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# Possible Mechanisms of Primary Angle-Closure and Malignant Glaucoma

Harry A. Quigley, MD, David S. Friedman, MD, MPH, and Nathan G. Congdon, MD, MPH

*Glaucoma Service and the Dana Center for Preventive Ophthalmology, Wilmer Ophthalmological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland*

## POPULATION STUDIES AND RISK FACTORS

During the last 5 years, population-based prevalence surveys, large-scale clinical evaluations, and technological advances in diagnostic methods have contributed to our understanding of primary angle-closure glaucoma (PACG). During the early 20th century, the association between eyes with high tactile pressure, pain, and rapid blindness was called "acute congestive" glaucoma. Eighty years ago, Curran[1] documented the beneficial effect of iridotomy in these eyes and proposed that they had impaired aqueous humor flow into the anterior chamber. Since these eyes represented the vast majority of those recognized to have glaucoma, he doubted that there were very many cases of glaucoma with no symptoms and lower levels of intraocular pressure (IOP), the condition that we now recognize as open-angle glaucoma (OAG).

Rosengren[2] performed a remarkably modern biometric analysis of the anterior segment in glaucoma eyes, detecting 2 groups of patients. Those with shallower anterior chambers had higher IOP and were symptomatic, while those with chambers of normal depth had asymptomatic glaucoma. This was the first quantitative separation of the 2 major forms of primary glaucoma. While Barkan popularized gonioscopy for glaucoma diagnosis and made seminal observations to distinguish PACG from OAG,[3,4] only his later publications show acceptance of the importance of resistance to aqueous humor movement through the pupil.[5] Instead, he stressed the need for broad removal of the iris during iridectomy, believing that this would prevent progressive closure of the angle.

Population-based surveys of the prevalence of eye diseases in Europeans directly contradicted Curran's belief that PACG was the dominant form of glaucoma. Hollows and Graham found much more OAG than PACG in the United Kingdom.[6] Additional surveys in European-derived and African-derived populations confirmed that PACG was approximately one-fifth as common as OAG in these ethnicities.[7–11] By contrast, detailed epidemiologic studies in Asia showed that Mongolians[12] and Chinese[13,14] had dramatically higher rates of PACG, nearly equaling those for OAG, while Indians[15] (and probably other Asians) also had PACG more often than Europeans and Africans.

The nomenclature for PACG is problematic and a new system for standardizing its definitions in prevalence surveys has recently been published.[16] In this system, PAC suspects are persons with bilateral, narrow angles, while PAC is defined when narrow angles are combined with 1) IOP above the 97.5th percentile for the population, 2) peripheral anterior synechiae, or 3) a past acute attack. PACG denotes bilateral narrow angles and glaucomatous optic nerve damage, indicated by a cup/disc exceeding the 97.5th percentile for the population and the presence of an automated visual field defect.

An estimate for the worldwide prevalence of the glaucomas[17] has been updated in light of new survey data, indicating that there are more than 50 million persons with glaucoma in the world, one third of whom have PACG. The proportion of those with PACG who become blind (by the World Health Organization definition, < 20/400 bilaterally) is over 25%,[18] more than twice as high as the estimated blindness proportion for OAG.

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Address correspondence and reprint requests to Harry A. Quigley, MD, Wilmer 122, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287. E-mail: hquigley@jhmi.edu

Consequently, more persons are blind from PACG than from OAG worldwide (about 4 million compared with 3 million). Glaucoma thus ranks as the second leading cause of blindness and PACG will soon become a more frequent cause of blindness than trachoma, making it the second leading cause of blindness in the world. In the developing world, the proportion of older adults is expected to increase, leading to even more persons with PACG.

Population-based studies also demonstrate that acute, symptomatic attacks represent only one fifth of all persons with PACG. The remainder has a chronic optic neuropathy, without symptoms. Other risk factors for PACG include older age and female gender; women are affected more than 3 times as often as men. Since cataract and trachoma also affect women more often, blindness worldwide is much more common among women than men. This disparity deserves more emphasis, especially in cultures in which more resources have typically been devoted to men.

Biometric research by Lowe[19] and Alsbirk[20] confirmed that PACG eyes are smaller in axial length, have flatter corneas, shallower anterior chambers, and thicker lenses. In recent research at the Singapore National Eye Center,[21] these differences were documented by ultrasound biomicroscopy and Scheimpflug photography. Consecutive persons presenting with a unilateral acute attack of PAC underwent immediate treatment to the affected eye and had detailed biometry and provocative testing in the fellow eye prior to prophylactic iridotomy. By comparison to age-matched persons randomly selected from the same geographic urban area, the fellow eyes had several differences: their axial length was 5% shorter, their lens was 7% thicker, their chambers were 24% shallower, and the resultant anterior chamber volume was 37% smaller. However, none of these statistically significant differences provided adequate predictive power to definitively separate those eyes with narrow chambers in which PACG will develop from the much larger proportion of small eyes that will not develop PACG. For example, gonioscopy provides a clue as to the presence of PAC, but does not give a definitive identification of these eyes.[22]

Further evidence that known anatomic factors do not fully explain PACG came from population-based data gathered by Congdon et al.[23] Since the prevalence of PACG among Chinese persons is 5 to 10 times higher than among other ethnicities, and since small eye size is a risk factor, it seemed likely that the Chinese population would have a higher proportion of small eyes. Yet when axial length, chamber depth, or other measures were compared, Chinese persons had distributions of ocular biometric parameters that were indistinguishable from those measured in persons of African or European descent (Fig. 1). In detailed comparisons of mean anterior chamber depth across populations that used historical data, other investigators suggested modest differences. The deepest chambers were found in Europeans, with shallower values for Chinese and the shallowest among Eskimos.[24] Clearly, smaller ocular biometry is a risk factor for PACG, but the differences among ethnicities in axial length or chamber depth are not dramatic enough to explain the large excess of angle closure in Chinese persons. Chinese eyes have more angle closure, but not because the Chinese population has a much higher proportion of small eyes. Rather, small eyes among the Chinese are more likely to develop PACG than small eyes among other groups. It is clear that the cross-sectional study of known anatomic factors in PACG eyes does not fully explain observed racial differences in PACG epidemiology. We must study the physiology of these eyes to discover contributing factors that cause some small eyes to develop PACG. This is the subject of this review.

## ESTABLISHED PHYSIOLOGY: PRIMARY ANGLE CLOSURE IS IMPROVED BY IRIDOTOMY

Curran's hypothesis that aqueous is somehow obstructed in moving through the pupil can be confirmed

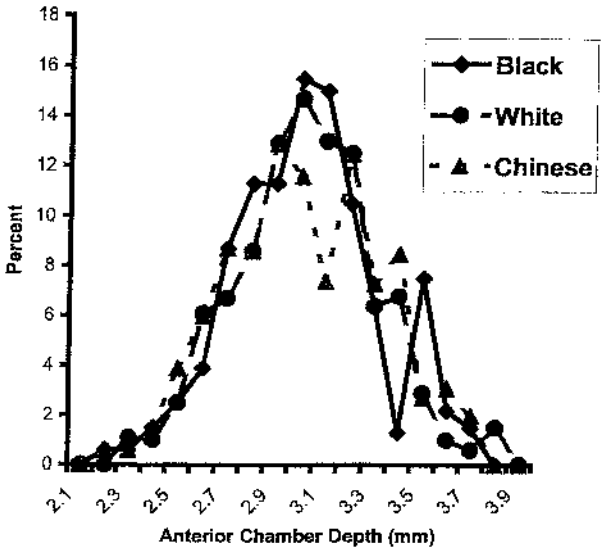


**FIG. 1.** The distribution of anterior chamber depth is shown for 3 population-based samples of adult persons, European-derived (white), African-derived (black), and Chinese (data drawn from Congdon[23]). There is no statistically significant difference among the groups; specifically, the Chinese persons from Taiwan did not have proportionately more shallow chambers compared with Baltimoreans (black and white). The high prevalence of PACG among Chinese persons must, therefore, derive from factors other than a simple excess of small eyes.

by observing the result of laser iridotomy. The iris has a forward convex shape that flattens dramatically in its periphery when a hole is made. The central iris settles down upon the lens (Fig. 2), and pigment can often be seen to flow from posterior to anterior chamber. But is this "pupillary block" a unique feature of certain unusual eyes, or is it present in most eyes to a greater or lesser degree?

