Primary open angle glaucomas in the rhesus monkey

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Abstract

Rhesus monkeys from the closed Cayo Santiago colony of the University of Puerto Rico demonstrate elevated (≥ 22 mm Hg) intraocular pressure in a pattern which significantly favours certain maternal lineage groupings. The colony had remained genetically pure since 1938. Of nine matriarchal lineages (matrilines) examined, two had an incidence of ocular hypertension of more than 40% and six of more than 10%. Information on 18 matriline is currently located in the colony data base which identifies each individual and its vital statistics. In 1990, six animals were moved to the laboratory in Florida. Among those from a low incidence matriline, we found abnormal optic nerve cups, pallor, reduced function of (mainly peripheral) fields, progression and loss of optic nerve axons in the presence of ocular hypertension. In another individual where the cup/disc ratio for the right eye was 0.7 and left eye 0.4 and outflow facility was normal, we excluded all other causes of optic nerve atrophy, and low tension glaucoma was diagnosed. This female was from a matriline with a low incidence of ocular hypertension. Relatively rapid aging (3-4 years/human year) monkeys with ocular hypertension and familial clustering produce a near ideal glaucoma research model.

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Since 1984, with the cooperation of the University of Puerto Rico, we have had a number of opportunities to examine members of the Cayo Santiago rhesus monkey colony for diseases of the posterior segment of the eye. Cayo Santiago is a small island off the east coast of Puerto Rico. The Cayo Santiago monkey colony is unique. It was established from African and Indian monkeys in 1938 and genetic purity has not been disturbed since that time. On this island the progeny of the original colony are maintained with all animals individually identified and a daily census recorded. The social history and matriarchal lineages (matrilines) for 8-12 generations are known for each animal. The history of the colony is described by Rawlins and Kessler.¹

Our earlier publications²⁻⁵ have established the high incidence of age-related macular drusen and disciform lesions in some matrilines and relatively low incidence in others. The findings on age-related macular drusen and associated changes have been summarised recently by Hope *et al.*⁶

In addition to macular disease, we have discovered high tension and low tension primary open angle glaucoma (POAG) in matrilines other than those showing high incidence of macular

disease. Some of the optic nerve pathology from an individual with high tension POAG was presented at ARVO in 1991.⁷ Here we describe two representative matrilines, the electrophysiological details of some loss in retinal function, characteristic optic disc changes, and optic nerve histopathology. These findings establish the Cayo Santiago macaques as the only non-human primates with known, naturally occurring POAG.

Methods

No monkeys have been introduced into the Cayo Santiago colony since the original importation in 1938. All monkeys have been individually identified since 1956. Daily census records are maintained. In addition to natural forage, assayed commercial diet and rainwater are provided on the island. The original social anthropological mission of the colony has been maintained and only behavioural observations are allowed. However, during the annual medical round-up, examination, tattooing, and treatment some limited, non-invasive biological research is possible. When overpopulation becomes a problem, monkeys are removed from the colony to the parent facility on the Puerto Rican mainland at Sabana Seca. Here, the excess Cayo animals are accessible and maintained adjacent to other species and random source macaques. The Caribbean Primate Research Center (CPRC) maintains more than 2000 animals, the majority of them are of Cayo Santiago derivation.

SAMPLING/SCREENING

We have conducted 315 eye examinations on 246 monkeys of Cayo derivation. Sixty one of the examinations were repeated after 1-3 years and eight were accidental duplicates (after 1 or 2 days). Intraocular pressure (IOP) was measured on one or more days in 163 monkeys (326 eyes). Examinations were conducted both on Cayo Santiago and at Sabana Seca. Only data from animals of Cayo Santiago origin are included in the data base. No matriline information was available at times of examination therefore eliminating any measurement/pedigree bias.

