Age-dependent loss of accommodative amplitude in rhesus monkeys: an animal model for presbyopia

L. Z. Bito, C. J. DeRousseau,* P. L. Kaufman,** and J. W. Bito

The refractive power and axial dimensions of the eye were measured under resting and fully accommodated conditions in 123 caged rhesus monkeys ranging in age from 0.5 to >30 years. The mean resting refraction measured under ketamine anesthesia was −5 diopters. Accommodative amplitude, calculated as the difference between resting refraction and the most negative refraction measured 0.5 to 1 hr after topical application of a maximally effective dose of a cholinomimetic, showed an age-dependent decline. The mean accommodative amplitude of 1- to 5-year-old rhesus monkeys was a remarkable 34 D, while animals over 25 years of age averaged 5 D of accommodation. Some >25-year-old animals showed no measurable change in refraction regardless of the dose or the type of cholinomimetic (carbachol, pilocarpine, or echothiophate) used. The resting axial thickness of the lens was found to increase with age throughout adulthood, well past the end of the growth period. A strong correlation was found between pharmacologically induced change in the refractive power of the eye and change in lenticular thickness. These similarities to the human condition suggest that the rhesus monkey represents a highly suitable animal model for the study of accommodation and presbyopia.

Keywords: Macaca mulatta, presbyopia, accommodation, lens, aging, carbachol, pilocarpine, echothiophate iodide, ocular dimensions, anthropometry

A continuous decrease in accommodative amplitude and the development of presbyopia are generally considered to be inevitable consequences of aging, presumably related, at least in part, to the continuous growth of the lens. However, probably because of the lack of an adequate animal model, no basic studies have been conducted to support these conclusions; previous studies aimed at elucidating the mechanisms of lenticular growth were done on the rabbit, a species with little or no accommodative ability regardless of age.

Previous surveys of rhesus monkey populations at the Caribbean Primate Research Center in Puerto Rico have shown that the adult rhesus lens increases in axial thickness with age well past the period when maximal globe size is achieved. This pattern is similar to the age-dependent changes observed.
provided in the human lens\textsuperscript{5, 11-12} but is unlike lenticular growth in other mammals, which follows the growth curve of the whole globe.\textsuperscript{13-16} In addition to lenticular growth, these surveys\textsuperscript{6, 9} have also found that the mean intraocular pressure (IOP) and its variation with age in rhesus monkeys are similar to these parameters previously described for human populations.\textsuperscript{17, 18} These similarities suggested that the rhesus monkey might provide a highly suitable animal model for the study of age-related ocular dysfunctions, including the development of presbyopia.

The refractive power and axial dimensions of the eyes of 123 rhesus monkeys ranging from 0.5 to \textgreater 30 years of age were therefore measured under resting conditions and after maximum pharmacologically induced cholinergic stimulation. Other ocular parameters (corneal curvature, IOP, occurrence of cataracts) and age-related musculoskeletal changes were also surveyed to evaluate the relationships between ocular and more general somatic aging processes.\textsuperscript{19, 20} Findings pertaining to resting refraction, accommodative amplitude, and ocular dimensions in the rhesus monkey eye are presented in this article as functions of chronological age.

Methods

All rhesus monkeys examined for this study belong to and were used at the Wisconsin Regional Primate Research Center and the Primate Laboratory of the Psychology Department of the University of Wisconsin, which collectively house one of the largest known populations of aging and aged rhesus monkeys. Most animals in the current sample had previously been manipulated for a variety of studies, some strictly behavioral and others involving invasive techniques such as ovariectomy and hormone administration. However, no single procedural history predominated in the sample. Animals were excluded from the study only if their background included eye surgery and/or trauma.

Each animal examined was weighed in a transfer cage and then tranquilized with an average dose of 14.9 ± 1.6 (S.D.) mg/kg i.m. ketamine HCl. A second dose of ketamine equalling half the original dose combined with 0.3 mg of acepromazine maleate (Ayerst Laboratories, Inc., New York, N. Y.) was administered approximately 1 hr after initial anesthesia, and subsequent doses of ketamine were given as needed until completion of the examination. Neither the dose of initial anesthesia nor the duration of anesthesia showed a significant correlation with any of the parameters measured.