First, it is obvious that the pressure behind the iris must be greater than the pressure in front of the iris, since aqueous moves from the posterior to the anterior chamber. It is equally obvious that aqueous encounters finite resistance in passing through the narrow iris–lens channel. By placing reasonable estimates of the anatomic dimensions for the channel between the iris and lens into equations based on standard fluid dynamics analysis, Silver and Quigley suggested that the IOP in the posterior chamber could be substantially higher than that in the anterior chamber under certain circumstances.[25] Direct measurement of channel dimensions in vivo is not technically possible, but images from ultrasound biomicroscopy (UBM) show that the iris and lens are so close at the channel that their separation cannot be resolved with this instrument. In fact, users of UBM refer to this area as the iris–lens contact distance, suggesting that the iris actually rests on the lens[26] (Fig. 3). Some have suggested (without direct evidence) that flow through the pupil is episodic, with aqueous building up in the posterior chamber for a period of time, then passing through the pupil in a bulk movement. Whether movement is episodic or continuous, resistance to aqueous movement through the iris–lens channel is potentially substantial. The model proposed by Silver and Quigley assumes that there is a finite resistance and estimates its magnitude. For this model, continuous flow is assumed, through a fluid-filled area, shaped like a flat doughnut, in which the iris and lens are close, but not touching (Fig. 4). The theoretical, axial resolution of UBM has been estimated at 25 μ; therefore, the channel height must be less than this (since the images show no separation) and values from 3 to 20 μ were used in our calculations.[25] The length of the channel must also be at least as long as the area through which UBM fails to see a separation. In published data, this varies from 0.5 to 2.0 mm.[27]

Interestingly, under some realistic solutions of the channel dynamics, the pressure behind the iris is typically 1 or 2 mm Hg higher than that in the anterior chamber, and could be as much as 5 to 10 mm higher (Fig. 5). It will be important to determine if a difference of this magnitude does occur in human eyes. This is relevant to clinical management because standard tonometry measures IOP by applanating the cornea, which is subjected to the anterior chamber IOP. The posterior eye, including the retina and optic nerve, are exposed to the higher, posterior IOP. This could be a previously undetected risk factor in causing glaucomatous damage. In fact, there is not 1 "IOP", but at least 3 (the third will be discussed later).

The effect of iridotomy is to eliminate the posterior–anterior pressure difference across the iris. An opening of almost any visible size would effectively carry normal aqueous flow (2 μL/min) without significant resistance.[28] The typical behavior of the iris without a pressure differential is to assume a flat peripheral

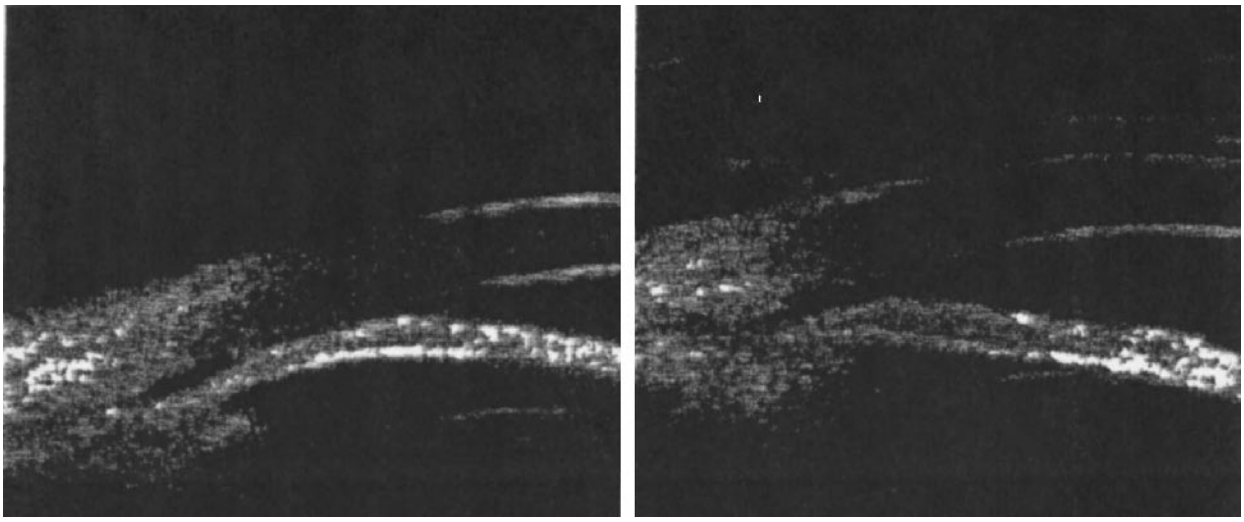

**FIG. 2.** Ultrasound biomicroscopy images of the cornea, iris, and lens of an eye with a forward convex iris configuration prior to iridotomy (left). After iridotomy (right), the iris appears to be closely apposed to the lens centrally, and in its periphery it takes on a flatter shape. These changes derive from the equalization of IOP on the 2 sides of the iris when the hole is made.

