ± 2.2

Source: Langham and To'mey.[9] Reprinted from *Experimental Eye Research*. Used with permission from Elsevier Science & Technology Journals

Table 27.3. Comparison of the IOP, the PA, the OAP, and the BrAP (mmHg) in two groups of healthy subjects with no apparent ocular pathology.

Parameters	**Age < 30 years**	**Age > 30 years**
Mean age	24.3 ± 1.25 (10)	55.85 ± 3.55 (13)
IOP (O.D.) (mmHg)	16.0 ± 0.54 (10)	16.8 ± 0.63 (13)
IOP (O.S.) (mmHg)	16.3 ± 0.56 (10)	17.2 ± 0.61 (13)
PA (O.D.) (mmHg)	2.15 ± 0.15 (10)	2.2 ± 0.12 (13)
PA (O.S.) (mmHg)	2.15 ± 0.15 (10)	2.2 ± 0.14 (13)
OAP (O.D.) (mmHg)	80.8 ± 2.3 (10)	88.4 ± 2.8 (13)
OAP (O.S.) (mmHg)	82.8 ± 2.6 (10)	89.7 ± 3.2 (13)
BrAP (syst) (mmHg)	123. ± 8.6 (10)	134. ± 6.6 (13)
BrAP (diast) (mmHg)	77.2 ± 5.2 (10)	79.4 ± 8.0 (13)
Ratio OAP/BrAP	0.67 ± 0.01 (20)	0.67 ± 0.01 (26)

Source: Langham.[10] Reprinted from *Glaucoma Contemporary International Concepts*. Used with permission from Masson Publishing USA

The IOPs are the mean of the minimal and maximal values of the IOP pulse; PA is the amplitude of the IOP pulse; OAP is the systolic ophthalmic arterial pressure, and BrAP is the brachial arterial pressure

28

The Relation Between the Ophthalmic Arterial Pressure and the Intraocular Pressure/Pulse Amplitude Relation

The internal carotid arteries supply the blood flow to the eyes and a major proportion of the blood flow to the brain. The circle of Willis connects to the carotid arterial vessels on each side of the body and includes connections of the internal carotid arteries to the anterior cerebral arteries and to the basilar artery, and is a pathway for maintaining flow to both eyes and to both hemispheres and thereby minimizes asymmetry of flow and pressure.

The vascular network supplying blood flow to the brain is without doubt the most important of the body. The adult human brain weighs about 1,400 g and receives approximately 750 ml min^{-1} of arterial blood, compared with the approximately 2 ml min^{-1} that flows to the two eyes. The oxygen uptake of the brain is approximately 42 ml min^{-1}, i.e., approximately 20% of that available for the whole body at rest.

The internal carotid and vertebral arteries forming the basilar artery unite in the circle of Willis at the base of the brain and supply the entire blood supply to the brain in man. The circle of Willis gives rise to six cerebral arteries for distribution to the cortex, subcortex, and upper stem, while the basilar artery directly supplies the occipital lobes, the cerebellum, pons, and the medulla. The limitation of the cervical arteries in supplying the needs of the brain is underlined by the fact that total occlusion of one internal carotid artery may reduce the blood supply to the corresponding hemisphere so severely that it causes the neurological deficit of stroke.

The ability of the brain to compensate for relative ischemia brought about by changes in composition of the blood or from decreased blood flow is due to a very efficient autoregulation involving both chemical and localized perfusion parameters. The chemical factors include the carbon dioxide and oxygen tensions in the blood and the interstitial fluids. The cerebral precapillary smooth muscles are highly sensitive to stretch and to local shifts in their immediate

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chemical environment. Changes in the CO_2 tension in the interstitial fluids modulate the hydrogen ion concentration, which induces cerebral vasodilatation. Thus, the pH acts as a negative feedback to counteract the myogenic tone of the cerebral resistance vessels. Similarly, changes in the pO_2 induce dilatation of vessels at low values and vasoconstriction at high pO_2 values.

The oxygen uptake of the brain goes predominantly to the cell-rich gray matter and comparatively little goes to the cell-poor white matter. Consequently, the gray matter of the cortex and some areas of the brain stem have a very rich blood supply and a high density of capillaries (3,000–40,000 mm^3). Active autoregulation can increase the cerebral blood flow by three to four times. In these conditions there may be a "steal" of blood from the eye to the brain and is associated with a decrease in the ophthalmic arterial pressure.

The presence of a very active autoregulation of the cerebral blood flow was first shown by Fog[11] and then in more detail by Haggendahl and Johansson.[12] Cerebral vasodilatation occurs in response to decreased perfusion pressure, increased pCO_2, and decreased pO_2. The smooth muscle of the precapillary vessels is highly sensitive to the chemical environment including the hydrogen ion concentration.[13] The response to lowered carbon dioxide tension, such as induced by hyperventilation, causes vasoconstriction; lowered oxygen tension causes cerebral vasodilatation and abnormally increased oxygen tension induces vasoconstriction.

Unlike the eye, adrenergic neurons play little role in the control of blood flow within the brain. Adrenergic innervation is present around the larger cerebral vessels exterior to the brain but their ability to induce increased blood flow does not exceed 30%, compared with increases of 200–300% or more induced by increased carbon dioxide tension. The volumetric changes associated with vasodilatation in the rigid cranium are readily compensated by changes in the cerebral veins and in the cerebral ventricles.

Physiologically, there are several ways by which substantial changes in the ocular blood flow to the eye and to the brain may be modified. First is the resistance to flow in the internal carotid arteries proximally to the ophthalmic artery. Second is the level of the central arterial blood pressure, and third is the cerebral vascular resistance.

The dynamic aspects of the influence of increased vascular resistance on flow through arteries with high velocity such as the internal carotid artery have been examined mathematically by Berguer and Hwang.[14] In their theoretical studies, they were able to predict and confirm experimentally the effect of increasing resistance on the lateral pressure in the poststenotic region (**Fig. 28.1**). Also in an "in vivo" arterial system, Berguer and Hwang showed how the relation between the degree of stenosis and the pressure gradient changed with either low or high flow rates. In arteries having a relatively slow rate of flow there is a critical degree of stenosis of 60–70%,

