

Accommodation dynamics in aging rhesus monkeys

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¹*Department of Ophthalmology and Visual Sciences, Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, Wisconsin 53792; and* ²*Department of Ophthalmology, Columbia University, New York, New York 10032*

Croft, Mary Ann, Paul L. Kaufman, Kathryn S. Crawford, Michael W. Neider, Adrian Glasser, and Laszlo Z. Bito. Accommodation dynamics in aging rhesus monkeys. *Am. J. Physiol.* 275 (*Regulatory Integrative Comp. Physiol.* 44): R1885–R1897, 1998.—Accommodation, the mechanism by which the eye focuses on near objects, is lost with increasing age in humans and monkeys. This pathophysiology, called presbyopia, is poorly understood. We studied aging-related changes in the dynamics of accommodation in rhesus monkeys aged 4–24 yr after total iridectomy and midbrain implantation of an electrode to permit visualization and stimulation, respectively, of the eye's accommodative apparatus. Real-time video techniques were used to capture and quantify images of the ciliary body and lens. During accommodation in youth, ciliary body movement was biphasic, lens movement was monophasic, and both slowed as the structures approached their new steady-state positions. Disaccommodation occurred more rapidly for both ciliary body and lens, but with longer latent period, and slowed near the end point. With increasing age, the amplitude of lens and ciliary body movement during accommodation declined, as did their velocities. The latent period of lens and ciliary body movements increased, and ciliary body movement became monophasic. The latent period of lens and ciliary body movement during disaccommodation was not significantly correlated with age, but their velocity declined significantly. The age-dependent decline in amplitude and velocity of ciliary body movements during accommodation suggests that ciliary body dysfunction plays a role in presbyopia. The age changes in lens movement could be a consequence of increasing inelasticity or hardening of the lens, or of age changes in ciliary body motility.

presbyopia

ACCOMMODATION, the mechanism by which the normal eye changes its focus from distant to near objects, is lost with increasing age in humans and monkeys. This phenomenon, called presbyopia, is the most common human ocular affliction, and its pathophysiology is poorly understood. The classical theory of accommodation proposes that the ciliary muscle moves forward and axially in the eye during contraction, thereby releasing tension on the anterior zonular fibers and allowing the lens to round up and thicken axially (59). This increases the eye's refracting power and permits focus on near objects. During disaccommodation the ciliary muscle relaxes, allowing the elastic choroid and posterior zonular fibers to pull the muscle posteriorly, increasing the tension on the anterior zonules to flatten the lens. Theories to explain the pathophysiology of presbyopia fall into two main categories, involving dysfunction of either the lens or the ciliary muscle.

Changes in Lens Properties With Age

There are numerous changes in the properties of the lens that occur with age and that have been put forth as the basis for presbyopia. The lens itself undergoes sclerosis or hardening (13, 15, 16, 19, 42), and there is evidence for loss of capsular elasticity with age (14, 32). Lenticular hardening/sclerosis and/or loss of the lens capsule's elasticity would lead to the inability of the elderly lens to change shape during accommodation. This view is supported by evidence showing that young human lenses undergo changes in focal length with stretching whereas older ones do not (19). A shift in zonular insertion onto the anterior surface of the lens (12) and continued growth of the lens with age (51, 63) have been suggested as possible causes of presbyopia (28, 29, 45), but no experimental evidence exists in support of this theory. Another lenticular theory is based on a controversial view of the accommodative mechanism (53), which proposes that the ciliary muscle increases rather than decreases equatorial zonular tension during accommodation, causing the equatorial edge of the lens to move toward rather than away from the sclera. Presbyopia is then attributed to the continued growth of the lens and an inability of the ciliary muscle to tense the equatorial zonules. Surgical expansion of the sclera in the region of the ciliary body has been suggested to improve accommodative ability in presbyopes (52, 65).

Ciliary Muscle Dysfunction

Ciliary muscle dysfunction has been suggested to contribute to presbyopia, possibly due to age-related neuromuscular (33) or configurational (34) changes, or to a loss of elasticity of the posterior muscle tendons, posterior zonular fibers, or choroid (56). Histological examination of ciliary muscle from elderly rhesus monkeys shows evidence of age-related degenerative changes, but they are subtle (33) and almost certainly insufficient to explain the almost complete immobility of the muscle *in situ* (40). There are no age-related changes in the number and binding affinity of the muscarinic receptors or in the activity of the biosynthetic and degradative enzymes for the cholinergic neurotransmitter acetylcholine, which mediates ciliary muscle contraction (18). There is no age-dependent loss of the contractile response to pharmacological stimulation by muscarinic agonists in excised monkey ciliary muscle (47). Collectively, these findings indicate that the parasympathetic neuromuscular mechanism remains normal. The posterior elastic tendons of the ciliary muscle are thicker and have increased amounts of microfibrils and collagen fibrils in aged monkey eyes, consistent

with decreased elasticity (57). Furthermore, ciliary muscle mobility in response to muscarinic agonists in older monkey eyes was fully restored when the muscle's posterior attachments were partially cut (56). Thus presbyopia might involve progressive age-related restriction of the ciliary muscle motility, due to an increasingly inelastic posterior attachment. Clearly, lenticular and ciliary muscle immobility contributions to presbyopia are not mutually exclusive (19, 34, 56), and the condition may be multifactorial (60–62).

Technical Aspects

Much remains unknown about human accommodation and its age-related decline due to lack of dynamic measures and difficulties imaging the component ocular elements in vivo (i.e., lens, ciliary muscle, zonules, and choroid). Indirect external observations via electrical recordings such as impedance cyclography (49, 50, 55), in vivo scleral transillumination (38), or in vitro postmortem passive manipulations (15–17, 19) provide no insight into the real-time dynamics of ciliary muscle, zonular, and lenticular mobility. Automated photorefractors (54) measure dioptric refractive changes dynamically, but provide no insight into structural dynamics. Dynamic A-scan ultrasonography (1) generates data on changes in lens thickness, but does not directly measure other accommodation-relevant structures. Previous dynamic and static studies of accommodation are limited by the nature of the experimental models (21, 36, 64) and imaging techniques (21, 35, 43, 46) or provide information only about the axial region in the vertical meridian of the lens (4–6, 25, 26, 29–31).

Subprimate animals accommodate either very little or by mechanisms anatomically and physiologically different from the human (11, 22, 31, 34, 39, 48). However, the rhesus monkey has an accommodative apparatus structurally and functionally identical to the human (2, 23, 33), a pharmacologically stimulated accommodative amplitude of 30–40 diopters in youth, and an age-related loss of accommodation with a similar relative age course as in humans (2, 23).

In rhesus monkeys, the iris may be surgically removed via a small limbal incision (24). This allows direct transcorneal visualization, imaging, and recording of the ciliary muscle-zonular-lenticular system in real-time by Scheimpflug- and goniovideography (40). Accommodation can be stimulated via the normal efferent neuronal pathway by means of an electrode permanently implanted in the midbrain Edinger-Westphal (E-W) nucleus (8). These previously described survival techniques permit repeated real-time study of accommodation dynamics and presbyopia in an animal model meaningfully comparable to the human. We describe here the quantitative image analysis methodology and initial findings obtained using this model.

