

Presbyopia and Glaucoma: Two Diseases, One Pathophysiology? The 2017 Friedenwald Lecture

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Presbyopia, the progressive loss of near focus as we age, is the world's most prevalent ocular affliction. Accommodative amplitude is at its maximum (~15 diopters) in the teen years and declines fairly linearly thereafter (Fig. 1).¹ By age 25 about half the maximum accommodative amplitude has been lost, by age 35 two-thirds are gone, and by the mid-40s all is gone. Clinical symptoms usually begin at age ~40. The accommodative apparatus of the rhesus monkey is very similar to the human structurally and functionally and develops presbyopia at the same rate relative to lifespan (Fig. 1).

In primates, accommodation occurs in response to intent to focus on a near object. The efferent arc of the reflex involves stimulation of the parasympathetic efferent neurons in the midbrain Edinger-Westphal nucleus, whose axons terminate and synapse in the orbital ciliary ganglion. The 2nd order parasympathetic neurons innervate the ciliary muscle (CM) and the iridial pupillary constrictor muscle.²⁻⁴ The CM is tethered by true tendons anteriorly to the scleral spur, trabecular meshwork (TM)/Schlemm's canal (SC), and the Schwalbe's line at the junction of the cornea and TM (Figs. 2, 3).⁵⁻⁹ Posteriorly, the CM is also tethered by true elastic tendons inserting into the elastic lamina of Bruch's membrane at the ora serrata (Figs. 2-4),^{5,10} where the pars plana zonules, the intermediate vitreous zonules,¹¹ and the posterior vitreous zonule insertion to lens equator (PVZ INS LE) strands¹² (the vitreous strands that extend from the intermediate vitreous zonule posterior insertion zone to the lens equator) all come together in a small region that we call the intermediate vitreous zonule posterior insertion zone (Fig. 3).^{11,13,14} From there, the elastic network of the choroid extends posteriorly to the elastic fiber ring that surrounds the optic nerve, in turn sending elastic fibers into the lamina cribrosa (Fig. 2).¹⁵ Thus, in effect the CM and the choroid form an elastic network¹⁶ that extends from the TM, SC, and the limbal corneosclera posteriorly to the scleral canal/lamina cribrosa, through which the optic nerve passes (Figs. 2, 3). During accommodation as the muscle contracts and moves forward and inward, the posterior insertion zone of the vitreous zonule as well as the vitreous zonule, the pars plana zonule, the PVZ INS LE, and the choroid are all pulled forward (Supplementary Video S1).

The posterior tendons insert into the elastic network of the choroid, which is continuous with the elastic fibers of Bruch's membrane.¹⁶ Bruch's membrane contains the basement membrane of the retinal pigmented epithelium (PE) and, therefore, is attached to the retina.^{17,18} Thus, in the in vivo eye the

choroid and the retina stretch in parallel with each other during the accommodative response. The question remains how far back the accommodative choroid/retina movement goes.

By "marking" points on retinal photographs (e.g., vascular bifurcations) in aphakic (to avoid lens magnification artifacts during accommodation) monkey eyes, movement of the retina during accommodation can be quantified in terms of both direction and magnitude (Fig. 5). Optical flow analysis shows that the center of movement is at the optic nerve head, and the magnitude of movement increases progressively toward the periphery (Fig. 5).¹⁹ Thus, with every accommodation effort, a peripheral "pull" is exerted on the nerve. Given that accommodation involves constant contraction/relaxation of the CM to adjust the "zeroing in" focusing mechanism, the forces exerted on the nerve head are complex.

Between the optic nerve and the lens lies the vitreous, which until recently has not been imaged during accommodation. Dynamic imaging of the vitreous during the accommodative response is possible in the monkey eye by using contrast agents (triamcinolone, Triesence; Alcon, Fort Worth, TX, USA) suspended inside the vitreous fluid/gel and clinging to the vitreous membranes and ultrasound biomicroscopy (UBM) (Supplementary Videos S2-S12). Still images (UBM and endoscopy) show that there are interconnections between the accommodative apparatus and the vitreous (Fig. 6). During accommodation, the central vitreous, including Cloquet's canal (Supplementary Video S9), moves posteriorly (Supplementary Videos S7-S9) while the peripheral vitreous is pulled forward by the CM (Supplementary Videos S2, S5, S6, S10; Fig. 7). The iris bows backward, collapsing the posterior chamber (Supplementary Videos S3-S5) and fluid flows posteriorly around the lens equator toward the anterior hyaloid and then further into the cleft between the intermediate vitreous zonule and the pars plana. These intravitreal movements occur in the presence or absence of the iris (Supplementary Videos S2, S3, S5-S9). We cannot understand how these data are consistent with the catenary theory of accommodation,^{20,21} and these incompatibilities need further exploration.

Aging of the Accommodation Apparatus

The proximate cause of presbyopia is a loss of crystalline lens deformability,²² which proceeds along the same timeline as the loss of accommodation with age (Fig. 8).²² However, there is also an age-related loss of morphologic responses to pilocarpine in rhesus monkey and human CM (Figs. 9, 10).²³⁻²⁵ In both



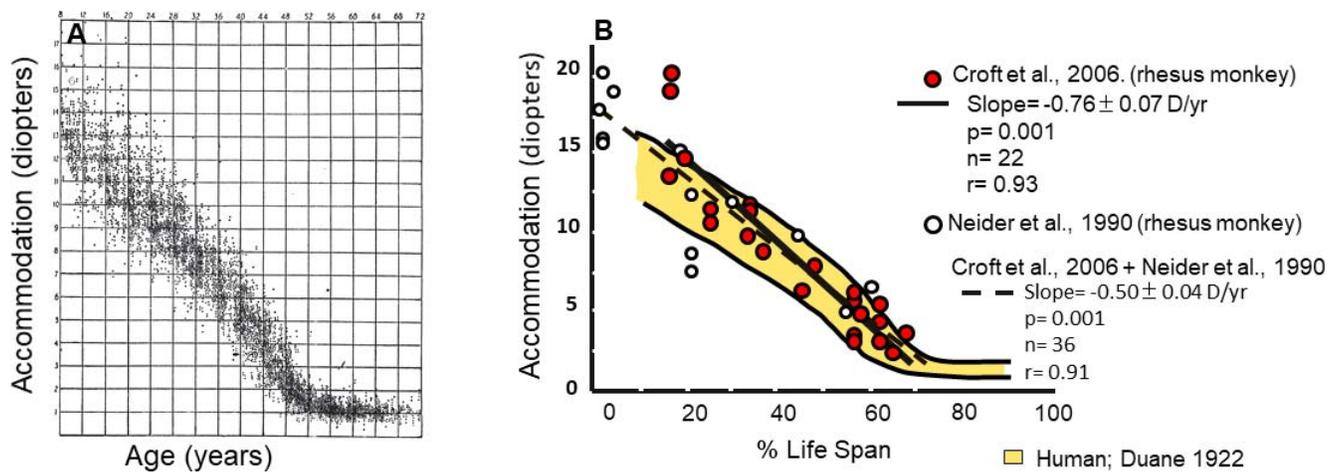


FIGURE 1. (A) Duane's curve showing accommodative amplitude (subjectively measured) of 4,200 patient eyes plotted versus age. Reprinted from Duane A. Normal values of the accommodation at all ages. *JAMA*. 1912;59:1010–1013. (B) Rhesus monkey % lifespan plotted versus accommodative amplitude (objectively measured) induced by central electrical stimulation of the Edinger-Westphal nucleus superimposed over Duane's curve (reprinted with permission from Neider MW, Crawford K, Kaufman PL, Bito LZ. In vivo videography of the rhesus monkey accommodative apparatus: age-related loss of ciliary muscle response to central stimulation. *Arch Ophthalmol*. 1990;108:69–74. © 1990 American Medical Association and Croft MA, Glasser A, Heatley G, et al. Accommodative ciliary body and lens function in rhesus monkeys, I: normal lens, zonule and ciliary process configuration in the iridectomized eye. *Invest Ophthalmol Vis Sci*. 2006;47:1076–1086. © 2006 Association for Research in Vision and Ophthalmology).