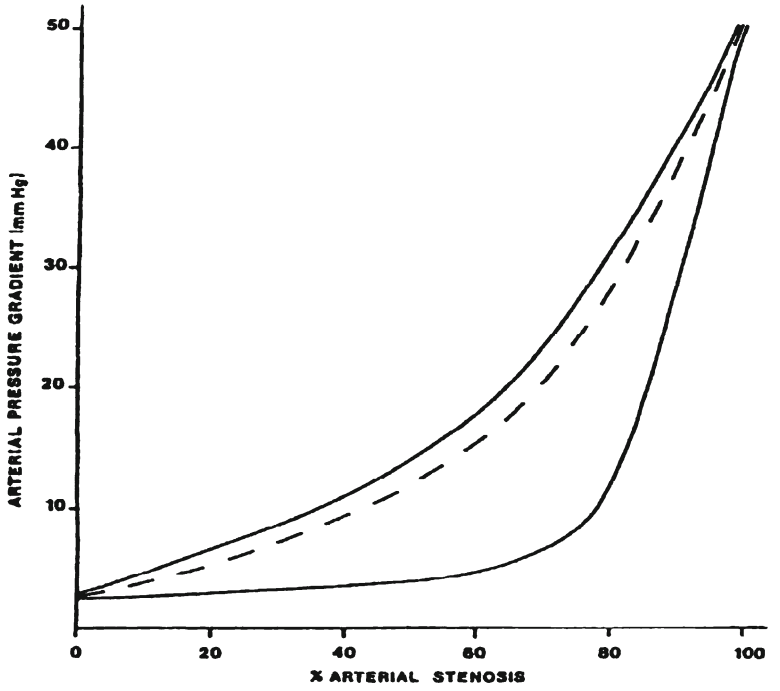

FIGURE 28.1. Comparison of the theoretical and the experimental curves relating the effect of increasing arterial stenosis on the arterial pressure gradient. The ordinate (arterial pressure gradient) of 50 mmHg reflects the decrease in the ophthalmic arterial pressure induced by an increasing stenosis of the proximal portion of the internal carotid artery. In the fully patent artery the corresponding pressure gradient is assumed to be 3 mmHg. The *dotted line* reflects the results on patients with radiologically determined increasing degrees of stenosis. Data from Langham and Preziosi.[15] The continuous lines are the theoretical values for arteries with either high (*upper line*) or low (*lower line*) flow rates, respectively. Data from Berguer and Hwang[14].

above which the lateral pressure begins to decrease rapidly (**Fig. 28.1**). By contrast, in arteries with a high flow velocity and high flow rates, even relatively small degrees of constriction caused substantial change in the pressure gradient.

In the internal carotid artery the relation between the constriction and the pressure gradient across the stenosis of the artery has been found to agree qualitatively and quantitatively with the conclusions of Berguer and Hwang (see Fig. 17.19). In this figure, the ordinate is the pressure gradient between the common carotid artery and the ophthalmic artery. With the internal carotid fully patent, the pressure gradient between the heart and the ophthalmic artery is small (approximately 4 mmHg). This gradient increases to approximately 40–50 mmHg when

arterial stenosis is 100% (**Fig. 28.1**). This is based on the observations that a total unilateral occlusion of the internal carotid artery causes the ophthalmic arterial pressure to decrease from the normal mean value of 84 mmHg to approximately 40 mmHg (see later). The dotted line in **Fig. 28.1** reflects data on a series of 100 patients with mild to severe stenosis (0–100%) of the internal carotid artery.[15,16] The dotted line corresponds closely to the upper solid line taken from the paper of Berguer and Hwang, of the relation between the percentage of stenosis and the pressure gradient across a constriction in arteries with high flow rates.[14]

The important physiological question arises whether increasing stenosis of the internal carotid artery affects the steady state IOP, the IOP/PA relation, and the pulsatile blood flow. This has been answered on healthy eyes of adult subjects with increasing degrees of unilateral and bilateral stenoses of the internal carotid arteries.

29

Modulation of the Intraocular Pressure/Pulse Amplitude Relation in Subjects with Stenosis of the Internal Carotid Artery

Unilateral Complete Occlusion of the Internal Carotid Artery

Table 29.1 summarizes the findings in a group of ten subjects with unilateral, complete occlusion of the internal carotid artery. The intraocular pressures (IOPs) were in the range in healthy subjects and there was no evidence of ocular disease. However, there was small but significantly lower IOP in the eyes on the occluded side. The ophthalmic arterial pressures (OAP) were abnormally low in eyes on the side with the occlusion. The pulse amplitudes (PAs) and the pulsatile blood flows were abnormally low in all eyes and especially in the eyes on the occluded side. Similarly, the OAP/brachial artery pressure (BrAP) ratios were abnormally low in all eyes and especially in the eyes on the occluded side.

It is evident that the unilateral occlusion had a substantial effect on the ocular circulation and on the IOP in both eyes, and that collateral blood flow through the vertebral arteries was insufficient to compensate fully for the reduction in arterial flow due to the arterial occlusion. The rates of pulsatile blood flow in the affected eyes were extremely low but it is evident that the pulsatile blood flows in the contralateral eyes were also low. The abnormally low ophthalmic arterial pressure on the occluded side implies that there was also a significant decrease in the perfusion pressure to the brain. This relative cerebral ischemia may account for the clinical symptoms, characteristic of stroke suspects in all these subjects, including transient ischemic attacks, dizzy spells, etc.

Figure 29.1 is a representative graph of the IOP/PA relations in pairs of eyes of one of the subjects with a unilateral complete occlusion of the internal carotid artery. The IOP/PA on the intact side is similar to the S-shaped IOP/PA relation of normal subjects indicating the presence of autoregulation.

M.E. Langham, *Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases: A New Perspective*, DOI: 10.1007/978-0-387-09716-9_29,

Table 29.1. The results on a series of ten patients (age 65 ± 3 years) found by arterial angiography to have a unilateral occlusion of the internal carotid artery with a fully patent internal carotid artery on the contralateral side.

Parameter	Eye 1	Eye 2	Eyes 2–1
Stenosis (%)	100	0	100
IOP (mmHg)	16.3 ± 2.4	17.6 ± 2.0	1.4 ± 0.1
PA (mmHg))	0.35 ± 0.1	1.51 ± 0.1	1.16 ± 0.1
OAP (mmHg)	45.4 ± 8.0	89.3 ± 6.1	43,9 ± 2.7
POBF (μl min^{-1})	229 ± 32	465 ± 75	263 ± 7.7
OAP/BrSyst BP	0.37 ± 0.05	0.58 ± 0.1	0.14 ± 0.04
Brach BP (mm Hg)		153 ± 6.7/78 ± 1.6	

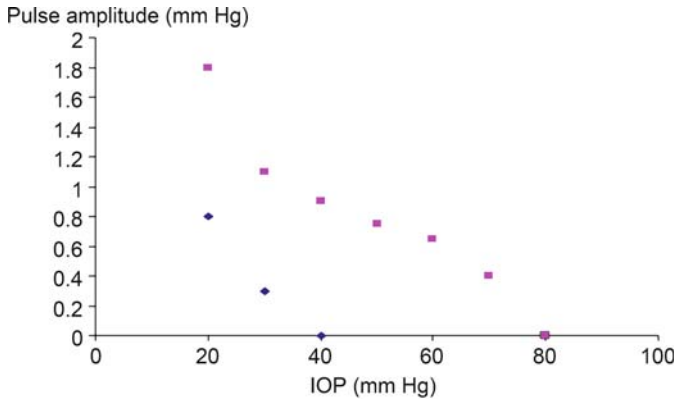

FIGURE 29.1. The IOP/PA relations in pairs of eyes of a subject with a complete occlusion of the right internal carotid artery (*diamonds*) and a fully patent left internal carotid artery (*squares*). The mean IOP (the mean of the maximum and minimum pressures of the pulse) on the supine subject was 18 mmHg (patent side) and 16.5 mmHg (occluded side).

