ANIMAL MODEL OF HUMAN DISEASE

Primary Open Angle Glaucoma

Inherited Primary Open Angle Glaucoma in the Beagle

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Biologic Features

Primary open angle glaucoma in man is a leading cause of blindness and visual impairment in the United States. This type of glaucoma is the most frequent in human adults, occurring in 2% of the population over 40 years of age. Blindness resulting from glaucoma is estimated to occur in 0.5% of persons in the United States.[1]

Investigations in glaucoma have been hampered by a lack of suitable spontaneous animal models. Past experimental methods to produce glaucoma in laboratory animals yielded variable results; some methods failed, while others produced transient to prolonged elevations in intraocular pressure. Unfortunately all methods resulted in varying amounts of inflammation.[2]

Recently glaucoma following the intraocular injection of α-chymotrypsin in rabbits, owl monkeys, and dogs was investigated, following reports of a transient elevation in intraocular pressure in man after intracapsular extractions with α-chymotrypsin.[3-5] Experimental glaucoma was produced in the rhesus monkey by repeated circumferential argon laser photocoagulation of the trabecular meshwork area of the anterior chamber angle[6] and intracameral injections of autologous fixed red blood cells.[7]

Spontaneous glaucoma in the New Zealand rabbit has been studied for nearly two decades, although reported in 1886. The glaucoma appears associated with congenital goniodysgenesis.[8]

Since 1972 our laboratories have established a strain of beagles with glaucoma.[9] Breeding experiments, still in progress, suggest an autosomal recessive inheritance. The elevation in intraocular pressure develops bilaterally in beagles at 1-2 years of age; tonographic recordings and constant pressure perfusions indicate a concurrent reduction in the coefficient of aqueous humor outflow.

Intraocular pressure, as measured by applanation tonometry, reveals a chronic insidious glaucoma (IOP 30 to 40 mm Hg). Mean coefficients (μl/mm Hg/min) for aqueous outflow in normal dogs are 0.24 (SD $\pm$ 0.07) compared to 0.13 (SD $\pm$ 0.05) in beagles with glaucoma at 4-6 months of age, which eventually decreases to 0.07 (SD $\pm$ 0.03) at 31-36 months of age. Gonioscopically the disease has two phases: open iridocorneal angle during the onset and the first 2-4 years of the disease and closed iridocorneal angles associated with lens subluxation and displacement from the patella fossa.[10-12]

Changes of the optic disc include cupping and eventually atrophy. Buphthalmia, cataract formation, vitreous syneresis, and eventually phthisis bulbi are additional effects.

Beagles with glaucoma have also demonstrated greater sensitivity to selected drugs that reduce intra-

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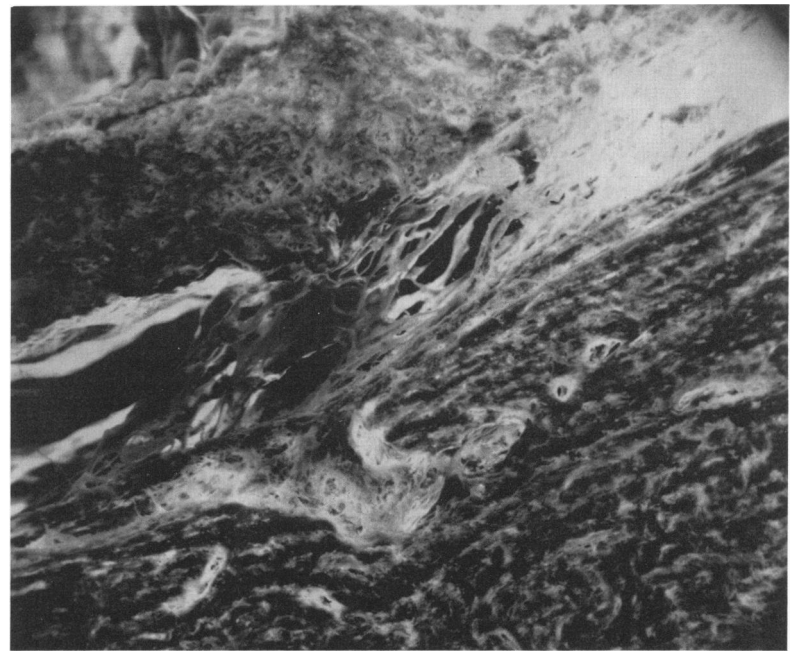