Animal sedation and management methods are similar to those used in several studies of induced monkey ocular hypertension and have minimal effects on blood pressure or IOP.⁸⁻¹⁰ All procedures were approved by the Institutional Animal Care and Use Committee and observed the NIH guidelines. Monkeys were sedated briefly (about 40 minutes) by intramuscular injections of ketamine hydrochloride (12 mg/kg, Vetalar). Pupils were dilated with phenylephrine (10%, Neo-Synephrine) and tropicamide (1%, Mydracil). Corneas were maintained with

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artificial tears and anaesthetised with proparacaine (0.5%, Alcaïne).

During the eye examinations abnormalities of the external eye and anterior segments were noted. IOP was measured by an applanation technique using a Tono-pen (Bio-Rad, Ophthalmic Division). The Tono-pen contains a calculator chip which estimates the adequacy of the individual measure and produces a digital mean pressure measure and an estimate of variance. Measures were discarded when the variance was more than 5%. Ophthalmoscopy was completed with both the direct and indirect ophthalmoscope. Conditions allowed the estimation of optic disc pallor and cup/disc (C/D) ratio in about half the animals. In some animals macular drusen were counted⁶ and gross refractive errors were noted when detected by the direct ophthalmoscopy. In some animals with normal anterior segment, fundus Ektachromes were made using a KOWA RC-2 fundus camera and fluorescein angiograms were occasionally done with that fundus camera's fluorescein accessories.

In 1990, six Cayo Santiago derived animals (including A25, 950, and I91) from matriline 091 were taken from the island as excess to the population limits and were examined further at the University of Florida.

PATHOPHYSIOLOGY

Losses of visual function were detected electrophysiologically in monkey I91 and monkey A25. The basis for electrical measurements has been previously described by Dawson *et al.*¹¹ for monkeys and by numerous papers which have described human electrophysiological losses in response to early fields changes from POAG.^{12,13} Briefly, the animals were sedated by the injection of ketamine hydrochloride (12 mg/kg), anaesthetised by thiamylal (Biotal), intubated, and maintained on a mixture of 25% oxygen, 75% nitrous oxide, in the presence of a muscle relaxant (pancuronium bromide, Elkins-Sinn, 0.1 mg/kg/h) and intravenous saline. Core temperature, electrocardiogram, and end tidal CO₂ were monitored and held approximately constant. The fundus was visualised through a highly modified Zeiss fundus camera which was fitted with a third optical channel. Through the third channel, computer generated video grating patterns of various special frequencies (5 minutes of arc per phase to 300 minutes of arc per phase) were projected upon the fundus under visual control and centred upon the fovea. The stimulated fields were 15 and 30 degrees in diameter. Electrical signals produced by counterphasing of light and dark grating bars produced in this way were indicators of the functional nature of the visual fields of the retina as the retina and visual cortex responded to the stimulation. The root mean square (RMS) amplitudes were calculated off line and provided an unbiased estimate of the magnitude of the responses.

Cup/disc ratios were calculated from examination by the direct and indirect ophthalmoscopes. Photographs of the optic discs were made from normal monkeys and from rhesus I91 and 950. The Ektachrome positives were digitised and the

cup rim was drawn. Digital measures of the cup and disc were used to calculate cup area and cup/disc ratio. Possible intracranial disease was rejected after a radiography and a magnetic resonance (MRI) series with gadolinium contrast was completed. I91's axial intraocular length was measured by ultrasonography and corneal curvature by keratoscopy.

Total outflow facility (C) was measured as described by Wickham *et al.*¹⁴ Following measurement of basal IOP (Tono-pen), the anterior segment was tapped by a single cannula. Balanced salt solution was injected to maintain constant pressure 3 and 10 mm Hg above the basal level for 4 minutes. Total facility was calculated from the amount of fluid infused per minute at these pressures. The result (C=0.18 left and C=0.29 right) is similar to the mean value (C=0.214 $\mu\text{l}/\text{min}/\text{mm Hg}$) for 21 rhesus eyes reported by Wickham *et al.*¹⁴

