Accommodative Ciliary Body and Lens Function in Rhesus Monkeys, I: Normal Lens, Zonule and Ciliary Process Configuration in the Iridectomized Eye

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PURPOSE. The underlying causes of presbyopia, and the functional relationship between the ciliary muscle and lens during aging are unclear. In the current study, these relationships were studied in rhesus monkeys, whose accommodative apparatus and age-related loss of accommodation are similar to those in humans.

METHODS. Centripetal ciliary body and lens equator movements were measured during accommodation in 28 eyes of 21 rhesus monkeys (ages, 5.7–26 years) by goniovideography. Ultrasound biomicroscopy was performed in 21 eyes of 17 monkeys. Narrowing of the angle between the anterior aspect of the ciliary body and the inner aspect of the cornea was used as a surrogate indicator of forward ciliary body movement during accommodation.

RESULTS. Average centripetal ciliary body movement in older eyes (age ≥17 years, $n = 16$) was ~20% (0.09 mm) less than in young eyes (age, 6–10 years, $n = 6$), but not enough to explain the 60% (0.21 mm) loss in centripetal lens movement nor the 76% (10.2 D) loss in accommodative amplitude. Average forward ciliary body movement was 67% (49°) less in older ($n = 11$) versus young ($n = 6$) eyes. Maximum accommodative amplitude correlated significantly with the amplitude of centripetal lens movement (0.02 ± 0.003 mm/D; $n = 28$; $P < 0.001$) and with forward ciliary body movement (3.34 ± 0.54 deg/D; $n = 21$; $P = 0.01$).

CONCLUSIONS. Decreased lens movement with age could be in part secondary to extralenticular age-related changes, such as loss of ciliary body forward movement. Ciliary body centripetal movement may not be the limiting component in accommodation in the older eye. (*Invest Ophthalmol Vis Sci.* 2006;47: 1076–1086) DOI:10.1167/iovs.04-1523

Fundamental elements of the accommodation mechanism (focusing from far to near objects) have been debated, notably in regard to the change in lens equatorial diameter. The classic Helmholtz theory of accommodation postulates that the ciliary muscle moves forward and inward, releasing tension on the zonula, allowing the lens equator to move away from the sclera.[1] The lens equatorial diameter decreases and the lens anterior–posterior (A-P) thickness increases.[1]

The functional relationships between the ciliary muscle, zonular fibers, and lens and their changes with age are unclear, impeding elucidation of the pathophysiology of presbyopia (the loss of accommodative ability with age). Rhesus monkeys have an accommodative apparatus virtually identical with the human[2–6] and exhibit an age-related decline in pharmacologically and centrally stimulated accommodation that, adjusted for lifespan, is comparable to the loss of visual stimulus-driven accommodation in the human.[3,7–10] The rhesus monkey is therefore an excellent model for accommodation and presbyopia.

In living rhesus monkeys, after surgical iridectomy, the tips of the ciliary processes (CPs), the zonular fibers, and the lens equator can be observed, and accommodative movements can be measured by goniovideographic imaging upon onset of electrical stimulation to the Edinger-Westphal (E-W) nucleus.[7–9] The tips of the CPs and the lens equator move away from the sclera.[9] Both lens equator and CP movement are highly linearly related to refractive change.[9] These techniques also permit studying age-related changes in the accommodative structures. Herein, we describe age-related changes in the functional interaction between the ciliary muscle and lens and the direction and extent to which these structures move during accommodation.

MATERIALS AND METHODS

Animals

Twenty-eight eyes of 22 rhesus monkeys (*Macaca mulatta*) of both sexes weighing 5.7 to 14.8 kg, with normal eyes (assessed biomicroscopically) were studied. Their age range at entry was 5.7 to 24 years, with experiments conducted between 2 weeks and 5 years thereafter. One eye of a 6-year-old cynomolgus monkey (*Macaca fascicularis*) weighing 4.5 kg was also included. The ages given are those at which the particular experiment was performed and thus range from 5.7 to 26 years. Longitudinal comparisons were not performed. All experiments adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Surgical and Experimental Preparations

Total iridectomy was performed[11] in both eyes, and a bipolar stimulating electrode was implanted into the E-W nucleus of each monkey.[12] The accuracy of electrode placement during surgery was ensured by obtaining the maximum accommodative response.[12] After surgery, the monkeys behaved normally with no evidence of neurologic deficit or photic discomfort. Anesthesia was induced before all surgical and

FIGURE 1. Goniovideography images of normal lens and CP configuration in the accommodated and unaccommodated states. To obtain quantitative measurements, a 9-0 nylon suture placed at the corneoscleral limbus served as a reference point (*left solid vertical line*) from which to measure distances to the lens equator (*right solid vertical line*) and the CPs (*cross-hairs*) for each image during a 2.2-second stimulus period.
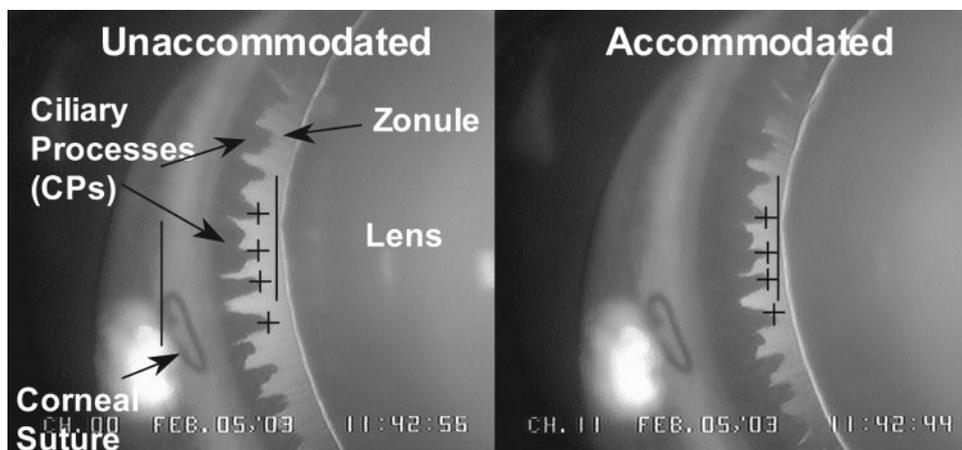
experimental procedures: (1) total iridectomy, slit lamp examination, routine photography, and refractions were performed in animals under intramuscular (IM) ketamine 10 mg/kg with or without IM diazepam 1 mg/kg, supplemented by ketamine 5 mg/kg every 20 to 30 minutes as needed; (2) midbrain electrode implantation was performed under IM ketamine 10 mg/kg+inhalant isoflurane 1% to 2%; and (3) central electrical stimulation and video recording of accommodative apparatus were performed under IM ketamine 10 mg/kg+IM or intravenous (IV) pentobarbital sodium (35 mg/kg IM, supplemented by 10 mg/kg IM per hour beginning at 2 to 3 hours, as needed; 10 to 15 mg/kg IV, supplemented by 10 mg/kg IV per hour beginning at 0.5 to 1.0 hours). A Hartinger coincidence refractometer (aus Jena, Jena, Germany) was used to measure resting refractive error and accommodation in response to stimulation of the E-W nucleus. Goniovideographic imaging and ultrasound biomicroscopy of the ciliary body, CPs, and lens equator were recorded during accommodation between 3 weeks and 5 years after electrode implantation. In 20 eyes of 16 monkeys, these experimental sessions were undertaken between 3 weeks and 10 months after electrode implantation. Eight eyes of five other monkeys were imaged at 1 ($n = 2$), 2 ($n = 4$), 4 ($n = 1$), and 6 ($n = 1$) years after electrode implantation. One monkey did not undergo goniovideographic imaging because the stimulating electrode stopped working.

Goniovideographic Imaging

For the experimental imaging sessions, the anesthetized monkey was held in a head holder with the head upright and facing forward. The body was placed prone on heating pads to maintain temperature at 36 °C to 38°C. When necessary, the medial and either the superior or inferior rectus muscles were paralyzed with an injection of botulinum A toxin at least 2 days before the recording session, to minimize eye movements; the effect typically lasted 3 to 6 months. Any residual eye movements not eliminated by the toxin injections were dampened by applying tension to a 5-0 Dacron suture passed beneath the lateral rectus muscle. Suture tension sufficient to minimize eye movements, but without dampening the accommodative response, was applied.