All eyes were routinely examined by slit lamp, and animals that showed any ocular abnormalities, including even slight lenticular opacity, were thoroughly examined by an ophthalmologist (P. L. K.). IOP was measured with an Alcon floating-tip pneumatonograph after the topical application of 0.5% proparacaine HC1. Two animals that had IOPs \textgreater 8 mm Hg higher than the mean IOP of 15.7 mm Hg previously reported for this species\textsuperscript{6, 9} were excluded from the accommodation study, and together with the occurrence of cataracts in animals \textgreater 20 years of age, are described elsewhere.\textsuperscript{21} Cataractous eyes were not excluded, since they did not seem to behave differently than other eyes with respect to the development of presbyopia.

Baseline measurements of corneal curvature, resting refraction, and dimensions of the globe were taken, in that order. Corneal curvature was measured with a keratometer (Bausch and Lomb Co., Rochester, N. Y.), with a +1.25 diopter (D) spherical lens to extend its range, and drum readings were converted to dioptries of corneal power according to conversion tables published by Bausch and Lomb Co. (1.1659 \times the drum reading). A Hartinger Coincidence Refractometer (Zeiss-Jena) was used to measure resting refraction and drug-induced accommodation of the globe; a \textminus 7.25 D hard (polymethylmethacrylate) corneal contact lens was used on some eyes to extend the negative dioptric measuring range of the refractometer, and the instrument readings were corrected appropriately. Axial lengths of the anterior chamber, lens, vitreous cavity, and whole globe were measured with an A-scan ultrasonic device (Digital Biometric Ruler, Model 300; Sonometrics System, Inc., New York, N. Y.) as previously described.\textsuperscript{9}

In preliminary experiments during the first day of the survey, seven animals were treated topically with increasing doses of carbachol, pilocarpine, echothiophate, or acetylcholine to find the drugs and doses that caused maximum accommodation. In one set of animals, atropine applied to one eye 15 to 45 min after the application of carbachol or pilocarpine to the contralateral eye did not cause a consistent change in the refractive state of the eye and was therefore not used in the standard protocol. Topical application of two drops of 10%
phenylephrine HCl solution was found to maintain an adequate pupil diameter (1.5 to 2 mm) for measuring refraction without having a notable effect on resting refraction or on the extent of drug-induced accommodation. Since these preliminary experiments were not based on a standardized protocol, their results were excluded from the analyses presented here.

The following protocol was established for the remainder of the survey. After all baseline readings were taken, both eyes were treated with two drops of 10% phenylephrine HCl, and in most cases the animal received 0.01 mg/kg i.m. atropine sulfate, a dose found here and previously (P. L. Kaufman, unpublished observation) to be sufficient to minimize the systemic, but not the accommodative, effects of the topically applied cholinomimetics. One eye then received five consecutive corneal applications (5 μl each) of a 40% solution of pilocarpine HCl about 0.5 min apart, for a total dose of 10 mg. An identical regimen of carbachol was applied to the contralateral eye. One eye of 12 animals received four applications of 5 μl of 2.5% echothiophate iodide (total dose of 500 μg/eye) instead of pilocarpine. In all cases, blinking was prevented for 0.5 min after each drug application. These doses of pilocarpine and carbachol were at least 10 times greater, while the dose of echothiophate was at least 5 times greater, than their respective minimum doses required to cause maximal accommodation in these macaques.

Refraction and all ultrasonic measurements were repeated 0.5 to 1 hr after drug application. To verify the refractoriness of old animals to cholinomimetic-induced changes in refraction, the entire protocol of drug applications and measurements was repeated on several old monkeys 1 hr after the application of the first dose. In some cases, to minimize the systemic side effects caused by these cholinomimetics (e.g., lowered blood pressure), a second larger dose (0.02 mg/kg) of atropine was administered intramuscularly 1 hr after pilocarpine or carbachol application, and refraction was measured 15 to 30 min later.