HISTOPATHOLOGY

Eyes from monkey 950 were enucleated within minutes after cardiac failure. Immediately, a 4 mm opening was made at the ora serrata and 5 ml of chilled 2% cacodylate-buffered glutaraldehyde solution was injected into the vitreous chamber. After a few minutes the anterior segment was removed. The anterior segment, the posterior segment, and optic nerve were stored together in a 2% cacodylate-buffered glutaraldehyde solution at 4°C for 1 week. Sections of the anterior chamber angle showed it to be normal. A 2 mm long portion of the optic nerve was removed and marked for vertical and posterior orientation. The optic nerve was post osmicated (1%) for 1 hour at room temperature, washed, dehydrated, and embedded in a Medcast-Araldite epoxy resin. One μm thick

Figure 1 Demographic data on ocular hypertension in Cayo Santiago macaques. (A) Incidence of pressures in our sample of eyes. (B) Incidence of hypertension (IOP ≥ 22 mm Hg) in nine matrilines of the 18 matrilines available. Individual and analysis by eye is presented.

Each field was 30 by 40 μm for an area of 1200 μm^2 per field. Within each field, axons were counted by the IBAS system and their mean minimal diameters were measured. Any axon that touched the left and inferior border of the area being measured was not included. Pial components were also excluded. The diameter measures were sorted into 20 bins, ranging from 0.2 to 4.0 μm .

Results

INTRAOCULAR PRESSURE

Intraocular pressures were measured by applanation tonometry in late morning or early afternoon. Pressures were measured one or more times on 163 monkeys (326 eyes). Examinations of 43 of these were repeated 1–3 years later. IOPs from individuals dilated for subsequent fundus examination were not significantly different from 49 other individuals undilated but otherwise treated identically. The IOP differential between dilated and undilated groups was 0.62 mm Hg. There was no significant difference between the groups in numbers of animals with pressures ≥ 22 mm Hg, which totalled 31 individuals. This value is widely accepted as the threshold for IOP abnormality in conscious humans.^{18,19}

It seems unlikely that any of our results are contaminated by anaesthetic or time cycle influences. Bito *et al.*²⁰ reported losses in IOP (17.6–11.3 mm Hg) in a trained rhesus after the injection of a small amount of sodium pentobarbitone. Normal or high doses of ketamine had no significant effect on this monkey or on the IOP of 35 others studied for dose rate, duration of anaesthesia, and effects on final IOP. In a sample of 102 animals, aged 7 months to 21 years, there were peaks (about 1–2 mm Hg) in the time of day/IOP function at 9 am and 3 pm. These were not significant.

IOP, optic disc pallor, and the C/D were estimated in 132 monkeys. Of this number, 24 exhibited pallor and C/D ≥ 0.4 . Six monkeys exhibited asymmetric pallor and C/D ≥ 0.5 . Some showed asymmetrical cup shapes. There was high subjective agreement between the extent of pallor and the optic cup size. Thirty eight eyes (30 individuals) had C/D ≥ 0.4 . Twenty nine eyes (21 individuals) had IOP values ≥ 22 mm Hg. Thirty one eyes (24 individuals) had C/D ≥ 0.4 where IOP ≤ 20 . Five animals showed combined C/D, IOP abnormality. C/D estimations were repeated on successive years (in the absence of previous records) and on the same visit (accidentally). Measures of C/D were made on 68 eyes/34 monkeys on successive years by any of three examiners. The mean difference between annual estimates was 0.054 (SD 0.125). For repeated measures on the same visit (12 eyes/six monkeys) the mean difference was 0.042 (SD 0.082).

The mean age of our sample of Cayo Santiago rhesus monkeys was 11.6 (SD 5.2) years. Ordry and Brizzee²¹ have estimated that one monkey year of life is equal to 3–3.5 human years. Therefore, our sample covered approximately 10–95 human years. The frequency distribution

of IOPs in our sample of 326 eyes is shown in Figure 1A. The distribution mean IOP is 16.9 (SD 3.8) mm Hg. We found no significant dependence of IOP on age. Mean IOP in the eyes of males (17.4, SD 3.9 mm Hg) were significantly higher ($p < 0.05$) than in those of females (16.45, SD 3.65 mm Hg). However, the difference was small and tests for differences in IOP based upon individuals rather than eyes were insignificant.