Accommodation was stimulated centrally via the implanted electrode. Goniovideography images (using a Swan-Jacob gonioscopy lens) were obtained with an infrared-sensitive, high-resolution CCD video camera (model 4915; Advanced Video Technology, COHU, Inc., San Diego, CA). The camera was mounted on a modified stereo photograph slit-lamp microscope (Carl Zeiss Meditec, Inc., Dublin, CA), and recordings were made with an SVHS videocassette recorder (SVO-9500MD; Sony Medical Systems, Montvale, NJ). A time–date generator was used to record the E-W stimulus onset and termination and to place a time–date stamp on the videotape. Care was taken to ensure that the observation tube of the slit lamp was always aligned with the A-P axis of the eye, allowing the circumlental space to be visualized through the Swan-Jacob gonioscopy lens. This standardization allowed detection of CP movement centripetally and comparisons between

experimental sessions on the same or different days. Details of all equipment and procedures for iridectomy, electrode implantation, and central stimulation have been described.[7,11–13]

To account for movement of the eye (if any), a 9-0 nylon suture placed in the cornea at the nasal or temporal limbus served as a reference point (Fig. 1) from which to measure centripetal movement of the lens equator and the CPs during accommodation. The amount of residual eye movement induced for each quadrant was quantified as the absolute amount the suture moved in the image from the baseline unaccommodated state to the maximally accommodated state.

Further, to determine whether residual eye movement affected the amplitude of the measured CP and lens centripetal accommodative movement, artificial eye movements were induced without accommodation by pulling on the extraocular muscle sutures in two rhesus eyes. Artificial movement was induced several times for each quadrant, and the position of the CPs and lens equator relative to the corneal suture position was measured.

Imaging through the gonioscopy lens introduced a small amount of prismatic distortion, but this did not affect overall results or conclusions, because the CPs and lens were always oriented in the middle of the field of view through the gonioscopy lens. For calibration of the extent of CP and lens movements, a 30-gauge needle was inserted into the anterior chamber just slightly anterior to the level of the zonular fibers in one eye, and the image was recorded goniovideographically. The gonioscopy image of the known-diameter 30-gauge needle in the anterior chamber was then measured to provide a calibration in pixels per millimeter. This calibration technique used the true in vivo situation (i.e., true anterior chamber depth and distance to CP/lens equator interface) and was also validated by ultrasound biomicroscopy (50 mHz).[14]

The movement values presented are the millimeters of change from baseline. The lens and CP movements were measured from 3 to 4 seconds of recorded videotape with a frame-by-frame analysis spanning the ~2.2-second stimulus period. An image-management program (Optimas; Media Cybernetics Inc., Silver Spring, MD) was used to save images from tape to hard drive and to analyze movements. Time to the nearest one thirtieth of a second and onset and termination of electrical stimulation were electronically encoded on the videotape. The measurements, together with the corresponding video frame numbers and the times of onset and termination of the stimulus, were recorded in a data file. CP movements were measured from the corneal marking suture to the tips of three to five well-defined CPs (Fig. 1). Lens movement was measured from the corneal marking suture to the vertical position corresponding to the lens equator (Fig. 1). Lens equator and CP movements were measured on the same images. Data were collected only from image sequences where the measurement reference points could be viewed throughout the entire accommodation/disaccommodation sequence. Video sequences of three responses were analyzed for each stimulus amplitude and were averaged. The

maximum amplitude of the centripetal CP and lens movement was calculated by averaging the measurements from 20 consecutive frames beginning 25 frames before termination of the stimulus (i.e., when the eye was in the stable accommodated state) and subtracting the measurements of the eye in the unaccommodated state (taken from a single image, 11 frames before the stimulus onset).

E-W Stimulation

The stimulus current amplitude (at constant frequency of 100 Hz, with a 500-μs pulse duration) versus accommodative response relationship was established for each monkey. Goniovideography recordings of the CPs, zonule, and lens equator movements were then made during stimulation at several current amplitudes. Beginning at threshold (the level needed to induce a minimum level of accommodation), the stimulus was increased by consistent increments available on the stimulus isolation unit until maximum accommodation was reached (maximal stimulus level). The stimulus level was then increased again by the same increment above the maximal stimulus (supramaximal stimulus level). This method was used, not only to ensure that maximum accommodation was achieved, as measured refractometrically, but also to determine whether maximum CP and lens movement had been achieved. Because of technical limitations, the amount of current increase above the maximal stimulus was not immediately known during each experiment but was retrospectively calculated. The supramaximal stimulus was calculated to be a current 0.1 to 0.2 mA or 26.2% $\pm$ 3.9% above that necessary to induce maximum accommodation.

Ultrasound Biomicroscopy

The anesthetized monkeys were placed supine with the head stabilized facing upward in a head holder and a saline fluid-well was placed around the eye.[15,16] The eye was rotated using a suture passed beneath the lateral rectus muscle.[16] A 50-MHz ultrasound biomicroscopy (UBM) instrument (model 840; Carl Zeiss Meditec, Inc., Dublin, CA) was used to image the lens, zonule, and ciliary body configuration at rest and during accommodation[16] while recording to SVHS tape. Measurements taken from the tape are accurate to within a few pixels (i.e., 4 pixels = 0.046 mm), as a result of the ultrasound's passing through tissues of different densities. However, the error should not influence the results appreciably, since the anterior–posterior ends of the ciliary body were oriented in a horizontal direction within all images. Comparisons were made between the images in the unaccommodated and accommodated states. The angle between the anterior aspect of the ciliary body (CB) and the inner aspect of the cornea (CB–cornea angle) was measured in the unaccommodated (resting) eye and during supramaximal stimulation. CB–cornea angle change was defined as the CB-cornea angle in the unaccommodated (resting) state minus the CB-cornea angle in the supramaximally stimulated state. Narrowing of the CB-cornea angle in the accommodated versus the unaccommodated state was used as a surrogate indicator of forward CB movement and will be referred to as such hereafter.

All analyses, images and data refer to the rhesus monkey eyes except where the single cynomolgus eye is specifically indicated (UBM images only).

Statistical Analysis

Simple linear regression (i.e., CP movement versus age, lens movement versus age, CP movement versus accommodation, and lens movement versus accommodation) and multiple regression analysis (i.e., accommodation versus age and CP movement; accommodation versus age and lens movement) were undertaken in all monkeys. The multiple regression analysis adjusted for the relatedness between two observations (i.e., instances where there were two eyes from the same monkey). Regression analysis that adjusts the relatedness between two observations has no associated correlation coefficient.

The model due diligence diagnostics were performed, and, based on the residual plots, the proposed models are not unduly affected by
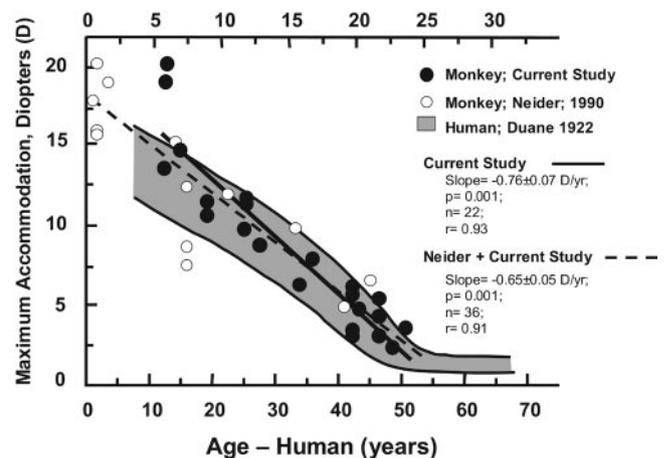

FIGURE 2. Comparative age-related decline in accommodative amplitude in the rhesus monkey (centrally stimulated, objectively measured) and human (voluntary; subjectively measured) accommodation based on a lifespan of 35 and 75 years, respectively. *Solid circles*: maximum centrally stimulated accommodation versus age in 22 rhesus monkeys (age range, 5.7–24 years) 2 weeks after midbrain electrode implantation for the present study. *Solid line*: least-squares regression of centrally stimulated accommodation on age (*solid circles*). Centrally stimulated maximum accommodative amplitude declined with age by -0.76 ± 0.07 D/y ($P = 0.001$). Rhesus monkey data (*open circles*) represent maximum accommodation induced by central stimulation in data collected by Neider et al.[7] (adapted, with permission, from Neider et al. *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. © *American Medical Association*). Human data (*shaded area*) represent the range of maximum voluntary accommodation (adapted, with permission, from Duane. Studies in monocular and binocular accommodation with their clinical applications. *Am J Ophthalmol.* 1922;5:867–877, © Elsevier). *Dashed line*: least-squares regression of all monkey data (Neider et al.[7] and current data).

variance fluctuations. There was no specific pattern in the residual plots and therefore no concern as to the validity of the model.

The expected lifespan of the rhesus monkey in captivity is ~35 years. In a separate analysis, monkeys up to 10 years of age (at ≤25%-30% of their expected lifespan) were grouped into a "young" age category, and monkeys 17 to 26 years of age were grouped in an "older" age category (at ≥45% of their expected lifespan). The mean $\pm$ SEM CP and lens movement were calculated for each group. The intermediate age group (11–16 years) was not included in this analysis.

Definitions

Maximal stimulus: the level of E-W stimulus current necessary to induce maximum refractometrically measured accommodative change. Supramaximal stimulus: a level of E-W stimulus current 26.2% $\pm$ 3.9% (or ~0.10–0.20 mA) above the maximal stimulus. Circumlental space (CLS): the average distance from the tips of four to five CPs to the equatorial edge of the lens, as measured in the goniovideography images.