MATERIALS AND METHODS

Data Collection

Six rhesus monkeys (*Macaca mulatta*) of either sex, aged 4–24 yr and weighing 1.7–11.3 kg, were studied. Each animal underwent total iridectomy (24) in one or both eyes and permanent implantation of a bipolar stimulating electrode

into the E-W nucleus as previously described (8). Postoperatively the animals behaved normally, with no evidence of neurological deficit or photic discomfort. All experiments were performed under surgical depth anesthesia (methohexital sodium 15 mg/kg im followed by pentobarbital sodium 35 mg/kg im, with a supplemental pentobarbital sodium dose of 10 mg/kg im as required after 2–4 h). Resting refractive error and accommodative responses to graded central electrical stimulation were determined with a Hartinger coincidence refractometer (aus Jena, Jena, Germany). Video image analysis was performed no less than 3 wk, and up to 3 yr, after electrode implantation. Animal ages given in RESULTS represent the age at which the imaging data were acquired. We did not perform longitudinal studies in any animals.

The anesthetized animal was placed prone in a head holder with the eyes in the primary position. Body temperature was maintained at 36–38°C by heating pads. Botulinum A toxin was injected into the medial and either the superior or inferior rectus muscle 2–7 days before the recording session to minimize eye movements by paralyzing the extraocular muscles. At the start of each experimental session, a 5–0 Dacron suture was passed beneath the lateral rectus muscle to allow tension to be applied to reduce any residual eye movements not eliminated by the toxin injections. Accommodation was stimulated centrally via the implanted electrode. Imaging and video recording of the anterior segment (Scheimpflug- and goniovideography, the latter employing a Swan-Jacobs gonioscopy lens) were accomplished using a modified Zeiss stereo photo slit-lamp microscope, equipped with a low-light, black and white video camera or a color video camera, a 3/4-in. VHS video recorder/player, and a time-date generator. Details of the equipment and procedures, as well as anesthesia, analgesia, and treatments for iridectomy, electrode implantation, and central stimulation have been described in detail previously (8, 24, 40) and in the interests of brevity are not repeated here.

The stimulus current amplitude (at constant frequency of 100 Hz)-accommodative response relationship was established for each animal. Scheimpflug video recordings of lenticular changes were then made during stimulation at four different current settings that yielded minimally suprathreshold, approximately one-third maximal, approximately two-thirds maximal, and maximal accommodative amplitude. Stimulus duration was 2.2 s, with videographic recording for at least 4 s to record the time course of onset and relaxation of accommodation. After the entire set of responses was recorded two or three times, the Scheimpflug camera was replaced with the gonioscopy lens to image movements of the ciliary body, zonule, and lens periphery, using the same stimulus parameters. Time to the nearest 0.01 s and onset and termination of electrical stimulation were electronically encoded on the videotape.

A millimeter rule was placed in the plane of focus for image calibration. The absolute magnification of the Scheimpflug and gonioscopic images within the eye could not be established, because in the former the cornea itself, and in the latter the gonio lens, alters the magnification of the image. However, uncertainty of magnification could have no effect on delay time or on observed time course of the various movements, the determination of which was the primary objective of the study. The values presented are therefore given as approximate millimeter change from baseline. Because in most cases interlace video mode was used, our time resolution was 1/30 s. Using noninterlaced video mode to obtain 1/60-s resolution did not yield observable effects on the time course curves; hence this mode was abandoned because the loss of spatial resolution offset any gain from improved temporal resolution.

The lens and ciliary body movements were measured on frame-by-frame playback of video recordings from a Panasonic model AG-6300 video recorder and model WV5350 video monitor using an electronic caliper (Fowler; Max-Cal, Newton, MA) connected to an Apple IIe computer. The caliper was fitted with transparent plastic plates with hairlines to allow these markers to be placed as close to the images as allowed by the thickness of the glass face of the cathode ray tube (CRT). The measured values, together with the frame numbers and the times of onset and termination of the stimulus, were recorded in the computer.

In a later phase of the study, individual frames were entered into a Sun Microsystems model 150 computer via a Matrox (Montreal, PQ) frame grabber and graphic support boards. After image enhancement, similar measurements as described above were made using a mouse-controlled cursor. This technique eliminated possible parallax errors introduced by the thickness of the glass or the CRT when the electronic caliper was used to make this measurement. Because no systematic differences in measurement were observed between the use of the cursor versus the caliper, the data obtained with the caliper were accepted as accurate without corrections.

Data were collected only from image sequences where the measurement reference points could be viewed throughout the entire accommodation/disaccommodation sequence. For ciliary body movement, this measurement was the distance between a single, well-identified point on the ciliary body and a fixed point at the edge of the sclera. Lens thickness was measured as the distance between the slit-lamp beams reflected from the apexes of the lens anterior and posterior surfaces. Anterior chamber depth was measured as the distance between the slit-lamp beams reflected off the apex of the cornea and the apex of the anterior lens surface. Lens movements were measured relative to the static corneal slit-lamp reflection. Because lens thickness and ciliary body movements were measured using different imaging techniques, they were necessarily measured during different stimulations, although during the same session and at the same stimulus parameters. A running average of the last three data points was calculated and a best fit curve vs. time was plotted by the computer.

Statistical Analysis

Simple, reasonable, and informative statistical models based on the data and the physiology of the system were selected. Where the parameter vs. age or vs. time relationship appeared nonlinear, we analyzed the data by an exponential decay model, where a_0 , a_1 , a_2 are variables in the exponential decay curve/model equation to predict y , where a_0 is the asymptote of the curve, a_1 is the rate of decay, and a_2 is a scaling parameter (see Fig. 4). Our goal was to determine whether the response amplitude or velocity changed significantly with age. For example, in Figs. 4A (ciliary body) and 8A, where we wanted to know whether the evident nonlinear decay in response amplitude with age or time was significant, the probability associated with the a_1 variable tests for the presence of such a decline. Disaccommodation showed evidence of a sigmoid decline with age, so we tested varying sigmoid models to fit these data. Linear models were used when data appeared to change in a linear fashion over time or age. Where linear regression was used, P is the probability that slope or intercept (coefficient \pm SE) = 0.0. Velocity of ciliary body movement during accommodation was measured over the time interval when it was constant (linear portion of trace). Data points where velocity was clearly nonconstant (i.e., near the beginning or end of the response, or during transition between first and second phase of the ciliary body

response) were excluded. Although velocity on the nonconstant portions of the response trace can be measured, we could not identify any trends with animal age or duration of stimulus train (fatiguing experiment) with so few data points; a larger number of animals would be needed to discern trends in these regions. Group data are reported as means \pm SE and compared by the two-tailed, two-sample t -test.

RESULTS

Accommodation

Figure 1, A–D, shows progressive change in position of the ciliary body during stimulation of the E-W nucleus in a young animal. In this 4-year-old monkey accommodating \sim 14 diopters, the first observable change, beginning at \sim 0.05 s after stimulus onset, was a rapid centripetal movement of the ciliary processes (i.e., increasing distance between fixed points on the sclera and the inner surface of the ciliary body) (Fig. 2 and Table 1). Increasing lens thickness, decreasing anterior chamber depth (i.e., the distance between the anterior corneal surface and anterior lens surface), and increasing distance between the anterior corneal and posterior lens surfaces began after \sim 0.1 s. All four parameters reached their new steady state within less than 1.0 s of stimulus onset, but the greatest and most rapid excursion was ciliary body movement. Ciliary body movement appeared to be biphasic, with the first half of the excursion proceeding more rapidly (2.41