Statistical analyses were done with the SCSS Conversational System\(^2\) on the DEC-20 computer at the Columbia University Center for Computing Activities. Resting refractions and most ultrasonic measurements obtained on the right and left eyes were not statistically different; all baseline parameters were therefore averaged and analyses were performed on these averages. Means ± S.D. are presented, and correlations are defined as significant if \(p < 0.05\).

Results

The mean resting refraction of these rhesus monkeys was \(-5\) D, with a mode of \(-4\) D, and the regression of resting refraction on age was not significant (Fig. 1). However, the percentage of animals showing a resting refraction 1 S.D. below the mean increased from 0% in \(<5\)-year-olds to 36% in \(>27\)-year-old animals. Three animals (noted by arrows in Figs. 1 and 2) who showed resting refractions 2 S.D. below the mean also showed unusually long globes, and in one case (the shortest globe of the three) corneal curvature was 5 D steeper than the average of 53.2 ± 1.9 D. Resting refraction was in general highly correlated with axial length of the globe \((r = -0.50, p < 0.001)\), longer globes showing more myopic refractions, but no consistent relationship was observed between resting refraction and corneal curvature.

Axial length of the globe (anterior surface
Fig. 2. Axial length of the globe as a function of age in rhesus monkeys. Globe growth, represented by the regression of axial length on age in years (Y = 0.33X + 17.23; r = 0.70, p < 0.001), appears to slow around 6 years of age. Adults show no significant change in globe size with age (Y = 0.01X + 19.16; r = 0.12, p = 0.174). Some adult variability can be explained by sex differences in globe size, with males generally possessing a larger globe than females. Individuals with resting refractions more myopic than 2 S.D. from the mean are indicated by arrows.

Fig. 3. Lens thickness as a function of age in rhesus monkeys. The slope of the regression of lens thickness on age in years was negative in 1- to 5-year-old rhesus monkeys (Y = — 0.07X + 3.89; r = -0.48, p < 0.05) and positive in adults (Y = 0.03X + 3.05; r = 0.66, p < 0.001).

markable 34.4 D; after this age the amplitude gradually decreased (Fig. 4). Some of the >25-year-old animals showed little or no measurable change in refraction from baseline values even when treated with echothiophate iodide or with two doses of pilocarpine or carbachol about 1 hr apart, each treatment using doses that were 10-fold greater than the minimum dose required to cause up to 40 D of accommodation in younger animals. Likewise, a small supplemental dose of systemic atropine given to reverse possible cardiovascular effects of the cholinergic drugs induced no changes in the refraction of these older individuals.

Although the decrease in accommodative amplitude as a function of age showed a very high statistical significance (r = — 0.85, p < 0.001), variability in accommodative amplitude within each age group was notable. For example, a few old monkeys (>20 year) showed over 10 D of accommodation, and one 24-year-old female with a resting refraction of -16 D and an unusually long globe, accommo-
Fig. 4. Accommodative amplitude as a function of age in rhesus monkeys. Amplitude of drug-induced accommodation decreases linearly with age in 1- to 25-year-old animals (\( Y = -1.31X + 39.54; r = -0.85, p < 0.001 \)), tapering off to a residual accommodative capacity of <5 D in most old individuals. Note, however, that many old individuals showed some accommodative amplitude and one 24-year-old female, indicated by the arrow, accommodated over 30 D. Accommodative amplitude is defined as the maximal drug-induced accommodative response of an individual minus the resting refraction averaged from both eyes of that individual.

Fig. 5. Relationship between accommodative amplitude and accommodative change in lens thickness in rhesus monkeys. Change in refractive state in response to application of cholinergic drugs is significantly correlated with a corresponding change in lens thickness (\( r = 0.78, p < 0.001 \)).

dated over 30 D (Fig. 4, arrows). In younger animals, some variability could be explained by differences in the type of cholinomimetic drug applied to the eye, carbachol inducing somewhat more accommodation (36.0 ± 5.2 D in 1- to 5-year-olds) than did pilocarpine (31.1 ± 5.6 D in 1- to 5-year-olds). In older animals, however, differences between the effects of the various drugs were not significant.