humans and nonhuman primates, CM structure and function is preserved long after presbyopia is complete. In monkeys there is little to no histologic or ultrastructural change,²⁶ the number of muscarinic cholinergic receptors and their intrinsic activity is unchanged,²⁷ and the value of the Michaelis constant (Km) and the maximum rate of reaction (Vmax) of the enzymes responsible for the synthesis and degradation of the cholinergic neurotransmitter acetylcholine (choline acetyltransferase and acetyl cholinesterase) are unchanged (Fig. 11).²⁷ In short, nothing suggests that the CM is incapable of normal contraction. Indeed, isolated CM strips from monkeys of all ages, placed in a perfusion chamber/tissue bath and connected to force transducers/strain gauges, generate the same contractile force in response to the same dose of the cholinomimetic drugs carbachol and aceclidine throughout the lifespan (Fig. 11).²⁸ Yet, in situ by histologic metrics after tissue fixation in the presence of pilocarpine or atropine^{23,25} or in live monkeys by UBM video imaging in real time with stimulation of CM contraction via an electrode permanently implanted in the midbrain Edinger-Westphal nucleus,^{29,30} CM movement progressively decreases with aging, more so in the forward vector than the centripetal vector) (Table 1).²⁹ This constellation of findings suggests posterior restriction of CM forward and inward movement, so that in essence the contraction becomes isometric.^{19,23} This has obvious implications for presbyopia pathophysiology—essentially a lens and CM double hit against accommodation, but that discussion is for another day. Of more immediate interest is the nature of the restriction and its implications for the optic nerve.

In the rhesus monkey, which develops presbyopia on the same time scale relative to lifespan as the human, the posterior CM tendons and the elastic lamina of Bruch's membrane become "collagenized" and stiffen with age (Figs. 4, 9, 10).^{16,25} Consequently, the CM's mobility when it contracts is limited, whether measured histologically postmortem²⁵ or in vivo by UBM.^{13,29,30} In both humans and monkeys, the forward movement in young eyes at the ora serrata is ~1.0 mm (Supplementary Video S1; Table 2),²⁴ declining gradually to about 0.40 mm and 0.15 mm in elderly monkeys²⁴ and humans,¹³ respectively. Near the optic nerve head, the movement is considerably less, about 0.13 mm in the young

monkey, declining to ~0.02 mm in the elderly (Tables 2, 3)¹⁹ (Croft MA, et al. *IOVS* 2014;55:ARVO E-Abstract 2647). Engineering/physical principles tell us that if the "rubber band" in the young eye becomes a "steel cable" in the older eye and if the contractile force generated by the muscle is unchanged, the force transmitted to the insertion (i.e., the lamina cribrosa and perhaps the optic nerve itself) is dramatically increased.¹⁹ At present, we have no method for measuring these forces at the nerve head or the nerve, but techniques in development may allow that, at least in the monkey (Fernandes J, et al. *IOVS* 2019;59:ARVO E-Abstract 2434). The effects that these forces or their change with age might have on the healthy functioning of the optic nerve are unknown. Interestingly, the prevalence of POAG in humans begins to rise from essentially 0% at about the same age that the last vestiges of accommodation are lost (i.e., the mid-40s), to ~5%, ~10%, and ~25%, respectively, in elderly (over 75 years) Caucasians, African Americans, and pure blood Black Afro-Caribbeans.³¹ In older (aged ≥80) Latinos living in the Los Angeles area, the prevalence of POAG is 21.8%.³²

Other forces are also at play. Outstanding histologic and other research has been reported regarding the vitreous structure^{20,21,33–45} and its possible role in accommodation and presbyopia.⁴⁶ Jongbloed and Worst³³ reported on the cistern structure within the vitreous compartment. The base of the cistern resides in the optic nerve (ON) region and the branches of the cistern extend forward to the anterior vitreous. In the in vivo rhesus monkey, we have shown that the tips of the cistern branches in the anterior vitreous attach to the intermediate vitreous zonule (Croft MA, et al. *IOVS* 2016;57:ARVO E-Abstract 1378; Supplementary Videos S2, S5, S6). As the CM contracts and moves forward and inward, the lens thickens (the anterior lens pole moves anteriorly and becomes more sharply curved) and the central posterior lens pole/capsule moves backward (Supplementary Video S12),^{12,21} the fibrillar structures within the central vitreous¹⁹ (Croft MA, et al. *IOVS* 2014;55:ARVO E-Abstract 2647) (Croft MA, et al. *IOVS* 2015;56:ARVO E-Abstract 3568) (Croft MA, et al. *IOVS* 2016;57:ARVO E-Abstract 1378) (Croft MA, et al. *IOVS* 2017;58:ARVO E-Abstract 2477) (Croft MA, et al. ESCRS Abstract 2014 FP-5069) (including the anterior hyaloid,¹⁴