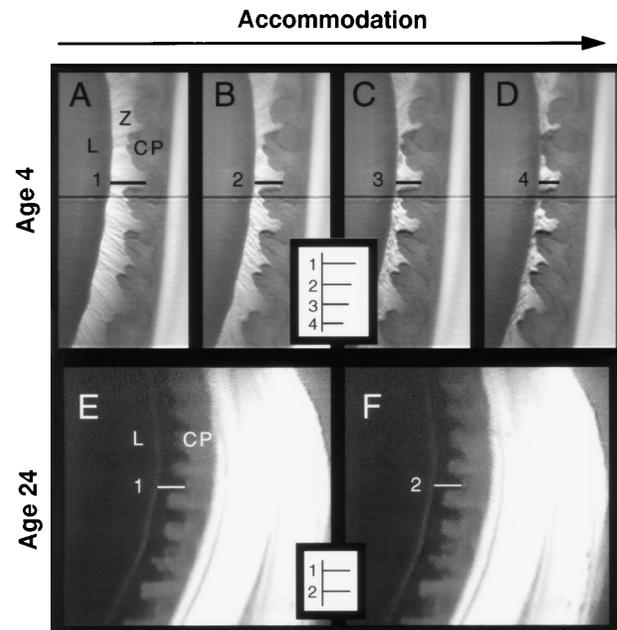


Fig. 1. Goniovideography of 4 (A–D)- and 24 (E and F)-yr-old rhesus monkey anterior segments following total iridectomy and midbrain electrode implantation. A and E: nonaccommodated ciliary process (CP), zonular fibers (Z), and lens (L) just before stimulation of Edinger-Westphal nucleus. B–D and F: after stimulation, accommodation progresses from B to maximum in D. In C, zonules fold and ciliary processes touch the lens. In D, ciliary ring continues to narrow even after tips of processes touch the lens. Line 1: distance between ciliary valley and lens. Lines 2–4, progressive narrowing of lens-ciliary body space during accommodation in 4-yr-old monkey. Lines 1 and 2 in 24-yr-old animal (E and F) indicate no change in lens-ciliary body space following stimulation.

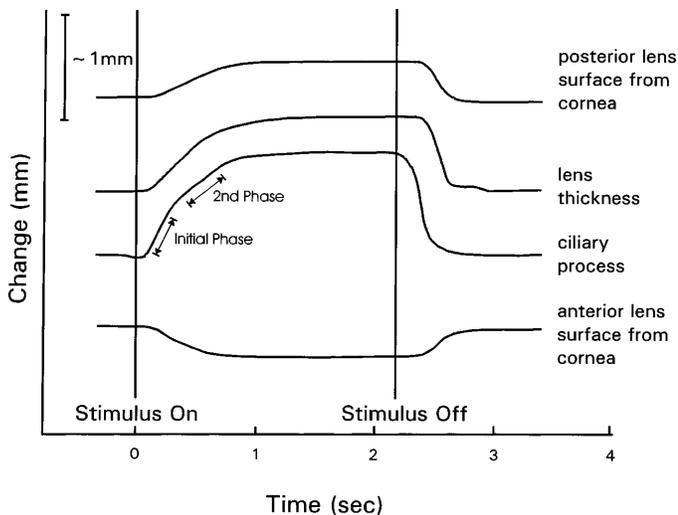


Fig. 2. Time course of lens and ciliary body movements during 14 diopters of centrally stimulated accommodation and disaccommodation in a 4-yr-old rhesus monkey. Stimulus parameters were supramaximal for accommodation in young animals (1,000 μ A at 100 Hz). Reference points on ciliary muscle that did not disappear during accommodation or disaccommodation were selected to determine amplitude and velocity of movement from sclera.

mm/s) than the second half (0.91 mm/s). Lens thickening seemed more nearly monophasic, at a rate of 1.14 mm/s. Ciliary body and lens movements all slowed as steady-state positions were reached, rather than ceasing abruptly.

Disaccommodation

Disaccommodation at the end of the 2.2-s stimulus train commenced with ciliary body centrifugal movement, beginning virtually immediately on stimulus cessation. Lenticular movements began \sim 0.2 s later, a longer latent period than for accommodation. Ciliary body movement was again faster than the three lens parameters (Table 1). All velocities were faster during disaccommodation than during accommodation (Table 1). Unlike accommodation, all movements during disaccommodation appeared to be monophasic, but again with gradual slowing near the end point (Fig. 1).

Aging

Accommodation. Figure 1, *E* and *F*, shows the almost total lack of movement of the ciliary body during

Table 1. Ciliary body and lenticular response time, amplitude, and velocity in a young monkey

Anatomic Structure	Velocity, mm/s		Lag Time, s		Amplitude, mm
	Accom	Disaccom	Stim on	Stim off	
Posterior lens surface	0.52	1.75	0.10	0.17	0.36
Lens thickness	1.14	3.27	0.07	0.18	0.73
Ciliary process					
Initial phase	2.41	6.27	0.05	0.00	0.98
2nd phase	0.91				
Anterior lens surface	0.53	0.94	0.08	0.17	0.31

Accom, accommodation; Disaccom, disaccommodation; Stim, stimulation. See Fig. 2.

stimulation of the E-W nucleus in an old animal. Figure 3 shows the trends of ciliary body and lens movement during the entire stimulus train and the overall changes with age. Figures 4A and 5 show that the decline of both the lens and ciliary body response (amplitude and velocity) were significantly correlated with age, so that neither structure can be entirely excluded from involvement in the pathophysiology of presbyopia.

With a stimulus (1,000 μ A at 100 Hz) producing maximal accommodation in young animals, both the amplitude and the velocity of lens thickening declined gradually with age, while the latent period increased (Figs. 3, 4A, 4B, 5C; Table 2). The 24-yr-old animal, capable of accommodating <2 diopters, exhibited virtually no lens thickening at maximal stimulus strength. The velocity of lens thinning during disaccommodation also declined with age, but the latent period was not clearly age dependent (Figs. 3, 4B, 5C; Table 2).

An age-dependent decline in the amplitude and velocity and increased latent period of ciliary ring constriction in response to the same (supramaximal) stimulus was also evident (Figs. 3, 4A, 4C, 5A; Table 3). Minimal ciliary body movement (0.06 mm) occurred in the 24-yr-old monkey that accommodated <2 diopters without any measurable change in lens thickness. The apparent discrepancy here is perhaps due to the resolution limits of the lens measurement technique or to a small lens translation. In the three youngest animals (ages 4, 9, and 10 yr), ciliary body movement was again biphasic, an initial rapid phase being followed by a second slower one. The velocity, duration, and magnitude of the initial phase were all greatest in the 4-yr-old animal (Figs. 3, 5A; Table 3). The second phase was of comparable velocity, duration, and magnitude in all three young animals (Figs. 3, 5B; Table 3). The velocity of the second phase of ciliary body movement in the three young animals was also comparable to the monophasic velocity in the three older animals, so that these six velocities collectively exhibited no age-related decline (Figs. 3, 5B; Table 3). The biphasic nature of ciliary body velocity is seen in the 4-yr-old animal in three separate experiments (Figs. 2, 3, and 6; 0 min stimulus train) and in the other two youngest animals aged 9 and 10 yr (Fig. 3).

Disaccommodation. When the stimulus terminated, ciliary body relaxation was clearly slower in the three oldest compared with the three youngest animals (0.48 ± 0.06 vs. 4.75 ± 0.13 mm/s, respectively; $P < 0.002$) and was again essentially monophasic, but with slowing toward baseline state (Figs. 3, 5A; Table 3). Ciliary body disaccommodation velocity declined rapidly with age from \sim 10 yr to 15 yr (Fig. 5A). Composite ciliary body velocity in younger animals was greater during disaccommodation than during accommodation, both velocities declined with age, and the rate of decline was more rapid for disaccommodation, so that by the age of \sim 20 yr the velocities were about equal (Fig. 5, A and B; Table 3).

