The development of glaucoma in rabbits

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In an attempt to study the development of glaucoma in rabbits, animals with established glaucoma and buphthalmos were bred, and their offspring followed with tonography at monthly intervals. Findings indicated that: (A) The animals developing glaucoma, as determined by a corneal diameter of 17 mm. or more at 1 year of age, had elevated intraocular pressures at 5 to 6 months of age, and impaired outflow facilities as early as 3 months of age. (B) Animals with corneal diameters of 15 mm. or less at 1 year showed no pressure elevations, and had much higher outflow facilities throughout the first year of life.

In 1955, Constant and Becker noted the occurrence of elevated intraocular pressure and impaired outflow facility, both by tonography and perfusion, in rabbits with buphthalmos. In 1960, McMaster, working at the National Institutes of Health, reported the results of perfusion studies in eyes from 10 buphthalmic rabbits. Each of these eyes demonstrated a marked impairment of outflow, with the average facility of outflow measuring 0.10. In an attempt to learn more about the development of hereditary buphthalmia in rabbits, a strain of such animals has been bred. The original rabbits used for this purpose were obtained from McMaster, and were from the same stock as those used in his studies.

The study of buphthalmia in rabbits is not new. Reports have appeared in the literature since 1886 and many aspects of the disease have been well documented. The condition has occurred sporadically in normal strains of rabbits bred for commercial purposes. These animals were usually killed and not used for rebreeding. Several studies have indicated that the disease was hereditary, and Smith, in 1944, bred a strain of such animals. Similar strains have been bred by others, and the disease was felt to be transmitted as a semilethal recessive gene. Histologic sections of buphthalmic eyes showed lack of development and abnormalities of the angle structures, atrophy of the ciliary processes, and deep excavation of the optic disc. Clinically, the animals had elevated intraocular pressures and decreased facilities of outflow, thus resembling glaucoma in the human. By studying the development of glaucoma in a strain of rabbits and having large numbers of such animals available for experimental studies, it was hoped that much might be learned about the pathogenesis of the disease, the stages of its development, and the effects of therapy in its prevention or cure.

This is a preliminary report on such a study.
Method

The original animals used for breeding were adult buphthalmic rabbits. They were of the New Zealand strain, all albino, and were identical to those of the strain previously shown to have impaired outflow facilities by perfusion studies. All had corneal diameters of 17 mm. or more, and all demonstrated elevated intraocular pressure and decreased facility of outflow by tonography. Buphthalmic rabbits were bred to each other, and to normal albino and pigmented rabbits. The offspring of these rabbits were followed with measurement of corneal diameter and with tonography at monthly intervals. Tonography was performed under topical anesthesia with a Mueller electronic tonometer and a Leeds and Northrup recorder, as described by Becker and Constant. Animals followed for at least one year from birth have been included in the study.

Since all animals studied did not develop glaucoma, it was necessary to define glaucoma arbitrarily. Once this was done, animals which developed the condition could be compared at various stages of the disease with nonglaucomatous rabbits of similar age. As in human populations, an elevation of intraocular pressure was the most outstanding characteristic of the glaucoma. However, definitions of glaucoma in terms of pressure have been difficult to defend unless the pressure has produced damage. Pressures pathologic to the eyes of one individual have been tolerated for years without damage by other individuals. In glaucoma of human beings, therefore, the definition has been based upon cupping of the optic disc and loss of visual field. In rabbits, the glaucoma developed at an early age when the fibrous coats of the eye were relatively elastic, resulting in marked enlargement of the eye. Therefore, it was easier to define glaucoma on the basis of ocular enlargement.

The corneal diameters of normal rabbits obtained from commercial breeders were determined. No measure of corneal diameter above 15 mm. was found at 1 year of age. It was thus felt that the corneal measurement at age 1 year could be used as the criterion for separating glaucomatous and normal eyes. For purposes of this study, a normal eye was defined as one with a corneal diameter of 15 mm. or less at age 1 year. The glaucoma group was limited to those eyes with a corneal diameter of 17 mm. or more at or before 1 year of age. The borderline group of rabbits with corneal diameters of 16 mm. at age 1 year has been ignored in this study for

Fig. 1. A buphthalmic rabbit compared with a normal rabbit. Both animals are 1 year old.
purposes of clearer definition of two groups. Fig. 1 compares a buphthalmic eye with a normal eye in rabbits 1 year of age.

Since some growth of the normal rabbit eye continued during the second year of life, corneal measurements at 2 years of age might be a better determination of normalcy. At the present time, however, we have not studied enough rabbits followed for this length of time.

Having defined two groups of eyes at age 1 year, it was possible to compare the two groups at various ages and stages of development of the disease. Because the breeding of animals was done at Northern Illinois University, some rabbits with corneal diameters of 17 mm. or more were transferred before 1 year of age for further breeding, and tonographic data are available for only the first 9 or 10 months of the animals' life.

Results

At the present time data are available on 54 eyes with corneal diameters of 15 mm. or less at age 1 year, and 15 eyes with corneal diameters of 17 mm. or more by age 1 year. The progressive growth of the corneas in these two groups is shown in Fig. 2. As can be readily seen, the two groups are only insignificantly separated (t = 1.66, P > 0.10) at age 3 months, but become progressively more distinct at each succeeding measurement (at 1 year, t = 13.5, P < 0.001). This agrees well with the findings of other observers who have noted that the condition cannot be detected clinically at birth, and is usually not obvious until 3 or 4 months of age.