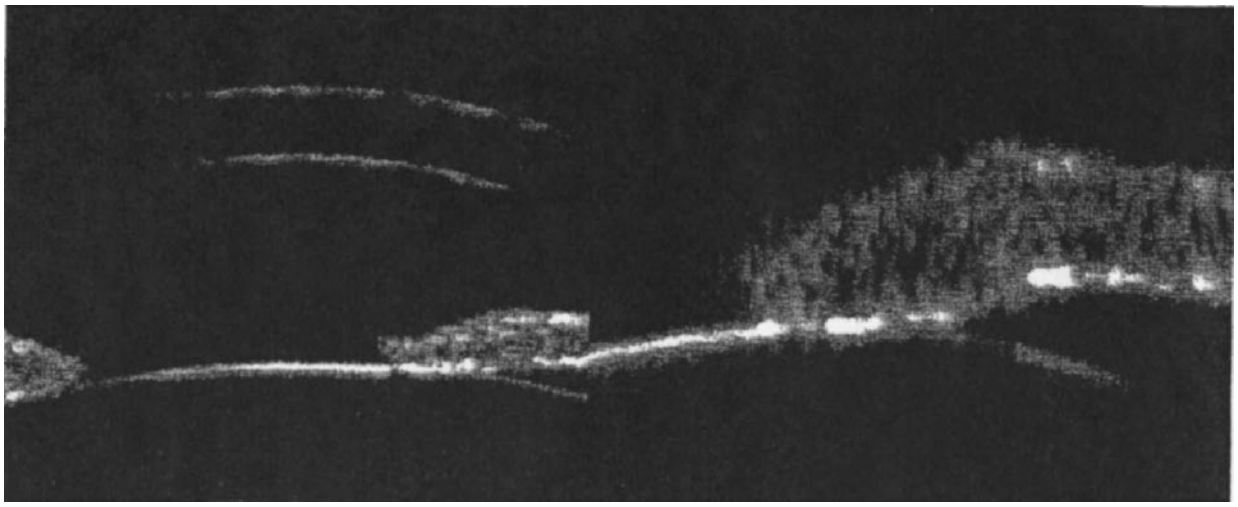

**FIG. 3.** Ultrasound biomicroscopy of the pupil area, showing the cornea, iris, and lens (left). At higher power (right), the iris appears to be in contact with the lens for more than 1 mm. There is, however, a flow of aqueous through this zone, indicating that there is in reality a fluid-filled iris–lens channel, whose height is less than the resolving power of the UBM (i.e., <25 μm).

configuration when viewed gonioscopically[29] or by photographic and ultrasound imaging (Fig. 2).[27,30–32] But the central anterior chamber depth has not been detected to change acutely with iridotomy in PAC suspect eyes.[30–33] Some studies show a 50-μ backward lens movement, though none of these investigations found a posterior lens movement after iridotomy that was statistically significant. We will return to this point later in this review.

## WHY IS THE IRIS CONVEX?

The iris is similar to a sail inflated by the wind. Tiedeman published an analysis of why the iris takes on a bowed forward configuration.[34] The fundamental iris contours calculated with his model agreed with observations using the Scheimpflug camera by Jin and Anderson.[31] The Tiedeman analysis treated the iris as a thin shell firmly attached at the iris root. The forces acting on it were those of the radially oriented dilator fibers, the centrally oriented sphincter, the force acting to hold it to the iris root, and the hydrostatic pressures in the posterior and anterior chamber. There is a force needed to lift the iris away from the lens that is equal to (pressure in posterior chamber − pressure in anterior chamber) times the area of the pupil. The lens is assumed, therefore, not to be in contact with the iris and exerts a force only as it determines the configuration of the iris–lens channel, whose resistance to flow is calculated in the Silver analysis described previously. The iris in the model takes on a convex shape, which increases in forward bowing when the lens is more anterior relative to the iris root (Fig. 6).

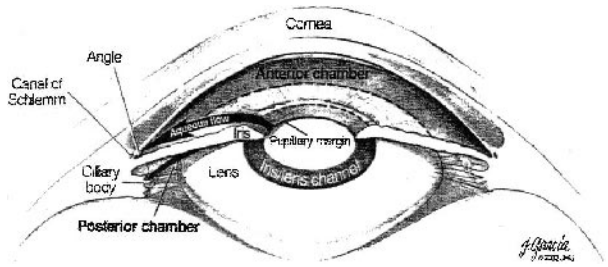


**FIG. 4.** Schematic diagram showing the movement of aqueous humor through the iris–lens channel (doughnut-shaped area just inside the pupil).

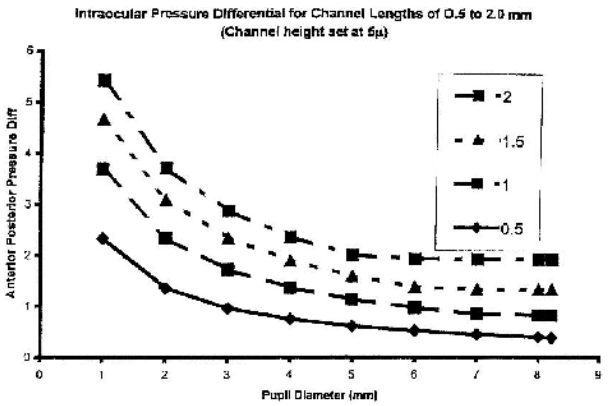


**FIG. 5.** From models that use fluid dynamics equations, Silver and Quigley estimated how the pressure differential between the posterior and anterior chamber (y-axis) increases as pupil size decreases (x-axis)[25]. The calculation is shown for 4 possible lengths of the iris–lens channel at a channel height of 5 μm (the distance separating the iris and lens). The pressure in the posterior chamber under these conditions can be as much as 6 mm Hg higher than that measured by tonometry on the cornea (expressing anterior chamber pressure).

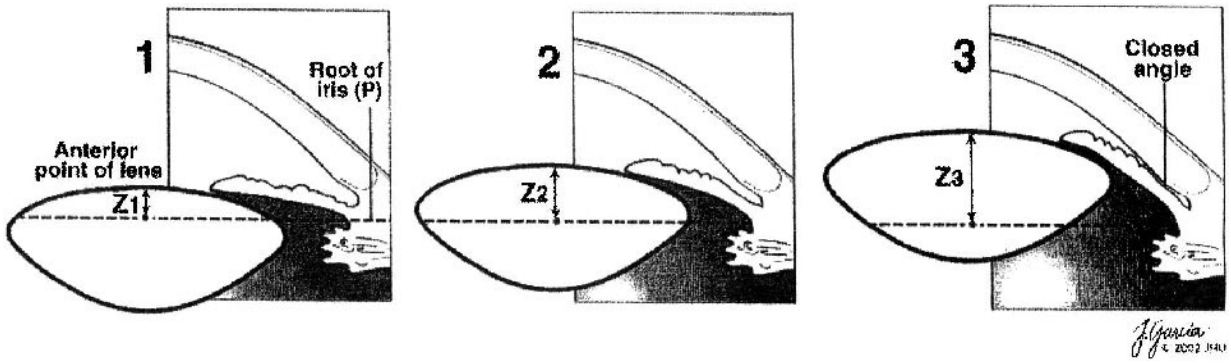


**FIG. 6.** Tiedeman[34] modeled the shape of the iris under a variety of conditions, predicting that the more anterior the surface of the lens (along the z-axis), the more anteriorly bowed (convex) will be the iris shape.

The model also predicts that the iris shape will come closest to closing off the angle when the pupil is in the mid-dilated position (Fig. 7), a feature that coincides with clinical observations during acute attacks.

Combining the Tiedeman and Silver models, we can say that resistance to aqueous movement through the iris–lens channel is a normal phenomenon that leads to a pressure gradient between the posterior and anterior chambers. The force needed to overcome this resistance powers aqueous flow. The pressure differential between the chambers, combined with the physical properties of the iris, accounts for the existence of iris convexity. In effect, "relative pupillary block" is not an uncommon condition, but is present in most phakic eyes. It is those eyes with high levels of resistance in the channel, more anterior lens position, or other risk factors that develop an iris shape that appositionally closes the angle.

It is interesting to speculate whether the shape of the iris depends upon its thickness. Tiedeman argued that a thicker iris stroma would not affect iris shape, but would increase the pressure differential between posterior and anterior chambers. Indeed, in a laboratory model that simulated the anterior segment structures with artificial materials, doubling the iris thickness did not alter its shape, but did increase the posterior to anterior pressure differential.[35] The dark-brown irises of African, Asian, and Hispanic persons may therefore generate a larger difference between posterior and anterior chamber IOP at the same tonometric IOP and the same iris shape (gonioscopic appearance) compared with eyes with thin, blue irises. Again, this may represent an additional risk factor for glaucomatous damage that has not been previously recognized.