At this time, there are 18 matriline of Cayo Santiago derivation in Puerto Rico. In our sample, we found IOPs ≥ 22 mm Hg in individuals from nine matriline. Data from six other matriline have not been included because sampling in them involved fewer than 10 animals. Two of the nine matriline (Fig 1B; 092 and 076) produced 44% affected animals (χ^2 , $p < 0.001$). Yet, mean IOP did not vary significantly among matriline, nor did age or numbers of animals sampled, except for 091 which supplied a large number of individuals.

Figures 2 A and B show partial matriline diagrams (pedigrees) taken from our CPRC data base. There is a low incidence (091) and high incidence (076) matriline. Only lineages of 'examined' or affected animals are shown to conserve space. The 076 diagram covers seven generations and the 091 diagram covers eight generations. The animals which we have examined for intraocular pressure are symbolised with double boundaries and those which were affected (IOP ≥ 22 mm Hg) are shown with double boundaries and cross-hatching. Animals deceased are identified by 'X' and animal number. Animals not examined are identified by number of boundary only. Matriline 091 (Fig 2A) represents 280 monkeys. Of these only the 57 progeny of matriarch WE are shown since she had 36 siblings with many offspring. In the 091 sample, six of 31 examined monkeys had ocular hypertension or optic atrophy. Three of these are among the WE progeny (Fig 2A). Normotensive monkey I91 will be discussed later. Matriline 076 represents a smaller group with 188 individuals; 102 are shown in Figure 2B; 17 were examined and seven were affected.

Of the animals examined in group 091, 19% had ocular hypertension; and 41% in group 076 had ocular hypertension. One animal (I91) in matriline 091 had pronounced excavation of the optic disc in the absence of ocular hypertension. In Figure 2, IOP is indicated as two integers (left eye; right eye) immediately above the symbol. The animal number is indicated in the upper part of the interior of the symbol and date of birth in the lower portion. Date of birth is prefixed by an apostrophe.

During our visits to the island, we were able to examine the optic discs of 132 normotensive (IOP ≤ 20 mm Hg) animals. Of this number, 24 exhibited some pallor and C/D ≥ 0.4 and six ≥ 0.5 . All of the six were asymmetric for pallor/disc shape. In human infants of this physical size (< 3 years) CD ≥ 0.4 is rare in normals and common in patients with glaucoma.²²

Six animals from Cayo Santiago were brought to the University of Florida for further examination. Data from three are presented. Number 950 and its offspring, number I91, are from

matriline 091 (Fig 2B), as is female A25. A25 is a clinically normal female that was born in 1980. Her IOPs were taken on five occasions in January of 1989 and yielded a mean IOP of 12.2 (SD 1.2; range 11–14) in the right eye and mean = 12.5 (SD 1.3; range 10–14) in the left eye. Female I91 was born in 1985 and in January of 1992 displayed C/D ratios estimated to be 0.7 in the right eye and 0.4 in the left eye. Intraocular pressures measured ($\times 15$) in 1990 averaged 14 mm Hg (range 10–15) in the right eye and 13 mm Hg (range 6–19) in the left eye and were normal again in 1991–92 with a mean of 11.6 (SD 0.74; range 11–14, $n=12$) in the right eye and 12.0 (SD 0.92; range 11–15; $n=12$) in the left eye. Outflow facility of I91's right (C/D=0.7) and left eye (C/D=0.4) were within normal limits for rhesus,¹⁴ which is similar to values reported by Schuman²³ for human. Female rhesus 950 was born in 1978 and in January 1988 showed C/D ratios of 0.7 in the left eye and 0.5 in the right eye. At that time, IOPs were taken repeatedly to produce a mean IOP = 26.1 (SD 1.9; range 24–30; $n=6$) in the right eye and mean = 27.5 (SD 2.3; range 23–30; $n=6$) in the left eye. Subsequent measures (1991) of IOP for female 950 have yielded consistent results >25 mm Hg, bilaterally, measured morning and afternoon.