This patient underwent surgical endarterectomy on the occluded artery and 4 weeks later the ocular studies were repeated. The IOP/PA curves in the two eyes were approximately symmetrical and normal; the PAs and the pulsatile blood flows (576 and 634 ml min^{-1}) were within the range of normal eyes, and the OAP/BrAP ratios were normal. The IOP/PA on the intact side was similar to the S-shaped IOP/PA relation of healthy subjects, indicating that blood flow to the eyes and to the brain had improved substantially.

Bilateral Complete Occlusions of Both Internal Carotid Arteries

The effect of bilateral, complete occlusions of the internal carotid arteries on the physiology of the eyes and brain is severe and the findings on a group of seven patients are summarized in Table 29.2.

Table 29.2. Results on seven subjects found by arteriography to have complete occlusions of both internal carotid arteries.

Parameter	Eye 1	Eye 2	Eyes 2–1
Stenosis (%)	100	100	0
IOP (mmHg)	11.2 ± 1.3	11.3 ± 1.6	0.2 ± 0.4
PA (mmHg))	0.82 ± 0.05	0.84 ± 0.6	0.15 ± 0.06
OAP (mmHg)	49.5 ± 7.8	49.8 ± 641	0.15 ± 0.6
POBF (µl min^{-1})	ca. 375	ca. 375	ca. 0
OAP/BrSyst BP	0.32 ± 0.05	0.30 ± 0.04	0.02 ± 0.02
Brach BP (mmHg)		153 ± 6.7/78 ± 1.6	

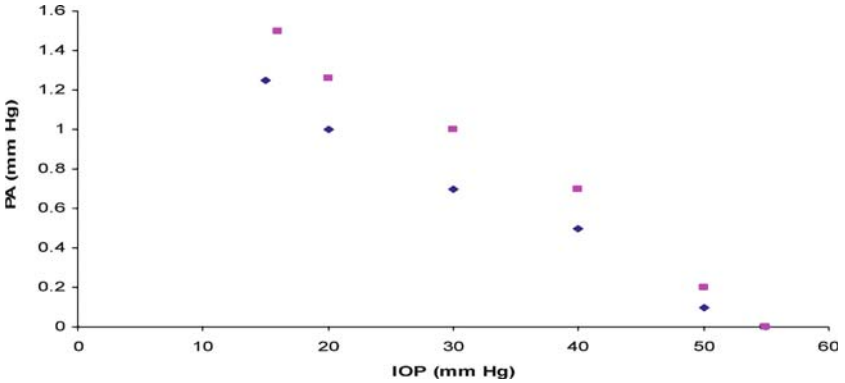

FIGURE 29.2. These results are from a female of 67 years, seen 4 years earlier with a diagnosis of cerebral vascular disease. At that time, the IOP/PA curves showed a severe stenosis on the right side and moderate stenosis in the left internal carotid artery. One year later, the patient underwent bilateral endarterectomies. The present study was made 1 year after the bilateral endarterectomies on both internal carotid arteries. The IOP/PA relations indicated severe stenosis in both internal carotid arteries. The IOPs of 13 and 15 mmHg and the PAs of 1.8 mmHg and the rates of pulsatile blood flows of 367 and 356 ml min^{-1} were well below the range in normal subjects. The brachial arterial systolic pressure was 156/85 mmHg and the OAP/BrAP ratios of 0.33 and 0.32 are well below the values in normal subjects. The evidence of severe bilateral occlusions of the internal carotid arteries was confirmed in subsequent arteriography.

Because both internal carotid arteries were occluded in this series of patients, the eyes and the brain had to be dependent on blood flow through the vertebral arteries. The IOPs and the PAs in this group were extremely low as were the rates of pulsatile blood flows (mean approximately 375 ml min^{-1}). The mean OAP/BrAP ratios of 0.32 and 0.30 were substantially less than the mean of 0.67 in normal subjects. The ophthalmic arterial pressures were similar in pairs of eyes and approximately 35 mmHg below the mean of normal healthy subjects. The IOP/PA relations in pairs of eyes of one of the subjects are shown in Fig. 29.2.

Moderate Unilateral Stenosis of the Internal Carotid Artery

Significant changes on the circulation to the eyes and the brain have been found in patients with moderate unilateral partial stenosis of the internal carotid arteries (Table 29.3).

With this degree of stenosis, the IOPs were in the range of normal but there was a small but significant asymmetry, with lower IOP in the eyes on the affected side. The PAs and the rates of ocular pulsatile blood flow were in the range in normal subjects but the pulsatile blood flows were lower on the affected sides.

A more unusual case in this group was a patient who suffered from systemic hypertension and had a history of abnormally high IOPs with a diagnosis of open angle glaucoma and had been on treatment with 2% pilocarpine (Fig. 29.3).

The patient had systemic hypertension and had been diagnosed with open angle glaucoma and placed on 2% pilocarpine. At the time of the present tests, the IOPs were 20 mmHg in both eyes but the PAs (1.5 and 1.45 mmHg) and the rates of pulsatile blood flow were asymmetric (610 and 545 μl min^{-1}) in the left and right eyes, respectively. The ophthalmic arterial pressure in the left eye was abnormally high and consistent with abnormally high cerebral vascular resistance. The IOP/PA relations were consistent with a unilateral stenosis and this was confirmed in arteriography.

Moderate Bilateral Stenoses of the Internal Carotid Arteries

This group of ten patients had experienced typical ischemic attacks including transient ischemic attacks (TIAs), carotid bruit, and transient numbness. The IOPs were normal, but the PAs and the rates of pulsatile blood flow were at the low end of normal and well less than the mean pulsatile blood flow in healthy subjects (Table 29.4).

Table 29.3. Results on a group of ten subjects found to have a unilateral partial stenosis of the internal carotid artery.