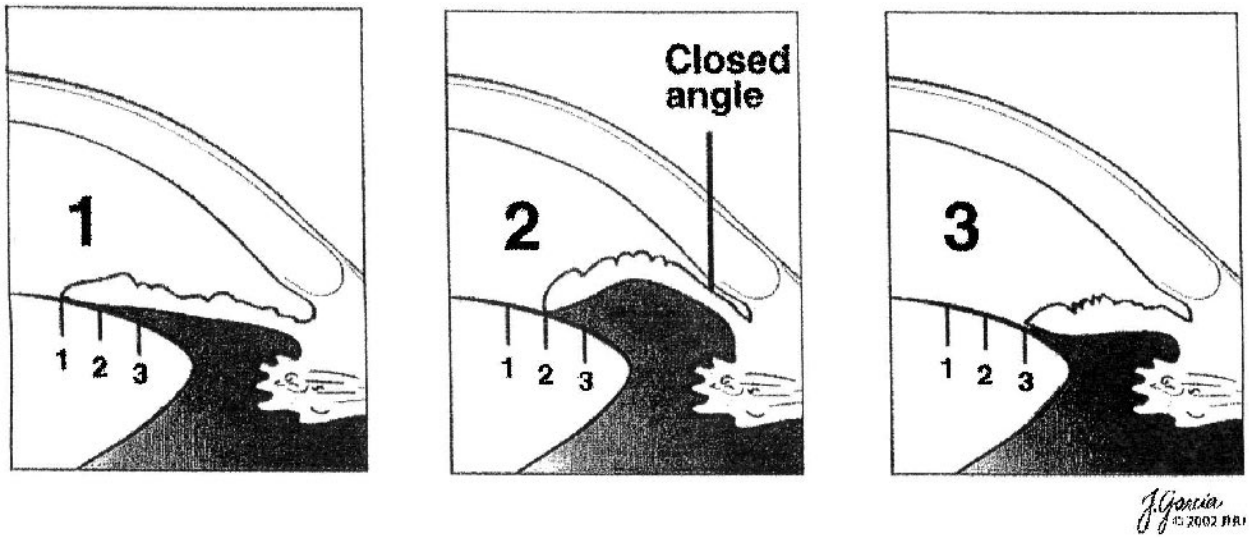


**FIG. 7.** Another prediction of the Tiedeman model is that the iris will take on its most anteriorly bowed (convex) shape when it is in the mid-dilated position, as illustrated schematically.

## EYES WITH PRIMARY ANGLE-CLOSURE GLAUCOMA ARE STILL PHYSIOLOGICALLY ABNORMAL AFTER IRIDOTOMY

All anterior segment surgeons are familiar with a tendency that is present in some eyes known as "positive pressure". In these eyes, during cataract or glaucoma surgery, when an incision is made into the anterior chamber, the iris prolapses, the lens moves forward, and the eye can develop a high IOP. One might be tempted to ascribe this behavior to "pupillary block," as if this were a unique attribute related to high iris–lens channel resistance and convex iris shape. But positive pressure is present in many PAC eyes after iridotomy[36] and is seen in some non–angle closure eyes as well.

In extreme examples, surgeons have detected choroidal expansion in these eyes and have reported removal and study of the extravascular fluid that accumulated.[37,38] The tendency for iris and lens to move forward in PAC eyes probably contributes to the higher prevalence of flat anterior chambers after glaucoma surgery (now mitigated by suturelysis and releasable suture techniques).[39] The extreme form of this phenomenon occurs in nanophthalmos.[40] Since this occurs in the presence of an iridotomy, it must be a physiological behavior not directly related to high iris–lens channel resistance. The amount of force observed is all the more remarkable when we consider that in the operating room the body is supine and the lens and iris mass must be overcome to more them forward against gravity.

Perhaps related to the tendency for forward movement of the iris and lens are 2 other behaviors of some PAC eyes. In the condition known as plateau iris syndrome, eyes have recurring attacks of high IOP even after iridotomy (often in response to pupil dilation). A second phenomenon is continued synechial closure of the angle after iridotomy, known as creeping angle closure. These issues deserve much more intensive study in longitudinal studies to determine their frequency and course. The present report will not attempt to delineate how their mechanisms differ from primary angle closure. However, it is possible that continued forward iris–lens movement after iridotomy plays some role here as well.

In summary, there are abnormal physiological features of eyes with PAC that remain after iridotomy, exemplified by the positive pressure phenomenon. We propose that these risk factors contribute to the initiation of the disease and provide sufficient cause for PAC to occur in small eyes.

## WHAT MOVES THE LENS FORWARD?

Both positive pressure and flat chambers after surgery involve a lens position that is quite anterior. Therefore, we should investigate what might induce the lens to move forward. The lens position is likely to be determined by physiological differences among eyes. Recent evidence suggests that eyes with acute attacks of PAC are physiologically different from normal.[21] These eyes are not just smaller, nor do they simply have narrower angles; compared with control eyes of the same size and with similar angle depth, they respond to provoking stimuli in dysfunctional ways. For example, from the same starting angle depth in room light, when placed in the dark, they become 50% narrower than controls. Likewise, when treated with pilocarpine, their angles open 50% less than control eyes with the same baseline biometry. These findings indicate that there are dynamic, physiological differences between PAC eyes and eyes with the same anatomic measurements at baseline.

There is direct evidence that these physiological differences derive, at least in part, from forces that act on the lens (Gazzard G, personal communication, 2002). Anterior chamber depth was measured in both eyes of persons who had undergone a unilateral acute PAC attack, and the chamber depth was remeasured 4 months after laser iridotomy had resolved the attacks. The mean chamber depth increased quite significantly several months after the attack. Fellow eyes, which had also undergone iridotomy, had shallow but deeper chambers than the attack eye at baseline, and deepened by only about 50 μm on average afterward. Thus, the attack eye not only had a shallower chamber, but deepened by a statistically significant magnitude, becoming nearly the depth of the fellow eye after resolution of the acute event.

Previous studies that measured central anterior chamber depth before and after iridotomy found no significant deepening, though each found that the peripheral iris configuration became flatter. As with the fellow eyes in the previously cited data, the central chamber depth increased by 50 μm at most.[30–32] While some studies were confounded by the use of miotic eyedrops,[33] the prevailing conclusion was that the lens did not move posteriorly after iridotomy. In fact, the simple elimination of the trans-iris pressure differential might alter lens position (and deepen the chamber) slightly. The lens is subjected to the posterior chamber pressure over its posterior surface and over all of its anterior surface except that portion in the pupil—for which the lower anterior chamber ambient pressure is operative. Iridotomy would eliminate

any differential pressure exerted on the lens (the pupillary zone would have equal pressure to that in the posterior chamber), which would perhaps allow a slight posterior movement (perhaps equal to the 50 μm or so that is seen in our data and other studies). By contrast, we hypothesize that the greater difference in chamber depth (lens position) at the time of the acute attack compared with 4 months later in the eyes with acute attacks is due to the fact that a forward movement of the lens contributes to the initiation of the attack, causing greater iris convexity. In this view, the attacks result from small anatomic dimensions and an additional physiological event that causes anterior lens movement. This lens movement was not seen in prior studies of chamber depth after iridotomy because they were carried out in prophylactic iridotomy eyes that were not in acute appositional closure at the time of laser surgery.