RESULTS

Accommodation versus Age

Maximum accommodative amplitude ranged from 20.1 D (age, 6 years) to 3.4 D (age, 24 years). Centrally stimulated maximum accommodative amplitude declined with age by 0.76 $\pm$ 0.07 D/y ($P = 0.001$; $n = 22$; $r = 0.93$; Fig. 2). Previous findings in rhesus monkeys (Fig. 2; Neider et al.[7]) and humans (Fig. 2; Duane[10]) were compared with the current findings (see the
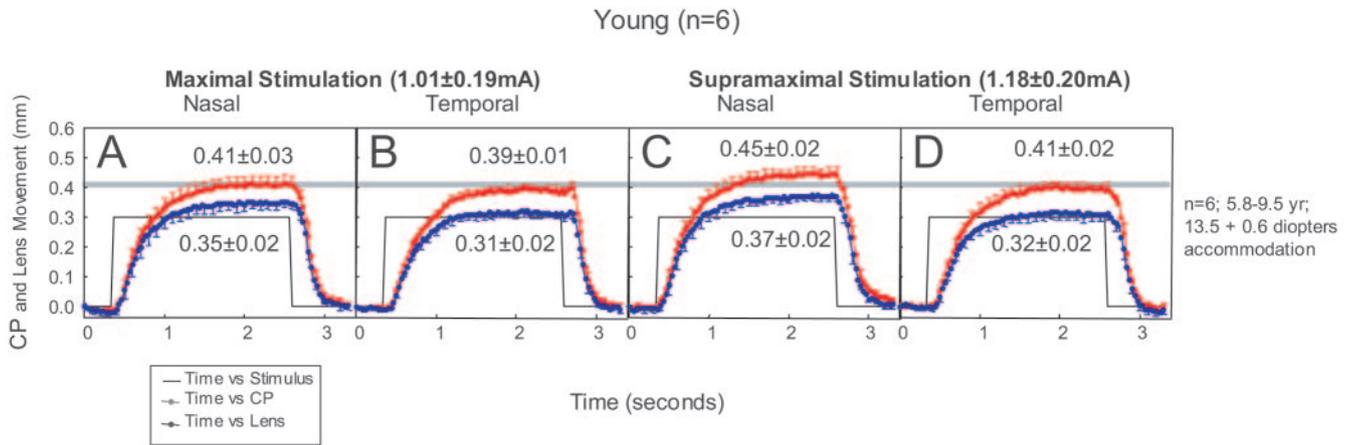
FIGURE 3. Data are the mean ± SEM centripetal CP and lens movement away from the sclera in six eyes of five young monkeys (age range, 5.8–9.5 years) during maximal (**A, B**) and supramaximal (**C, D**) central electrical stimulation to induce accommodation. Maximal stimulus: The amplitudes of the centripetal CP and lens movement were 0.41 ± 0.03 and 0.35 ± 0.02 mm, respectively, in the nasal quadrant and 0.39 ± 0.01 and 0.31 ± 0.02 mm, respectively, in the temporal quadrant. Supramaximal stimulus (stimulus setting ~0.10–0.20 mA above that which induces maximum accommodation): The amplitudes of the centripetal CP and lens movement were 0.45 ± 0.02 and 0.37 ± 0.02 mm, respectively, in the nasal quadrant and 0.41 ± 0.02 and 0.32 ± 0.02 mm, respectively, in the temporal quadrant. The eyes accommodated 13.5 ± 0.6 D.

Discussion section). Accommodative amplitude did not decline significantly after botulinum toxin injection (9.13 ± 1.28 D; n = 7) compared with the baseline (preinjection) amplitude (10.6 ± 1.73 D; n = 7).

Average Centripetal CP and Lens Movement

The Young Eye. In the young eyes (age range, 5.8–9.5, years; average, 7.2 ± 0.7 [mean ± SEM]), the lens equator moved in close association with CP movement (Fig. 3). The average maximum accommodation was 13.50 ± 0.06 D. At the maximal stimulus (Figs. 3A, 3B), the amplitude of the centripetal CP and lens movement was 0.41 ± 0.03 and 0.35 ± 0.02 mm, respectively, in the nasal quadrant and 0.39 ± 0.01 and 0.31 ± 0.02 mm, respectively, in the temporal quadrant. The nasal (but not temporal) CP centripetal movement amplitude increased slightly during supramaximal versus maximal stimulation (CP by 0.055 ± 0.016 mm; $P < 0.05$). The nasal and temporal lens centripetal movement amplitude did not increase significantly during supramaximal versus maximal stimulation.

The Older Eye. In the older eyes (age range, 17–26 years; average age, 21.6 ± 0.7), the average maximum accommodation was 3.3 ± 0.4 D. The lens equator did not move in as close association with the CPs (Fig. 4) as in the young eye. The amplitude of the lens and CP movement reached a maximum of 0.14 and 0.36 mm, respectively. The CP, but not lens, centripetal movement amplitude further increased during supramaximal versus maximal stimulation (nasal CP by 0.089 ± 0.017 mm, $P < 0.0001$; temporal CP by 0.083 ± 0.017 mm, $P < 0.0002$).

Group A. In 8 of the 16 older monkey eyes ($n = 8/16$; Figs. 4E–H; age range, 17–26 years; average 21.1 ± 1.1), the CPs came in contact with the lens as accommodation progressed in the temporal quadrant, but not the nasal quadrant, and more so at the supramaximal than at the maximal stimulus amplitudes. Their average accommodation was 3.0 ± 0.7 D. At maximum accommodation (Figs. 4E, 4F), CP and lens movement (but not the accommodative optical change) tended to be higher in these eight eyes than in group B (Figs. 4I, 4J; see next section). In the unaccommodated eye, temporal CPs were closer to the lens than nasal CPs by 0.21 ± 0.03 mm ($P = 0.005$) and touched the lens during supramaximal stimulation (Figs. 4G, 4H). The temporal CPs continued to move centripetally after

they came in contact with the lens (Fig. 4H), causing the lens to shift nasalward (Fig. 4G), perhaps because the CPs were not in contact with the lens nasally.

Group B. In 7 of the 16 eyes ($n = 7/16$; Figs. 4I–L; age range, 20–26 years; average, 22.9 ± 0.9), the CPs did not touch the lens during accommodation. The average accommodation was 2.9 ± 0.5 D, nearly identical with group A. However, the amplitude of CP movement was less in both quadrants (nasal, $P = 0.062$; temporal, $P = 0.01$) in this group (Figs. 4K, 4L versus Figs. 4G, 4H), and the temporal, but not nasal, lens equator movement was also significantly less (nasal, $P = 0.51$; temporal, $P = 0.006$; Figs. 4K, 4L versus 4G, 4H).

In one other monkey eye (age, 22 years), the temporal CPs were in contact with the lens at rest, and the nasal CPs came in contact with the lens 0.75 second after the onset of stimulation. The lens did not shift nasalward (data not shown). The eye accommodated 4 D.

Compared with the younger eyes, during maximal stimulation the older eye CP movement was 41% (0.17 mm) and 31% (0.12 mm) less in the nasal and temporal quadrants, respectively. Lens movement was 66% (0.23 mm) and 65% (0.20 mm) less in the nasal and temporal quadrants, respectively. During supramaximal stimulation, the older eye CP movement was only 27% (0.12 mm) and 12% (0.05 mm) less in the nasal and temporal quadrants, respectively. Lens movement was 65% (0.24 mm) and 57% (0.18 mm) less in the nasal and temporal quadrants, respectively. The older eye accommodated 3.3 ± 0.4 D (76%, 10.2 D) less than the young eye (Figs. 3, 4).

Residual Eye Movements and Variance

The mean ± SEM amount of eye movement that occurred during supramaximal stimulation was 0.17 ± 0.03 mm in 27 monkey eyes. A small amount of variability was introduced by convergence eye movement, but the values were close to or less than the SD of the experimental measurements (±0.05 mm) and cannot account for the accommodative movements observed. The error bars (SEM) were small compared with the amplitude of movement (Figs. 3, 4). If there were an effect from eye movement, one would expect consistent, significant differences in CP and lens equator movement between nasal and temporal quadrants, irrespective of age.

