Intraocular pressure of rhesus monkeys
(Macaca mulatta)

I. An initial survey of two free-breeding colonies

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As part of an ophthalmic and anthropometric survey of two free-breeding rhesus monkey
(Macaca mulatta) populations, intraocular pressure (IOP) of 114 animals was measured under
ketamine catalepsia with the use of a floating-tip pneumatonometer. The mean IOP of the 102
animals included in the main analyses was 14.9 ± 2.1 (S.D.) mm Hg. The age distribution of
animals in this sample ranged from 7 months to 21 years and reflected reasonably well the
estimated age distribution in the total population (approximately 1600 macaques). Since
ketamine does not have a barbiturate-like effect on IOP, this value can be regarded, as a
good, estimate of the normal IOP of rhesus monkeys. No significant differences were found between
left and right eyes nor between males and females. However, the mean IOP of infants and
juveniles (7 months to 3 years) was significantly higher (15.7 ± 2.0 mm Hg; n = 33) than that
of young adult and adult rhesus monkeys (14.5 ± 2.0; n = 69). The IOP of young animals (≤6
years) showed a decline between 9 A.M. and 2 P.M., whereas the IOPs of older animals showed
only small fluctuations between 8 A.M. and 5 P.M. This study shows that the normal IOP of
macaques is remarkably similar to that of humans and demonstrates the feasibility of surveying
IOP in free-ranging primates.

Key words: eye, primates, Macaca mulatta, intraocular pressure, IOP,
development, aging, diurnal variation, ketamine, anesthesia

Anthropoid primates, especially vervet,
cynomolgus, and rhesus monkeys, have been
used extensively in glaucoma-related re-

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The facilities used were supported by National Institutes
of Health contract N01-RR-7-2115 to the University of
Puerto Rico. This project was also supported by U.S.
Public Health Service research grants EY00333 and
EY00404 from the National Eye Institute; the cost of
the expedition was borne in part by Biotrics, Inc.,
New York, N.Y.
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0146-0404/79/080785-09$00.90 © 1979 Assoc. for Res. in Vis. and Ophthal., Inc.

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iological experiments using primates frequently mention "normal" IOPs3, 4 but these studies, too, lack background information on individuals and, furthermore, were done on groups too small to adequately describe the general population.

The present study represents a preliminary survey of a large sample of free-breeding rhesus monkeys (Macaca mulatta) maintained on two islands off the coast of Puerto Rico. Most of these animals are of known age and maternal genealogy, and at least one of the populations is expected to be available for long-term follow-up studies.

Methods

Description of the population and the sample surveyed. Two free-breeding rhesus monkey colonies are maintained on the islands of Cayo Santiago and La Cueva (east coast of Puerto Rico, near Humacao, and south coast, near La Parguera, respectively) by the University of Puerto Rico's Caribbean Primate Research Center (CPRC). Both colonies are provisioned with Monkey Chow and water, although the animals are also free to forage on island vegetation.

All the animals on Cayo Santiago and many La Cueva monkeys were born on the islands. Annually since 1959, each crop of infants in the Cayo Santiago colony has been trapped and tattooed for identification; date of birth, sex, maternal genealogy, and social group affiliation are known for most individuals.5 Although census information is collected less regularly on La Cueva, records on most animals include year of birth, sex, and some genealogical and social information.6, 7

Between Jan. 9 and 14, 1978, 70 monkeys from Cayo Santiago (total population 537) and, between Jan. 15 and 20, 44 monkeys from La Cueva (total population approximately 1100) were examined. During these days, sunrise and sunset occurred at approximately 6:00 A.M. and 5:00 P.M. (EST), respectively, and all animals were examined between 8:00 A.M. and 5:00 P.M. The exact time of IOP measurement was noted for each animal.