The tendency for the lens to move anteriorly in acute attacks and potentially in the chronic form of the disease as well may derive from expansion of the choroid. There are many clinical syndromes in which expansion of choroidal volume leads to shallowing of the anterior chamber, including inflammations (uveal effusion, Vogt-Koyanagi-Harada, pan-retinal photocoagulation), infections (HIV), suprachoroidal hemorrhage, high vortex vein pressure (Sturge-Weber, scleral buckling surgery, orbital tumor, central retinal vein occlusion), extremely small eye size (nanophthalmos), metastatic choroidal tumor, pharmacological reactions (sulfa-based antibiotics and topiramate), and arteriovenous malformations (carotid–cavernous sinus fistula).[41–51]

Nanophthalmos is the extreme end of a continuum in which choroidal expansion leads to forward lens movement. It is our contention that many eyes share this feature, even if they are not small enough to be considered nanophthalmic. The choroid is a highly vascular structure whose choriocapillaries are somewhat permeable to small proteins. The choroid has one of the highest ratios of blood flow to tissue volume in the body. Its thickness is approximately 400 μm in the human eye when measured in vivo. However, its volume (thickness) is variable and is regulated by several parameters, including arterial and venous pressure in choroidal vessels, colloid osmotic pressure of the choroidal extracellular space, and IOP.

Normally, pressure in the vitreous cavity is 2 mm Hg higher than that in the potential space between the choroid and the sclera.[52] Taken together with the previous delineation that the anterior chamber IOP is lower than the posterior chamber IOP, this means that there are at least 3 separate IOPs, not just 1. The existence of a pressure differential between the choroidal potential space and the vitreous cavity indicates that there is a natural tendency for the choroid to expand inward that is opposed by the IOP in the posterior eye. The choroid is known to change its thickness in a regulated and active manner in response to form deprivation.[53,54] This seems to be a physiological mechanism to place the retina closer to the point of clearest focus. In the monkey, this regulated choroidal expansion can be more than 50 μm. Other observations have shown that the human anterior choroid expands substantially with acute elevation of episcleral and orbital pressure induced by playing the trumpet (increasing from 371–440 μm).[55] This acute change probably results from an expansion of choroidal blood volume. Increases in orbital venous pressure would necessitate increases in choroidal venous pressure, expanding the intravascular space of the choroid. However, as soon as orbital venous pressure was restored to normal, the expansion would cease. Thus, an increase in intravascular volume would explain choroidal expansion only in situations with sustained elevation of outflow venous pressure (e.g., carotid–cavernous sinus fistula).

A more likely cause of sustained choroidal expansion is an increase in the volume of the extravascular space of the choroid. Normally, there is a relatively low concentration of small protein molecules in the choroidal stroma (and even fewer large proteins). Some clinical situations increase the levels of large proteins in the extravascular choroid.[56] These situations are precisely those in which choroidal expansion occurs in association with high IOP. If abnormal concentrations of protein leak into the choroidal extravascular space, the normal osmotic pressure difference that moves fluid back into the choroidal vessels is diminished, allowing choroidal expansion. Proteinaceous fluid must exit this space by passing through the sclera or via its emissary channels that carry the vortex veins. This would occur more slowly in eyes with thicker sclera or, whose sclera had lower fluid conductivity. There is qualitative evidence that nanophthalmic eyes have altered scleral properties,[57] and smaller eyes do, in general, have thicker sclera. The surface area for fluid to leave through the sclera is lower in small eyes—in fact dramatically so, since the surface area decreases by the square of the ocular radius. Thus, choroidal expansion would affect any eye in which it occurred, but would be more long-lasting in smaller eyes. It is possible that some small eyes have abnormal choroidal vascular permeability or low scleral conductivity, providing a physiological weakness that compounds the disadvantages of their anatomic size.

Increases in choroidal volume could move the lens forward very dramatically (Fig. 8). In the average human eye, the vitreous volume is approximately 5000 μL, the choroidal volume is about 480 μL, and the anterior

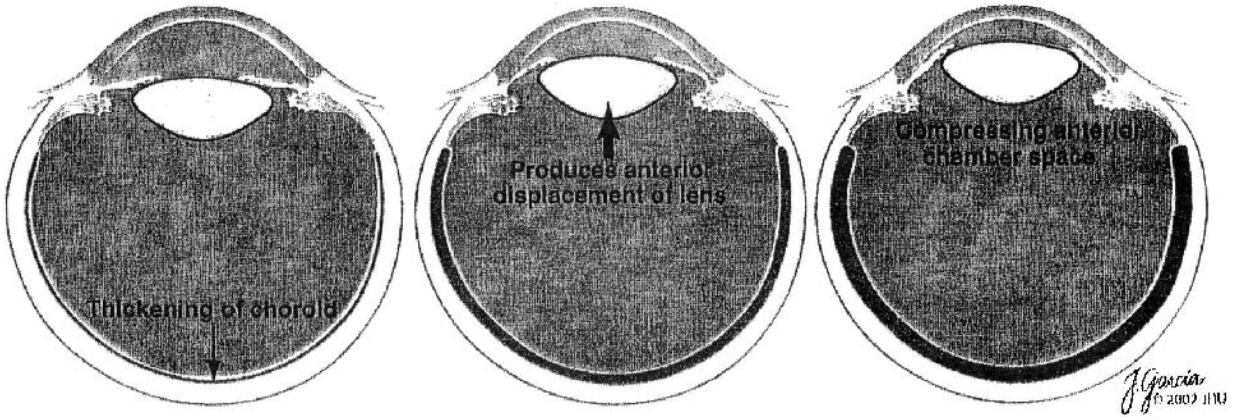


**FIG. 8.** Schematic illustration shows the substantial effect of choroidal expansion on the eye. The example presumes that an increase in choroidal volume is accommodated by immediate exit of aqueous humor from the anterior chamber (as in the situation during surgery when a corneal track incision is made). With a 20% increase in choroidal thickness, there is 100 μL in volume displacement—equal to the volume of the anterior chamber in a typical PAC eye. If there is no anterior wound, the pressure–volume relationship of the human eye suggests that IOP would rise to 60 mm Hg with a similar expansion.[59]

chamber volume is about 150 μL. If an incision is made into the anterior chamber, and the choroid expands by 20%, it would occupy 100 μL of space, equal to two thirds of the normal anterior chamber volume. In a small eye, the anterior chamber volume is only 100 μL; hence, all aqueous would exit, with the iris forced against the cornea. This is precisely the situation in eyes exhibiting positive pressure. If the choroid expands in a closed eye, there would be a significant IOP increase that is predictable by knowing the pressure/volume relationship of human eyes.[58]

If the choroidal volume increases, pressure within the corneoscleral shell would rise. It is likely that as aqueous humor exits from the trabecular meshwork under this increased pressure, the choroid would maintain its expanded state or even expand further, causing the lens to move forward. Clearly, forward movement of the lens (shallowing of the anterior chamber) occurs in a number of clinical settings when anterior outflow of aqueous (e.g., through a filtering site) is driven by normal or elevated IOP. But in the eye with high iris–lens channel resistance and forward convexity of the iris at baseline, such forward lens movement would exacerbate the existing situation, adding this physiological event to the basic anatomic disadvantage of the small eye. In summary, PAC could be a result of small anatomic size and an additional expansion of the choroid.