Mean ± SEM centripetal lens and CP movements calculated over three successive responses at maximal and supramaximal
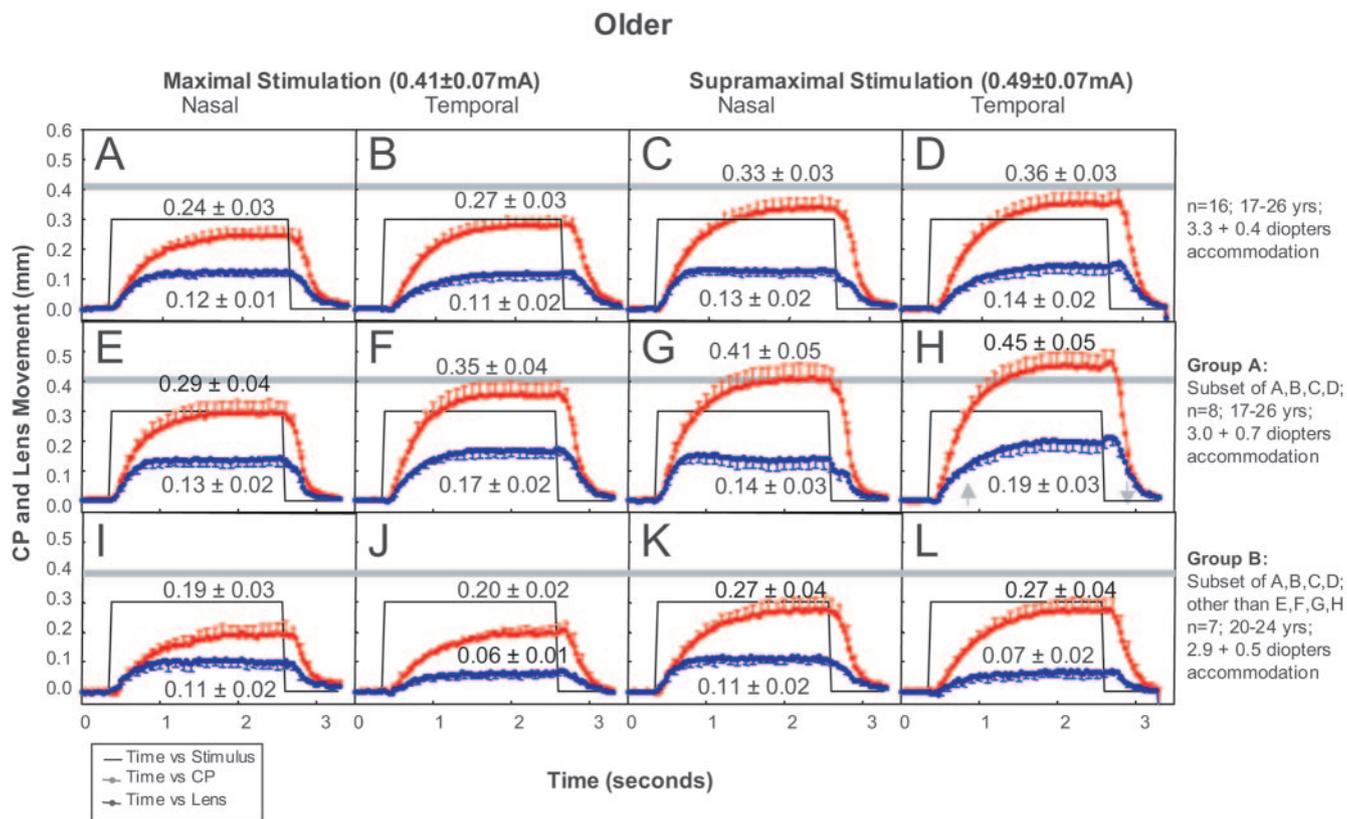
Older

FIGURE 4. (A–D) Data are mean ± SEM centripetal CP and lens movement away from the sclera in 16 eyes of 10 older monkeys aged 17 to 26 years during central electrical stimulation at maximal (**A**, **B**) and supramaximal (**C**, **D**) stimulus settings. (**E–H**) Group A (*n* = 8/16): In this group the temporal CPs touched the lens equator in all eight eyes during the supramaximal stimulus. After the onset of the supramaximal stimulus, the average time point at which the temporal CPs (**H**) touched the lens was 0.90 ± 0.12 seconds (*up arrow*). The CPs no longer touched the lens after 2.8 ± 0.02 seconds (*down arrow*) after stimulus onset. (**I–L**) Group B (*n* = 7/16): The CPs did not touch the lens during accommodation in this group.

stimulus levels delivered to the E-W nucleus were plotted (Supplementary Fig. S1, available online at http://www.iovs.org/cgi/content/full/47/3/1076/DC1) versus time for one young rhesus monkey eye. At each time point during the stimulation, the SEM of the three values was typically small (i.e., 0.005–0.02 mm), indicating fairly consistent CB and lens movement for a given stimulus level and monkey eye.

Stimulus Amplitudes

The older eye required lower stimulus levels to achieve maximum accommodation than did the young eye (Table 1, Fig. 5A). The average increase in stimulus current between the maximal and supramaximal stimulus settings was 0.10 ± 0.01 mA or 26.2% ± 3.9% for the young and the older monkeys combined (Table 1A). The mean difference between the supramaximal and maximal current amplitudes was 0.17 ± 0.03 mA (21.1% ± 7.4%) for the young eye and 0.08 ± 0.01 mA (28.2% ± 4.7%) for the older eye. The mean increase in absolute current amplitude (maximal versus supramaximal stimulation in mA) was higher for the young eye versus the older eye (*P* = 0.016) but not when expressed as a percentage of current increase (Table 1A). Although the change in stimulus amplitude from maximal to supramaximal was significantly greater in the young eye than in the older eye (when expressed in milliamperes), the magnitude of increased CP movement was significantly higher in the older eye (Figs. 3, 4, 5B; Table 1B). Further, in some older eyes only able to accommodate 2 to 4 D, the magnitude of the CP centripetal movement was in the range of that in the young monkey (Fig. 5B) during the supramaximal stimulus. There was no significant increase in lens

centripetal movement between the maximal and supramaximal stimulus current in either age group (Figs. 3, 4, 5C; Table 1C). The average current necessary to induce 3.0 ± 0.6 D of accommodation in the young eye was 0.45 ± 0.11 mA, similar to the current (0.41 ± 0.07 mA) necessary to induce maximum accommodation of 3.0 ± 0.5 D in the older eye.

The amplitude of maximum accommodation correlated significantly with the magnitude of stimulus current needed to achieve it in 21 eyes of 14 monkeys ranging in age from ~6 to 26 years (Fig. 5A). The maximal and the supramaximal stimulus currents were 59% (0.60 mA) and 58% (0.69 mA) less, respectively, in the older eye than in the younger eye.

Ciliary Body Configuration by UBM

The Young Eye. During accommodation, the anterior aspect of the CB moved forward past the scleral spur at higher accommodative amplitudes (Fig. 6D), and formed an acute angle with the inner aspect of the cornea (CB-cornea angle) in both quadrants. We used the same supramaximal stimulus level as given during goniovideography, not only to ensure that we had reached maximum accommodative CB movement but also for comparison to the CP centripetal movement. The analysis in the temporal quadrant was used to compare forward versus centripetal (CP) CB movement, because the amount of centripetal CP movement was reduced by only 12% (0.05 mm) in the older eye versus the young eye (Figs. 3, 4). The average temporal CB-cornea angle in the unaccommodated and supramaximally stimulated young eye was 157.5 ± 3.8° and 84.1 ± 2.8°, respectively (*n* = 6 eyes of five monkeys; Table 2A).

TABLE 1. Average Maximal and Supramaximal Stimulus Currents and the Corresponding Average Ciliary Process and Lens Movements

| | A. Average Current Amplitudes (mA) | | | | Accommodation (D) | n | B. Ciliary Process Movement (mm) | | | | C. Lens Movement (mm) | | | |
	Max	Smax	Smax-Max	% Current Increase			Max	Smax	Smax-Max	% CP Movement Increase	Max	Smax	Smax-Max	% Lens Movement Increase
Young + older														
Mean	0.58	0.69	0.10	26.2	NA	21	0.30	0.38	0.08	29.5	0.18	0.19	0.01	11.4
SEM	0.09	0.10	0.01	3.9			0.03	0.03	0.01	5.8	0.02	0.02	0.01	7.6
Young														
Mean	1.01	1.18	0.17	21.1	13.5	6	0.40	0.43	0.03	7.9	0.33	0.34	0.01	3.7
SEM	0.19	0.20	0.03	7.4	0.6		0.02	0.02	0.01	3.6	0.02	0.02	0.01	3.5
Older														
Mean	0.41	0.49	0.08	28.2	3.0	15	0.26	0.36	0.09	38.1	0.12	0.13	0.01	14.5
SEM	0.07	0.07	0.01	4.7	0.5		0.03	0.04	0.02	6.8	0.01	0.02	0.01	10.6
Young vs. older *P*	0.027	0.019	0.016	0.439	0.001		0.001	0.096	0.008	0.001	0.001	0.001	1.000	0.350