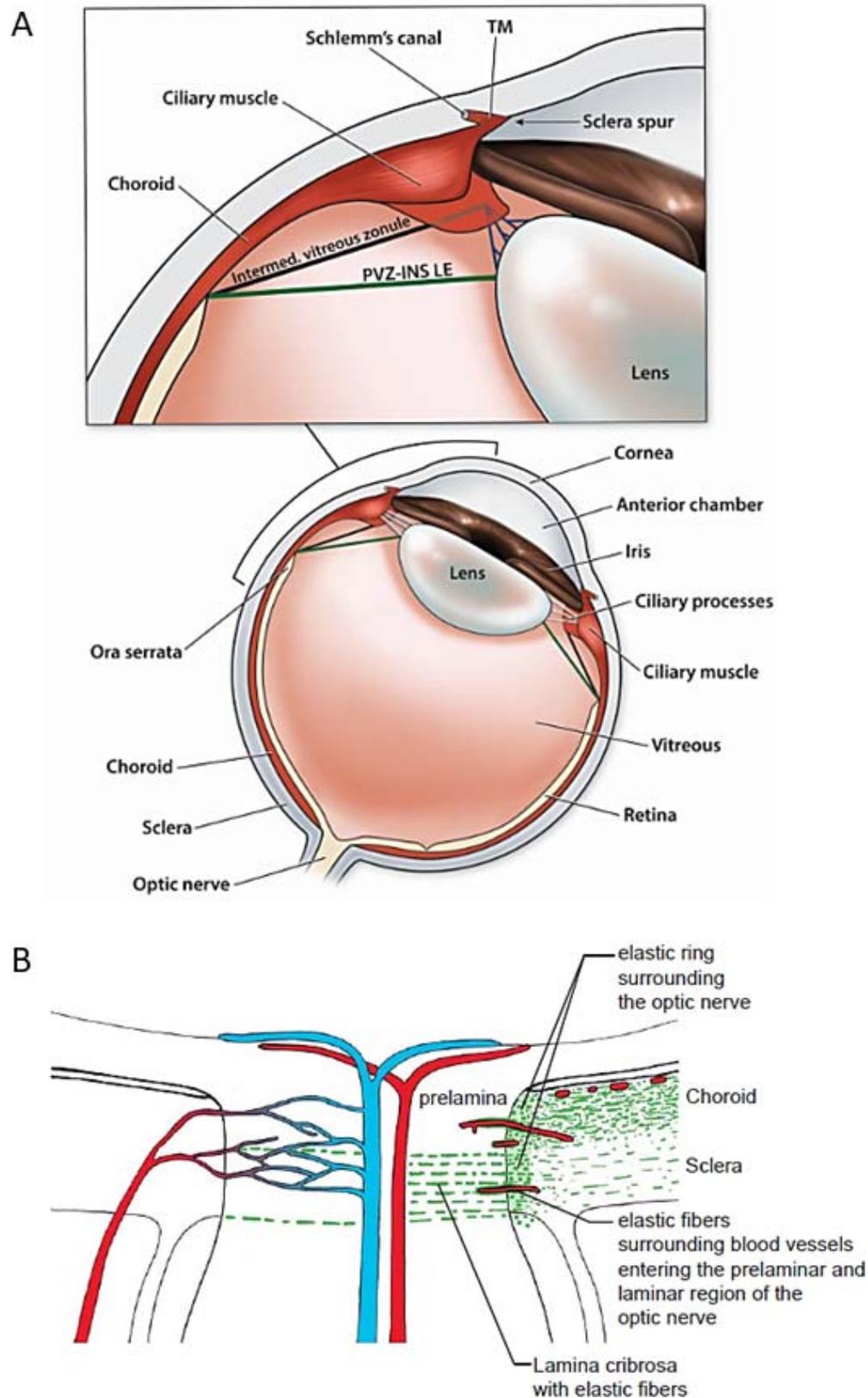


FIGURE 2. The CM and the choroid functionally form an elastic network that extends from the TM to the back of the eye (A) and ultimately attaches to the elastic fiber ring that surrounds the optic nerve and to the lamina cribrosa through which the nerve passes (B). (A) PVZ INS LE is the vitreous strand that extends from the intermediate vitreous zonule posterior insertion zone to the lens equator. (B) Reprinted with permission from Croft MA, Lütjen-Drecoll E, Kaufman PL. Age-related posterior ciliary muscle restriction - A link between trabecular meshwork and optic nerve head pathophysiology. *Exp Eye Res.* 2017;158:187-189. © 2016 Elsevier Ltd.; and Tektas O-Y, Lütjen-Drecoll E, Scholz M. Qualitative and quantitative morphologic changes in the vasculature and extracellular matrix of the prelaminar optic nerve head in eyes with POAG. *Invest Ophthalmol Vis Sci.* 2010;51:5083-5091. © 2010 Association for Research in Vision and Ophthalmology.

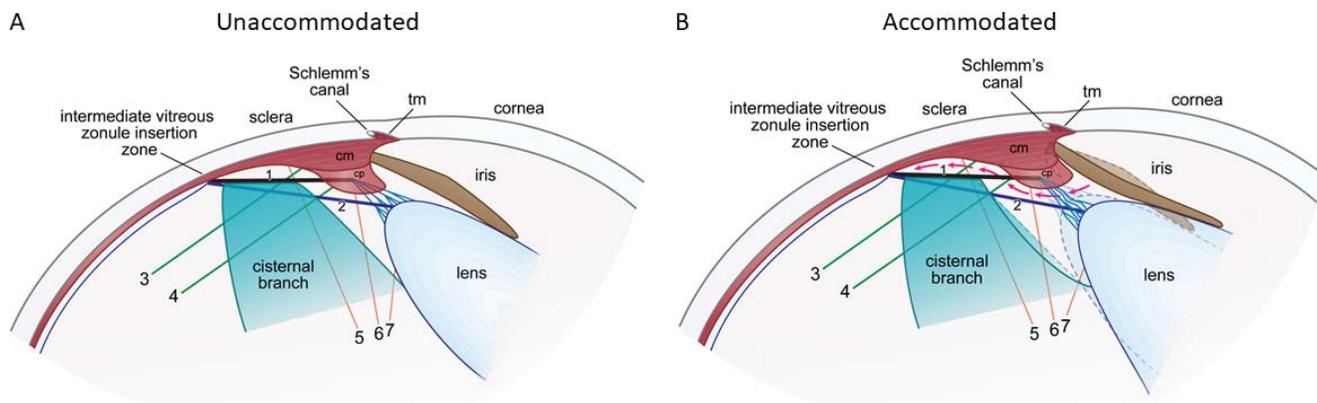


FIGURE 3. Accommodation summary: CM, lens, iris and cisternal branch tip close-up. **(A)** Unaccommodated state. *Thick black line (1)* represents the intermediate vitreous zonule that extends between the intermediate vitreous zonule posterior insertion zone and the zonular plexus (which resides between the walls of the ciliary processes). *Thick blue line (2)* represents the vitreous strand that extends from the intermediate vitreous zonule posterior insertion zone and attaches to the posterior lens equator (PVZ INS-LE).¹² *Thin green lines* represent other vitreous strands that extend from the posterior vitreous body to the pars plana region (3) or the pars plicata region (4). *Thin pink lines (5, 6, 7)* represent vitreous strands that extend from the anterior vitreous to the pars plana (5), the pars plicata (6), or the posterior lens surface (7). **(B)** Accommodated state. Legend as for **(A)**, but structures are now in the accommodated state. Note backward bowing of the iris and anterior hyaloid. The lens is thickened and the lens equator has moved away from the sclera. The muscle apex is in a more forward and inward position. Fluid flows around the lens equator toward the anterior hyaloid and then further into the cleft between the intermediate vitreous zonule and the pars plana region during accommodation, as represented by the *red arrows*.