Fatiguing. When the 4-yr-old animal was maximally stimulated with repeated trains of 2.2-s duration separated by 2-s rest intervals, the magnitude of lens

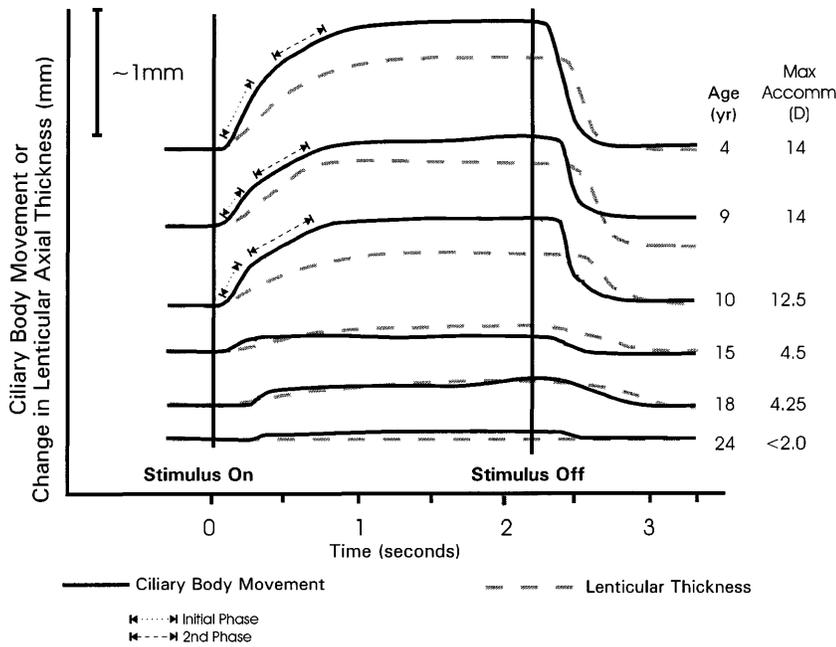


Fig. 3. Age-dependent loss of lens thickening and ciliary body movement during centrally stimulated accommodation and disaccommodation in rhesus monkeys. Stimulus parameters were supramaximal for accommodation in young animals (1,000 μ A at 100 Hz). Max Accommm, maximum accommodation; D, diopters.

thickening declined progressively (Fig. 6, 7A; Table 4). After 4 min, maximum lens thickening was reduced by two-thirds and was reached within 0.5 s after stimulus onset. From 0.5 s after stimulus onset the lens tended to thin slightly whereas lens thickness increased con-

tinuously throughout most of the first stimulus period. The latent period for lens thickening remained essentially constant with repeated stimulation while the latent period for thinning decreased progressively over time (Fig. 6, 7B; Table 4). With repetitive stimulation,

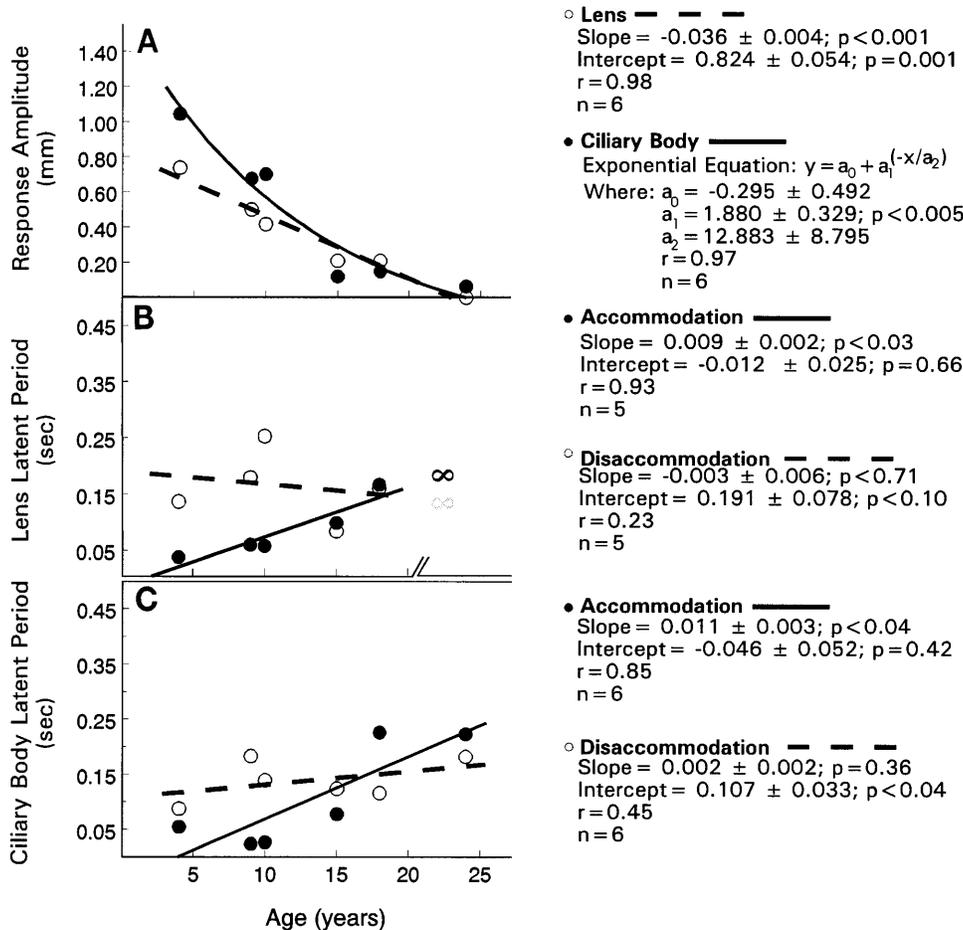
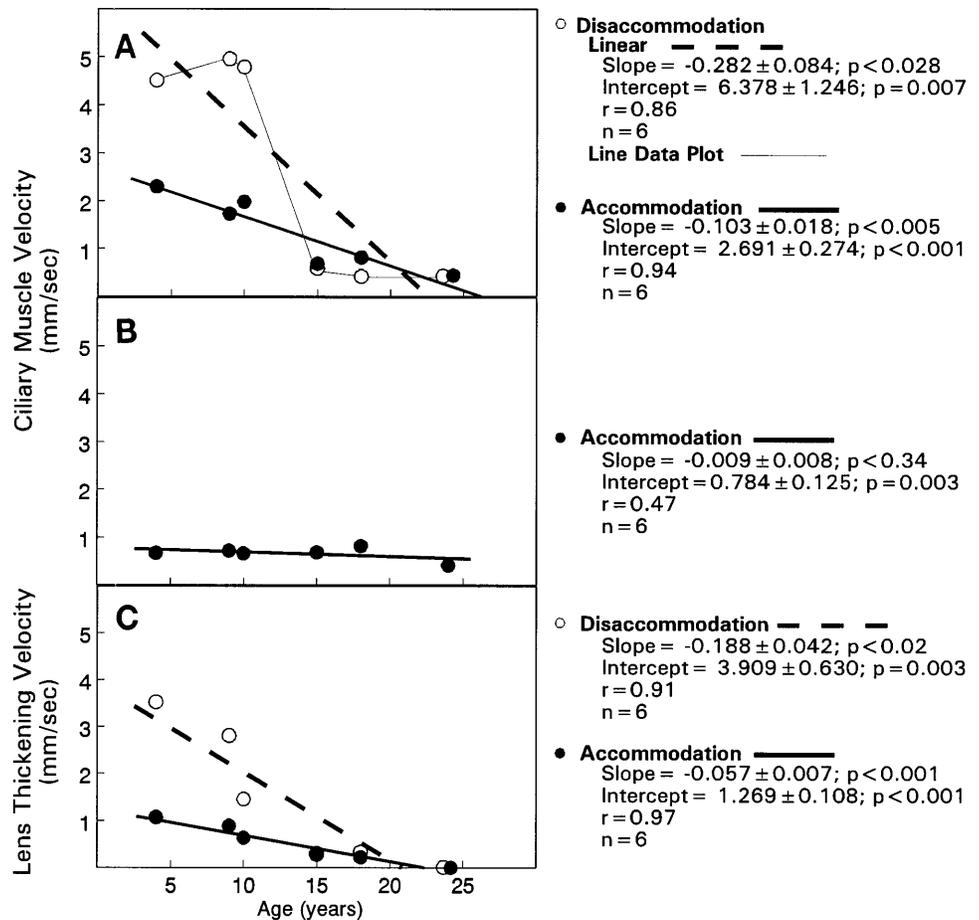