Figure 3 shows the optic discs of the right eyes of each animal. These are reproduced digitally from transparencies. The very light areas normally associated with the optic cups are shown as the darker regions of the papilla. These are digitally outlined and marked with arrows. Note especially the poor resolution and/or absence of temporal fibre-layer striations of the papillomacular bundle in female I91. The MRI series, cranial radiographs, anterior segment and gonioscopic examination, and general neurological results on I91 were all normal. The high I91 C/D was a chance finding among animals shipped to Florida. Clinical and digital calculations of C/D values are presented in Table 1.

Figures 4A and 4B describe the eye and visual cortical responses produced (sequentially) by 50/50 gratings of seven sizes projected upon the fundus during intervals over approximately 8 minutes. Figures 4A and 4B describe the responses from normotensive female I91. Data for Figure 4A were collected in 1990 and Figure 4B in early 1992. The data shown in Figure 4A are typical of normal cortical and retinal responding to counterphased gratings of several spatial frequencies. The spatial tuning function (STF) is very similar to that produced by normal female A25. Typically, there is a minimum which is approached at the smaller sizes, a subsequent peak, and a second minimum at the largest stimulus size. The 1992 STF from I91 differs mainly by reduced response amplitude, both at the visual cortical recording site and from

Fig 3A

Fig 3B

Fig 3C

Figure 3 Optic disc photographs have been digitised and are presented as negative prints from Kodachrome positives. Cup rims are outlined and marked by arrows. (A) Normal rhesus A25, right C/D=0.4. (B) Abnormal disc, rhesus 950, right C/D=0.6. (C) Abnormal disc, rhesus I91, right C/D=0.7. Digital values were used to produce Table 1.

the eye itself. The loss may be more profound at the eye electrode than at the cortical electrode.

Figure 5 summarises the STFs originating from the right retinas of I91 and A25. Eye data from the earlier and later recordings from animal I91 and from the normal A25 are shown. The histograms represent the mean values of all of the STF components over the full range of grating sizes. That is, the 30° STF (Fig 5A) represented on the fields ordinate for animal I91 is the equivalent of summing all the eye data points

Table 1 Cup/disc ratios of three monkeys measured clinically and digitally (two methods) from photographs

Animal	Clinical	Digital area	Digital width
A25 (normal)	0.4	0.21	0.36
950 (IOP >25 mm Hg)	0.6	0.22	0.54
I91 (atrophy)	0.7	0.57	0.85

Figure 4 Spatial tuning functions produced by contrast evoked signals of retinal (●) and cortical (▽) origin in response to a range of counterphased gratings (5–750 minutes of arc) projected onto the right fundus. (A) Measures from I91, right eye in mid-1990. (B) Measures from I91, right eye in early 1992.

Figure 6 Peripheral optic nerve axons of POAG female 950, left and right eye counted in regions and scaled by diameter. (A) Dorsal periphery (see inset) including four divisions of equal area. (B) Ventral periphery. Abscissa values are mean axons/size/unit area. Abscissa mean numerals are provided below the ordinate (size-range).

Figure 5 Mean spatial tuning function values for the right eye of I91, C/D=0.7 and A25, C/D=0.3. STF means were calculated for a central 30° diameter field, a 15° diameter field and a toroidal field derived from the 30° result minus the 15° result. (A) Data are from I91 in 1990 and 1992. (B) Data are from normal female A25.

shows the STF result from a 15° field stimulus centred (as others) upon the fovea. Toroid values in Figure 5 are the result of a subtraction of the 30° mean and the 15° mean. Spatially, this represents the response of a toroidal field around the macula. Changes in cortical responses are not significantly different from those from the retina. Normal A25 STF means (Fig 5B) are shown for comparison.

