Animal models for glaucoma

The scientific community has for several decades recognized the value of animal models as substitutes for the study of human diseases. The similarity of the disease process in the animal may have differed in some aspects from that in man but frequently provided additional information and understanding relative to the human counterpart. Animal models with either induced or spontaneous diseases often permit extensive and invasive investigations not usually possible in the human patient. Current limitations and possible future, more stringent constraints on investigations involving human patients accentuate the need to develop animal models, especially those with spontaneous diseases that closely mimic the human syndrome.

The search for animal models with different types of glaucoma has not been highly fruitful. Most studies have utilized the rabbit and to a lesser extent subhuman primates. The dog has attracted attention more recently. It can be argued that the iridocorneal angle anatomy of most animal species, except for subhuman primates, differs extensively from that of man. Phylogenetically, the development of iridocorneal angle structures has been ranked from Rodentia (rabbit and rat), Ungulata (ox and pig), Carnivora (dog and cat), to Primata (subhuman primate and man).[1] Although the iridocorneal angles of the many animal species possess overt topographic differences such as pectinate ligaments, limited ciliary body musculature, and the scleral venous plexus (instead of Schlemm's canal), they all have a continuous endothelial lining of the aqueous outflow channels like those of man.[2] Davson[3] commented, "There is nothing in the physiological phenomena associated with the passage of material into, and out of, the anterior chamber that permits us to draw a sharp line of distinction between the primates and the lower mammals."

Investigators have subjected the animal eye to a variety of insults to induce glaucoma since as early as 1870. Some methods failed; others produced transient to prolonged elevations of intraocular pressure. Most of the methods produced varying amounts of inflammation and abrupt elevations in intraocular pressure. Techniques to block outflow channels from the anterior chamber included the injection of air, methylcellulose, bacteria, cotton fragments, mineral oil, and other substances. Methods to impede the "outer" aspects of aqueous humor outflow included ligation of individual vortex veins, ligation of all blood vessels posterior to the globe, and diathermic and chemical cautery of the subconjunctival tissues at the limbus. Other techniques which produced varying amounts of intraocular inflammation included blunt trauma to the globe, encircling rubber bands about the equator of the globe, and aqueous chamber paracentesis with mechanical stimulation of the iris.

The observations of a transient elevation in intraocular pressure in man after cataract extraction has recently stimulated research in experimental glaucoma, associated with intraocular alpha-chymotrypsin in rabbits and owl monkeys. Pathogenesis of the enzyme glaucoma has been attributed to blockage of the trabecular meshwork by lysed zonular material as well as atrophy of the ciliary body in primates.[4] The enzyme

in dead human eyes did not affect aqueous outflow resistance. Blockage of the outflow channels by trabecular precipitates is apparently the primary mechanical impediment, although the enzyme can produce a reasonably intense iridocyclitis.

The alpha-chymotrypsin glaucoma in rabbits also provides an experimental model to study long-term effects of elevated intraocular pressure.[5] In addition to the initial intraocular inflammation associated with the enzyme injections, lens dislocations and vitreous disturbances are also associated with the glaucoma.

Experimental glaucoma was recently produced in the rhesus monkey by repeated circumferential argon laser photocoagulation of the trabecular meshwork area of the anterior chamber angle.[6] Although the two to four treatments initiated a mild to moderate iridocyclitis, seven of the 10 treated eyes developed elevated intraocular pressure. Outflow facility, as determined by in vivo constant-pressure perfusion, was impaired and ranged from 0.02 to 0.11 μl/min./mm. Hg (normal values: 0.33 to 0.75 μl/min./mm. Hg). Histopathologic examination revealed localized scarring of the anterior chamber structures. The retinal and optic nerve changes perhaps were most remarkable and simulate those of human glaucoma.

This experimental glaucoma will probably be most useful for the study of posterior segment changes. The extensive iridocorneal angle scarring will, for the most part, minimize many physiologic and pharmacologic studies affecting aqueous outflow. The subhuman primate is typically difficult to handle and expensive to maintain.