Figure 1—Sagittal section of a 32-month-old beagle with glaucoma. The iridocorneal angle and sclerociliary cleft are open and the trabecular meshwork is normally developed. (SEM, × 131)

ocular pressure, eg, pilocarpine, epinephrine, dipivalyl epinephrine, acetazolamide, ethoxzolamide, methazolamide, and dichlorphenamide.[13-16] Intraocular pressure in these affected dogs decreased to a greater extent in both mm Hg and percentage of drop than normal dogs. Water loading also produces abrupt elevations in intraocular pressure of a greater magnitude and a longer period of time than in normal control Beagles.[17] Serum cortisol in beagles with glaucoma is higher than control dogs but within the normal range for the radioimmunoassay test. These slightly increased cortisol levels coincided with increases in the diurnal changes in intraocular pressure in the glaucomatous beagles.[17]

The cause for the initial elevation in intraocular pressure has not been ascertained by light microscopy and scanning electron microscopy.[19] The iridocorneal angle appears normally developed and devoid of

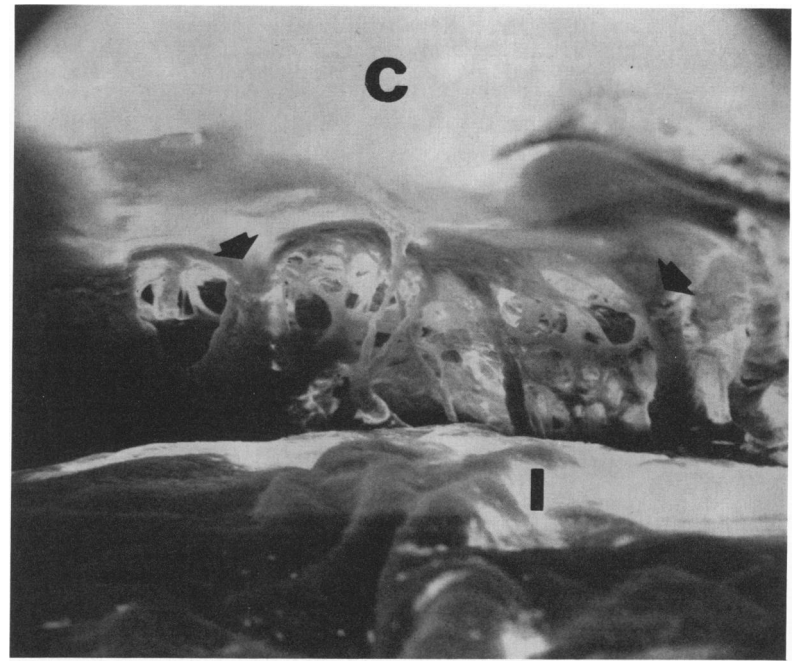

Figure 2—Frontal section of a 32-month-old beagle with glaucoma. The iridocorneal angle is open and pectinate ligaments normal (*arrows*) I = Iris; C = posterior cornea. (SEM, × 125)