Cloquet’s canal, and possibly the cistern trunk³³) move posteriorly toward the optic nerve head (Supplementary Videos S2, S5–S8, S12). The accommodative posterior movement of the central vitreous includes the region of the vitreous very near the optic nerve head itself (Supplementary Videos S7–S9). This strongly suggests that there is a fluid wave—and

consequently a pressure change—impacting the nerve head. Simultaneously, the fibrillar peripheral vitreous, some of which is attached to the intermediate vitreous zonule (including the tips of the cistern branches near the anterior vitreous³³; Supplementary Videos S2, S5, S6), moves anteriorly and inwardly (Supplementary Videos S2, S5, S6, S10).¹⁴ Disaccom-

TABLE 1. Average Maximum Amplitudes of Accommodation, Forward Ciliary Body, Ciliary Process, and Lens Movement in Young, Middle-Aged, and Older Eyes

Age	Accommodation, D	FCB (°)*	n*	Centripetal Movement, mm*		% Decline†				
				CP	Lens	Accommodation, D	FCB	CP	Lens	
Young, 6–9.5 y										
Mean	15.2	61.8	8	0.44	0.31	-	-	-	-	-
SEM	1.0	5.7		0.02	0.01					
Middle-aged, 12–15 y										
Mean	8.1	27.9	7	0.35	0.22	46.7	54.8	19.4	30.4	
SEM	0.5	4.4		0.03	0.03					
Middle-aged vs. young										
P	0.001	0.001		0.012	0.022					
Older, 17–26 y										
Mean	2.4	23.9	8	0.32	0.14	84	61.3	26.7	54.3	
SEM	0.6	3.0		0.05	0.03					
Older vs. young										
P	0.001	0.001		0.08	0.001					
Middle-aged vs. older										
P	0.001	0.258		0.584	0.166	37.3	6.5	7.3	23.9	

Data are mean ± SEM accommodative amplitude (diopters) at supramaximal (~25% above that necessary to induce maximum accommodation) stimulus levels in 28 eyes of 23 rhesus monkeys. Reprinted with permission from Croft MA, McDonald JP, Nadkarni NV, Lin TL, Kaufman PL. Age-related changes in centripetal ciliary body movement relative to centripetal lens movement in monkeys. *Exp Eye Res.* 2009;89:824–832. © 2009 Elsevier Ltd.

* Data are mean ± SEM forward ciliary body movement (FCB: in units of degrees as previously defined [Fig. 2] [Ref. 30]), centripetal ciliary process movement (CP), and lens movement amplitude (mm) at standard supramaximal stimulus settings. Age ranges: young eyes (6–9.5 years), middle-aged eyes (12–15 years), and older eyes (17–27 years). A *P* ≤ 0.05 represents a significant difference between the young age group versus the other age groups by two sample *t*-test.

† Percent decrease is calculated as $([\text{middle-aged} / \text{young}] - 1) \times 100$ or $([\text{older} / \text{young}] - 1) \times 100$ for each variable. For instances in which there were two eyes from one monkey, the data were averaged to provide one data point. A subset of the CP and centripetal lens equator movement data (16 eyes of 12 monkeys) was adapted with permission from Croft et al. Accommodative ciliary body and lens function in rhesus monkeys. *Invest Ophthalmol Vis Sci.* 2006; 47:1076–1086. © Association for Research in Vision and Ophthalmology.

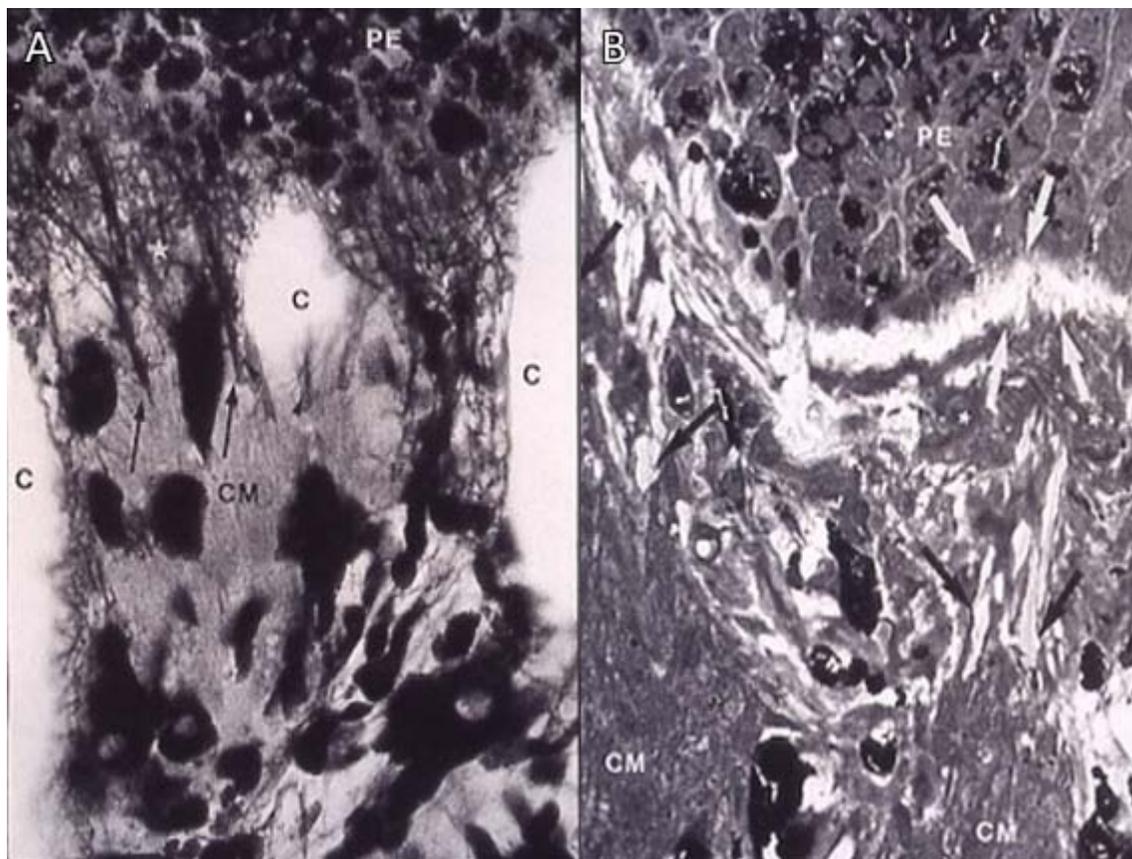


FIGURE 4. (A) Oblique-tangential section of the posterior attachment of the CM in a young monkey. The elastic tendons (*arrows*) that originate from the muscle bundles (CM) are connected by smaller elastic fibrils to a network of elastic fibers (*asterisk*) surrounding the vessels of the posterior ciliary body. This network is continuous with the elastic layer of Bruch's membrane next to the PE. Due to the obliquity of the cut, the elastic lamina is partly resolved into its substructure, which consists of a meshwork of elastic fibers. In some areas, elastic tendons are in close contact (*arrowheads*) with the walls of the pars plana capillaries (C) (paraffin section, resorcin-fuchsin/van Giesson stain, $\times 1000$). (B) Oblique-tangential section of the posterior attachment of the CM in a 34-year-old monkey. Region and orientation of the section are comparable with (A). The elastic tendons (*arrows*) that originate from the muscle bundles (CM) are thickened and have an irregular shape with fuzz borders and a notched appearance. Although a histologic stain for elastic fibers is used, neither the elastic tendons nor the elastic lamina of Bruch's membrane (*white arrows*) stain positive. The connective tissue between the elastic tendons and the ciliary PE is thickened and hyalinized (*asterisks*) (semithin section, resorcin-fuchsin stain, $\times 1000$). (A, B) Reprinted with permission from Tamm E, Lütjen-Drecoll E, Jungkunz W, Rohen JW. Posterior attachment of ciliary muscle in young, accommodating old, presbyopic monkeys. *Invest Ophthalmol Vis Sci.* 1991;32:1678-1692. © 1991 Association for Research in Vision and Ophthalmology.