Fig. 4. A: age-dependent loss of ciliary body and lens response amplitude during centrally stimulated accommodation and disaccommodation vs. age in rhesus monkeys. Stimulus parameters were supramaximal for accommodation in young animals (1,000 μ A at 100 Hz). ∞ , no lens response at age 24 yr. Solid curved line in A represents exponential decay model (see *Statistical Analysis*) to determine whether nonlinear decay evident in data was significant; the probability associated with the a_1 variable (reported as coefficient \pm SE) tests for presence of such a decline. Straight solid or dashed lines in A, B, and C represent least-squares regression of lens response amplitude (A), lens latent period (B), or ciliary body latent period (C) on age during accommodation (B and C, solid lines) and disaccommodation (B and C, dashed lines). Slopes and intercepts are coefficients \pm SE; P, probability that slope or intercept = 0; r, correlation coefficient.

Fig. 5. Age dependence of ciliary body (A and B) and lens (C) velocity during centrally stimulated (1,000 μ A at 100 Hz) accommodation and disaccommodation. A: plot of first-phase velocity for young animals and monophasic velocity for older animals vs. age. B: plot of second-phase velocity for young animals and monophasic velocity for older animals vs. age. Straight solid or dashed lines in A, B, and C represent least-squares regression of ciliary muscle velocity (A and B) or lens thickening velocity (C) on age during accommodation (solid lines) and disaccommodation (dashed lines). Slopes and intercepts are coefficients \pm SE.



velocity of lens thickening during accommodation did not clearly decline, but velocity of lens thinning during disaccommodation declined (Fig. 6, 8C; Table 4).

The amplitude of ciliary ring constriction also declined by $\sim 60\%$ with repetitive stimulation (Fig. 6, 7A; Table 5). The second (slower) phase of contraction was lost with time, so that the peak response was reached within ~ 0.3 s of stimulus onset (Fig. 6). This time to first-phase peak did not lengthen during the 4-min stimulus train. During the first minute, the maximum response was maintained until the end of the 2.2-s stimulus. However, during the last 2–3 min, the response declined during the second half of each stimulus, the decline beginning progressively earlier (Fig. 6). The decline from the maximum response amplitude by

the end of the 2.2-s stimulus became proportionally greater for the ciliary body than for the lens with time (Table 5 vs. 4). Ciliary body velocity during accommodation did not change appreciably over time, but velocity during disaccommodation slowed marginally (Figs. 6, 8A, 8B; Table 5). The latent period for the ciliary body did not change over time for either accommodation or disaccommodation (Fig. 7C).

DISCUSSION

Technical Considerations

Accommodative changes in lens thickness and surface curvatures as a function of age have been reported for animals from this colony (25, 31). Lens thickening was measured by static A-scan ultrasound and lens surface curvatures were measured by Scheimpflug still photography (25, 31). However, still photography does not allow establishment of time courses and assessment of dynamic changes.

Total iridectomy is necessary for goniovideographic imaging of the lens equator and ciliary body. Complete removal of the iris reduces the maximal pharmacologically stimulated accommodative amplitude in rhesus monkeys, perhaps because the intense contraction of the iris enhances the normal accommodative response by either pinching the anterior lens or dragging the ciliary body still farther axially (9). Implanting a

Table 2. Age and lens response

Age, yr	Velocity, mm/s		Lag Time, sec		Amplitude, mm
	Accom	Disaccom	Stim on	Stim off	
4	1.07	3.53	0.04	0.14	0.74
9	0.89	2.81	0.06	0.18	0.50
10	0.63	1.46	0.06	0.25	0.42
15	0.27	0.30	0.10	0.08	0.21
18	0.22	0.33	0.17	0.16	0.21
24	0.00	0.00	NA	NA	0.00

Data represent 6 different animals ranging in age from 4 to 24 yr old. NA, not applicable. See Fig. 3.

Table 3. Age and ciliary body response

Age, yr	Velocity, mm/s		Lag Time, s		Total Amplitude, mm	Response Separated by Phase	
	Accom	Disaccom	Stim on	Stim off		Duration, s	Amplitude, mm
4							
Initial phase	2.30	4.51	0.05	0.09	1.04	0.20	0.49
2nd phase	0.68					0.37	0.24
9							
Initial phase	1.73	4.96	0.02	0.18	0.68	0.12	0.27
2nd phase	0.72					0.39	0.26
10							
Initial phase	1.98	4.79	0.03	0.14	0.70	0.13	0.29
2nd phase	0.66					0.42	0.27
15	0.69	0.59	0.08	0.12	0.12		
18	0.82	0.42	0.23	0.12	0.15		
24	0.41	0.43	0.22	0.18	0.06		

Data represent 6 different animals ranging in age from 4 to 24 yr old. See Fig. 3.

stimulating electrode in the living monkey brain and maintaining it for extended periods theoretically might injure the accommodative center, but no other methodology exists for repeatedly inducing rapid physiological accommodation and disaccommodation in subhuman primates. Minor week-to-week variability in the accommodative response occurs (8), both increases and decreases, perhaps due to variations in anesthetic depth, hydration, or the exact position of, or fibrosis surrounding, the electrode tip within the E-W nucleus. However, given all the theoretical sources of variability and systematic long-term effects on the ocular and central components of the mechanism, it is remarkable how consistent the responses of a given animal are over time (8). It is also remarkable how closely the cross-sectional age-dependent decline in electrically stimulated accommodation follows that for 1) pharmacologically induced accommodation in noniridectomized, non-electrode-

implanted rhesus monkeys (2) and for 2) voluntary accommodation in humans, relative to lifespan (10, 29). Furthermore, the methodology was identical for all animals, and there is no evidence that young and old animals were affected differently by the procedures. Therefore, we conclude that our data reasonably reflect the true accommodative mechanism and its dynamics and aging. Ideally, one would like to observe the course of presbyopia in individual animals longitudinally. However, presbyopia is a continuous process and would require many years before discernible differences in accommodative amplitude became apparent in an individual animal. From the standpoints of both completing the study within a reasonable time period and maintaining a monkey with a functioning indwelling electrode in the midbrain, it was far more realistic to undertake a cross-sectional study.

Lens and Ciliary Body Dynamics and Their Relationship

This study shows that the time-course and magnitude of lens and ciliary body deformation during centrally stimulated accommodation can be measured using Scheimpflug- and goniovideography in totally iridectomized living rhesus monkey eyes to provide a better understanding of accommodative dynamics, their aging, and the pathophysiology of presbyopia.

The amplitude of the ciliary body movement declined exponentially while the lens thickening declined linearly (Fig. 4A). This indicates greater rate of age-dependent restriction of movement for the ciliary body than for the lens, especially in youth (Fig. 4A). The increasing inability of the lens to thicken might be caused by the increasing ciliary muscle restriction with age or by a hardening of the lens occurring separately but with a similar time course.