One impediment to the acceptance of this hypothesis is the frequent association of clinically visible choroidal expansion (choroidal detachment) with low IOP. We have strongly associated choroidal detachment and low IOP in our thinking. There is both a terminological issue and a physiological issue. Duke-Elder stated that, in hypotony "the choroid is not in the strictest sense detached from the sclera but . . . oedematous: cilio-choroidal edema would be a more accurate term [than choroidal detachment]."[59] Hypotony is frequently associated with breakdown of the blood–aqueous and blood–retinal barriers, and it is not unreasonable to assume that there is breakdown of the blood/choroidal barrier as well. When IOP is low, the choroid expands extravascularly with increased protein followed by passive water retention. The choroid's normal tendency for expansion into the eye is permitted by lower pressure in the vitreous cavity. Furthermore, the fluid in the extravascular choroid would take considerable time to exit via the sclera when the normal pressure head driving across the sclera is reduced during hypotony.

The association between low IOP and choroidal expansion in hypotony does not at all preclude choroidal expansion as a cause of high IOP. In the situations listed above that are known to have increased choroidal volume (e.g., with elevated orbital venous pressure), the additional choroidal volume cannot be rapidly accommodated by exit of fluid. The intact eye responds to these choroidal expansions with significant IOP elevation. Choroidal expansion can, therefore, be associated with low or high IOP. When IOP decrease is the first event, low IOP is cause of expansion of the choroid (low IOP is the cause). Alternatively, if the first event is expansion of the choroid, this leads to high IOP (choroidal expansion is the cause).

## WHAT IS THE EVIDENCE FOR CHOROIDAL EXPANSION CAUSING ANTERIOR LENS MOVEMENT IN PAC AND PACG?

The most obvious clinical example of this phenomenon that is familiar to most ophthalmologists occurs

during surgery on an eye with nanophthalmos. Choroidal expansion is associated with high IOP and anterior lens movement. Until recently, however, the same physiological behavior had not been documented in the more typical PAC eye. Gazzard et al.[60] found choroidal expansion to be present in several PAC eyes studied shortly after acute attacks; the choroid had become thicker by 140 to 400 μm in these eyes. While it is possible that choroidal expansion was unrelated to the attacks or even resulted from pressure-lowering treatment, we believe that the expansions preceded and contributed to the attacks, and persisted thereafter. At present, we cannot determine how frequently and how actively choroidal expansion contributes to acute PAC attacks because of a lack of accurate measurement systems for this parameter. The measurement of choroidal thickness is possible in the anterior globe by ultrasound biomicroscopy. Laser-Doppler interferometry, ocular coherence tomography, or other methods should be used to test this hypothesis more rigorously.

## WHEN THE CHOROID EXPANDS, HOW IS FORCE TRANSMITTED TO THE LENS?

An increase in choroidal volume would simply raise the pressure uniformly within all ocular compartments if there was no loss of fluid from any of the compartments. But, there is a continuous outflow of aqueous from the conventional outflow pathway. Choroidal expansion would to increase the absolute IOP in each compartment, increase the absolute pressure differences within the eye (higher in the posterior globe than in the anterior chamber), and induce a volume loss from the anterior chamber to compensate. If water normally passed through the vitreous without any resistance, the volume increase posteriorly would be accommodated by fluid exit from the anterior chamber without any shift in iris or lens position. The choroid would occupy a larger proportion of the posterior globe at a new equilibrium IOP.

But, the chemical structure of the vitreous does limit free diffusion of water. The vitreous consists mostly of water with some collagen and glycosaminoglycans. Persons with PAC are typically older adults, with a high prevalence of posterior vitreous detachment. Not only is the fluid conductivity of the vitreous finite, but an increased pressure differential across the vitreous decreases its ability to transmit fluid.[61,62] In an important experimental study, Epstein et al.[62] found that substantial differences in pressure across the vitreous body lead to decreases in vitreous fluid conductivity in human eye bank eyes. This could lead to a disequilibrium situation, since the increased demand for posterior to anterior fluid flow would not be relieved by sufficient fluid movement. Any further choroidal expansion would set up a vicious cycle of higher pressure difference and poorer vitreous conductivity. The vitreous gel would compress and move forward, carrying the lens with it. The forward movement of the lens could cause abnormalities in 2 ways. In small eyes that are predisposed to PACG, forward lens movements of even a modest amount would further increase resistance in the iris–lens channel, intensify forward iris convexity, and make angle closure more likely. Thus, poor vitreous fluid conductivity could contribute to the causation of PAC. The second situation would pertain in eyes not typically predisposed to PAC. The lens would move forward much more dramatically, without producing iris convexity, as the angle configuration is not that of PAC. The lens would come far forward until the chamber was nearly flat before the iris blocked the angle (Fig. 9).

The second clinical picture that has just been described is malignant glaucoma, with pooled fluid in the posterior chamber, a relatively opaque, forward displaced vitreous, the lens and iris far forward of their normal positions, and high IOP.[63] Malignant glaucoma has been said to be due to "misdirected aqueous," but this explanation violates the laws of physics. If aqueous humor could move from the ciliary body through the vitreous gel to the fluid compartment behind it to cause a pressure differential, it would be able to move back the opposite way just as easily. A functional ball valve would somehow need to be invented to propose a 1-way, posterior movement of aqueous humor, and none has ever been documented. Rather, we believe that the inciting event for malignant glaucoma is more likely to be the inability to generate fluid flow across the vitreous sufficient to compensate for aqueous outflow anteriorly under the higher pressure conditions that are generated by choroidal expansion. Malignant glaucoma would be more likely to occur in an eye with higher than normal resistance to vitreous fluid flow. Hence, it is possible that limited fluid flow through the vitreous could contribute to PAC in eyes with other risk factors for that disorder, and could be the major predisposing factor for malignant glaucoma in eyes of normal size.

Anteriorly, the vitreous gel is in direct contact with the lens. For water passing through the vitreous humor from posterior to anterior, the zone through which it exits the vitreous gel is delimited peripherally by the apposition of the vitreous to its insertion and centrally where it contacts the lens. The area through which fluid may pass is shaped like a doughnut with the lens occluding the central area and the ciliary body forming its outer perimeter. Epstein et al.[62] have pointed out that as the vitreous