Eight monkeys at Cayo Santiago and four at La Cueva were used in preliminary experiments and dose-response studies. In the total of 102 monkeys included in the main analyses, there were 50 males and 52 females; of the females, 15 were found, when palpated, to be pregnant. The age distribution of the 102 animals is shown in Fig. 1. This figure also shows an estimate of the age distribution of the overall population constructed from life tables for Cayo Santiago females.5 Although this distribution is based on 1973-1974 records of females alone, ages of Cayo Santiago males also approximate the skewed distribution of our main sample (R. G. Rawlins, personal communication).

Procedures. Animals were trapped at feeding stations each day by CPRC staff. They were kept in cages for no longer than 20 hr (typically 2 to 5 hr) before transfer into a squeeze cage, where they were injected i.m. with approximately 10 to 30 mg of ketamine per kilogram of estimated body weight (Ketalar, ketamine hydrochloride in a solution equivalent to 100 mg/ml ketamine; Parke-Davis & Co., Detroit, Mich.) by a CPRC veterinarian. Each animal was weighed after anesthesia so that

![Fig. 1. Age distribution of male and female rhesus monkeys in the study sample compared with the overall age distribution of the total population. The latter was estimated from the life table for Cayo Santiago females, calculated from 1973-1974 census records.5](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933087/)
the exact dose of ketamine administered could be calculated. The mean dose based on a sample of 42 animals was found to be 18.7 ± 4.3 (S.D.) mg/kg.

The IOP of only one eye was measured on the first eight animals examined (not included in the 102 animals used for data analysis) because of the concern that the probe might cause microscopic corneal damage sufficient to interfere with slit-lamp and other examinations of the eye by accompanying investigators.8 Since such damage was not detected, the IOPs of both eyes were measured in all subsequent animals.

On the first 50 animals, measurements were made in both the supine and seated postures. Applying the probe to the cornea horizontally with the animal seated on a table and held by an assistant, or seated between the knees of an assistant, was found to give reproducible readings if approximately 30 sec were allowed to pass after the animal was raised to the seated position. This position was selected because sitting is a normal resting posture for this species and is similar to the position in which the IOP of human subjects is measured in current clinical studies.

The following procedure was used in measuring IOP of the 102 animals used for the main analysis. A drop of the local anesthetic proparacaine HCl 0.5% (Alcaine; Alcon Corp., Fort Worth, Texas) was administered to each eye following the intramuscular administration of ketamine. The animal was held in the seated position by an assistant while the investigator held the upper lid and head of the animal with the left hand and the probe of a floating-tip9 applanation pneumatomograph (Alcon) with the right hand. Several measurements, each about 3 to 4 sec in duration, were taken on each eye at an average of 13 min following administration of ketamine, and values based on steady-state segments of the recordings were averaged.

The IOPs of 35 animals were measured again between 1 and 3 hr (104 ± 25 min) after the initial readings. During the interim, a drop of the mydriatic cyclopentolate HCl (Cyclogyl, 1%; Schieffelin & Co., New York, N.Y.) was applied to the eye, and the animals passed through four other stations for ophthalmoscopy, slit-lamp examination, and electroretinography8 and for anthropometric measurement.10

Effect of ketamine on IOP. The possibility that ketamine used for anesthesia could have had a dose-dependent effect on IOP was studied on four monkeys at La Cueva. Injection of a small dose (about 3 mg/kg i.m.) of ketamine, which was just sufficient to inhibit overt aggression, was followed by repeated IOP measurements at 5 and 10 min. Then approximately three times the maximum recommended dose (35 mg/kg i.m.) of ketamine was administered, and the IOP was measured again at 5, 10, and 30 min.

Another study of the effect of ketamine on IOP was conducted in our New York laboratory on a female rhesus monkey (4.6 kg; estimated age, 4 years) that was accustomed to handling and to sitting in a primate chair. For 2 days, frequent IOP measurements were made on the conscious animal while it was seated in the primate chair. Following application of a drop of local anesthetic (Alcaine), the investigator applied the tonometer probe with
To one hand and steadied the monkey's head gently with the other. Once the animal was accustomed to tonometry, a comparison of IOP in the conscious and anesthetized state was made on 6 separate days over a 2-week period. Six IOP readings were taken each day at 30 to 60 min intervals, followed by intramuscular injection of the recommended dose of ketamine (10 mg/kg). IOP was then measured at 5, 10, and 30 min while the animal remained in the chair.