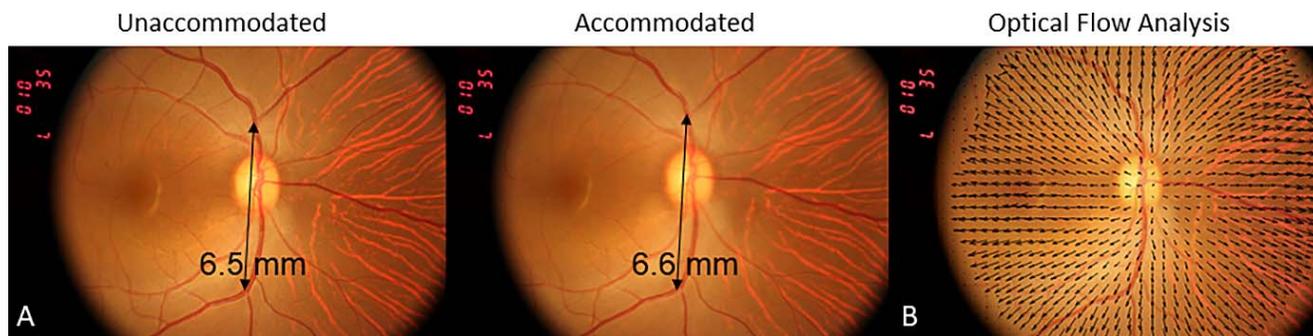


FIGURE 5. (A) Removal of the lens substance by extracapsular lens extraction allowed direct measurement of the accommodative movement of the choroid/retina by using known landmarks. Very little accommodative movement of the choroid/retina in the region of the optic nerve. (B) Results of optical flow analysis in one young monkey (courtesy of Bosco Tjan) shows that the choroid/retina is stretched and that the center of the stretch is centered around the optic nerve region, and choroid/retina moves by 0.1 mm in the optic nerve region during accommodation.¹⁹ Reprinted with permission from Croft MA, Lütjen-Drecoll E, Kaufman PL. Age-related posterior ciliary muscle restriction - A link between trabecular meshwork and optic nerve head pathophysiology. *Exp Eye Res.* 2017;158:187-189. © 2016 Elsevier Ltd.

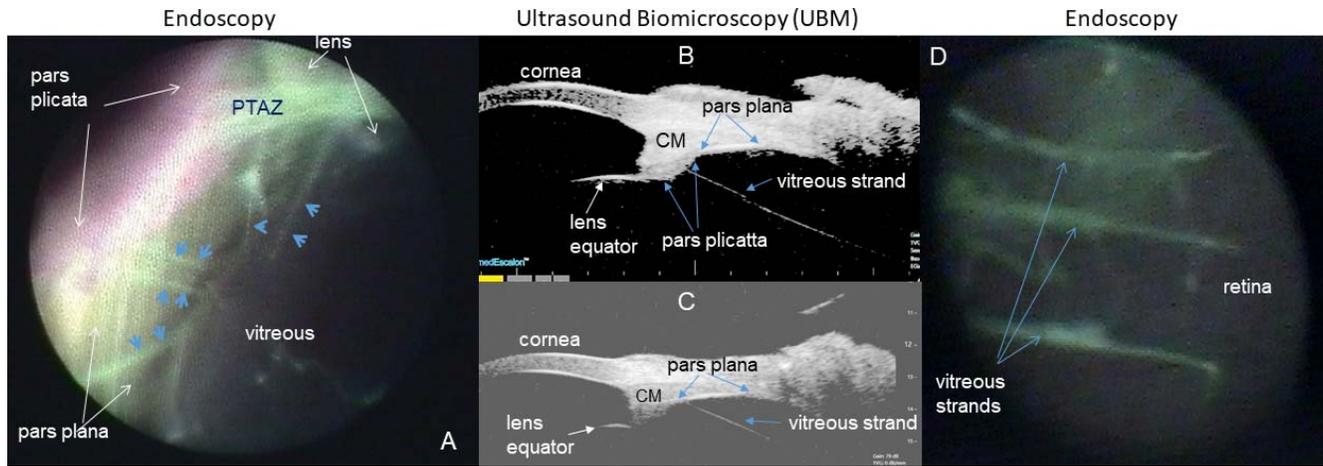


FIGURE 6. (A) Endoscopy image in the same 28-year-old monkey as panel D, showing vitreous strands (blue arrowheads) that attach to the accommodative apparatus in the region of the pars plana and pars plicata. PTAZ, posterior tine of the anterior zonula. (B, C) Ultrasound biomicroscopy images obtained using the Sonomed VuMax (UBM-V) in a 6-year-old rhesus monkey shows newly visualized vitreous strands that extend from the vitreous body and attach to the accommodative apparatus in the region of the pars plicata (B) and pars plana (C). See also the schematic drawing in Figure 3. (D) Endoscopy image in a 28-year-old rhesus monkey shows vitreous strands that are attached to the choroid/retina and extend anteriorly toward the central anterior vitreous body.