Figures 6A and 6B show the relative left optic nerve axon loss counted by the IBAS analysis system in regions of the optic nerve of female 950. The left eye had a 0.7 C/D ratio and the right eye was relatively normal with C/D=0.4. The vertical axis scale is axons measured in 1000 μm² samples within the measured optic nerve zones as shown in the inset. The abscissa represents axon diameter ranges into which the counts were subdivided. The range 0.2 relates to all fibres with sheath diameters of 0.2 units or less. The values below each range are means for the samples from left or right eyes. Figures 7A and 7B present similar data from the centre of this optic nerve.

Figure 8 shows a cross section of the left optic nerve 4 mm behind the disc and cup, from female 950. Losses from the central regions of the section are clear. Some abnormal axons remaining showed profoundly low stain uptake. Axon debris and unstained margins could be identified but did not reproduce photographically.

The left optic nerve, dorsal ventral diameter was 2.81 mm and horizontal was 2.3 mm. In the total area of measurement we found 52 027 axons in 0.307 mm² of tissue. From this our Zeiss IBAS system calculated that the whole nerve (5.08 mm²) contains approximately 860 000 axons. This is notably fewer than in the total of axons in the right optic nerve (C/D=0.4 with little pallor) where 1.22 million total axons were calculated. Potts *et al*²⁴ counted each fibre in sections of rhesus optic nerve and obtained totals of about

Figure 7 Central optic nerve axon size spectrum of POAG female 950. Otherwise as Figure 6. (A) Dorsal centre. (B) Ventral centre.

1.6 million. Also using the Zeiss IBAS system, Sanchez¹⁶ reported about 1.2 million axons in a normal, cynomolgus macaque (*Macaca iris*) optic nerve.

Calculations on the Sanchez *et al*¹⁶ data show that 28% of the axons are >1 μm in diameter in

the normal eye. By comparison, our rhesus 950 optic nerve samples showed only 16% of the fibres >1 μm in diameter in naturally occurring, progressive POAG. We found moderately reduced axon densities at various sites on the left optic nerve face, except in the superior central and superior peripheral portions of the left samples where counts were reduced by 50% or more.

Discussion

The Puerto Rican monkeys' ocular pressures have been studied before. A sample of 114 animals from Cayo Santiago and La Cueva island was measured by Bito *et al.*²⁰ They report a mean IOP of 14.9 (SD 2) mm Hg, which is 2 mm Hg below those we report. Since the La Cueva colony no longer exists and several whole Cayo matriline have been sold in recent years, it is unlikely that animals from their 1979 study are included in our sample. Nevertheless, neither set of measures are significantly different from human (for example, refs 17 18). Bito *et al.*²⁰ reported no evidence of optic disc cupping or other glaucomatous changes in their samples of the Cayo rhesus population.

Authoritative reviews of the principles and concepts involved in classification and treatment of human glaucomas have been provided by a number of authors. Newell²⁵ states that, 'glaucomas are a family of ocular diseases in which increased IOP may cause optic atrophy with excavation of the optic disc and characteristic loss of visual field'. This definition includes both open angle and closed angle glaucomas. In a schematic presentation of POAG classes, Newell lists low tension glaucoma (LTG) among others but provides no detail. Chandler and Grant²⁶ describe glaucoma as a disease characterised by IOP, 'sufficient to cause either temporary or permanent impairment of vision'. They treat LTG briefly – 'in uncommon so-called low-tension glaucoma the intraocular pressure may not be abnormally high'. However, they comment that the other signs/symptoms of the disease may be the same as are found in high tension glaucoma. More recently, Werner²⁷ traces the identification of LTG to Von Graefe in 1857 and provides a table which compares the prevalence of glaucoma with normal IOP to open angle glaucomas. Seven publications are listed, totalling 860 diagnoses. The average percent incidence of low pressure glaucoma was 43% (SD 12%). The lowest percentage reported in 45 glaucoma patients was 6.7 with the highest reported as 68% of 189 diagnoses of glaucoma. From this, we have adopted a multifactorial criterion for the identification of glaucoma in the rhesus macaque.