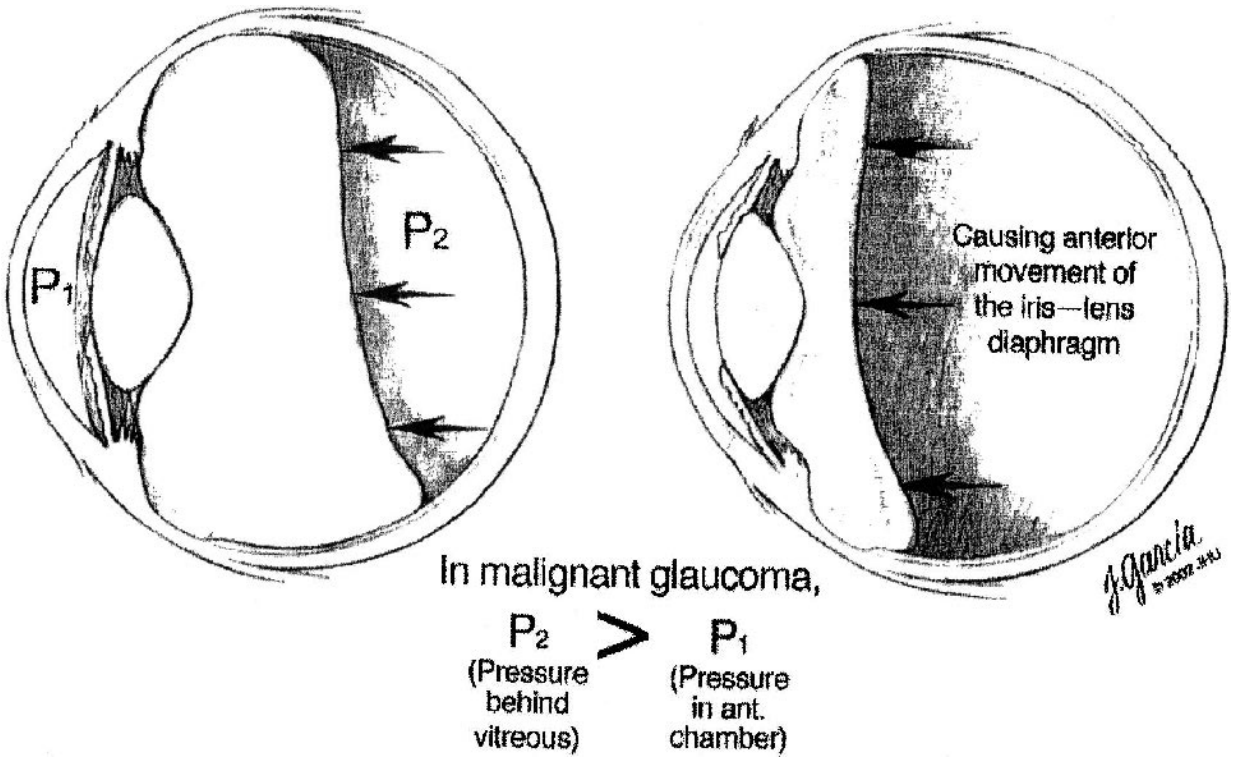


**FIG. 9.** A proposed mechanism of malignant glaucoma is illustrated schematically. In the left diagram, the normal pressure in the posterior vitreous cavity is higher than that in the posterior and anterior chamber. With an expansion of the choroid, the pressure within the corneoscleral shell increases and anterior outflow increases. There is a finite ability to transmit fluid through the vitreous cavity, allowing anterior movement of the compressed vitreous humor and the iris and lens. When transvitreous flow is insufficient to equalize the pressure differential, the vitreous compresses more, further decreasing its fluid conductivity and establishing a vicious cycle. The vitreous moves forward, carrying the lens and iris with it (right diagram). In eyes that are predisposed to PAC, the forward movement of the lens would need to be only a modest shift to potentiate iris bowing and cause angle closure. In larger eyes with no PAC tendency, the picture of malignant glaucoma with a deep-chambered fellow eye would result.

humor presses forward, the anterior diffusional area would decrease, making malignant glaucoma more likely to happen. They provided an additional reason why this anterior fluid diffusion might be even more limited in PAC eyes (Fig. 10): the axial length of PAC eyes is smaller, making the outer diameter of the doughnut smaller. We point out a second element, that the lens in angle closure eyes is thicker and potentially larger, so that the inner, blocked area is bigger. The typical PAC eye probably has only half the forward diffusional area of a normal eye. Even without this disadvantageous anatomy, vitreous collapse could result from poor conductivity in a normal-sized eye. Malignant glaucoma is known to occur in phakic eyes of normal size. However, it is sometimes recognized in a subject with small eyes presenting with an acute attack that is not cured by iridotomy alone.

If this theory is correct, choroidal expansion should be detected with malignant glaucoma. Indeed, the coexistence of a picture identical to malignant glaucoma with annular uveal swelling has been observed by ultrasonic biomicroscopy.[64] The so-called choroidal detachments seen in this setting are interpretable in the present context as expansions of choroidal volume that contribute to forward lens movement, aided by poor vitreous fluid conductivity.

The therapies for malignant glaucoma all fit this hypothesis well. Cycloplegia widens the ciliary body diameter, increasing the forward diffusional area for fluid to leave the posterior vitreous cavity. Osmotic agents remove fluid from the eye, and it is quite possible that their site of action is the extravascular space of the choroid. A bolus of hyperosmotic fluid initially would pass through the choroidal vessels, permitting it to generate a high osmotic gradient between vessels and the choroidal stroma. Finally, it is obvious that vitrectomy would remove the resistance to fluid movement by removing the vitreous.

In summary, a second contributing cause in positive pressure is poor vitreous fluid conductivity. This may occur as a dominant feature of eyes that are not initially at risk for PAC (and have deep chambers in the fellow

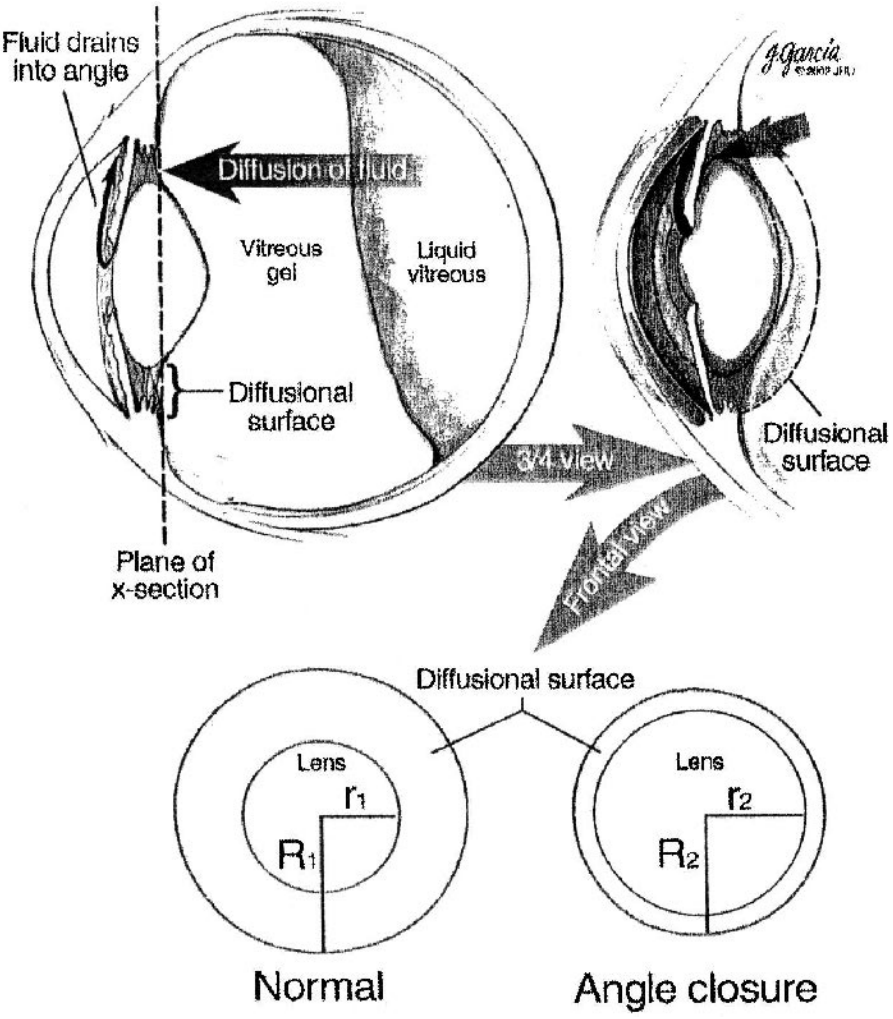


**FIG. 10.** In the mechanism described in Figure 9, the fluid that must traverse the vitreous body from posterior to anterior can only exit the vitreous gel from an anterior surface that is delimited by the vitreous base peripherally (shown by radius R) and the vitreous–lens contact zone centrally (determined by lens–vitreous contact zone radius, r). If this doughnut-shaped diffusional surface area is smaller, the malignant glaucoma mechanism is more likely to be operative as described in Figure 9. Eyes predisposed to PAC have smaller axial lengths and possibly larger lenses, making the surface area for anterior diffusion substantially smaller. Calculations suggest that PAC eyes might have only 50% of the area found in eyes of average size.