Glaucoma can be induced in chickens by exposure of chicks during rearing to continuous light (20 L/OD).[7] Light-induced avian glaucoma is associated with increased eye weight and diameter, reduced corneal curvature, impaired outflow facility, and elevated intraocular pressure. Eye enlargement and refractive errors are detectable several weeks before outflow facility is impaired, and intraocular pressure is elevated still later in the disease process. Affected birds exhibit reduced aqueous flow, reduced corneal lactic dehydrogenase (LDH), and increased aqueous humor LDH. The pathogenesis of light-induced avian glaucoma is unclear, but the disease can be reproduced at will in the laboratory.

Animals with spontaneous glaucoma have been infrequently identified and even less frequently developed into effective models. Buphthalmia in the rabbit has received most of the attention, perhaps because of the preoccupation of ophthalmic research in this species. More recent investigations in the dog indicate additional promising models. Perhaps, in the search for animal models with glaucoma, the dog has inadvertently been overlooked and may represent the prime source since this species exhibits, at least clinically, most of the types of glaucomas that occur in man. The frequency of the glaucomas in the dog, based on presentations to veterinary medical teaching hospitals of the colleges of veterinary medicine in North America, is 0.05% or 1 case for every 204 patients presented.

An ideal spontaneous glaucoma animal model should exhibit at least the following characteristics. (1) The animal should be easy to maintain in a laboratory environment and (2) easy to handle without special equipment and sedation. (3) The glaucoma should be transmitted by a simple mode of inheritance without other additional objectionable traits. (4) The glaucoma should exhibit a predictable onset and clinical course and (5) should have a reasonably long course before destruction of the eye, thereby permitting various anatomic, physiologic, pharmacologic, and pathologic studies.

Of the animal models with spontaneous glaucoma, buphthalmia in rabbits has yielded the most information to date because of the most extensive research. Buphthalmia in rabbits appears to have been described as early as 1886 by Schloesser.

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Since then several investigators have reported on the disease. Buphthalmia in the rabbit is inherited as an autosomal recessive trait as a semilethal condition. Affected animals exhibit reduced offspring per litter, higher mortality, and about 20% incidence of other congenital anomalies (hydrocephalus, prognathism, microphthalmia, herniation, limb and/or sacral abnormalities, strap ovary, flexed tail, etc.) suggesting that the buphthalmia is part of a systemic developmental defect. The disease is exhibited bilaterally (68%) as well as unilaterally (32%) and occurs in both the albino and, to a lesser extent, the pigmented rabbit.

The glaucoma is believed to be of the congenital type because of undifferentiated uveal tissues in the iridocorneal angle. The disease exhibits elevated intraocular pressure, impaired outflow facility (by tonography and perfusion), and corneal enlargement.[8] Aqueous outflow is impaired early in the disease even before elevation of intraocular pressure. Hyposecretion of aqueous humor appears to occur during this phase, perhaps to compensate for the outflow impairment. As this mechanism fails, intraocular pressure gradually elevates, with development of buphthalmia and other changes. Tonographic studies of water loading in the buphthalmic rabbit result in greater pressure elevations and fall in the outflow facility.

Aqueous humor ascorbate concentrations are lower than normal in buphthalmic rabbits with and without clinical signs. Aqueous ascorbate levels progressively decrease as the disease worsens. The relationship of aqueous ascorbate levels to the pathogenesis of buphthalmia is unclear.

Spontaneous glaucoma has been primarily investigated in the dog in three breeds: American cocker spaniel, basset hound, and the beagle. Glaucoma in the American cocker spaniel is generally believed the primary narrow-angle type. Persistent solidification of focal areas of pectinate ligaments can also occur but have not been related directly to the disease.

Glaucoma in the cocker occurs in dogs from 6 to 13 years of age and in both sexes. Attempts to produce affected offspring from glaucomatous patients have not been reported. Preliminary water provocative responses as well as tonographic results indicate differences compared to controls. The disease clinically is exhibited as an acute congestive glaucoma, although the history may signal brief, intermittent episodes of mild "attacks." On the basis of present information, the American cocker spaniel has not to date emerged as a good animal model for studying glaucoma.