Parameter	Eye 1	Eye 2	Eyes 2–1
Stenosis (%)	0	37.1 ± 5.2	37
IOP (mmHg)	16.7 ± 1.7	15.4 ± 1.3	–2.0 ± 0.7
PA (mmHg))	1.61 ± 0.33	1.35 ± 0.35	–0.25 ± 0.1
OAP (mmHg)	89.3 ± 4.4	90.0 ± 641	5.0 ± 2.9
POBF (μl min^{-1})	626 ± 93	535 ± 79	–91 ± 7.7
OAP/BrSyst BP	0.67 ± 0.1	0.67 ± 0.05	0.2 ± 0.4
Brach BP (mmHg)		123 ± 6.7/7.8 ± 1.6	

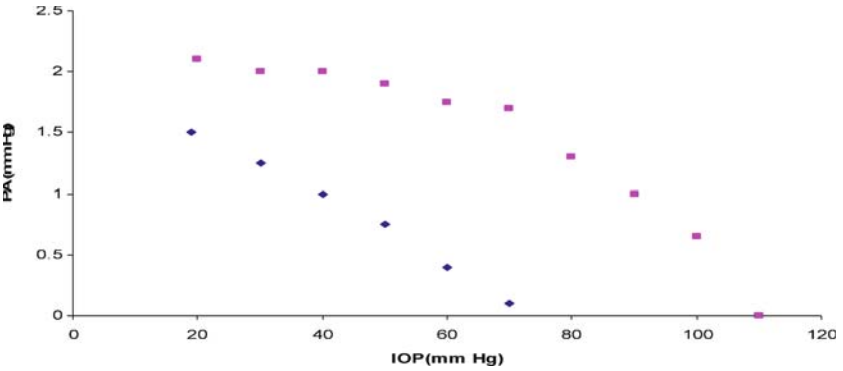

FIGURE 29.3. The IOP/PA recordings on a male subject with systemic hypertension complaining of dizziness, vertigo, and transient visual loss in left eye and who had been considered to be glaucomatous and treated with 2% pilocarpine in both eyes. The *squares* and the *diamonds* are the results on the left and right eyes, respectively. The IOPs were normal; the postural effect on the IOP was 2 and 1 mmHg in the right and left eyes, respectively. The PAs and the rates of pulsatile blood flow were abnormally low in both eyes. The brachial blood pressure was 130/80 mmHg in both arms. The IOP/PA relations were asymmetric and indicated a moderate stenosis of the internal carotid artery on the right side. The IOP/PA relation on the left side indicated a loss of autoregulation but no stenosis. Subsequent arteriography showed a unilateral stenosis in the internal carotid artery of approximately 40%.

Table 29.4. Results on a group of ten subjects found to have bilateral moderate partial stenosis (25–50%) of the internal carotid arteries based on arteriography.

Parameter	Eye 1	Eye 2	Eyes 2–1
Stenosis (%)	30 ± 1.8	34 ± 2.2	4
IOP (mmHg)	17.8 ± 1.3	16.8 ± 2.0	–2.0 ± 0.7
PA (mmHg))	1.66 ± 0.30	1.60 ± 0.29	–0.6 ± 0.1
OAP (mmHg)	87.4 ± 4.1	87.0 ± 4.4	–0.4 ± 2.9
POBF (µl min–1)	549 ± 93	536 ± 79	–13.0 ± 7.7
OAP/BrSyst BP	0.62 ± 0.1	0.63 ± 0.05	0.2 ± 0.4
Brach BP (mmHg)		123 ± 6.7/7.8 ± 1.6	

Representative IOP/PA relations in pairs of eyes in one of these patients are shown in Fig. 29.4. The curves are similar in pairs of eyes and of abnormal shape and consistent with a loss of autoregulation. The systemic ophthalmic arterial pressures in the two eyes were normal as were the OAP/BrAP ratios. Despite the normal ophthalmic and ocular perfusion pressures, the ocular pulsatile blood flows of 432 µl min^{-1} in both eyes were below the range in normal eyes and consistent with abnormally high ocular vascular resistance.

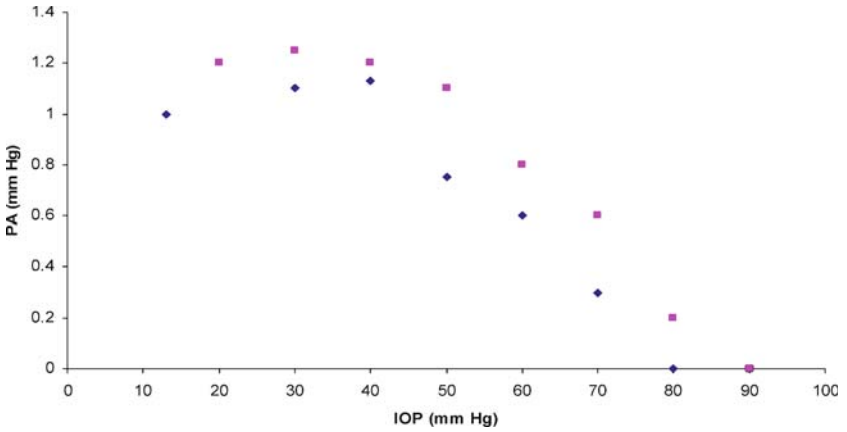

FIGURE 29.4. A male subject of 69 years with bilateral carotid bruits. Patient was seen by a neuro-ophthalmologist and was considered to have a left optic neuropathy. Central visual fields in both eyes were normal. The PAs were slightly asymmetric and below the range in normal subjects. The brachial blood pressure was 140/90 mmHg and the BAP/OAP ratio was approximately 0.60. Subsequent arteriography revealed stenoses of approximately 25% in both internal carotid arteries.

Abnormally High Cerebral Vascular Resistance

Among the subjects with clinical signs of a stroke suspect, there were those with apparently no demonstrable stenoses of the internal carotid arteries based on arteriography studies but suffered from abnormally high OAP/BrAP ratios. Table 29.5 summarizes the findings on a series of eight patients in this category. The steady state IOPs were normal and identical in pairs of eyes. Similarly, the PAs and the pulsatile blood flows were symmetrical in pairs of eyes and within the range in normal eyes. The mean ophthalmic arterial systolic pressure of 106 mmHg in these patients was significantly higher than the mean of 84 mmHg in healthy eyes, and the mean OAP/BrAP ratios of 0.82 ± 0.1 were significantly higher than the normal range.

This abnormally high ophthalmic arterial pressure and the high AOP/BrAP ratio imply an increase of approximately double the cerebral vascular resistance distal to the ophthalmic artery (including the brain). The abnormally high ophthalmic arterial pressures mean that the pressure gradient between the arterial pressures feeding the eye and the brain was only approximately 20 mmHg compared with the normal of 40 mmHg. A representative recording of the IOP/PA relation in one of the patients in this group is shown in Fig. 29.5 .