There was a high degree of correlation between accommodative amplitude and the corresponding changes in lens thickness (\( r = 0.78, p < 0.001 \); Fig. 5), anterior chamber depth (\( r = -0.55, p < 0.001 \)), and vitreous depth (\( r = -0.20, p < 0.05 \)). Axial length of

Discussion

Our results clearly show that rhesus monkeys undergo an age-related decrease in pharmacologically induced accommodative amplitude highly comparable to the age-dependent decrease in physiologically induced accommodative amplitude in humans. Taking into consideration differences in life span and maximum accommodative capacity, the patterns of decrease in accommodative amplitude as a function of chronological age are strikingly similar in these two species (Fig. 6). In both humans and rhesus monkeys the greatest amplitude of accommodation is found in juveniles, well before either species attains skeletal maturity at 5 to 6 years of age in rhesus and around 18 years in human populations. Both species show the greatest rate
Fig. 6. Human and rhesus patterns of age-dependent loss in accommodative amplitude. The mean (± S.D.) rhesus monkey accommodative amplitude for each age group (3 year intervals), superimposed on the time curve of decrease in accommodative amplitude in humans, reveals a remarkable similarity in the patterns of age change in the two species. The curves representing human accommodative capacity (shaded area) were taken from figures constructed by Duane (1912) to include most “normal” cases.

of decline in amplitude in the second trimester of their respective life spans. Postmenopausal age groups, >25 years old in rhesus monkeys and >45 years old in humans, show a relatively stable residual accommodative capacity. It should be noted that the technique used by Duane to generate the curve for development of human presbyopia (reproduced in Fig. 6) may have overestimated accommodative amplitudes by approximately 1.5 D. However, this error appears to be a constant and should not appreciably affect the shape of the curve presented by Duane.

The age-dependent decline in accommodative amplitude in humans has been considered to be the result of declining ciliary muscle function, continuing increase in the size and a concomitant flattening of the lens, changes in elasticity of the lens substance and capsule, and/or changes in the distribution of zonular insertions with respect to the lens equator. Some evidence has been presented indicating that the first factor, declining ciliary muscle activity, cannot account for the loss of accommodative capacity in humans. Although the relative contributions of the remaining lenticular factors remain to be elucidated, it should be noted that most and possibly all of these factors can be directly or indirectly related to the continuous growth of the lens. In this and in a previous study on free-ranging rhesus monkeys, lenticular thickness was found to increase with age well past the period of rapid general and ocular growth, mimicking human lenticular growth. Thus there is no reason to believe that in rhesus monkeys the etiology of the age-dependent decrease in accommodative amplitude is basically different from that of humans.

The maximal accommodation of over 40 D observed in some rhesus juveniles in this study is more than the accommodative amplitude previously reported for any terrestrial mammal. Anecdotal reports suggest that human infants may similarly possess the largest accommodative amplitudes for their species, as much as 20 D, although reported surveys of human populations do not include young children or infants. The lack of adequate population data on human juveniles cannot, however, explain the discrepancy in maximal accommodative amplitude noted between the two species, since not only juveniles but also older age groups of rhesus monkeys show about twice as much accommodative capacity as those reported for humans of comparable ages (see Fig. 6).