On the last day of these experiments, the effect of ketamine on IOP was compared to that of another anesthetic, sodium pentobarbital. One milliliter of Diabutal (60 mg/ml sodium pentobarbital; Diamond Laboratories, Des Moines, Iowa) was injected intravenously 1 hr after injection of ketamine, and IOP was measured at 1, 5, 10, 30, and 60 min thereafter.

**Tonometer calibration.** The tonometer was calibrated in the field with an artificial membrane at the beginning and end of each day. Calibration of the tonometer on a rhesus monkey eye was done in our laboratory in New York. A 7 kg female rhesus monkey was anesthetized (0.7 ml of Ketalar i.m.) and seated in a primate chair. A drop of local anesthetic (Alcaine) was applied to one eye, and the anterior chamber was cannulated with a 26-gauge hypodermic needle which was connected by flexible tubing to a reservoir of heparinized saline. The height of the saline reservoir relative to the midpoint of the eye was gradually increased by intervals corresponding to 5 mm Hg. IOP within the range of 5 to 40 mm Hg was measured on the cannulated eye; then the level of the reservoir was varied in random sequence throughout the range. The tonometer probe was held in a horizontal position similar to the position used throughout these studies. In the range of 5 to 35 mm Hg, the plot of the reservoir setting vs. the chart paper reading yielded a straight line with a slope of one and an extrapolated intercept of zero. Since all values measured in Puerto Rico fell within this range, the values presented here were read directly from the tonometer tracings.

**Analysis of data.** All IOP data and relevant information were entered into the CDC 6600 computer at Vogelback Computing Center, Evanston, Ill., where anthropometric data were already stored. Factors considered in the analysis of the IOP data included age, weight, skin fold thickness, sex, pregnancy, dose of ketamine, time between ketamine injection and IOP measurement, and time of day. For all statistical analyses, standard procedures as described in Nie et al. were used, and relationships between variables were considered significant only if p < 0.05. All values presented with limits in the text represent means ± 1 S.D., and N = the number of animals on which the value is based. Unless otherwise stated, the mean IOP of the two eyes of each ani-
normal (one mean IOP value per animal) was used for data analysis.

Results

Correlation of IOP with population parameters. The frequency distribution of all individual IOP values in the total sample studied (204 eyes of 102 monkeys) is shown in Fig. 2, A. The overall mean IOP was 14.9 ± 2.1 mm Hg. No significant differences in IOP were found between Cayo Santiago and La Parguera animals or between different social groups. Furthermore, a strong positive correlation \((r = 0.88, p < 0.001)\) was found between the IOPs of the left and right eyes. Therefore all subsequent analyses were based on the total sample of 102 animals and used the mean IOP of the two eyes of each animal (i.e., one value per individual).

An overall negative correlation was found between IOP and age. This correlation could be best described by linear regressions when the total sample was divided into growing (7 months to 6 years of age) and adult (7 to 21 years) animals (Fig. 3). There was a significant negative correlation between age and IOP in the former age group \((p < 0.05)\) but not in the latter \((p > 0.2)\). These relationships remained the same when time of day (see Apparent diurnal variations) was held constant with partial correlation analysis. When the population was broken into three age groups of approximately equal size, the mean IOP of 33 juveniles (7 months to 3 years) was 15.7 ± 2.0 mm Hg, of 42 adolescents and young adults (4 to 9 years) 14.6 ± 1.9, and of 27 adults (10 to 21 years) 14.3 ± 2.1. The difference between the mean IOP of juveniles and that of the remainder of the animals was statistically significant \((p < 0.01)\). In addition, the IOP frequency distribution in the juveniles was skewed to the right, whereas that of the rest of the population more closely resembled a normal distribution (Fig. 2, B).