The latent period increased with age at virtually the same rate for the ciliary body and lens responses (Fig. 4, B and C). This may indicate increasing ciliary body restriction, perhaps due to an increasingly inelastic posterior attachment (33, 56). The increase in lens latent period could be due to the ciliary body restriction or, separately, to lens hardening. Figure 5 shows an age-dependent decline of ciliary body and lens veloci-

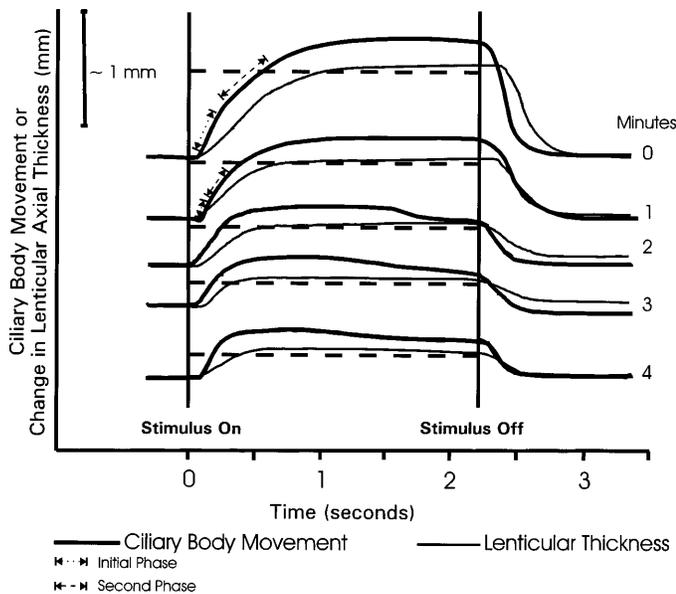
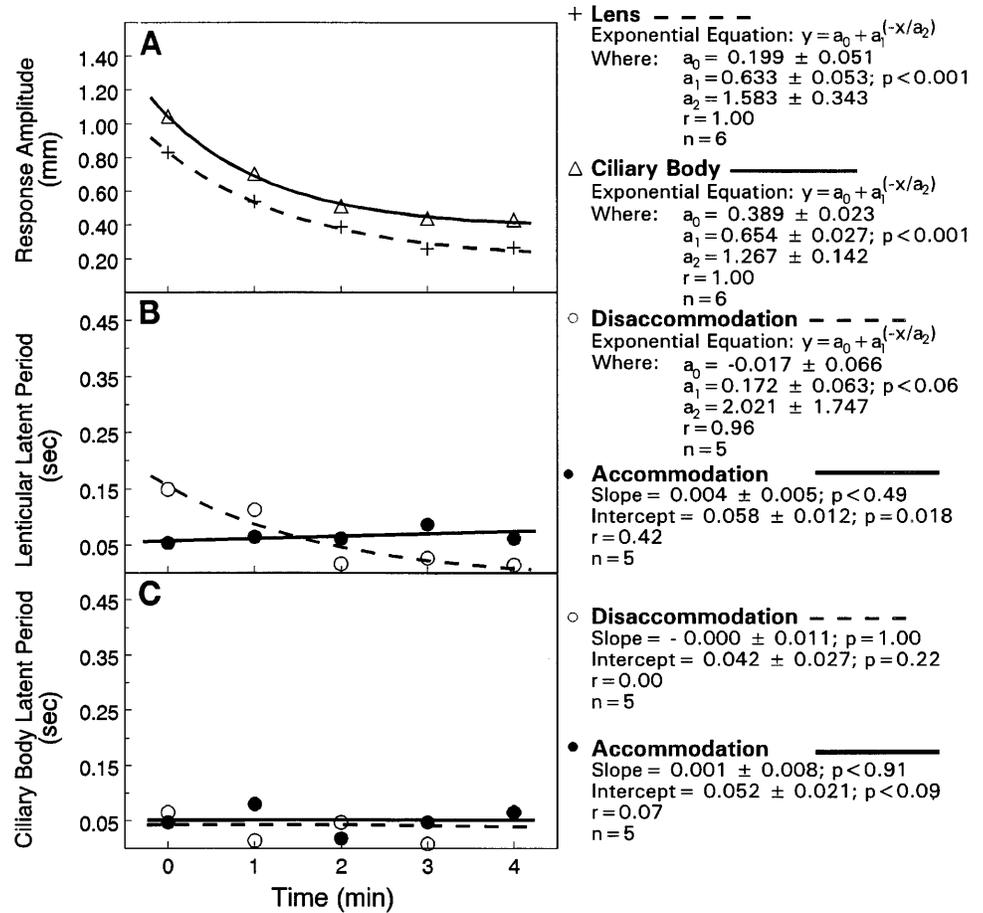


Fig. 6. Time-dependent loss of lens and ciliary body movements during repeated centrally stimulated maximum accommodation and disaccommodation in a 4-yr-old rhesus monkey. Stimulus parameters were 1,000 μ A at 100 Hz, administered in a 2.2-s on, 2.0-s off sequence for 4 min. Dashed horizontal lines drawn to delineate subtle lens and ciliary body changes during stimulus train relative to the horizontal.

Fig. 7. Amplitude (A) and latent period (B and C) of lens and ciliary body movement vs. time in a 4-yr-old rhesus monkey during repeated central stimulation. Conditions as in Fig. 6. Straight solid or dashed lines in B and C represent least-squares regression of lens latent period (B) or ciliary body latent period (C) on time during accommodation (dark, solid lines) and disaccommodation (dashed lines). Slopes and intercepts are coefficients \pm SE.



ties for both accommodation and disaccommodation, again consistent with restriction of the ciliary body; the reduced speed of lens deformation could again be due either to the ciliary body restriction or to lens hardening itself. The ciliary body velocity declines more rapidly with age than does lens velocity, suggesting a primary ciliary body-related component in presbyopia.

Figure 7A shows a nearly identical exponential decline in the amplitude of ciliary body and lens movement during repetitive stimulation in a young animal, reflecting the dependence of lens deformation on ciliary body movement and fatigue of the ciliary muscle with time. The ciliary body showed no time-dependent change in the latent period for disaccommodation, but the lens exhibited a decrease in latent period. Possibly the fatiguing ciliary body had progressively less antero-inward movement at the end of minutes 2, 3, and 4

during the stimulus train (Fig. 6), so that when the stimulus was turned off, return of zonular tension sufficient to deform the lens occurred sooner. Normally humans can accommodate to focus on near objects at a comfortable working distance for long periods of time, as during reading. The decline in amplitude of ciliary ring constriction and lens thickening within <4 min in our animal was most likely due to supramaximal stimulation, analogous not to normal near work but rather to maintaining sharp focus at or even closer than the near point of accommodation.

One might expect the velocities for both ciliary body and lens to change in parallel. However, they differed in the young animals; the ciliary body response was consistently biphasic (Figs. 2, 3, 6), whereas the lens responded monophasically, without a clear linear second phase in which to measure a constant velocity.

Table 4. Ciliary body fatigue and lens response

Minutes	Velocity, mm/s		Lag Time, s		Response Amplitude			
	Accom	Disaccom	Stim on	Stim off	Max, mm	At 2.2 s, mm	Time at max, s	LRA _{2.2} /LRA _{Max}
0	1.13	1.86	0.05	0.15	0.83	0.83	2.20	1.00
1	1.20	1.43	0.07	0.13	0.54	0.54	2.20	1.00
2	0.99	0.86	0.06	0.02	0.39	0.38	1.80	0.97
3	1.17	0.48	0.09	0.03	0.26	0.25	0.58	0.95
4	0.69	0.75	0.06	0.01	0.27	0.25	0.81	0.92

Max, maximum; LRA, lens response amplitude. See Fig. 6.