(A) Average of the minimum current amplitudes required to induce maximum accommodation and supramaximal stimulation. Data are the mean ± SEM milliamperes at maximal (Max) and supramaximal (Smax) stimulus levels in 21 eyes of 14 rhesus monkeys. (**B**, C) Data are the mean ± SEM CP and lens movement amplitude (mm) at Max and Smax stimulus settings. For this analysis, the average movement amplitude of nasal and temporal quadrants was calculated for each monkey individually, and a mean value was calculated for all the monkeys. Young eyes ranged in age from 5.8 to 9.5 years and older eyes ranged in age from 17 to 26 years. $P \leq 0.05$ represents a significant difference between young and older monkey eyes by two-sample *t*-test. The percentage increase is calculated as [(Smax/max) − 1] · 100.
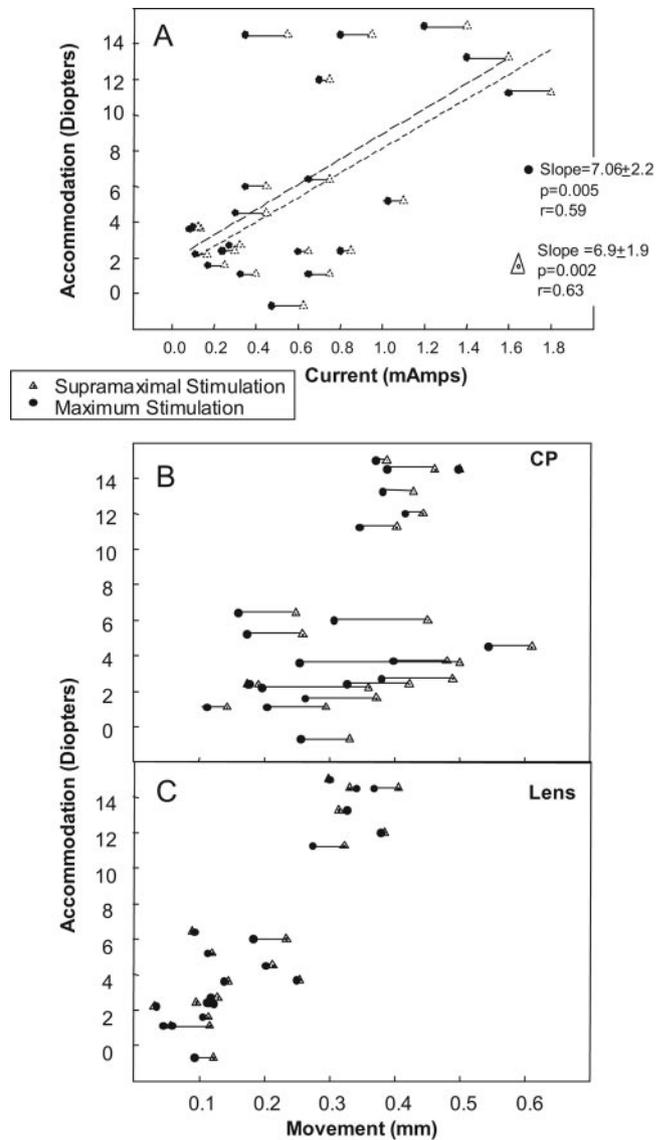

FIGURE 5. Data are maximum accommodation plotted versus stimulus current (**A**), CP (**B**), and lens movement (**C**) in 21 rhesus monkey eyes. The amount of current delivered to the E-W nucleus that is necessary to induce maximum accommodation (maximal stimulus) and a slightly higher stimulus level (supramaximal stimulus) and corresponding responses are plotted in (**A**) *Solid horizontal line*: connection of corresponding stimulus data points (at maximal and supramaximal stimulus) for each monkey eye in (**A**) and (**B**). These lines do not all appear in (**C**) because the data points are so close. (**A**) *Dashed lines*: least-squares linear regression of accommodation versus age for maximal (*long dash*) or supramaximal (*short dash*) stimulus levels. Negative accommodation occurred in one rhesus monkey. In this one monkey eye, the CPs touched the periphery of the anterior lens surface, and the anterior chamber deepened during accommodation (data not shown), but the CP and lens equator moved away from the sclera, as is normal.

The Older Eye. In the older eye the anterior aspect of the CB did not move past the scleral spur (Fig. 6F) in either quadrant. The average temporal CB-cornea angle in the unaccommodated and supramaximally stimulated older eye was 147.5 ± 2.5° and 123.5 ± 3.1°, respectively (*n* = 11 eyes of eight monkeys; Table 2A).

The magnitude of the forward movement in the younger eye (73.0 ± 6.4°, *n* = 6) was significantly greater (*P* = 0.001) than in the older eye (24.0 ± 3.0°, *n* = 11) by 67.1% (49°)
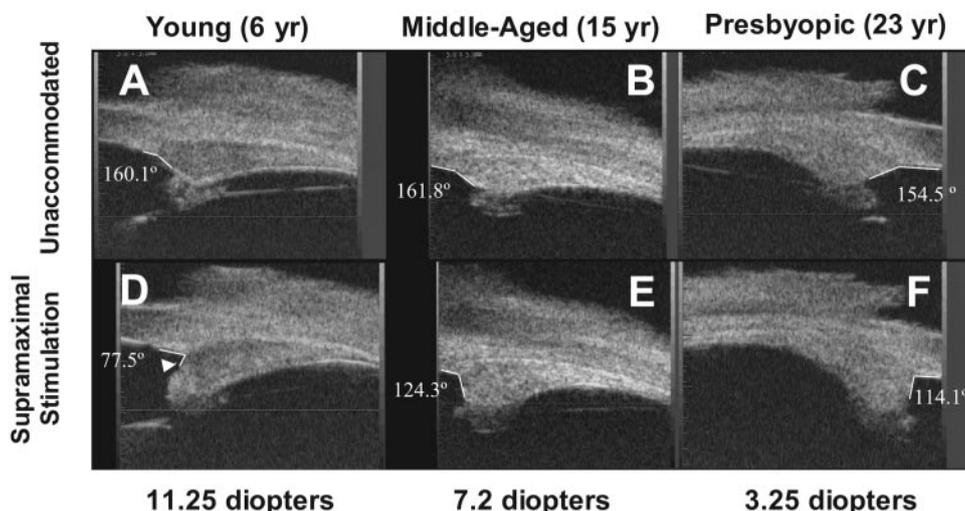
FIGURE 6. UBM images of the temporal quadrants in three normal iridectomized monkey eyes ages 6 (**A, D**), 15 (**B, E**) and 23 (**C, F**) years in the unaccommodated and accommodated states. The degrees represent the angle between the anterior aspect of the CB and the inner aspect of the cornea (CB-cornea angle). During centrally stimulated accommodation, the CB moved forward and inward, and its anterior aspect (**D**, *white arrowhead*) moved past the scleral spur at higher accommodative amplitudes in the young eye but not in the older eye. The anterior aspect of the CB did not move past the scleral spur at any stimulus current in the older presbyopic eye and did not form an acute angle with the inner aspect of the cornea. The young eye accommodated 11.25 D and the older presbyopic eye accommodated 3.25 D.

during supramaximal stimulation. In these same eyes (stimulated at the supramaximal level) centripetal CP movement (as measured from goniovideography images) was only 22.5% (0.09 mm) less in the older eye than in the young eye (Table 2B; $n = 5$ young rhesus eyes, $n = 11$ older rhesus eyes). Centripetal lens equator movement was 49.3% (0.15 mm) less in the older eye than in the young eye. See the following section for the results of regression analysis involving CB forward movement.

Regression Analysis

Centripetal Lens and CP Movement during Accommodation. The amplitude of gonioscopically measured CP centripetal movement during maximum accommodation declined significantly with age in both the nasal ($P < 0.005$) and temporal ($P < 0.02$) quadrants (28 eyes, 21 monkeys; Figs. 7A, 7B). At the supramaximal stimulus level, the amplitude of the temporal CP movement did not decline significantly with age ($P =$

TABLE 2. CB-Cornea Angle and Temporal Centripetal Movement

| | A. Temporal CB-Cornea Angle Measurements (degrees) | | | | | B. Smax Temporal Centripetal Movement (mm) | | |
| | | | Accommodative Angle-Narrowing | | | | | |
	Resting (°)	Smax (°)	Resting-Smax (°)	*n*	Accommodation (D)	CP	Lens	*n*
Young								
Mean	157.5	84.1	73.0	6	15.2	0.41	0.30	5
SEM	3.8	2.8	6.4		1.1	0.02	0.01	
Older								
Mean	147.5	123.5	24.0	11	2.4	0.32	0.15	11
SEM	2.5	3.1	3.0		0.5	0.05	0.03	
Young vs. older *p* =	0.065	0.001	0.001		0.001	0.109	0.001	
Decline Older vs. Young (%)			67.1		84.1	22.5	49.3	