A significant negative correlation was also found between IOP and body weight in the total population. Further analysis indicated, however, that this was due to a correlation between age and body weight rather than to weight per se. In full-grown animals (6+ years), there was no significant correlation between IOP and body weight or between IOP and skin fold thickness, a measure that can be used as an index of obesity.\(^{10}\)

Fifty males and 52 females showed mean IOPs of 14.9 ± 2.1 mm Hg and 14.9 ± 2.0, respectively, whereas the subset of 15 females with palpable fetuses had a mean IOP of 14.1 ± 1.4. This last value is statistically different \((p < 0.05)\) from the mean IOP of all other females \((15.3 ± 2.1 \text{ mm Hg})\), but when IOPs of pregnant females were compared to IOPs of either females in the same age range (4 to 15 years) with no palpable fetuses or to males in the same age range, no significant differences were found.

Apparent diurnal variations. Highest IOP values were measured between 9 and 10 A.M. (Fig. 4, A). The mean IOP of 24 animals mea-
sured between 9 and 11 A.M. was 16.1 ± 2.0 mm Hg, whereas that of 26 animals measured between 12 and 2 P.M. was 14.4 ± 1.9. The difference between these two values is statistically significant (p < 0.01). A partial correlation to eliminate the effect of age on IOP continued to show a significant negative relationship between IOP and time of day (p < 0.002). Dividing the sample into growing (0 to 6 years) and adult (6+ years) animals showed that diurnal variations in IOP were more pronounced in the young age group; the IOPs of the older group fluctuated within a much smaller range during the day (Fig. 4 B).

**Effect of anesthetics on IOP.** The mean IOP of the four animals given first a low and then a high dose of ketamine was 13.9 ± 1.3 and 15.2 ± 0.8 mm Hg within 10 min after injection of the low and high doses, respectively. The difference between these means is not statistically significant. In the 24 growing individuals and 19 adults (included in main sample of 102 animals) for which accurate dose information was available, the relationship between initial dose of ketamine (mg/kg) and mean initial IOP was not statistically significant. The IOPs of 35 of these animals were measured a second time, at an average of 104 ± 25 min after the initial IOP determination. These animals received additional ketamine at a mean dose rate of 8 mg/kg per hour. The mean of these second IOPs was 16.3 ± 2.1 mm Hg, and the mean change between initial and second readings was 1.3 ± 2.2. There was no significant correlation between the dose-rate of ketamine and change in IOP or between the total dose of ketamine, duration of anesthesia, and final IOP.

The trained rhesus monkey studied in our laboratory had a mean preanesthetic IOP of 17.8 ± 0.4 mm Hg based on 24 determinations taken 30 to 60 min apart on 6 different days. The mean IOP of 18 determinations taken 5 to 30 min after administration of the recommended dose of ketamine on 6 different days was 18.1 ± 0.4 mm Hg. The difference, based on these six experiments, was not statistically significant. Five IOP readings taken within 60 min after the intravenous injection of a small dose (12 mg/kg) of sodium pentobarbital gave a mean IOP of 11.3 ± 0.8 mm Hg, which was found to be significantly lower (p < 0.05) than the mean of nine IOP readings (17.6 ± 0.3) taken after the induction of ketamine anesthesia, but before the pentobarbital administration.

**Discussion**

The results of this initial survey of two free-breeding rhesus monkey populations clearly demonstrate the feasibility of conducting large-scale IOP determinations under field conditions. Trapping and handling the animals caused only a brief period of apparent excitement, and all animals recovered from ketamine anesthesia rapidly and without complications.

Ketamine proved to be a particularly useful anesthetic for IOP studies, not only because it has a large safety margin but also because it does not appear to affect IOP. In our survey, no significant correlations were found between dose of ketamine and IOP. Likewise, IOP did not change significantly with duration of ketamine anesthesia (in the range of 5 min to 2 hr). Furthermore, our results on one trained rhesus monkey in New York showed that there are no significant differences between IOPs measured before (on the conscious animal) and 5 to 30 min after administration of an anesthetic dose of ketamine. On the other hand, intravenous injection of a small dose of barbiturate, when this animal was already under ketamine-induced catalepsia, resulted in an immediate and significant reduction in IOP, indicating that ketamine itself does not have a barbiturate-like effect on IOP.