Patent Internal Carotid Arteries Despite Clinical Signs of Strokes

This group of subjects is of special interest, for they had experienced typical signs of the stroke suspects, including a history of TIAs and/or local numbness, but had been found to have patent

Table 29.5. The results on a group of eight adults with clinical signs of stroke suspects.

Parameter	Eye 2	Eye 1	Eyes 2–1
Stenosis (%)	0	0	0
IOP (mmHg)	17.4 ± 1.1	17.2 ± 1.2	0.71 ± 0.3
PA (mmHg)	1.81 ± 0.21	1.72 ± 0.2	−0.1 ± 0.04
OAP (mmHg)	106 ± 3.5	104 ± 2.8	1.4 ± 1.3
POBF (μl min^{-1})	629 ± 91	575 ± 87	−47 ± 23
OAP/BrSyst BP	0.82 ± 0.01	0.82 ± 0.01	0.004 ± 0.004
BrABP (mm Hg)		128 ± 3.5/78 ± 3.3	

Arteriography indicated a complete absence of stenoses of the internal carotid arteries. The measurements in pairs of eyes did not differ significantly and were within the range for eyes in healthy subjects except for the abnormally high ophthalmic arterial pressure and the abnormally high OAP/BrAP ratios. These high values are consistent with an increase of approximately 100% in the normal cerebral vascular resistance

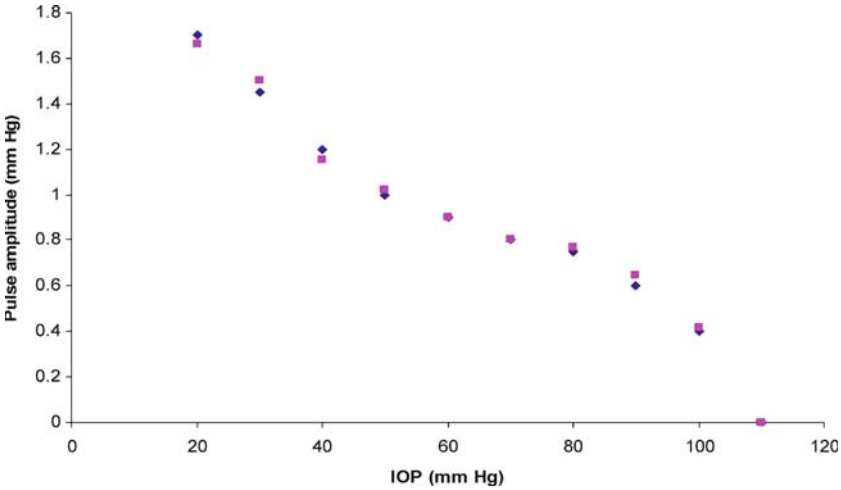

FIGURE 29.5. The IOP/PA relation in an adult male (65 years) with abnormally high ophthalmic arterial pressure and abnormally high AOP/BrAP ratio. The patient suffered from recurrent episodes of right side weakness and left side numbness. The IOP/PA curves were symmetrical and of the S-shape, typical of normal eyes.

internal carotid arteries. The results on this group of ten subjects are summarized in Table 29.6. The IOPs were normal but not identical in pairs of eyes. The PAs and the rates of pulsatile blood flow were substantially below normal, but the ophthalmic arterial systolic pressures were close to the mean of normal.

The symmetries of the PAs and the presence of normal OAPs indicate an absence of stenoses of the internal carotid arteries and are in agreement with the results of arteriography.

However, the PAs and the rates of pulsatile blood flow are below the range found in healthy eyes and consequently, because the arterial

Table 29.6. A series of subjects with subjective and clinical signs of stroke suspects but with completely patent internal carotid arteries.

Parameter	Eye 2	Eye 1	Eyes 2–1
Stenosis (%)	0	0	0
IOP (mmHg)	18.4 ± 1.6	17.6 ± 1.5	−0.8 ± 0.7
PA (mmHg))	1.05 ± 0.2	1.04 ± 0.4	−0.07 ± 0.03
OAP (mmHg)	86.7 ± 9.8	88.3 ± 7.7	−1.58 ± 7.3
POBF (ml min−1)	444 ± 91	451 ± 89	32 ± 21.4
OAP/BrSyst BP	061 ± 0.05	0.61 ± 0.05	0.01 ± 0.01
Brach BP (mmHg)		144 ± 6.7/76 ± 4.4	

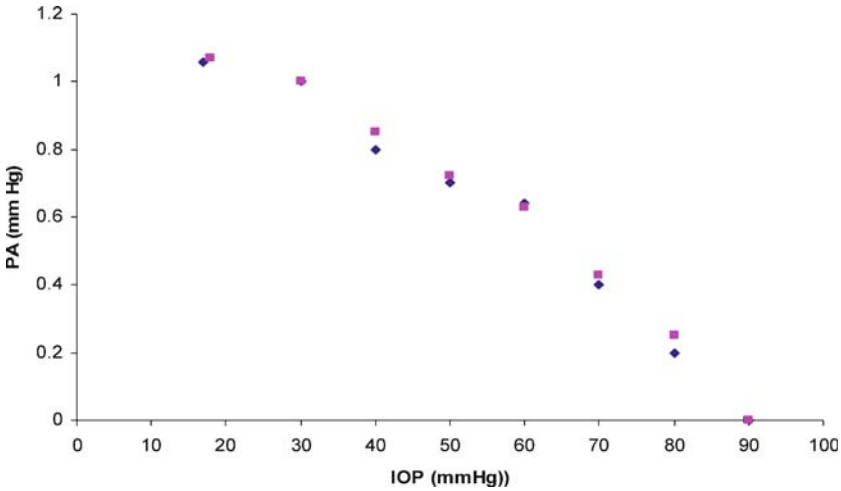

FIGURE 29.6. The IOP/PA relations in pairs of eyes of a patient with a history of TIAs but found to have fully patent internal carotid arteries by arteriography. The PAs and the rates of pulsatile blood flow were abnormally low in the undisturbed eyes and the IOP/PA relations were also abnormally low and consistent with a loss of autoregulation.

perfusion pressures were normal, the vascular resistance in these eyes must have been abnormally high. A typical IOP/PA relation in one of the subjects in this group is shown in Fig. 29.6. The presence of clinical signs of the stroke suspect in the absence of internal carotid stenosis points to the possibility of high vascular resistance in both the eyes and in the brain as the cause of the relative ischemia, loss of autoregulation, and the neurologic abnormalities.