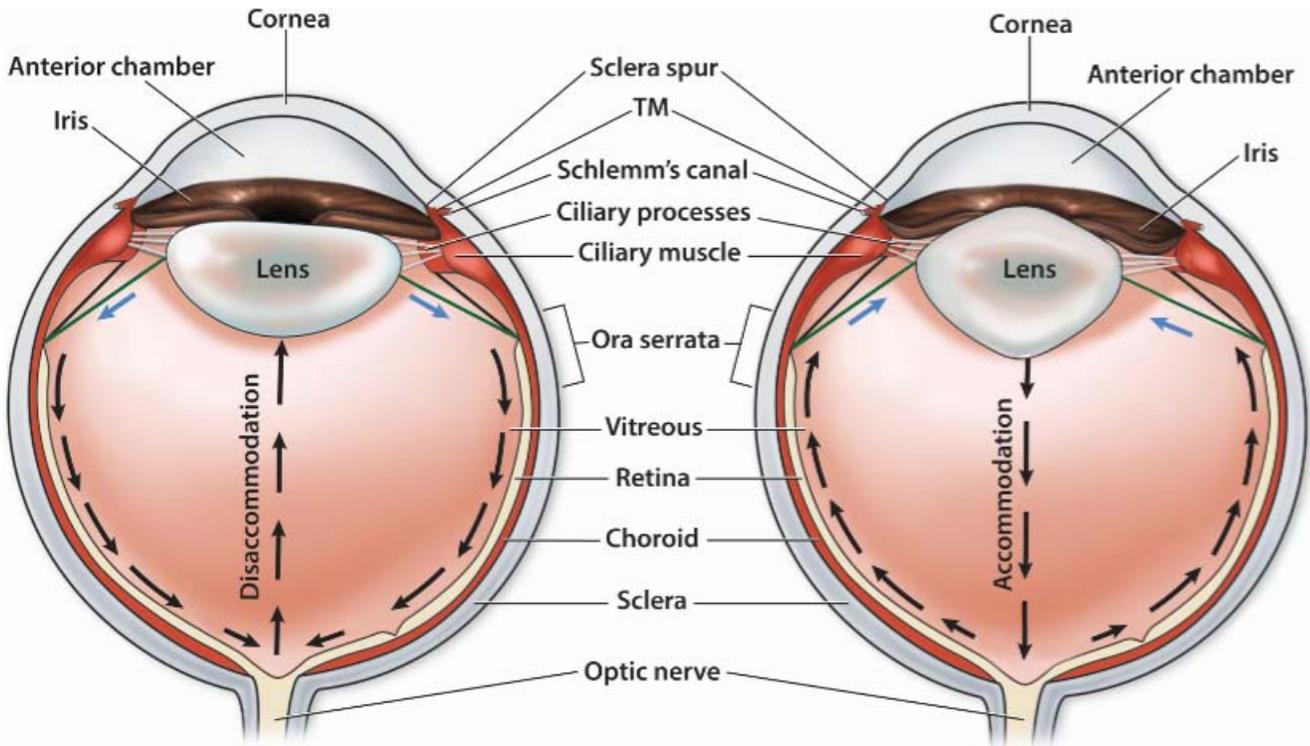


FIGURE 7. Accommodation: diagram demonstrating the accommodative/disaccommodative movements inside the vitreous. During accommodation, the CM contracts and moves forward and inward, releasing tension on the anterior zonula and, thus, facilitating lens thickening. In addition, during accommodation, the CM pulls the intermediate vitreous zonule (black line), the choroid, and the peripheral vitreous forward; the central vitreous moves backward (including Cloquet's canal, see Supplementary Videos S7-S9) toward the optic nerve head, and the backward movement of the central vitreous also facilitates lens thickening. During accommodation, the capsule facilitates lens shape change into a more spherical form and we view close range objects. The PVZ INS-LE strand (green line) is pulled forward by the CM contraction, supporting the accommodative forward movement of the posterior lens equator and also facilitating lens shape change.¹² Fluid flows around the lens equator toward the anterior hyaloid and then further into the cleft between the vitreous zonule and the pars plana region during accommodation (see Fig. 3). The reverse for everything just described in this figure is true during disaccommodation. TM, trabecular meshwork.

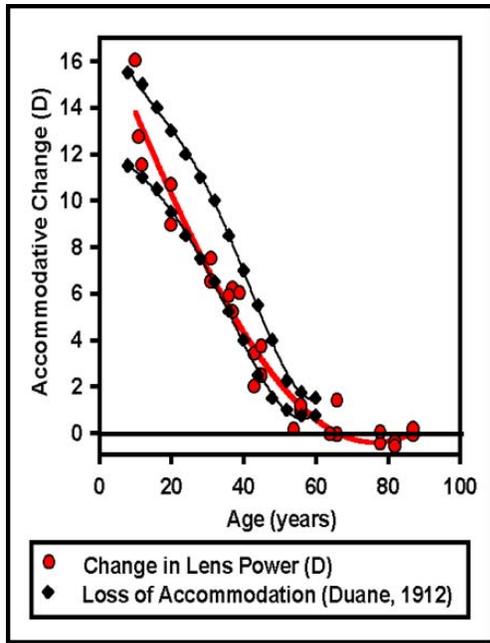


FIGURE 8. The age-dependent decline in the ability of the human lens to undergo accommodative changes with mechanical stretching matches and can fully account for the decline in accommodative amplitude over the human life-span. Reprinted with permission from Glasser A, Campbell MC. Presbyopia and the optical changes in the human crystalline lens with age. *Vision Res.* 1998;38:209-229. © 1998 Elsevier Ltd.

modation gives the reverse movements (Fig. 7).¹⁴ In addition to pressure gradients, these fluid movements may generate shear stress at the nerve head. Whether these vitreal forces are bad, good, or irrelevant for the nerve is impossible to say, but we can say that they likely gradually decrease with age (see below)

and become small once presbyopia becomes complete, again at about the age when POAG begins to appear.^{47,48} And, of course, any of the effects may not be on the nerve directly but rather on the astrocytes and other glial elements associated with the nerve head and the lamina.⁴⁹ Although accommodative vitreous movements may be reduced to a small amount with age, several other phenomena occur with age and also need to be considered. There is an age-related increase in lens thickness. The anterior lens pole encroaches on the anterior chamber, and the posterior lens pole is in a more posterior position in the older eye, encroaching on the anterior central vitreous. With age, the CM moves far less in a forward direction (65% and 85% loss in monkeys and humans, respectively), but the movements in the centripetal direction are less reduced (i.e., ~20%).^{29,30} Furthermore, the central vitreous liquifies with age,⁵⁰ perhaps allowing more pressure on the optic nerve via the fluid current, lens position, and accommodative pressure spikes.

During accommodation in both young monkeys and humans, there is a slight change (a small notch) in the scleral contour in the region of the limbus (Fig. 12).¹⁴ In older resting presbyopic eyes, there is inward bowing (increased concavity) of the sclera in the region of the limbus, and the inward bowing is more pronounced during accommodation (Fig. 12).¹⁴ Although older forward muscle movements are reduced, a substantial amount of centripetal muscle movement remains. Coupled with the posterior lens pole being positioned more posteriorly with age, the inward bowing of the sclera and the presence of the cisternal trunk in the region of the optic nerve (with the branches of the cistern extending to and attaching to the vitreous zonule) may all contribute to a greater pressure spike toward the optic nerve during accommodation in the aged eye.

Focusing requires a continuous zeroing in on the target, much as a gunner acquires a target's range. This constant, high frequency, microcontraction/relaxation generates its own force

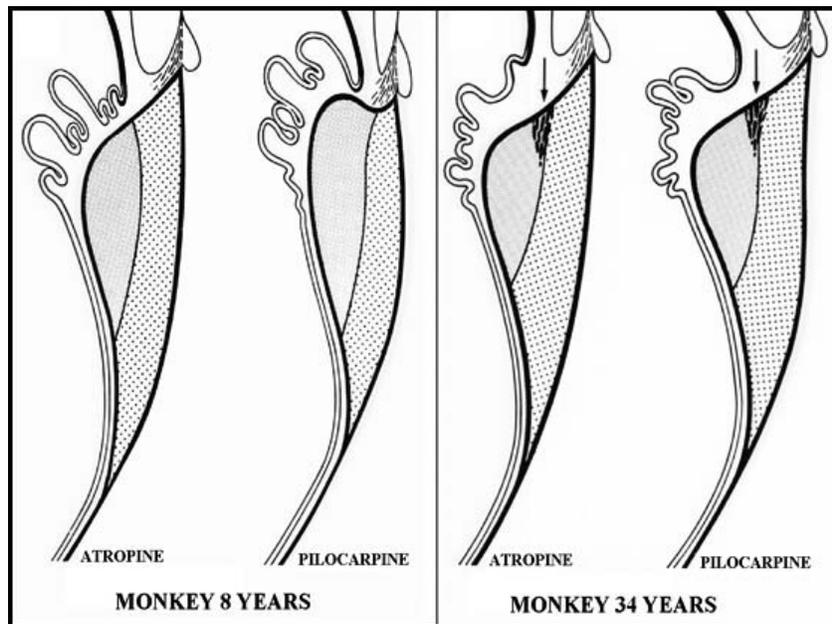


FIGURE 9. Ciliary muscle shape from an 8-year-old and a 34-year-old enucleated rhesus monkey eye placed in atropine or pilocarpine solution. The young 8-year-old monkey eye undergoes pilocarpine induced accommodative configurational change. The older eye fails to undergo an accommodative configurational change due to the loss of elasticity of the choroid which attaches to the posterior end of the ciliary muscle. Reprinted with permission from Lütjen-Drecoll E, Tamm E, Kaufman PL. Age-related loss of morphological responses to pilocarpine in rhesus monkey ciliary muscle. *Arch Ophthalmol.* 1988;106:1591-1598. © 1988 American Medical Association.