(**A**) Data are the mean ± SEM angle between the anterior aspect of the ciliary body and the inner aspect of the cornea (CB-cornea angle) in the temporal quadrant measured in degrees. Measurements were taken from UBM images in the unaccommodated (resting) eye and during supramaximal (Smax) stimulation in 5 young rhesus and 1 young cynomolgus (age range, 5.8–9.5 years), and in 11 older rhesus monkey eyes (age range, 17–26 years). The farther the ciliary body moved forward during accommodation, the more narrow the CB-cornea angle. (**B**) Data are the mean ± SEM centripetal CP and lens movement amplitude (mm) in the unaccommodated eye and during supramaximal stimulation as measured from goniovideography images taken in the same eyes as in (**A**). $P \leq 0.05$ denotes a significant difference between young and older monkey eye by the two-sample *t*-test. Percentage of decline older versus young is calculated as [(older/young) − 1] · 100. Loss of forward ciliary body movement as represented by accommodative CB-cornea angle change was more pronounced than loss of centripetal movement in the temporal quadrant.
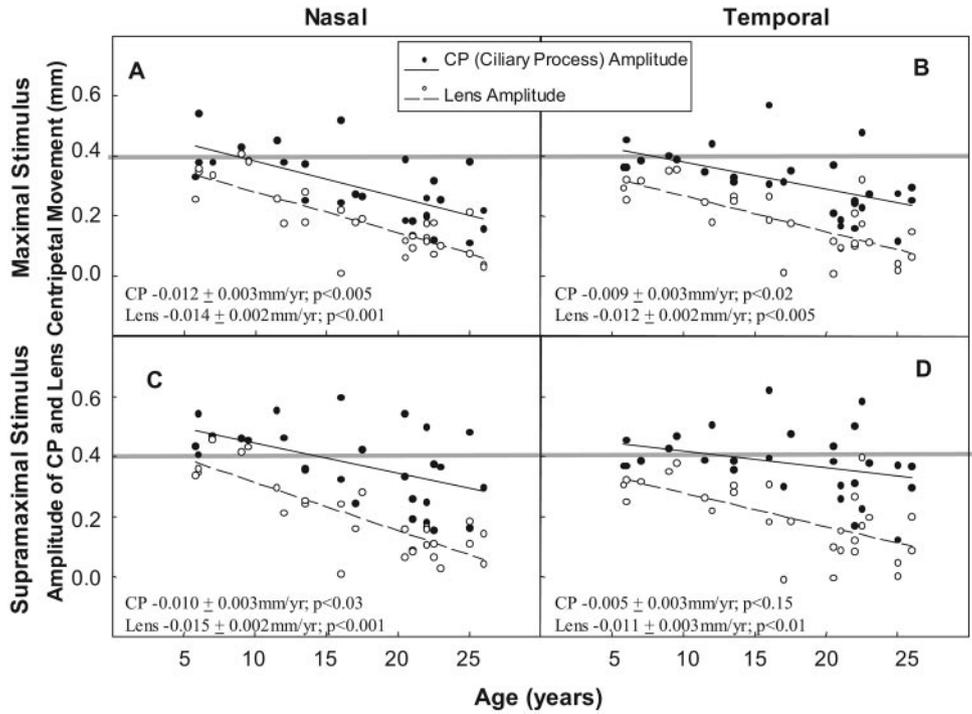
FIGURE 7. CP or lens centripetal movement versus age in 28 eyes of 21 monkeys (age range, 5.8–26 years). Least-squares regression of the amplitude of the CP (*solid line*) or lens (*dashed line*) centripetal movement versus age (adjusted for the relatedness between two observations; i.e., instances where there were two eyes from the same monkey). Slopes are coefficients ± SE; p, probability that the slope = 0.0.

0.15; Fig. 7D). The amplitude of CP centripetal movement was significantly correlated with accommodation (Fig. 8A, 8B) at the maximal but not at the supramaximal stimulus level (Figs. 8C, 8D). Because CP movement and accommodation covaried with age, we modeled accommodation as a linear function of age and CP movement, by using a multiple regression analysis. The multiple regression coefficient of nasal or temporal CP centripetal movement (at either stimulus level) was not significantly different from 0.0 (Supplementary Table S1A, http://www.iovs.org/cgi/content/full/47/3/1076/DC1), indicating that age and CP movement together could not predict accommodation better than age alone.

At the maximal stimulus level, the amplitude of gonioscopically measured lens centripetal movement significantly declined with age in both nasal ($P < 0.001$) and temporal ($P = 0.005$) quadrants (Figs. 7A, 7B). The multiple regression coefficient of averaged (nasal and temporal) lens centripetal movement was different from 0.0 (Supplementary Table S1B, http://www.iovs.org/cgi/content/full/47/3/1076/DC1), indicating that age and average lens equator movement (nasal and temporal) could predict accommodation better than age alone. Similar results were recorded at the supramaximal stimulus level.

Forward CB Movement. In the temporal quadrant (the only quadrant thus far studied), the amount of UBM-measured
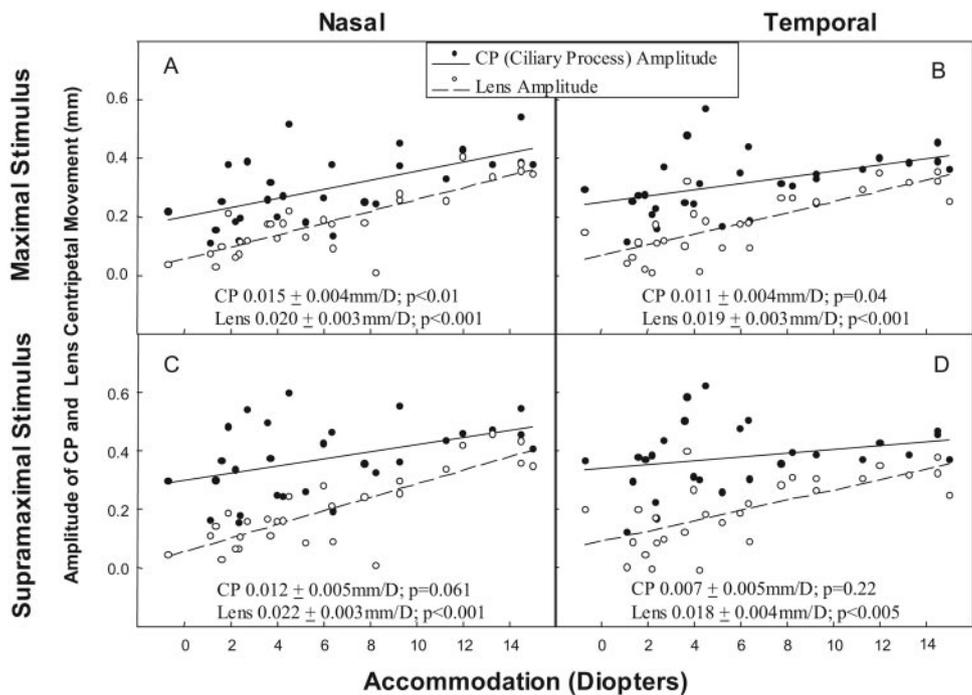

FIGURE 8. Data represent the mean amplitude of the CP and lens movement at maximal and supramaximal stimulus levels plotted versus maximum accommodation in 28 eyes of 21 monkeys (age range, 5.8–26 years). Numbers represent slope ± SE of the slope; p, probability that the slope = 0.0. Negative accommodation occurred in one monkey (see Fig. 5 for explanation).
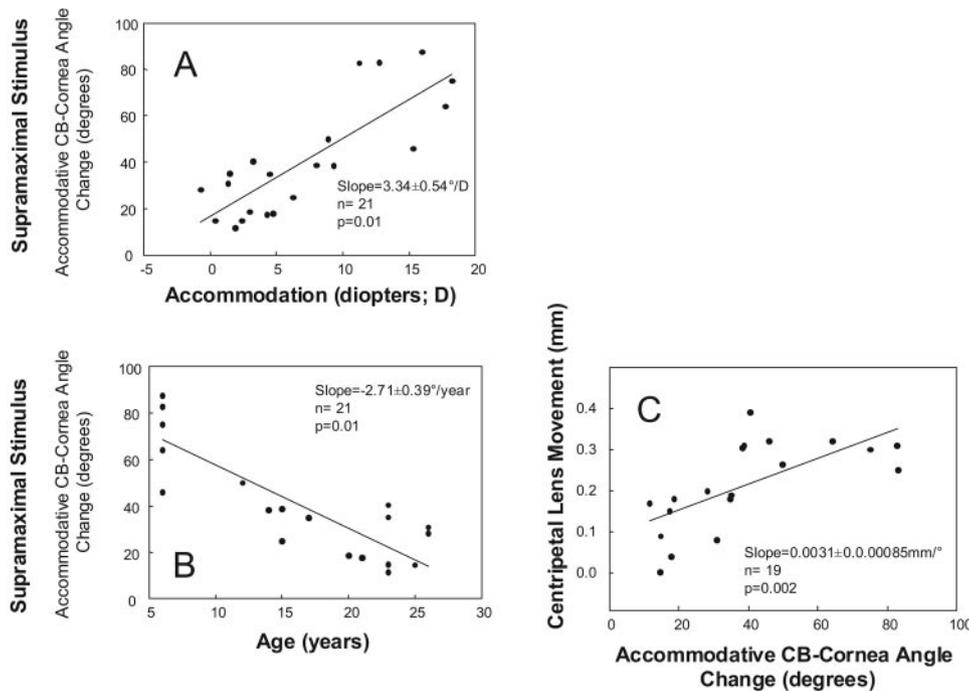
FIGURE 9. Temporal accommodative CB-cornea angle change versus accommodation (A) and age (B) in 20 eyes of 16 rhesus monkeys (age range, 5.8–26 years) plus one cynomolgus monkey eye aged 6 years. Accommodative CB-cornea angle change is defined as the CB-cornea angle in the unaccommodated eye minus the CB-cornea angle in the supramaximally stimulated eye. (C) Amplitude of centripetal lens movement versus accommodative CB-cornea angle change in 19 supramaximally stimulated eyes of 15 rhesus monkeys. *Solid line*: least-squares linear regression. Numbers represent slope ± SE of the slope; p, probability that the slope = 0.0. Accommodative CB-cornea angle change (reflecting forward CB movement) was significantly related to centripetal lens equator movement and accommodative amplitude and declined significantly with age at the supramaximal stimulus level. Regression analysis that adjusts for the relatedness between two observations (i.e., two eyes from the same monkey) has no associated correlation coefficient.