The Effect of Surgical Endarterectomy on the IOP/PA Relation

The measurement of the IOP/PA relation prior to and following surgical endarterectomy on the internal carotid artery provides quantitative data on the immediate success of the operation in restoring patency of the internal carotid artery and ocular blood

flow. Also, the measurements provide a simple means to follow the long-term success of the surgery.

In a review of 15 cases of surgical endarterectomy in subjects with a unilateral moderate to severe stenosis of the internal carotid artery, the ocular blood flow was improved substantially on the operated sides and was associated with a modest increase of flow in the eye on the contralateral side.

However, patency of the artery was not always maintained and the development of a further stenosis was seen, in some cases, 6 months to 12 years after the original surgery. A typical example of the recovery of the blood flow in the undisturbed eye and in the IOP/PA curve after surgical endarterectomy is shown in Fig. 29.7a, b.

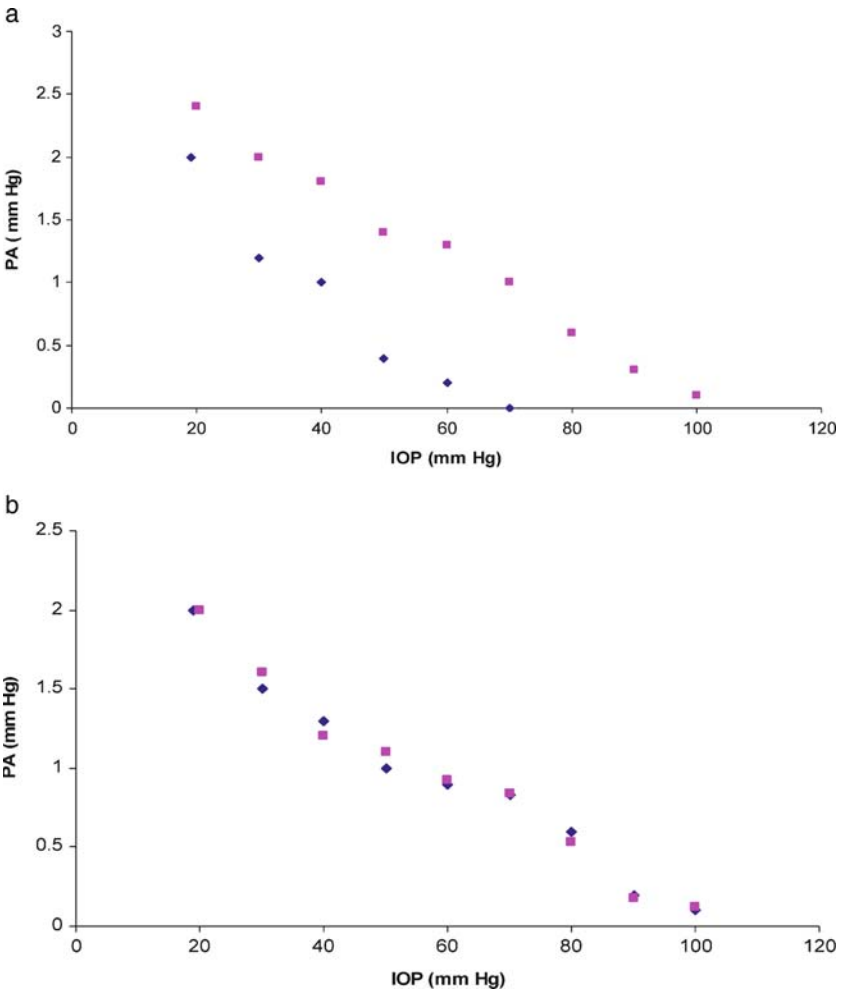

FIGURE 29.7. The effect on the IOP/PA relations in a patient with a severe stenosis of the right internal carotid artery (*diamonds*) and patent left internal carotid artery (*squares*) before (**a**) and after surgical endarterectomy on the right internal carotid artery (**b**).

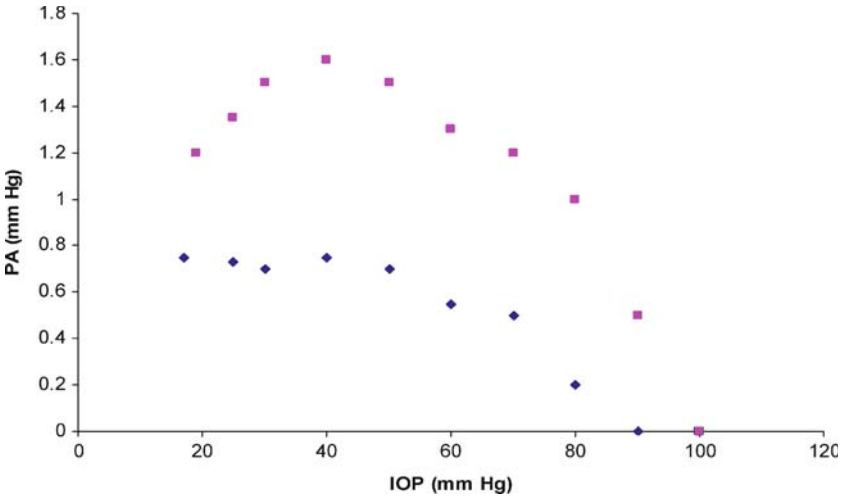

FIGURE 29.8. The IOP/PA relation in pairs of eyes of a patient who had developed symptoms of an impending stroke 12 years following successful bilateral endarterectomy. Arteriography revealed bilateral partial stenoses of both internal carotid arteries and more severe on the left side. (The *diamonds* and the *squares* are the PAs on the left and right eyes, respectively.) The brachial blood pressure was 165/90 mmHg.

In another example, a male of 66 years with severe bilateral stenoses of the internal carotid arteries of approximately 75% was reported to have successful bilateral endorectomy based on Doppler studies. Twelve years later, the patient began to have TIAs and symptoms consistent with a possible renewal of the arterial stenosis and was referred for IOP/PA studies. Doppler studies indicated bilateral moderate stenoses with greater severity on the left side. The IOP/PA curves were measured (Fig. 29.8). The IOPs were asymmetric and the pulsatile blood flows were abnormally low in both eyes (450 and 346 ml $min^{-1)}$. The IOP/PA curves were abnormal and consistent with loss of autoregulation. The BrAP/AOP ratio of 0.54 in the left eye is abnormally low and consistent with stenosis, and the ratio of 0.62 is consistent with a smaller stenosis on the right side.