The clinical literature reports either a small increase in IOP as a result of ketamine anesthesia\(^1\)\(^2\)\(^3\) or no significant change.\(^4\) The reported increase in IOP may, however, be due to other noncontrolled factors. For example, Corssen and Hoy\(^1\)\(^3\) reported that the IOP measured under ketamine anesthesia (presumably in the morning) was high compared to the “normal” IOP measured the previous night or compared to the preopera-
tive IOP taken 35 min after premedication with barbiturates, morphine sulfate, or demerol. A difference between these IOP values may well reflect the effects of premedication and/or circadian variations rather than the effect of ketamine. In any case, such clinical studies indicate that ketamine may increase, but certainly does not decrease, IOP in the human.

In contrast, Hahnenberger reported a 12% decrease in the IOP of four cynomolgus monkeys (Macaca fascicularis) following intramuscular administration of a tranquilizing dose of ketamine and a 20% decrease following the injection of an anesthetic dose. These trained animals were removed from their cages just before tonometry and were manually restrained by an assistant while IOP was measured with a hand-held Draeger application tonometer. We found that even after our rhesus monkey had become accustomed to tonometry, manual restraint of her head or arms as she sat in a primate chair resulted in as much as a 5 mm Hg increase in IOP. Although it is possible that ketamine response varies among primate species, the disparity between Hahnenberger’s results and our observations may simply be due to differences in technique and the handling of the animals.

We can safely conclude that, in contrast to barbiturates, which are known to lower IOP in several species, including subhuman primates and man, and were found in this study to have a similar effect on the IOP of a rhesus monkey, ketamine catalepsia has little or no effect on the IOP of this species. Thus we may assume that the mean IOP (14.9 ± 2.1 mm Hg; S.E. = ±0.2) of the 102 animals in this survey is a good estimate of normal IOP of rhesus monkeys. This value is remarkably similar to the mean IOP of 15.7 ± 2.5 mm Hg reported and generally accepted for humans, considering that the human population studies were based on samples consisting of much older individuals.

The distribution of IOP in rhesus monkeys is skewed to the right, though it does not include unusually high (2 sigma or greater over the mean) values. This skewness is due primarily to the presence of juveniles, which have a mean IOP significantly higher than that of the rest of the population. This age difference is noteworthy and does not appear to be an artifact of anesthesia or diurnal variation. In humans, a similar negative correlation between age and IOP during the first 9 years of life is apparent. The similarity of both IOP distribution and mean IOP in man and rhesus monkeys underscores the usefulness of the rhesus monkey as a model for research on ocular fluid dynamics and glaucoma.

The facts that IOP values of animals over 3 years of age were more normally distributed than those for the total sample and that there was no correlation between age and IOP in adults (6 to 21 years) suggest that our sample contained no individuals with chronic simple glaucoma. It should be noted that although the accompanying investigations of the ocular fundus discovered a high frequency of macular degeneration, none of the animals showed cupping of the optic nerve head or other glaucomatous changes (G. Eisner, personal communication).

The absence of ocular hypertensive individuals in the group of 102 animals examined so far is not surprising, since it is known that the frequency of ocular hypertension in people over the age of 40 is 2% to 3% and much lower in younger age groups. Although it is difficult to draw parallels between different species, developmental stages and reproductive and total life-spans may be used to define comparable age groups. As is the case in humans, reproductive capacity in rhesus monkeys is achieved prior to the development of maximum body size and is lost prior to the maximum life-span. For example, female rhesus monkeys reach menarche around 2 years of age, but full body size is not assumed until the age of 5 or 6. Reproductive capacity begins to decline around age 15, ovaries may be sclerotic at 23 years, and menopause may occur at about 25 years of age. The average life-span of rhesus monkeys is stated to be approximately 24 years, and the oldest animals at Cayo Santiago are at least this old (R. G. Rawlins, personal communication). In a laboratory colony, rhesus...
monkeys have been maintained up to the age of 30 years. If, on this basis, we assume that the age of 16 in monkeys is equivalent to the age of 40 in humans and further assume that the frequency and age distribution of ocular hypertensive individuals is the same in these two species, we might expect only about 2% of the monkeys 16 years and older to have ocular hypertension. Since our sample contained eight animals in this age group, we had only a one in five chance to observe one individual with abnormally high IOP. Examination of much larger numbers of adults and old adults will be required before the possibility of naturally occurring ocular hypertension and glaucomatous changes in the rhesus monkey can be ruled out.