Glaucoma in the basset hound has been classified as a congenital type because of persistence of large, heavily pigmented bands of mesodermal tissues spanning the basal iris to the peripheral cornea.[9] Congenital glaucoma in the basset hound is familial; results of inheritance studies are still in progress. Gonioscopy in a basset colony maintained for glaucoma research revealed 63% of the iridocorneal angles contained mesodermal dysgenesis. However, these dogs are normotensive despite the abnormal angles. Outflow analyses by tonography and perfusion experiments in these anomalous angles have not been reported. The disease clinically has been divided into two general groups: acute congestive glaucoma and chronic glaucoma.

Glaucoma was first described in the beagle in 1972 in nine closely related dogs with advanced glaucoma.[10] Since then a colony of over 50 glaucomatous beagles has been investigated. Sixteen affected × affected matings have yielded 54 affected offspring. Other matings to laboratory-quality beagles support a simple autosomal inheritance, although the heredity studies are still incomplete.[11]

On the basis of gonioscopic examination, the glaucoma process in the beagle occurs in two distinct phases: (1) open-angle glaucoma and (2) approximately 1 to 2 years later, narrow- to closed-angle glaucoma. The glaucoma lasts 2 to 3 years before destruction of the eye, thereby per-

mitting other variable and serial numbers of investigations.

The first report of the nine affected beagles detailed advanced glaucoma, lens luxations, and even phthisis bulbi. In the laboratory these changes required 24 to 36 months to develop. Initial elevations in intraocular pressure occur in beagles at 6 to 18 months of age, with open iridocorneal angles and in the absence of other ocular abnormalities. Extensive persistent sheets of pectinate ligaments (mesodermal dysgenesis) have not been observed in the beagle. As the glaucoma progresses for 1 to 2 years, the lens dislocates, and the iridocorneal angle gradually closes.

Consecutive tonographic studies in the offspring of affected beagles indicate normal aqueous outflow for the first 6 to 12 months and then a gradual decrease in the coefficient of aqueous outflow until the end of the disease process.[12] Mean coefficients (μl/min./mm. Hg) for aqueous outflow are as follows: in normal dogs, 0.24 (S.D. ± 0.07), in preglaucomatous 4- to 6-month-old beagles, 0.13 (S.D. ± 0.05), in 19- to 24-month-old glaucomatous beagles, 0.08 (S.D. ± 0.04), and in 31- to 36-month-old glaucomatous beagles, 0.07 (S.D. ± 0.03). Preliminary constant-pressure perfusion studies support the tonographic results.

The clinical disease in the beagle is a chronic insidious glaucoma (IOP about 40 mm. Hg) with occasional acute further elevations (IOP 60 to 80 mm. Hg). Cupping of the optic disc also occurs in the beagles but appears delayed, perhaps because of stretching of the ocular tunics associated with mild buphthalmia.

The glaucomatous beagle eye is also sensitive to the common drugs that affect aqueous humor formation and outflow. Pilocarpine, epinephrine, and dipivalyl epinephrine as well as acetazolamide and dichlorphenamide reduce intraocular pressure in the affected beagle. Water loading in the beagle also elevates intraocular pressure above that of control dogs.

The glaucomatous beagle is the first breed of dog to exhibit an inherited glaucoma. Initial studies indicate impaired aqueous outflow. The glaucoma appears as a combination of primary open-angle initially and closed-angle later, depending on the stage of the disease.

Animal models with spontaneous glaucoma can provide additional information relative to the genesis of the different types of glaucoma in man. Because the dog exhibits many types of glaucoma clinically, further exploration and development of canine glaucoma models are recommended. Glaucomatous animal models may also be utilized for pharmacologic studies at various stages of the disease with drugs that may affect aqueous outflow, formation, or a combination. Spontaneous models can also provide the basis to investigate the effects of elevated intraocular pressure on the ocular tissues for long periods of time without the superimposed effects of experimental procedures and inflammations.

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