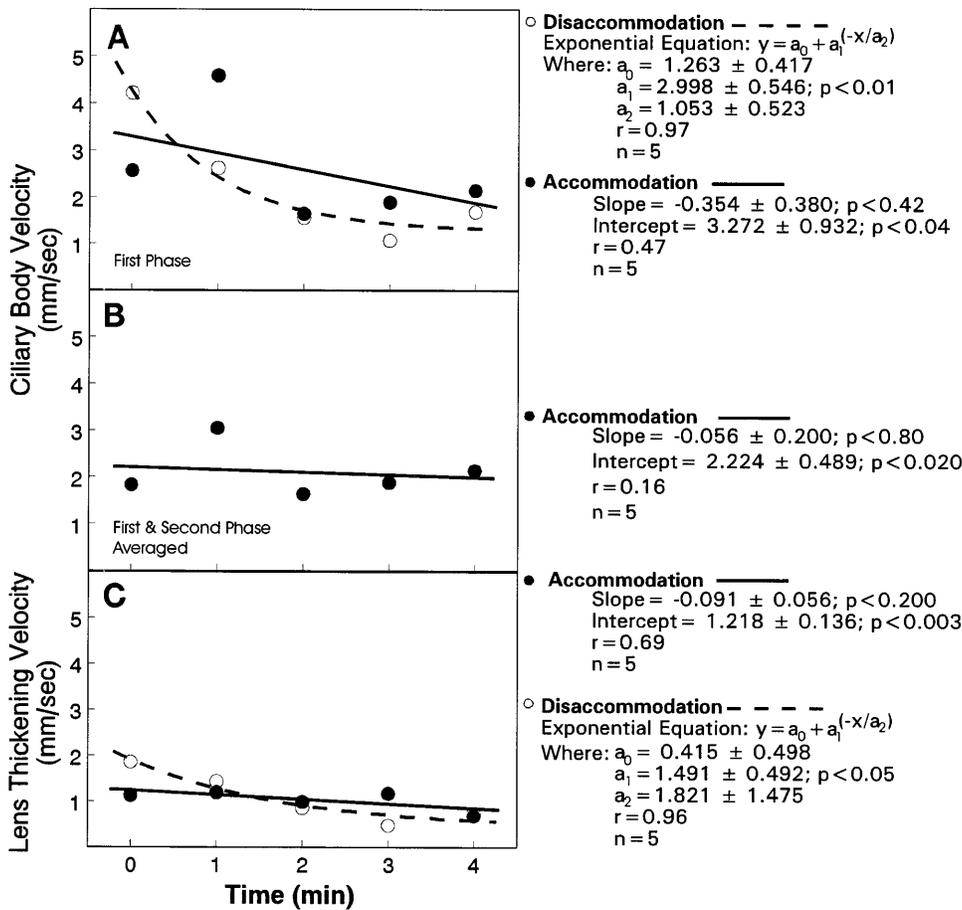


Fig. 8. Velocity of ciliary body (A: first phase; B: average of first and second phases) and lens movement (C) vs. time in a 4-yr-old rhesus monkey. Conditions as in Fig. 6. Solid lines in A, B, and C represent least-squares regression of ciliary body velocity (B) or lens thickening velocity (C) on time during accommodation. Slopes and intercepts are coefficients \pm SE.

Thus we did not analyze the lens response as having a first and second phase, as we did for the ciliary body in Table 1. The biphasic nature of the ciliary body response is likely real rather than artifact. In one animal a small transient baseline drop was occasionally observed near the stimulus onset. However, this occurred in only two traces (Fig. 2, immediately before stimulation; Fig. 7, 1-min stimulus train) and not in the 10 other traces examined in these young animals (Fig. 4; Fig. 7: 0-, 2-, 3-, and 4-min stimulus trains). The precise cause of this drop is uncertain, but in any event an

artificial change of this magnitude later during stimulation would be too small to account for the biphasic nature of the ciliary body response, which was biphasic both in the presence and absence of this apparent artifact.

The initial phase of ciliary muscle contraction appears to be lost with increasing age. We deduce this from three findings: 1) in the older animals, the ciliary body was slower to respond (longer latent period); 2) in the younger animals, the second-phase velocity was independent of age; and 3) the velocity of the monopha-

Table 5. Ciliary body fatigue and ciliary body response

Minutes	Velocity, mm/s		Lag Time, s		Response Amplitude, mm		CBRA _{2.2} /CBRA _{Max}	(LRA _{2.2} /LRA _{Max})/(CBRA _{2.2} /CBRA _{Max})
	Accom	Disaccom	Stim on	Stim off	Max	At 2.2 s		
0.00								
Initial phase	2.56	4.22	0.05	0.07	1.04	1.00	0.96	1.05
2nd phase	1.12	NA						
1.00								
Initial phase	4.59	2.62	0.08	0.01	0.70	0.70	0.99	1.01
2nd phase	1.51	NA						
2.00								
Initial phase	1.64	1.56	0.02	0.05	0.51	0.40	0.77	1.26
2nd phase	NA	NA						
3.00	1.89	1.07	0.05	0.01	0.44	0.29	0.66	1.44
4.00	2.14	1.69	0.07	0.07	0.43	0.35	0.81	1.14
Mean \pm SE								1.18 \pm 0.08

CBRA, ciliary body response amplitude. See Fig. 6.

sic movement in the older animals was similar to that of the second phase in young animals (Fig. 5B). Specifically, in the 18- and 24-yr-old animals the latent period (0.23 and 0.22 s, respectively) is as long or longer than the combined duration of the latent period and the first contraction phase in the 4, 9, and 10-yr-old animals (0.25, 0.14, and 0.16 s, respectively). However, it is also possible that the initial phase still exists in the older animals, but that the difference between the first and second phase is so small that we are not able to distinguish them.

Additionally, in the older animals, the combined duration of the latent period plus the remaining contraction period (0.40 ± 0.04 s; $n = 3$) is shorter than the entire biphasic contraction response in the younger eyes (1.06 ± 0.11 s; $n = 3$; $P = 0.028$), perhaps implying that at least some of the second contraction phase is also lost with age. The 15-yr-old animal appears to be intermediate in this regard (0.08-s latent period + 0.36-s remaining contraction period), perhaps because this animal has not completely lost its initial rapid phase. However, it also appears that ciliary movement latency changes may occur at a later age than the velocity and amplitude changes and therefore might be secondary to them. These various possibilities must remain tentative, because the findings are based on results from relatively few animals.

Our data also show that 1) maximum ciliary ring constriction in the young exceeds that needed for maximum lens rounding and thickening; 2) with fatigue during repetitive stimulation, the amplitude of ciliary body movement declines more rapidly than does lens thickening; and 3) despite the differences in lens and ciliary body dynamics, the maximum accommodative amplitude was virtually identical in all three young animals. The fatiguing experiment suggests that the rapid initial component is insensitive to fatigue, whereas the more slowly developing component is more sensitive.

On termination of the stimulus in the young animals, ciliary body relaxation begins almost immediately and continues in a rapid monophasic fashion but slows as the baseline state is approached (Fig. 3). The slowing (especially noticeable in the 10-yr-old animal) is most likely a consequence of the mechanical/elastic properties of the muscle-zonule-lens, rather than of gradual cessation of neuronal conduction and transmitter release and binding. Measuring this nonconstant deceleration might provide some insight into the elastic component of the accommodation apparatus and its change with age or fatiguing, but our limited data did not reveal any trends with age or duration of stimulus train here.