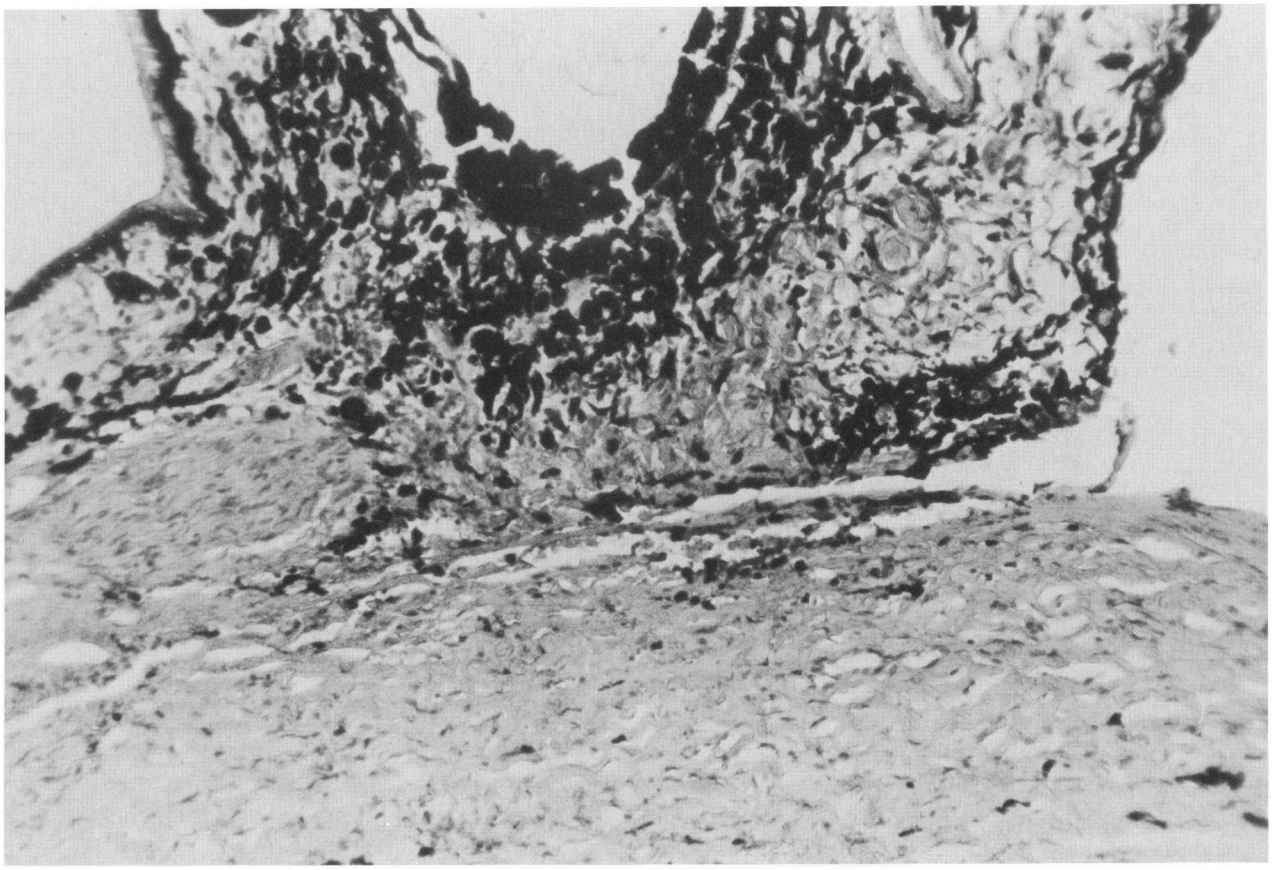

Figure 3—Advanced glaucoma in a beagle with a closed iridocorneal angle and collapsed sclerociliary cleft. (H&E, × 132)

congenital anomalies (Figures 1 and 2). Additional light-microscopic, histochemical, and transmission electron-microscopic studies are in progress.

As the glaucoma progresses, the iridocorneal angle closes and the sclerociliary cleft collapses (Figure 3). Peripheral anterior synechiae attenuate the outflow channels. These changes also impair the outflow of aqueous humor through the conventional trabecular and the unconventional uveoscleral pathways.

Other microscopic changes in moderately advanced glaucoma include optic atrophy with extensive demyelination, infiltration with pigment cells, excavation of the optic disk, and prominence of the optic nerve septums.

Comparison With Human Disease

Because the dog exhibits spontaneous glaucoma, second in frequency to that in humans, investigation in this species is timely. Inherited glaucoma in beagles is similar to primary open angle glaucoma in man initially and later in the advanced disease to chronic narrow angle glaucoma. Possible corticosteroid metabolic changes in beagles with glaucoma may be useful for further investigations, because persons with primary open angle glaucoma also exhibit corticosteroid metabolic abnormalities.