In contrast, Barany and Rohen found, in a population of 69 vervet monkeys, three individuals with elevated IOPs, two of them affected in only one eye and one bilaterally. The unilateral elevated IOP in the first two animals was classified as secondary glaucoma because earlier traumatization was evident. The third case apparently represented simple glaucoma; unfortunately, the ages of these animals were not known.

The existence of diurnal variation in IOP is apparent from an analysis of readings obtained on different animals between 8 A.M. and 5 P.M.; an apparent peak in IOP was found between 9 and 10 A.M. Further analysis of the data indicated, however, that only in young animals (age <6 years) was there a significant correlation between IOP and time. The fact that the young age group showed an essentially linear and highly significant decline in IOP between 9 A.M. and 2 P.M. whereas the older animals showed only much smaller fluctuations in IOP during the day is not entirely surprising, since it is known that in humans, the peaks and troughs of some circadian rhythms occur at different times of the day in children and adults. Differences in circadian rhythm have also been reported to exist between infant and adult rhesus monkeys. It is possible, therefore, that in our sample the older macaques show variation in IOP similar to that found in the younger group but that the peak IOP falls outside the 9 hr period during which our measurements were made.

Further studies on these and possibly other free-ranging rhesus monkeys will have to be undertaken before correlations between IOP and additional parameters can be examined. The macaque populations that form the base of this survey are especially valuable for future work because of the wide scope of background information available on each animal. Census records, including birthdates, genealogical relationships, and pregnancies, date from 1959 at Cayo Santiago and from 1961 at La Cueva. Ongoing behavioral observations on Cayo Santiago, and to a lesser extent at La Cueva, document dominance ranks, traumas, miscarriages, mating behavior, locomotion, etc. The genetic composition of the Cayo Santiago population has been studied with regard to red cell and serum proteins. In addition, the IOP survey of these populations was done in conjunction with anthropometric measurements and ophthalmic examinations. The former provided even more data on each animal, such as weight, crown-rump height, skin fold thickness, and the presence of joint diseases and/or trauma, the latter included ophthalmoscopic and/or slit-lamp evaluations of the anterior segment, lens, vitreous, and fundus. Such comprehensive descriptions of these monkeys will make it possible to examine a broad range of variables that may affect normal ocular fluid dynamics and that may be associated with the development of ocular hypertension and glaucoma.

In conclusion, the present study demonstrates the feasibility of conducting large scale IOP surveys on free-ranging primates under ketamine catalepsia and shows that rhesus monkeys have a mean IOP that is remarkably similar to that of humans. The finding that the mean IOP of juvenile macaques is significantly higher than that of adults may also be consistent with the similarity between rhesus monkeys and man with respect to IOP and underscores the usefulness of this species for studies on normal aqueous dynamics and its control. Longitud-
inal follow-up studies on some of the animals already examined and additional surveys focusing on older animals are planned in order to determine whether ocular hypertension occurs in rhesus monkeys with a frequency and course of development similar to that reported for man.

We thank the staff of the Caribbean Primate Research Center of the University of Puerto Rico for their cooperation and assistance throughout this study. We especially thank Dr. Bill Kerber, Scientific Director of the Primate Center, and Richard Rawlins and John Herbert, Scientists-in-Charge at Cayo Santiago and La Cueva, respectively. The assistance of Michael Evans, Sam Martinez, and Connie Reynolds is also appreciated.

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