Ciliary body movement during accommodation in the young animals was biphasic, with an initial rapid and a subsequent slower velocity. It is likely that the latter is due to the elastic components of the system (i.e., choroid, lens, etc.). The decline with age in disaccommodation velocity and the increase with age in latent period of the ciliary body response are in all likelihood related to changes in properties of the ciliary muscle or

lens, rather than to alterations in the neural signal. To verify this one could administer a cholinesterase inhibitor (i.e., eserine); if the latent period did not decrease in older animals it would point to a nonneural factor. The striking feature of the relationship of ciliary body disaccommodative velocity to age is its precipitous decline, rather than its linearity or sigmoidality.

Implications for Ciliary Body and Lens Involvement in Presbyopia

The age-dependent decline in accommodative lenticular deformation theoretically could be caused by changes in lens elasticity or viscosity. If the change in the accommodative apparatus were increased lens viscosity, lens deformation should be reduced very little in amplitude but would proceed at a much slower rate to reach the same end point. So age changes in viscosity alone cannot explain these data. A decrease in lens capsular elasticity or hardening of the lens substance could result in both decreased amplitude and velocity of lens deformation. However, the observed decline in amplitude and velocity of ciliary body constriction as a function of age is unlikely to be due to changes in lens properties alone. The lens cannot physically restrict ciliary body movement by reducing the perilenticular space as the lens grows with aging, because there is still sufficient space between the tips of the ciliary processes and the lens, even in the 24-yr-old animal, to allow further reduction in ciliary ring diameter (12, 40). Furthermore, it is difficult to imagine restriction by the lens being responsible for a reduced velocity of ciliary body constriction during the initial phases of accommodation; indeed, in young and middle-aged animals, the ciliary body continues to move during accommodation even after the soft, spongy ciliary process tips touch the lens (Fig. 1). However, if the hardened larger, immobile lens were unable to stretch the ciliary muscle centripetally during accommodation, the muscle might theoretically develop secondary changes. This in turn could reduce the amplitude and velocity of ciliary body constriction. Conversely, it is equally likely that some of the observed changes in lens mobility could be a secondary consequence of loss of ciliary muscle efficacy. Either way, our results strongly suggest an extralenticular contribution to presbyopia.

The basis for an extralenticular contribution to presbyopia is provided by the age-related loss of the movement of the rhesus ciliary muscle in response to pilocarpine stimulation, as measured *in situ* by histological criteria (33, 56). This loss of movement is believed to be due to a reduction in elasticity of the posterior tendons of the muscle and the elastic lamina of Bruch's membrane, the tissues that connect the ciliary muscle posteriorly to the sclera at a point near the optic nerve (56, 57). The diminished ciliary body response to pilocarpine is not due to any deficiency in the neuromuscular apparatus (47, 58). Furthermore, loss of muscle strength, especially as early in life as the loss of accommodation with presbyopia, is not characteristic of aging. The constancy of the pupillary light response throughout the rhesus lifespan (37) suggests that the

parasympathetically dominated intraocular smooth muscles are no exception. Collectively, these data indicate that nonmuscular extralenticular factors are involved.

The ciliary muscle might be restricted due to the posterior tendons becoming fixed and rigid (56) or fixed and flaccid (3). If the posterior tendons became fixed and rigid, the normal forward movement of the contracting ciliary muscle would be restricted by the inextensible posterior tendons, and no accommodation would occur (56). If the posterior and intramuscular elastic tissue became flaccid, as proposed by Bito and Miranda (3), rather than rigid, the force of contraction of the ciliary muscle becomes irrelevant, because the system is "stuck" in the accommodated position assuming the lens/capsule remains elastic and continues to pull the ciliary muscle into an accommodated state. This scenario would also predict that the lens in the elderly eye would always have an accommodated (more spherical) configuration, with the refractive consequences (6, 27, 28) compensated for by a decreased lens refractive index, maintaining focus at distance rather than near (7, 44). However, Glasser and Campbell (19) argue against this hypothesis on the basis of finding that no amount of stretching or releasing zonular tension of older, presbyopic human lenses results in any optical change, whereas the same stretch applied to young lenses produced substantial optical changes. Furthermore, some of the neuromuscular and connective tissue degenerative changes and altered muscular and lenticular geometry sometimes cited in support of the "flaccid posterior attachment" hypothesis may represent post-presbyopic secondary or aging changes. Indeed, the specimens studied histologically (58) did not include individuals under the age of 35 yr, and very few under the age of 40 yr, by which time two-thirds of the accommodative amplitude has already been lost (10).

Another consideration is the change in the geometry of the lens suspension with age. In the human, the distance between the anterior zonular insertion onto the lens and the lens equator increases with age, whereas the distance between the insertion ring and the ciliary body remains relatively constant (12). It has been suggested that the zonular fibers become less able to relax with accommodation or that they become less able to exert an influence on the lens (27), but there are no other data to support this geometric theory (19), and complete relaxation of the zonular tension *in vitro* does not cause presbyopic human lenses to become accommodated (19). It remains unknown whether this phenomenon is present in the rhesus monkey.

In addition to a slow loss of accommodation before the age of 10, our data also suggest the possibility that something dramatic may be happening between the ages of 10 and 15 yr, when there is a loss of 8 diopters of accommodative ability. Furthermore, the decline of ciliary body response amplitude (Fig. 4A) and velocity (Fig. 5A) with age happens at a much faster rate from ages 10 to 15 yr than either before or after this age range. It could be that incremental changes seen before age 10 yr lead to a critical point where a new state is

reached between ages 10 and 15 yr. However, a much more likely possibility is that of the few animals used, the 10 yr old had an unusually high accommodative amplitude and the 15 yr old an unusually low accommodative amplitude. The gradual decline in accommodation with the progression of presbyopia is such a characteristic feature of presbyopia [even in rhesus monkeys (2)] that it would be truly remarkable if something suddenly occurs between ages 10 and 15 yr in these animals.

Although our knowledge of the events that accompany the aging of the accommodative mechanism has increased vastly over the past decade, we still do not completely understand the age-related changes in any of the components, nor how they interact to produce presbyopia. Future studies utilizing the animal model and techniques described herein may enhance our insight into this most common of all ocular afflictions.

Perspectives

The presbyopia literature is rich with review articles, theories, and speculation but lacking in experimental data. Infrequently, techniques such as impedance cyclography, magnetic resonance imaging, or ultrasound biomicroscopy emerge to provide new information on varied aspects of human intraocular accommodative function and its age-related decline. These developments sometimes clarify and sometimes confuse the field. Studies on rhesus monkeys, the only known animal model for presbyopia (2), have consistently provided new and significant information not otherwise obtainable. Because accommodation is a dynamic process, presbyopia must inevitably affect its normal physiological dynamics. The present study has utilized optical imaging in living rhesus monkey eyes to quantify real-time movement of the lens and ciliary body, aspects of accommodation and presbyopia not previously studied. It has demonstrated the potential to differentiate relative pathophysiological contributions of these structures to the progression of presbyopia. This will ultimately improve our understanding of the primary root causes of this ubiquitous aging process and may identify or exclude possible targets for future pharmacological or surgical interventions. For instance, pliable polymeric intraocular lenses are designed to change shape and refractive power, with the hope of providing accommodative function when inserted or injected into the lens capsule in replacement of cataractous lens substance (20, 41). However, such artificial lenses will not restore accommodation in the absence of ciliary muscle function. Conversely, pharmacological intervention directed at the ciliary muscle, choroid, or their connective tissue would be futile in the face of a hardened, immobile lens. We look forward to extracting further information from this unique primate model.

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