Usefulness of the Model

Aqueous dynamics and outflow pathways and vascular routes have been investigated in the dog only recently. The dog has an intrascleral plexus, rather than Schlemm's canal. The significance of this anatomic difference is unknown and may be minor, because the site of impediment for aqueous humor outflow may involve predominantly the trabecular meshwork.

The use of dogs with spontaneous glaucoma may permit essential studies of aqueous humor dynamics, outflow pathways, pharmacologic trials, and changes in the optic disk and nerve that occur in glaucoma.

Availability

Colony size is limited; however, cooperative studies with other investigators may be possible with ongoing studies.

References

1. Kolker AE, Hetherington J Jr: Becker's and Schaffer's Diagnosis and Therapy of the glaucomas. 4th edition. St. Louis, C. V. Mosby, 1976
2. Gelatt KN: Animal models for glaucoma. Invest Ophthalmol Vis Sci 1977, 16:592–596
3. Lessell S, Kuwabara T: Experimental alpha chymotrypsin glaucoma. Arch Ophthalmol 1969, 81:853–864
4. Sears D, Sears M: Blood-aqueous barrier and alpha chymotrypsin glaucoma in rabbits. Am J Ophthalmol 1974, 77:378–383
5. Barrie KP, Gelatt KN, Gum GG, Merideth RE: Alpha chymotrypsin glaucoma in the dog. Invest Ophthalmol Vis Sci 1980, 19 (Suppl):123
6. Gaasterland D, Kupfer C: Experimental glaucoma in the rhesus monkey. Invest Ophthalmol 1974, 13: 455–457
7. Quigley HA, Addicks EM: Chronic experimental glaucoma in primates. Invest Ophthalmol Vis Sci 1980, 19: 126–136
8. Kolker AE, Moses RA, Constant MA, Becker B: The development of glaucoma in rabbits. Invest Ophthalmol 1963, 2:316–321
9. Gelatt KN: Familial glaucoma in the beagle dog. J Am Anim Hosp Assoc 1972, 8:23–28
10. Gelatt KN, Peiffer RL Jr, Gwin RM, Sauk J Jr: Glaucoma in the beagle. Trans Am Acad Ophthalmol Otolaryngl 1976, 81:636–643
11. Gelatt KN, Peiffer RL Jr, Gwin RM, Gum GG, Williams LW: Clinical manifestations of inherited glaucoma in the beagle. Invest Ophthalmol Vis Sci 1977, 16:1135–1142
12. Gelatt KN, Gwin RM, Peiffer RL Jr, Gum GG: Tonography in the normal and glaucomatous beagle. Am J Vet Res 1977, 8:515–520
13. Gwin RM, Gelatt KN, Gum GG, Peiffer RL Jr: Effects of topical 1-epinephrine and dipivalyl epinephrine on intraocular pressure and pupil size in the normotensive and glaucomatous beagle. Am J Vet Res 1978, 39: 83–86
14. Gwin RM, Gelatt KN, Gum GG, Peiffer RL Jr, Williams LW: The effect of topical pilocarpine on intraocular pressure and pupil size in the normotensive and glaucomatous beagle. Invest Ophthalmol Vis Sci 1977, 16:1143–1148
15. Gelatt KN, Gum GG, Williams LW, Gwin RM: Ocular hypotensive effects of carbonic anhydrase inhibitors in normotensive and glaucomatous beagles. Am J Vet Res 1979, 40:334–345
16. Whitley RD, Gelatt KN, Gum GG: Dose-response of topical pilocarpine in the normotensive and glaucomatous beagle. Am J Vet Res 1980, 41:417–424
17. Gelatt KN, Peiffer RL Jr, Jessen CR, Gum GG: Consecutive water provocative tests in normal and glaucomatous beagles. Am J Vet Res 1976, 37:269–273
18. Chen CL, Gelatt KN, Gum GG: Serum hydrocortisone (cortisol) values in glaucomatous and normotensive beagles. Am J Vet Res 1980, 41:1516–1518
19. Peiffer RL Jr, Gelatt KN: Aqueous humor outflow in beagles with inherited glaucoma: Gross and light microscopic observations of the iridocorneal angle. Am J Vet Res 1980, 41:861–867