CB forward movement (measured by accommodative CB-cornea angle change; 21 eyes, 17 monkeys) declined significantly with age (-2.71 ± 0.39 deg/y; $P = 0.01$; $n = 21$; Fig. 9B). Further, there was a significant relationship between the amplitude of UBM-measured CB forward movement and the amplitude of gonioscopically measured centripetal lens movement (0.0031 ± 0.00085 mm/deg; $n = 19$; $P < 0.002$; Fig. 9C), and between forward movement and maximum accommodative amplitude measured refractometrically (3.34 ± 0.54 deg/D; $P = 0.01$; $n = 21$; Fig. 9A). Thus, the greater the CB forward movement, the greater the lens equator movement and the higher the maximum accommodative amplitude. The multiple regression coefficient of CB forward movement was not different from 0.0 (Supplementary Table S1C, http://www.iovs.org/cgi/content/full/47/3/1076/DC1), indicating that age and temporal CB forward movement could not predict accommodation better than age alone.

DISCUSSION

Presbyopia has been attributed to increased hardness of the lens,[17–23] lens growth,[22,24–30] and loss of elasticity of the ciliary muscle's posterior attachments.[31,32] The ciliary muscle-body configurational change required to induce accommodation of the lens includes both inward and forward movement, allowing the lens to thicken and the lens curvatures to increase. The loss of elasticity of the ciliary muscle's posterior attachments may cause the age-related loss of the CB's ability to undergo configurational change to induce accommodation. In the enucleated old rhesus monkey eye, ciliary muscle configurational change in response to cholinergic agonist drug stimulation is lost, but is restored when the posterior attachments of the ciliary muscle are cut.[33] In the present study, centrally stimulated maximum accommodative amplitude declined linearly with age by 0.76 ± 0.07 D/y ($P = 0.001$, $r = 0.93$). This is similar to previous findings in rhesus monkeys (Fig. 2)[7] where centrally stimulated accommodation declined by 0.57 ± 0.10 D/y ($r = 0.85$, $n = 14$), and, when adjusted for lifespan, resembles the age-related decline in voluntary accommodation in humans (Fig. 2).[10] Combining the previous data[7] with the current data, centrally stimulated accommodation declined by 0.65 ± 0.05 D/y ($r = 0.91$, $n = 36$).

The centripetal CP movement data suggest that the neurologic pathway in the older monkey functions to induce centripetal CP accommodative responses at least as well as in the young monkey. The cholinergic neuromuscular mechanisms subserving the ciliary muscle remain intact with age.[34] Ciliary muscle contractile responses to pharmacological stimulation in vitro did not vary markedly with age in the coronal or longitudinal vector,[35] suggesting that the age-related decrease in ciliary muscle mobility in vivo was due to extramuscular restrictive factors rather than diminished muscular contractility.

In the present study, we used a consistent viewing angle along the A-P axis of the eye, important for quantitative comparisons. Prior gonioscopy studies of accommodation in the rhesus monkey[7] used a viewing angle of 35° from the A-P axis, which can result in the appearance of anomalous accommodative lens equator movements.

CP movement in older monkeys increased significantly at supramaximal versus maximal stimulation, but lens equator movement did not. Also, the amplitude of lens equator centripetal movement still declined significantly with age at both maximal and supramaximal stimulus levels. In addition, across the entire age range studied, age and lens centripetal movement together could predict accommodation better than age alone. Collectively, these data support the lens playing a role in presbyopia. However, the decreased centripetal lens movement may also be a consequence of decreased forward CB movement, given the significant correlation between them ($P < 0.002$).

The amplitude of CP centripetal movement that occurred with maximum accommodation declined significantly with age in both the nasal and temporal quadrants, corroborating previous qualitative observations.[7,8] However, the maximum possible centripetal CP movement (during supramaximal stimulation) was significantly greater (0.09 mm; $P < 0.05$) than that necessary to produce maximum accommodation in the older eye. The increase between supramaximal and maximal stimulus amplitudes produced a more dramatic increase in centripetal CP movement in the older eye versus the young eye (Fig.

3 versus Figs. 4, 5), perhaps because the CP movement in the young eye had reached its physiological limit and the CP movement in the older eye had not.

Age and CP movement together could not predict accommodation better than age alone. Collectively, these data suggest that CP centripetal movement may not be the limiting component in accommodation in the older eye. The older temporal CP centripetal movement during supramaximal stimulation was only 12% (0.05 mm) lower than in the young monkey (Figs. 3, 4), not enough to explain the 57% decrease in temporal lens centripetal movement or the 76% (10.2 D) loss in accommodative amplitude. Similar results were seen in the nasal quadrant. Accommodation involves both the centripetal and forward movement of the CB. Loss of forward CB movement in the older versus the young eye was more pronounced than loss of centripetal movement, at least in the temporal quadrant. Temporal CB forward movement (as measured by CB-cornea angle) change was 67.1% (49°) less in the older eye than in the young eye at supramaximal stimulation, perhaps sufficient to explain the 76% (10.2 D) loss in accommodative amplitude. The magnitude of the decline is similar and there is a significant correlation between the two parameters. In light of these findings, it may be that there are differences in the age effect on forward versus centripetal CB movement, perhaps consequent to stiffening of the ciliary muscle's posterior attachments (posterior tendons and/or the elastic lamina of Bruch's membrane) with age.[32,33] Morphologic studies showed an age-related decline in forward muscle movement (76.3%; as measured by apical position), but not centripetal movement (as measured by muscle width),[33] and that the ciliary muscle in the older monkey can move forward as in the young monkey when posterior attachments are cut.[33]

An alternative theory of accommodation postulated by Schachar et al.[30] and Tscherning[36] speculate that the lens equator moves toward, rather than away from, the sclera during accommodation. Schachar[28] also speculates that presbyopia is due to a putative age-related increase in lens equatorial diameter. These ideas have led to surgical interventions such as anterior ciliary sclerotomy and scleral expansion.[28] Recent reports, however, show that accommodation is not restored in these patients.[37-40]

Collectively, these data show that accommodation is related to both centripetal and forward CB movement. The fact that the age-related loss of centripetal movement is not as dramatic as the loss of forward movement suggests that the age-related loss of accommodation may be caused in part by something else, in addition to the loss of centripetal muscle movement. In relation to the Helmholtz theory,[1] accommodation requires both centripetal and forward movement of the CB, and the age-related loss of accommodation may be related to the loss of forward movement of the CB. In relation to the Coleman theory of accommodation, which suggests that accommodative changes in the lens are induced by vitreous pressure,[41-43] the age-related loss of centripetal CB movement may affect the vitreous support of the peripheral lens. However, normal accommodative changes occur in eye bank eyes that are devoid of vitreous forces.[18,44]

Researchers have reported that the forces necessary to mold the lens into a conoid shape are greater than the capsule could exert.[45] Coleman and Fish[43] suggest that the capsule does not have the elastic properties to round up the lens reproducibly and rapidly during accommodation but provide no evidence to support this statement. Krag et al.[46,47] suggest that the viscoelastic characteristics of the lens capsule are sufficient to perform the molding of the lens during accommodation. Their findings are supported by recent studies suggesting that the accommodative changes in the lens are produced by the capsule's molding the lens.[18,22,44,48,49]

The asymmetry of the lens equator movement in group A older monkeys (in which the CPs touched the lens in the temporal quadrant) resulted from (1) the loss of lens centripetal accommodative movement with age; (2) the smaller resting temporal CLS compared with the nasal quadrant[14]; (3) the still-substantial temporal CP centripetal accommodative movement; and (4) the nasalward shift in lens position. This asymmetry does not seem to affect accommodative amplitude, because accommodative amplitude was almost the same whether the asymmetry was present or not (group A versus group B older animals). During accommodation, before the lens movement reached a plateau or began its nasalward shift in position, there was greater lens movement per unit of CP movement in the nasal versus the temporal quadrant of the older eye. This could be due to nasal versus temporal CB configurational differences.[16]

Although the lens no doubt plays a major role in presbyopia, altered lens movement could be in part secondary to extralenticular age-related changes, such as loss of CB forward movement. The CB centripetal movement may not be the limiting component in accommodation in the older eye. The results show that accommodative centripetal movements of the ciliary processes and therefore the ciliary muscle are still present in the old rhesus monkeys, as they are in the presbyopic human,[50] despite the reduced accommodative amplitudes. Whether the remaining movement is sufficient to power the system and produce accommodation post-IOL implantation depends on the approach and the characteristics of the accommodating IOL material. Accommodating IOLs may be more effective in restoring accommodation in the presbyopic eye if they rely on centripetal CB movement rather than forward CB movement.