We may conclude, therefore, that rhesus monkeys possess a greater capacity for accommodation and have a much closer near point than do humans. This may be, in part, an allometric phenomenon related to species differences in body size and specifically in interpupillary distance, since the smaller rhesus monkey infant requires a much greater accommodation per given angle of convergence than does the larger human infant. It should be noted, however, that an emmetropic eye capable of 20 D of accommodation has a near point of 5 cm, whereas 40 D brings the near...
point only 2.5 cm closer to the eyes. Hence, the measured discrepancy between rhesus and human accommodative range may not imply an important difference in function. Although we cannot rule out the possibility that cholinergic drug-induced accommodation is greater than physiologic accommodation, maximum accommodation under eserine was found to be only 1 to 3 D greater than voluntary accommodation in humans.\textsuperscript{37} In addition, accommodation induced by electrical stimulation of the midbrain was found to be up to 27 to 29 D in cynomolgus (\textit{Macaca fascicularis}) and owl monkeys (\textit{Aotus trivirgatus}) of unspecified ages.\textsuperscript{38} Other authors, using electrical stimulation or local administration of cholinergic drugs, have also reported over 20 D of accommodation in non-human primates.\textsuperscript{39} Although considerably lower amplitudes (4 to 12 D) have often been noted in response to voluntary accommodation or to electrical or unspecified stimulation in monkeys,\textsuperscript{34, 41-43} these reports do not generally take into account the ages of the animals examined. Only one study\textsuperscript{39} appears to have considered the effect of age on accommodative amplitude in primates, finding that two cynomolgus monkeys, apparently old on the basis of general appearance and tooth wear, showed amplitudes of 9 to 10 D after topical application of carbachol as compared with values near 20 D in apparently younger animals. These considerations indicate that our results do not necessarily overestimate the physiologic capacity of the rhesus eye to accommodate.

Behavioral observations provide further evidence that a large amplitude of accommodation is normal for young macaques. Rhesus monkeys perform visual tasks ranging from social grooming and inspection of insects, dirt, etc. held very close to their eyes, to recognition of friend and foe at distances great enough to ensure safety (DeRousseau, unpublished observations). It tends to be the younger animals on the periphery of the group who most frequently act as "look outs" and also perform the greater proportion of near-vision tasks such as grooming; older individuals are more centrally located in the group and are more often the recipients rather than the givers of grooming.\textsuperscript{44} Thus, not only the range of visual behavior but also the age-dependent differences in behavioral patterns are consistent with our findings on accommodative amplitude in this species. In fact, although changes in social grooming behavior with age have been related to changes in dominance rank,\textsuperscript{44} our findings suggest that the decline in accommodative capacity must be considered in the interpretation of such age-dependent shifts in behavioral patterns.

The average resting refraction under ketamine of $-5$ D cannot be taken as an indication that rhesus monkeys tend to be normally myopic, since our "resting refraction" does not necessarily represent the far point of these animals. Monkeys have been shown to exhibit about 1.5 D of accommodation in darkness, corresponding to the well-described human syndrome of night myopia,\textsuperscript{45} and to accommodate still further, about 3 D, when anesthetized or asleep.\textsuperscript{46} Young\textsuperscript{47, 48} measured the resting refraction of the eyes of caged and "wild-captured" Old World monkeys after topical application of a cycloplegic and suggested that caged monkeys tend to show a higher frequency of myopia. In addition, Young\textsuperscript{49} reports that refractions were made more negative by placing animals in restricted visual spaces. Although Young's work is certainly suggestive, his reports did not or could not always take into account the age of the animals, while his experimental work was generally done on samples of insufficient size to control for all possible confounding factors. Furthermore, it is not clear whether under the conditions of his refractions a true far point was measured, and he did not attempt to measure accommodative amplitude.

The observed variability in accommodative amplitude in older monkeys in our sample, for example, the existence of a 24-year-old female that showed an accommodative amplitude of >30 D, suggests that presbyopia is not a totally predictable and inevitable consequence of aging in rhesus monkeys. This may appear to be in conflict with generally accepted textbook concepts about the predic-
tability of the development of presbyopia in humans. However, in Duane’s classic study of human accommodation,3 which is quoted in all current textbooks, almost a third of the subjects examined were excluded from his analyses. Thus, Duane’s population may have included greater variability than his published figures indicate; a more random sample of a human population may well show variability in the accommodative amplitude of older individuals similar to that observed in the present study on rhesus monkeys. Further longitudinal and more detailed cross-sectional studies may, in fact, isolate conditions that modify the time-course of accommodative loss and the onset of presbyopia. The results of this preliminary survey clearly indicate that the rhesus monkey can serve as an animal model for such studies and for basic studies aimed at elucidating the age-dependent decrease in accommodative amplitude and the etiology of presbyopia.

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Animal model for presbyopia


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