In the absence of macular or intracranial disease, the standard for POAG diagnosis is the progressive loss of optic nerve fibres. Also used is retinal functional loss and subsequent clinically detectable excavation of the optic disc. When data on optic nerve fibre loss are not available, we accept abnormal cup/disc ratios with the reduction of visual function as an indicator of inner retinal pathology and/or optic nerve damage. In view of the recent thinking prompted by the

Figure 8 Low magnification photomicrograph of a transverse section of the left optic nerve of rhesus 950 (C/D=0.7). Vertical diameter is about 2.3 mm. Plastic embedding, toluidine blue stain.

coalescence of data on the 'high' incidence of low pressure glaucoma in humans,²⁷ the presence or absence of hypertension (≥ 22 mm Hg) is of interest to us but is not required to diagnose glaucoma in the rhesus monkey. In this respect it is interesting that normotensive monkey I91 is the offspring of hypertensive 950 (Fig 2A).

As in humans, large scale screening for glaucoma is most efficiently pursued by heavy dependence on applanation tonometric measurements. We managed our large scale CPRC screening of the Cayo Santiago rhesus population in this way and with ophthalmoscopy obtained a great deal of data in a short period of time (Fig 1). Electrophysiological measurements of field losses were impossible with the tropical island conditions but were done on representative animals that were shipped to Florida as a courtesy by CPRC. In the laboratory, estimation of loss of rhesus visual function by the stimulation of the retina with gratings requires slightly less time (about 8 minutes, independent of anaesthesia and preparation) than automated perimetry in humans. Data from normal female A25 in Figure 4A are typical of the resolution/sensitivity we have seen in the past^{6,11} in the presence of good physiological optics. There is usually a STF that displays a minimum around 5 minutes of arc, a peak and reduced output at the largest grating sizes. The response magnitude of the eye signal is always greater than the cortical signal. However, the tuning and peak of the cortical signal is usually more developed. The general shape and amplitude of the right eye signals (C/D=0.7) from normotensive I91 were comparable with A25 (C/D=0.3) when I91 was first tested in 1990 (Fig 4A). There was a decline of about 50% in the central 30° field of the right eye signal with re-evaluation in 1992 (Fig 4B). In addition to the signal loss there was a shift of the tuning peak towards lower spatial frequencies. The left eye (C/D=0.4) changed very little.

However, the right eye's field losses (C/D=0.7) are not equal in all retinal areas. Figure 5 shows that the least progression occurred in the central 15 degrees and the greatest loss (about 60%) in the toroidal shaped periphery. Typical early progression of human POAG is often more evident in the mid peripheral fields. Earlier (1990) test results for I91 compare favourably (Fig 5) with those from normal female A25 where C/D is about 0.3. I91 cup dimensions changed minimally during the 2 year period; pallor was difficult to quantify. Function of the I91 left eye (C/D=0.4) did not change and remained comparable with the results from normal A25 (Fig 5).

In his review,²⁸ Schwartz considers enlargement of optic disc cupping as a common normal phenomenon often associated with aging. However, when pallor develops, visual field loss generally occurs. He considers 50% pallor as the upper extent of normality. In his drawings and figures pallor and cupping are highly correlated. He recommends patients with asymmetric pallor/cupping as 'suspect' glaucomatous patients. The pronounced pallor and cupping of the optic nerve head or its normal diameter which we see in I91 is not explained by the normal axial intraocular distance measured by ultrasound or by the normal corneal curvature

measured by keratoscope. Further, there was no evidence on MRI scan of an intracranial phenomenon (neoplasm or aneurism) that might contribute to I91's right optic nerve head abnormality (Fig 3). Aside from C/D, I91 appeared clinically normal.