References

1. von Helmholtz HH. Helmholtz's treatise on physiological optics. In: Southall JPC, ed. *Mechanism of Accommodation.* New York: Dover Publications; 1909:143–172.
2. Glasser A, Kaufman PL. Accommodation and presbyopia. In: Kaufman P, Alm A, eds. *Adler's Physiology of the Eye, Clinical Applications.* Vol. 5, 10th ed. St. Louis: Mosby; 2003:197–233.
3. Bito LZ, DeRousseau CJ, Kaufman PL, Bito JW. Age-dependent loss of accommodative amplitude in rhesus monkeys: an animal model for presbyopia. *Invest Ophthalmol Vis Sci.* 1982;23:23–31.
4. Koretz JF, Bertasso AM, Neider MW, Gabelt BT, Kaufman PL. Slit-lamp studies of the rhesus monkey eye: II. Changes in crystalline lens shape, thickness and position during accommodation and aging. *Exp Eye Res.* 1987;45:317–326.
5. Koretz JF, Neider MW, Kaufman PL, et al. Slit-lamp studies of the rhesus monkey eye: I. Survey of the anterior segment. *Exp Eye Res.* 1987;44:307–318.
6. Lütjen-Drecoll E, Tamm E, Kaufman PL. Age-related loss of morphologic responses to pilocarpine in rhesus monkey ciliary muscle. *Arch Ophthalmol.* 1988;106:1591–1598.
7. 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.
8. Croft MA, Kaufman PL, Crawford KS, et al. Accommodation dynamics in aging rhesus monkeys. *Am J Physiol.* 1998;44:R1885–R1897.
9. Glasser A, Kaufman PL. The mechanism of accommodation in primates. *Ophthalmology.* 1999;106:863–872.

10. Duane A. Studies in monocular and binocular accommodation with their clinical applications. *Am J Ophthalmol*. 1922;5:867–877.

11. Kaufman PL, Lütjen-Drecoll E. Total iridectomy in the primate *in vivo*: surgical technique and postoperative anatomy. *Invest Ophthalmol*. 1975;14:766–771.

12. Crawford K, Terasawa E, Kaufman PL. Reproducible stimulation of ciliary muscle contraction in the cynomolgus monkey via a permanent indwelling midbrain electrode. *Brain Res*. 1989;503:265–272.

13. Vilupuru AS, Glasser A. Dynamic accommodation in rhesus monkeys. *Vision Res*. 2002;42:125–141.

14. Croft MA, Glasser A, Heatley G, et al. The zonula, lens, and circumlental space in the normal iridectomized rhesus monkey eye. *Invest Ophthalmol Vis Sci*. 2006;47:1087–1095.

15. Pavlin CJ, Foster FS. Examination techniques. *Ultrasound Biomicroscopy of the Eye*. New York: Springer Verlag; 1995:30–46.

16. Glasser A, Croft MA, Brumback L, Kaufman PL. Ultrasound biomicroscopy of the aging rhesus monkey ciliary region. *Optom Vis Sci*. 2001;78:417–424.

17. Pau H, Krantz J. The increasing sclerosis of the human lens with age and its relevance to accommodation and presbyopia. *Graefes Arch Clin Exp Ophthalmol*. 1991;229:294–296.

18. Glasser A, Campbell MCW. Presbyopia and the optical changes in the human crystalline lens with age. *Vision Res*. 1998;38:209–229.

19. Fisher RF. Elastic constants of the human lens capsule. *J Physiol (Lond)*. 1969;201:1–19.

20. Fisher RF. The force of contraction of the human ciliary muscle during accommodation. *J Physiol (Lond)*. 1977;270:51–74.

21. Fisher RF. The elastic constants of the human lens. *J Physiol (Lond)*. 1971;212:147–180.

22. Glasser A, Campbell MCW. Biometric, optical and physical changes in the isolated human crystalline lens with age in relation to presbyopia. *Vision Res*. 1999;39:1991–2015.

23. Heys KR, Cram SL, Truscott RJ. Massive increase in the stiffness of the human lens nucleus with age: the basis for presbyopia? *Mol Vis*. 2004;10:956–963.

24. Farnsworth PN, Shyne SE. Anterior zonular shifts with age. *Exp Eye Res*. 1979;28:291–297.

25. Scammon RE, Hesdorfer MB. Growth in mass and volume of the human lens in postnatal life. *Arch Ophthalmol*. 1937;17:104–112.

26. Weale RA. The lens. In: *The Aging Eye*. New York: Harper & Row; 1963:68–102.

27. Willekens B, Kappelhof J, Vrensen G. Morphology of the aging human lens: I. Biomicroscopy and biometrics. *Lens Res*. 1987;4:207–230.

28. Schachar RA. Cause and treatment of presbyopia with a method for increasing the amplitude of accommodation. *Ann Ophthalmol*. 1992;24:445–452.

29. Schachar RA, Black TD, Kash RL, Cudmore MS, Schanzlin DJ. The mechanism of accommodation and presbyopia in the primate. *Ann Ophthalmol*. 1995;27:59–67.

30. Schachar RA, Tello C, Cudmore DP, et al. *In vivo* increase of the human lens equatorial diameter during accommodation. *Am J Physiol*. 1996;271:R670–R676.

31. Tamm S, Tamm E, Rohen JW. Age-related changes of the human ciliary muscle: a quantitative morphometric study. *Mech Ageing Dev*. 1992;62:209–221.

32. 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.

33. 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.

34. 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.

35. Poyer JF, Kaufman PL, Flügel C. Age does not affect contractile response of the isolated monkey ciliary muscle to muscarinic agonists. *Curr Eye Res*. 1993;12:413–422.

36. Tscherning ML. Accommodation. *Physiologic Optics*. 3rd ed. Philadelphia: Keystone; 1920:192–228.

37. Hamilton DR, Davidorf JM, Maloney RK. Anterior ciliary sclerotomy for treatment of presbyopia. *Ophthalmology*. 2002;109:1970–1977.

38. Mathews S. Scleral expansion does not restore accommodation in human presbyopia. *Ophthalmology*. 1999;106:873–877.

39. Malecaze FJ, Gazagne CS, Tarroux MC, Gorrand JM. Scleral expansion bands for presbyopia. *Am J Ophthalmol*. 2001;108:2165–2171.

40. Ostrin LA, Kasthurirangan S, Glasser A. Evaluation of a satisfied bilateral scleral expansion band patient. *J Cataract Refract Surg*. 2004;30:1445–1453.

41. Coleman DJ. Unified model for accommodative mechanism. *Am J Ophthalmol*. 1970;69:1063–1079.

42. Coleman DJ. On the hydraulic suspension theory of accommodation. *Trans Am Ophthalmol Soc*. 1986;84:846–868.

43. Coleman DJ, Fish SK. Presbyopia, accommodation, and the mature catenary. *Ophthalmology*. 2001;108:1544–1551.

44. Koopmans SA, Terwee T, Barkhof J, Haitjema HJ, Kooijman AC. Polymer refilling of presbyopic human lenses in vitro restores the ability to undergo accommodative changes. *Invest Ophthalmol Vis Sci*. 2003;44:250–257.

45. Fisher RF. The significance of the shape of the lens and capsular energy changes in accommodation. *J Physiol (Lond)*. 1969;201:21–47.

46. Krag S, Andreassen TT. Mechanical properties of the human lens capsule. *Prog Retin Eye Res*. 2003;22:749–767.

47. Krag S, Olsen T, Andreassen TT. Biomechanical characteristics of the human anterior lens capsule in relation to age. *Invest Ophthalmol Vis Sci*. 1997;38:357–363.

48. Roorda A, Glasser A. Wave aberrations of the isolated crystalline lens. *J Vision*. 2004;4:250–261.

49. Vilupuru AS, Roorda A, Glasser A. Spatially variant changes in lens power during ocular accommodation in a rhesus monkey eye. *J Vision*. 2004;4:299–309.

50. Strenk SA, Semmlow JL, Strenk IM, et al. Age-related changes in human ciliary muscle and lens: a magnetic resonance imaging study. *Invest Ophthalmol Vis Sci*. 1999;40:1162–1169.