eye) or as a contributing feature of PAC eyes. Its extreme example is malignant glaucoma, but the phenomenon may be contributory in other eyes, including those with PAC.

## ARE THERE OTHER CONTRIBUTORY FACTORS?

Since we have suggested 2 new physiological contributors to PAC, there may well be others. One major risk factor for PAC is female gender: women are 3 times more likely than men to develop the disease.[12,14] Women have slightly smaller mean axial length than men, but the calculated ocular volume of the average female eye is 10% less than that of men (volume depending upon the cube of the spherical radius). This factor alone might be important in intensifying the events described above. There is cross-sectional evidence that women develop shallower anterior chambers with age than do men. This might result from anatomic or physiological factors, but in either case, the chance for PAC to occur would be enhanced. Furthermore, other factors that may be more prevalent in women include tendencies toward altered vascular permeability or vasospasm (leading to choroidal expansion). In OAG, a history of migraine is a significant risk factor for progression of glaucoma, but only among women.[65]

Patterns in the rate of change of refractive status and biometry over life may contribute to our understanding of which individuals and racial groups are more prone to PACG. In population-based data from several groups, there is shallowing of the anterior chamber and increasing hyperopia during the fifth and sixth decades of life. Cross-sectional evidence among Eskimos[66] and Chinese,[23] 2 racial groups with high prevalence of angle-closure glaucoma, suggests that the apparent rates of anterior chamber shallowing and concomitant increase in

hyperopia are significantly more rapid than among persons of European or African descent. Interestingly, cohort studies among children demonstrate that the rate of progression towards myopia is significantly more rapid among Chinese children than other racial groups.[67] It may be that Chinese persons undergo more rapid, ocular biometric changes over their lifespan, and that this tendency is a risk factor for their higher prevalence of PAC.

Another likely factor may be looseness of the zonule. It is clear that if the lens is more mobile, it will be more easily repositioned anteriorly. Loose zonules are a feature of exfoliation syndrome, and this condition is known to have a higher prevalence of PACG.[68] These suggestions point out that we should be alert to investigate additional physiological contributions to PAC.

## SUMMARY

Previous analysis stressed 2 major elements in PAC: an anatomically small eye and "blockade" of aqueous movement at the pupil. Cases were differentiated mostly by their clinical course (intermittent, chronic, acute, or subacute). In addition, nanophthalmos and malignant glaucoma were treated as separate conditions from PAC.

PAC occurs in eyes with high resistance to aqueous movement through the iris–lens channel, leading to convex iris shape, and iridotomy relieves this component. But PAC eyes show continued dysfunction after iridotomy, pointing to additional contributory mechanisms. One candidate mechanism is expansion of choroidal volume, leading to increased vitreous cavity pressure; another is poor vitreous fluid conductivity. Each of these features can appear as isolated, dominant causes in a single condition (nanophthalmos and malignant glaucoma, respectively), or they may be contributory features in PAC.

These concepts can be illustrated in a Venn diagram format (Fig. 11). Consider that there are 3 components to the disorders that we are evaluating: small eye size, poor vitreous flow conductivity, and a higher-than-normal tendency for the choroid to expand. The diagram shows that an eye could exhibit one or more of these components. There are surely more components than those indicated here (e.g., deficient vascular permeability, female gender, loose zonules). PAC occurs among those with small eyes combined with at least 1 other component cause. The proportion of all small-eyed persons that has additional risk is small. Among those with very small eyes (nanophthalmos), the prevalence is higher than among all small eyes. Choroidal expansion could be a contributor without poor vitreous conductivity and vice versa. Malignant glaucoma could occur in either small eyes or in normal-sized eyes, but all cases would have dramatic choroidal expansion or vitreous flow abnormality.

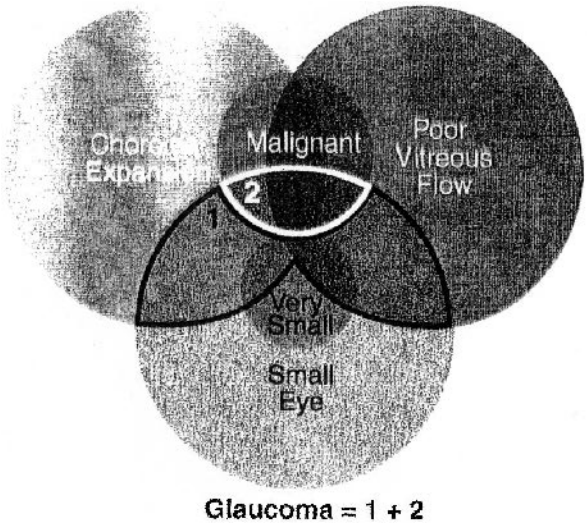


**FIG. 11.** The Venn diagrams indicate the interaction and coexistence of several contributing risk factors for PAC, including small eye size, poor vitreous fluid conductivity, and expandability of the choroid. Eyes that develop PAC probably share more than 1 of these risk factors, and eyes with malignant glaucoma and nanophthalmos are shown as extreme examples of the expression of these phenomena. See text for detailed discussion.

## THESE HYPOTHESES SUGGEST NEW METHODS FOR PROVOCATIVE TESTING

As discussed previously, provocative testing has been considered ineffective in the past. Possibly, its low predictive value results from using IOP as the outcome parameter. Video UBM observations show that the angle dramatically shallows immediately in some eyes when the lighting is dimmed in a room. But, the additional features that generate critical narrowing may not be induced by change in lighting or by dilation of the pupil. Furthermore, a measurable IOP increase may require a longer duration of apposition than is typically allowed.

If choroidal expansion is a contributing cause for PAC, then we should attempt to induce and measure changes in choroidal thickness as a provocative test. Choroidal thickness can now be measured anteriorly with UBM. Measurements of the posterior choroidal thickness are needed that can detect a change of 25 to 50 μm in the axial plane. Alternatively, anterior movement of the lens could be used as a surrogate measure, using optical or ultrasonographic anterior chamber depth measurement.

The Valsalva maneuver might induce an increase in choroidal volume by inverted body posture, neck compression, or alteration in serum osmolarity. While there

are practical issues in implementing each of these, we must try to improve diagnostic specificity for PAC. The imminent, worldwide increase in this disorder demands new ideas, new diagnostic approaches, and better therapy.

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