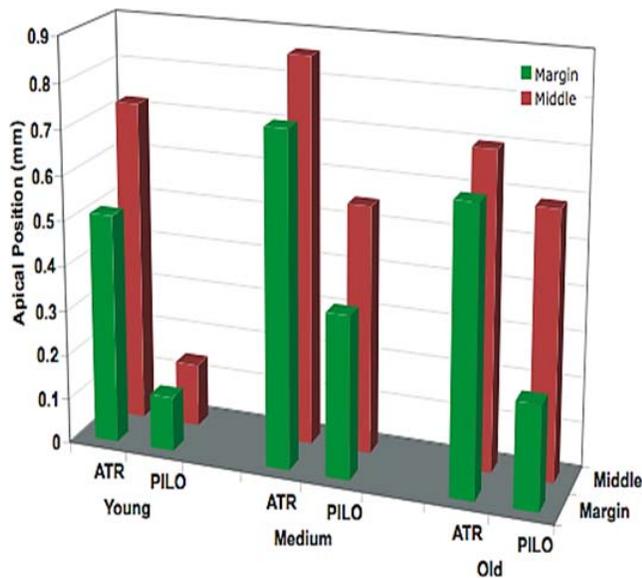


FIGURE 10. Data plotted are mean apical position of the CM grouped according to age, drug, and section location. *Red bars* represent sections obtained from the middle (farthest from the original meridional cut), where the CM posterior tendon is intact. *Green bars* represent sections taken from the margin (closest to the original meridional cut), where some of the posterior and outer attachments of the CM have been severed. These data show that there is an age-related posterior restriction. The restriction is removed once the posterior attachment is severed. Adapted with permission from Tamm E, Croft MA, Jungkunz W, Lütjen-Drecoll E, Kaufman PL. Age-related loss of ciliary muscle mobility in the rhesus monkey: role of the choroid. *Arch Ophthalmol.* 1992;110:871-876. © 1992 American Medical Association.

fluctuations on the surrounding structures and fluidics, which may also affect the optic nerve and may diminish with age.

The anterior longitudinal region of the CM, with its tendinous attachment to the scleral spur, TM, inner wall of SC, and Schwalbe's line, is also challenged by aging.⁵¹⁻⁵⁵ The TM stiffens⁵⁵⁻⁶² and forward CM movement is severely restricted²⁹ (more than is the centripetal vector) by the posterior stiffening,²³ so that the TM deformation and recovery associated with accommodation and disaccommodation are

TABLE 2. Presbyopia: Rhesus Monkey

Region		P Value of Two Sample t Comparison by Region		
Ora Serrata, mm, UBM	n	Optic Nerve, mm, Fundus Photos	n	Ora Serrata vs. Optic Nerve
Young, 6-9 y				
1.05 ± 0.07*	4	0.13 ± 0.03*	2†	0.009
Old, 17-24 y				
0.40 ± 0.12*	4	0.02 ± 0.02	2	0.049
Young vs. old		P = 0.205		
P = 0.024		Two sample t comparison by age group		
Young + old				
0.69 ± 0.14	8	0.08 ± 0.035	4	0.003

Data are mean ± SEM accommodative choroid/retina movement in the region of the ora serrata (measured from UBM images) and accommodative choroid/retina movement in the region of the optic nerve (measured from fundus photos following extracapsular lens extraction). Note accommodative choroid/retina movement is 10-fold greater in the ora serrata region than in the region of the optic nerve, and these movements decline with age (CM still generates force-isometric contraction). The accommodative stretching of the choroid may place accommodative tension spikes on the optic nerve region (...increased stress on optic nerve astrocytes...increase in transforming growth factor β [Ref. 49]...increase extracellular matrix... One hypothesis: optic nerve more susceptible to glaucomatous damage.).

* Reprinted with permission from Croft et al. Extralenticular and lenticular aspects of accommodation and presbyopia in human versus monkey eyes. *Invest Ophthalmol Vis Sci.* 2013;54:5035-5048. © Association for Research in Vision and Ophthalmology.

† Data include three eyes of two monkeys undergoing the same protocol (to minimize the number of monkeys used). The data from the two eyes of the same monkey were averaged and that number averaged with the eye of the other young monkey for an n of 2 in this table. P value of ≤ 0.05 indicates a statistically significant difference between groups (i.e., the amount of choroid/retina movement in the ora serrata region was significantly greater in the young eye vs the old eye [P = 0.024] by two sample t-test). Due to the small sample sizes collected in the region of the optic nerve, a separate analysis was using ANOVA and adjusting for repeated measures (two eyes from one young monkey), and the results are in Table 3.

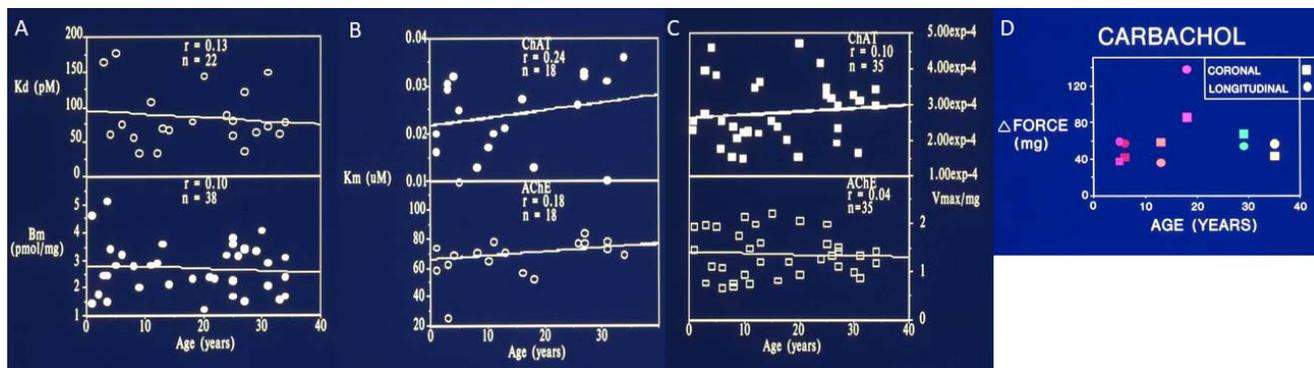


FIGURE 11. (A) The number of muscarinic cholinergic receptors (Bm) and their receptor affinity (Kd), (B) the Km, and (C) the Vmax of the enzymes responsible for the synthesis and degradation of the cholinergic neurotransmitter acetylcholine (choline acetyltransferase [ChAT] and acetyl cholinesterase [AChE]), are all unchanged with age; reprinted with permission from Gabelt BT, Kaufman PL, Polansky JR. Ciliary muscle muscarinic binding sites, choline acetyltransferase and acetylcholinesterase in aging rhesus monkeys. *Invest Ophthalmol Vis Sci.* 1990;31:2431-2436. © 1990 Association for Research in Vision and Ophthalmology. (D) There was no age-related change in contractile force of isolated rhesus monkey CM strips stimulated with muscarinic agonist carbachol (1 μM). From Poyer JF, Kaufman PL, Flügel C. Age does not affect contractile responses of the isolated rhesus monkey ciliary muscle to muscarinic agonists. *Curr Eye Res.* 1993;12:413-422. Reprinted with permission from Taylor & Francis Ltd.