30

Alzheimer's Disease and the Eye

An abnormal prevalence of glaucoma and retinal nerve degeneration in patients with Alzheimer's disease and the identification of beta amyloids in the eyes of glaucoma patients has led to the consideration that these two diseases have a similar underlying pathology.[17,18] This view has been supported by certain similarities between the histopathology of nerve fiber loss in the retina of glaucomatous eyes and in the brain of Alzheimer patients and the finding that vision is frequently affected in the early phase of Alzheimer's disease.[19,20] In addition, the onset of Alzheimer's disease is accompanied by decreased retinal blood flow and by decreased cerebral perfusion.[21–24] Further, Sadun and Bassi found degeneration and loss of axons in the optic nerve of patients with Alzheimer's disease, which differed from the normal effect of aging on the optic nerves of healthy subjects.[25]

The evidence of an impairment of the blood flow circulation in the eye and to the brain of Alzheimer's patients has been strengthened in observations of the blood flow, autoregulation, and the cerebral vascular resistance in patients with Alzheimer's disease.

Four patients diagnosed with Alzheimer's diseases with bilateral optic neuropathies had been referred for ocular vascular evaluation by the neuro-ophthalmologist. Typical intraocular pressure/pulse amplitude (IOP/PA) relations in pairs of eyes of one of the four patients are shown in Fig. 30.1. The IOPs in the two eyes were equal and normal, but the PAs were well below normal and asymmetric. The pulsatile blood flows in pairs of eyes were 299 and 330 µl min^{-1} and well below the range in healthy eyes. The brachial arterial blood pressures (BrAP) were 120/80 mm Hg, and the ophthalmic arterial pressures (OAP) were 105 mmHg in both eyes (Fig. 30.1) and approximately 20 mmHg higher than the mean ophthalmic pressure of 84 mmHg in normal subjects. These values imply that the vascular resistance is approximately twice normal,

M.E. Langham, *Ischemia and Loss of Vascular Autoregulation in Ocular and Cerebral Diseases: A New Perspective*, DOI: 10.1007/978-0-387-09716-9_30,

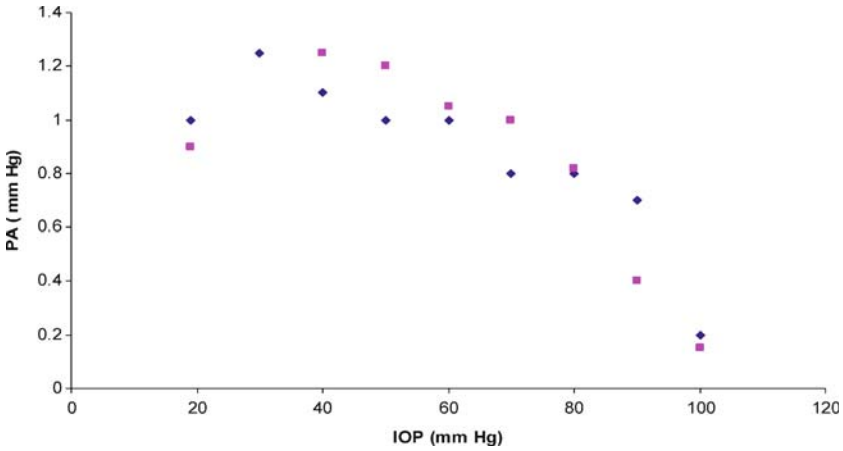

FIGURE. 30.1. Female of 65 years with a diagnosis of Alzheimer's disease with visual impairment. The pulsatile blood flows were 299 and 330 µl min^{-1} in the two eyes, which are substantially lower than the mean of 740 µl min^{-1} in healthy eyes. The brachial arterial blood pressure (BrAP) was 120/80 mmHg and the ophthalmic arterial pressures (OAP) were approximately 102 mmHg, giving OAP/BrAP ratios of 0.83, which are abnormally elevated and consistent with high cerebral vascular resistance. The IOP/PA relations in the two eyes were of abnormal shape and consistent with loss of autoregulation.

and the cerebral blood flow approximately 50% less than the mean in healthy subjects. The OAP/BrAP ratios of 0.87 compare with the mean of 0.67 in healthy subjects and are consistent with abnormally high cerebral vascular resistance.

A second patient was a male of 71 years with a history of a unilateral stenosis of the internal carotid artery, who had undergone surgical internal carotid artery endarterectomy 2 years ago. The surgery had been successful, based on arteriographic studies. The IOPs were normal but the PAs of 1.3 and 1.5 mmHg and the pulsatile blood flows of 464 and 414 µl min^{-1} were below the range in healthy subjects. The brachial blood pressure was 150/85 mmHg and the OAP was 116 mmHg, which is well above the mean of 84 mmHg in healthy subjects. These high OAPs are consistent with abnormally high vascular resistance in the brain and a loss of more than 50% of the normal rate of cerebral blood flow. The IOP/PA relations in the two eyes were similar in shape to that in Fig. 30.1 and indicative of relative ischemia and a loss of autoregulation in the eye.

The third patient had a diagnosis of retinal optic neuropathy. The pulsatile ocular blood flows in the two eyes were low (478 and 524 µl min^{-1}), and the IOP/PA relations in the two eyes showed absence of autoregulation. Further, the OAPs of approximately 105 mmHg in both eyes were abnormally elevated and consistent with high vascular resistance in the eye and the brain and abnormally low rates of blood flow.

The fourth Alzheimer's patient referred for evaluation of the ocular circulation had a diagnosis of nonneovascular age-related macular degeneration and was under treatment with the drug Aricept (donepezil HCI). The IOPs were 17 mmHg (measured with Goldmann and Langham tonometers), the PAs were 1.8 mmHg in both eyes, and the rates of pulsatile blood flow were 535 and 515 μl min^{-1}, values at the low end of the range of values in healthy eyes. The IOP/PA relations were abnormal and similar in shape to those shown in Fig. 29.8 and consistent with loss of autoregulation. The OAPs were approximately 110 mmHg compared with the mean of 84 mmHg in normal subjects and a brachial arterial pressure of 145/85 mmHg, values consistent with abnormally high vascular resistance and abnormally low blood flows to the eye and to the brain disease, there is the possibility that they result from changes in the structure and function of the endothelium in the microcirculation.

Histologically, changes in the endothelial cells include loss of mitochondria and a steady decline in endothelial modulated vasodilatation resulting in decreased blood flow in the microcirculatory network as is found with advancing age and, more specifically, with atherosclerosis. These impairments frequently lead to relative ischemia, hypoxia, and increased deposition of aggregates of beta-amyloid peptides, and finally neurodegeneration and neovascularisation.

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The Ocular Perfusion Pressure and the Visual Threshold

The active autoregulation of ocular blood flow in the healthy eye sustains the intraocular pressure (IOP) and the ocular blood flow within the normal range, despite abnormal low ophthalmic arterial and the ocular perfusion pressures. The important question arises on the extent to which the visual threshold is affected by a decreased ophthalmic arterial pressure and the ocular perfusion pressure.