If it is valid to apply human clinical criteria to the diagnosis of glaucoma in other primates, it seems certain that glaucoma is a significant factor in the visual health of certain Cayo Santiago macaque matriline. We have demonstrated the pressure component, the familial cluster component mentioned by several authors,^{29,30} the abnormal cup/disc ratio component, the normal angle, and the field loss diagnostic components typical of human POAG. In the case where the pathology data were available in female 950, we find an overall loss of approximately 25% of the optic nerve fibres in her left eye compared with published normal numbers in related macaque strains. Further, her left eye had a significantly lower optic nerve axon count than her right eye, which had 1.2 million fibres and a normal cup/disc ratio. It is interesting that significant loss appears in the large fibre portion of the spectrum as reported in the early histopathology of cases of human POAG by Quigley *et al.*¹⁷

Accurate animal models of human disease can be very useful. Yet, modelling of human spontaneous glaucoma has been limited. One useful model of POAG has been developed as an autosomal recessive trait in a strain of beagle dogs by Gelatt.³¹ Buphthalmic rabbits have been known for some time but have received relatively little attention.³² The older literature on the features of experimentally induced glaucoma is reviewed by Kalvin *et al.*³³ who produced ocular hypertension in owl monkeys by the injection of α chymotrypsin into the anterior chamber. More recently, Quigley and Hohman¹⁵ have succeeded in more controlled reduction of outflow by damaging the trabecular meshwork of cynomolgus monkeys with lasers to produce a partial functional angle closure with fluctuating elevations in IOP.

The implications of these models using induced angle closure glaucomas (IAG) for LTG or even POAG are not yet clear, although Quigley *et al.*¹⁷ have shown parallels between the monkey IAG pathology and the human optic nerve condition in POAG.³⁴ Fischer *et al.*³⁵ have reported that there is frequent spontaneous recovery from hypertension in this model after about 1.5 years. There does not appear to be a common human parallel to this phenomenon.

In the laser induced glaucoma monkey model, large diameter optic nerve axons were found to be damaged more easily than smaller axons in both the least and best preserved areas of the nerve.¹⁷ The data indicated that fibres with a diameter from 0.35 to 0.75 μ m survived better in the widely fluctuating elevations of IOP found in the IAG model, than fibres with diameters from 0.85 to 1.25 μ m. Study of 10 optic nerves from this model indicated a preferential loss (broad size range) of axons at the superior and inferior regions of the nerve head. The least damaged areas were found to be in the temporal centre, with the most severe damage localised to the nasal periphery of the superior and inferior

poles. The optic nerve damage to CPRC monkey 950 with naturally occurring POAG was most severe in the superior nasal quadrant with a 50% or larger reduction in the fibres smaller than 0.8 μ m and only slight reduction in the larger diameter fibres. The superior central regions of the nerve were similarly affected. The inferior peripheral and central areas were less affected than the superior regions, although the largest fibres in the inferior peripheral area were markedly reduced in number.

There are also reports of complex pathophysiology other than optic nerve fibre loss when IOP is elevated in (otherwise) normal eyes.^{36,37} Although in the past local ischaemia seemed to be related to early IAG,³⁸ a reliable relationship between vascular phenomena and low tension human glaucoma has not been clear³⁹⁻⁴¹ until recently.^{42,43} As more tissue from monkeys with naturally occurring POAG becomes available, it will be interesting to see if the other monkeys also demonstrate widespread loss of small diameter fibres as compared to larger axons. This naturally occurring disease, with its insidious elevations of IOP, may not be identical with the laser induced primate glaucoma model.

In view of the frequency of LTG,²⁷ an increment in the relative priority of LTG may be justified. A computer search of the world literature from 1985-90 yielded 3855 entries on the topic 'glaucoma'; of these 95 (2.5%) included 'low tension', 'lower pressure', or 'normotensive' in the abstract or as a key word. The errors involved in this literature search technique notwithstanding, an underemphasis on LTG is suggested.

The finding of open angle glaucomas (both high tension and low tension) and numbers of ocular hypertensive individuals in the Cayo Santiago macaque is very encouraging for the development of new diagnostic techniques, treatments, and the genetic study of these important human eye diseases. The relatively rapid aging of the macaque makes the study of decades of glaucoma progress a practical component of laboratory research not previously available.

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