TABLE 3. Choroid Movement in the Optic Nerve Region Results

Group Comparisons: Old vs. Young	Eyes, N	Outcome (95% CI)	P Value
Repeated measures ANOVA results			
Old, animals = 2	2	0.019 (−0.066, 1.04)	0.095
Young, animals = 2	3	0.131 (0.019, 0.244)	
	Eyes, N	Mean (SD)	P Value
Analysis treated as independent measures for the three young monkeys			
Old, animals = 2	2	0.019 (0.029)	0.031
Young, animals = 2	3	0.141 (0.037)	
Analysis independent measures, but averaged repeated measures			
Old, animals = 2	2	0.019 (0.029)	0.115
Young, animals = 2	2	0.130 (0.044)	

Due to the unknown effect of having one monkey with both eyes measured, a sensitivity analysis of different statistical methods was assessed. These methods included a repeated measures ANOVA and two independent two-sample *t*-tests, one with all measures treated as independent ($n = 2$ vs. $n = 3$), and the other with the two measures within the one animal averaged ($n = 2$ vs. $n = 2$). Data are mean and 95% CI or mean (SD) choroid/retina movement (mm) in the region of the optic nerve in rhesus monkeys. Although statistical significance varied between methods ($P = 0.095$ for RM-ANOVA, $P = 0.031$ for $n = 2$ vs. $n = 3$ *t*-test, and $P = 0.115$ for $n = 2$ vs. $n = 2$ *t*-test), all methods estimated close to a 7-fold decrease in movement of old eyes compared to young eyes. This decrease is substantial and indicates that there is significantly lesser choroid/retina movement in old versus young monkeys in the region of the optic nerve.

progressively lost. The deformation/recovery cycle may contribute to the “self-cleaning” ascribed to the TM,^{63–65} and thus, its loss may contribute to the TM stiffening^{59,60} and accumulation of collagen and other extracellular matrix materials seen with aging,^{51,66} especially in glaucomatous eyes.^{59,60} These changes may impede the outflow of aqueous

humor, as evidenced by and perhaps accounting for the age-related increase in outflow resistance seen in both monkeys^{56,67} and (at least in Western) human^{68,69} populations. We do not know whether the internal contraction/relaxation mechanisms possessed by the TM/SC⁶⁷ might change with age and affect CM movement and, thereby, the optic nerve. Although all the biomechanics at play are not clear, altered forces and decreased deformation of the TM during accommodative effort seem likely, perhaps contributing to increased outflow resistance.

CONCLUSIONS

The ocular anterior and posterior segments are linked both structurally and functionally, and their intellectual separation in both the clinical and research enterprises is counterproductive to advances. The accommodative mechanism and its aging are much more complex than generally realized, and extralenticular changes with age may play an important role in the pathophysiology of presbyopia, glaucomatous optic neuropathy, impaired aqueous outflow, and the frustrating inability of current intraocular lenses to provide more than 1.75 to 2.00 diopters of dynamic accommodation,^{70,71} which is not quite enough for fine near vision in subpar lighting conditions.

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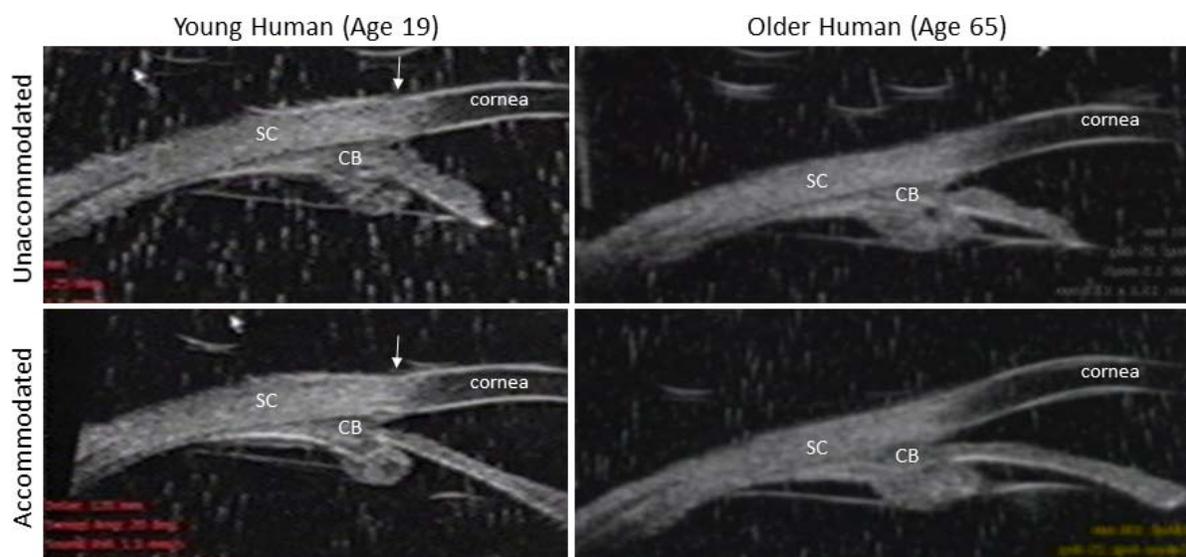


FIGURE 12. Note the deformation of the outer limbus (“notch”; arrow, upper left panel) in the accommodated young eye compared to the unaccommodated eye. In the older eye there is a discernable depression or “easy hammock” contour to the sclera. This occurs in the nasal but not the temporal quadrant. In the older eye the contour of the sclera (SC), ciliary body (CB), and zonula has changed and this may have an impact on the ability of the lens to change shape and the peripheral lens equator to move forward during accommodation. This phenomenon is also present in the monkey eye. The young accommodated muscle is clearly in the anterior inward position compared to the unaccommodated eye. In the older eye: unaccommodated versus accommodated not much different. Reprinted with permission from Croft MA, Nork TM, McDonald JP, Katz A, Lütjen-Drecoll E, Kaufman PL. Accommodative movements of the vitreous membrane, choroid and sclera in young and presbyopic human and nonhuman primate eyes. *Invest Ophthalmol Vis Sci.* 2013;54:5049–5058. © 2013 Association for Research in Vision and Ophthalmology.

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APPENDIX

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