In five subjects with healthy eyes but with unilateral severe stenosis of the internal carotid artery, the differential visual threshold in pairs of eyes was found to be equal and of normal values despite a mean decrease of more than 50% in the ocular perfusion pressure (Fig. 31.1). In a typical case with a unilateral stenosis of the internal carotid artery, the ophthalmic arterial pressures were 87 and 45 mmHg in the pairs of eyes, and the rates of pulsatile blood flows were 740 and 657 µl min^{-1}, respectively. Thus, the autoregulation was adequate to maintain a normal blood flow and a normal differential visual threshold.

The ability of autoregulation to modify the vascular resistance and increase ocular blood flow to nearly normal in patients with stenosis of the internal carotid artery is consistent with the numerous observations that stroke fails in the majority of patients to cause serious visual impairment. This contrasts with subjects who have ocular disease with moderate to severe loss of autoregulation and is seen dramatically in the loss of stability of the differential time-dependent visual threshold. For example, both in normal and low-tension glaucomatous eyes, loss of stability of the differential light sensitivity is found in the undisturbed eye, and a loss of sensitivity in discrete areas of the retina is found when the IOP is artificially increased. Similar findings have been observed in eyes of patients with age-related macular degeneration, diabetic retinopathy, and primary retinal detachment.

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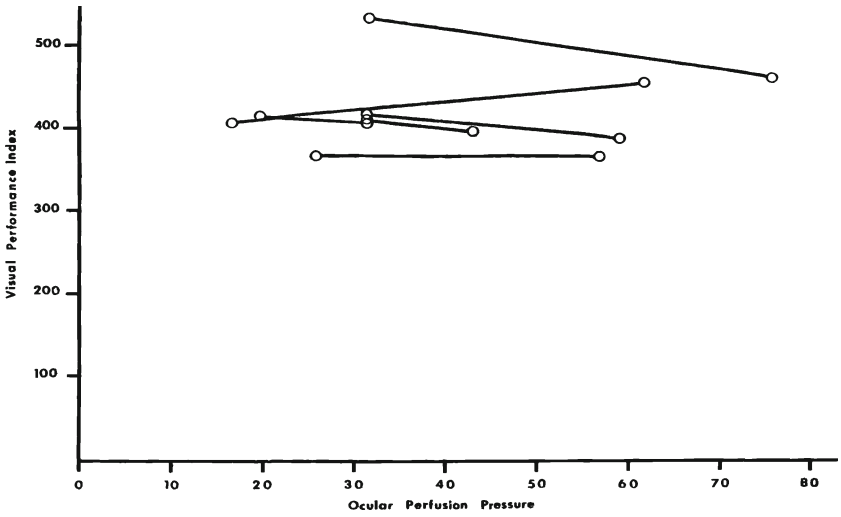

FIGURE 31.1. The visual performances in pairs of eyes of five patients with unilateral stenosis of the internal carotid artery. The results on pairs of eyes are represented by the *circles* joined by the *connecting lines*. The visual performance (central field) was measured using the Heijl-Krakau automatic perimeter (screening program) (From Langham. Visual sensitivity to intraocular pressure. In: Krieglestein GK, Leydhecker W, eds. *Glaucoma Update II/Glaucoma Society of the International Congress of Ophthalmology, Carmel/California.* October 22–27, 1982, Berlin, New York: Springer; 1983:161–167. Reprinted with permission from Springer Science + Business Media.).

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Concepts and New Perspectives

In the summer of 1665 and 1666, England was ravaged by plague and at the University of Cambridge the students, including a young promising undergraduate Isaac Newton, were sent home to avoid infection. In 1666 at the age of 23, Newton purchased a prism at a country fair to study the phenomenon of colors and on his return to Cambridge he assisted Dr. Barrow, his predecessor in the chair of mathematics, in revising his lectures on optics for publication. In 1669 at the age of 27, Newton succeeded to the chair of mathematics and in 1704 published an account of experiments, which established that white light comprised a spectrum of colors in the same order as that of a rainbow.[26] Newton showed how a small beam of sunlight passing through a prism spread out to form a series of colors, and this spectrum passed through a second prism at right angles to the first, retained the same colors and their identity. His conclusion that white light comprised a spectrum of colors was in disagreement with current views of leading physicists of the day, and Newton was fiercely attacked and involved in so much controversy that he nearly lost all interest in further publications. In the course of time, Newton's concept of the nature of light was accepted, and it was Einstein who justly recognized the genius of the man: "The conceptions which Newton used to reduce the material of experience from the beautiful experiments which he ranged in order like playthings." Einstein describes with an affectionate wealth of detail, "… In one person, Newton combined the experimenter, the theorist, the mechanic and, not least, the artist in exposition. He stands before us, strong, certain and alone."[27]

It was approximately 200 years later that the significance of colors to the physiology of vision was born, with the observation of Müller in 1851 of the reddish color of the outer segments of the rods of many vertebrate eyes.[28]

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Subsequently, the observations of Boll in 1876 established that the red color rapidly disappeared after the retina was separated from the choroid.[29] In the numerous studies of Kühne, the pigment was further characterized and given the name rhodopsin.[30] Later it was recognized that the absorption of light by this pigment gave rise to the formation and transmission of electrical signals to the neural layers of the retina and to the visual cortex.

One fundamental physiological aspect of vision is its stability, which is dependent on the blood flow and its autoregulaton maintaining the metabolic needs of the photoreceptors and the communicating nerves to the optic nerve and the visual cortex.

There is now overwhelming evidence from experimental and clinical research that relative ischemia leads to decreased visual sensitivity and instability of the time- and pressure-dependent differential light sensitivity. This new perspective opens up the prospect of new ways to treat the onset and progression of ocular and cerebral vascular diseases.

Open angle glaucoma, age-related macular degeneration, diabetic retinopathy, and Alzheimer's disease increase with age and are associated with a decreased ability of the vascular circulation to provide the required blood flow. The role of the transmural pressure acting across the capillary walls is unique in the eye and appears to play a major role in the onset and treatment of the vascular diseases of the eye. Endothelial cells play a role in the determination of the optimal transmural pressure through modulation of the vascular tone by humoral, neuronal, and mechanical stimuli, specifically through the release of vasodilators including nitric oxide, and vasoconstrictor molecule endothelin.[31,32] Finally, it is clear that pulsatility within the microcirculation plays a very important role in the maintenance of the status quo by modulating endothelial cell and function,[33] and loss of this pulsatility contributes to the onset of pathology of the ocular and cerebral vascular diseases.

The understanding of these fundamental physiological processes and their integration in maintaining the healthy steady state of the microcirculation is the exciting challenge for future progress in the prevention of the onset and progression of ocular and cerebral vascular diseases.

Section 3
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