Fig. 3 is a graph demonstrating the average intraocular pressure of the normal and glaucoma rabbits from the age of 3 months to 1 year. Tonography is very difficult to perform earlier than 3 months of age. As can be seen, the intraocular pressure in both groups is essentially identical until about 5 months of age, when the glaucoma group begins to have marked pressure elevations. While occasional pressure elevations are present before this time, they tend to be intermittent and do not reach extremely high levels until about 5 to 6 months of age. Even beyond this age, fairly large fluctuations are seen, but as a rule the pressure is usually high. The normal eyes, on the other hand, show little change throughout the time of measurement.

Fig. 4 shows the facility of outflow, as measured tonographically, for the two groups. The normal eyes demonstrate a gradual slight decrease in outflow with age, but always maintain a facility above 0.20. The glaucomatous eyes, on the other hand, show marked impairment of outflow, even as early as 3 months of age, at a time...
when their intraocular pressures are normal. Some progression of the outflow impairment with age is suggested, but the number of animals is too few to state this with any certainty.

Discussion

The number of litters is too small and the number of animals in the colony too few to make any definite statements about the hereditary aspects of glaucoma in the rabbit. Some of our findings, however, offer confirmatory evidence to the findings of other investigators. None of the offspring from matings of buphthalmic with normal animals showed any evidence of glaucoma as determined by corneal diameter, intraocular pressure, and outflow facility. These "hybrid" rabbits, however, when bred back to their buphthalmic parent, produced both normal and buphthalmic offspring. This is indicative of recessive transmission.

Most authors feel that buphthalmos is a bilateral disease, but a recent report indicates that almost a third of cases are unilateral. The fifteen glaucoma eyes in this study are from 10 rabbits. There is bilateral buphthalmos in 5 animals. Unilateral buphthalmos, by the criterion mentioned, was present in none. The possible unilateral cases are in rabbits in which the second eye is in the intermediate range (16 mm. at age 1 year), or in which the animal died before 1 year of age with only one eye reaching 17 mm. At this time of death. Our numbers are too few to make any definite statement about unilateral cases, except that the majority of cases are bilateral.

The gene for transmission of this disease is said to be semilethal, and affected offspring frequently are less healthy and grow and breed more poorly than their normal littermates. Possible confirmation of this observation is the 25 per cent mortality in the offspring obtained in this series. While this is suggestive of a semilethal characteristic, it must be remembered that these animals have undergone repeated handling and testing at frequent intervals, and many have been transported several hundred miles at young ages. In an attempt to produce a healthier strain of animals, normal pigmented rabbits were bred to albino buphthalmic rabbits. As noted, all offspring of such matings were normal, although several were pigmented. On breeding these pigmented carriers back to buphthalmic rabbits, we have succeeded in obtaining one pigmented buphthalmic male rabbit. This animal is now about 9 months old, and has corneal diameters of 17 and 18 mm., right and left eye, respectively. Similar attempts in other laboratories have not been successful, but several authors have reported the occurrence of buphthalmos in pigmented rabbits.

Of primary interest at present is the progression of the disease process in eyes which develop glaucoma. The eyes that show glaucoma at 1 year can be detected by pressure elevations at 5 to 6 months of age and by impairment of outflow at 3 months of age, or earlier. At this early time of 3 months, no significant difference between normal and glaucoma in either corneal diameter or intraocular pressure can be measured.

The question must be raised as to why intraocular pressure is not elevated in the glaucomatous eye at a time when the facility of outflow is decreased. Hyposecre-
tion of aqueous humor would account for the tonographic findings. Evidence exists that buphthalmic eyes are in a state of relative hyposecretion. Smith\(^2\) demonstrated that the appearance in the anterior chamber of subcutaneously injected fluorescein was delayed in buphthalmic eyes. Greaves and Perkins\(^6\) noted the delayed appearance of Evans blue in the episcleral veins following the injection of the dye into the anterior chambers of such eyes. Auricchio and Wistrand\(^1\) demonstrated that while in normal rabbit eyes the aqueous was hypertonic compared to the plasma, in buphthalmic eyes this osmotic gradient was eliminated, suggesting that the reduced flow allowed prolonged time for equilibration over the blood-aqueous barrier.

The present findings also suggest a possible series of events resulting in the final condition of buphthalmos. That the ability of aqueous to leave the eye is markedly impaired very early in life, possibly at birth, seems established. This is also suggested by histologic studies of the angle structures in the newborn offspring of buphthalmic rabbits.\(^6\) Under these circumstances, normal intraocular pressure can exist only when marked hyposecretion is present to compensate for this reduced outflow. At about 4 to 6 months of age, the compensatory mechanism either becomes deficient, or the outflow becomes even further embarrassed so that the compensatory mechanism is less effective, and pressure elevation occurs. This is associated with enlargement of the globe and the typical picture of buphthalmos. With outflow facilities as low as those measured, slight changes in secretory rate result in large changes in intraocular pressure. These fluctuations have been noted on repeated testing at frequent intervals.

Familial human chronic simple glaucoma often develops in a manner similar to that described above. An impairment of outflow is at first compensated by hyposecretion. As this mechanism fails, pressure elevation develops, and is eventually followed by ocular damage in the form of cupping and field loss. Studies of families of patients with chronic simple glaucoma have demonstrated impairment of outflow facility in a high percentage of close relatives at time when their intraocular pressures are normal.\(^2\)

There are a number of experiments planned on glaucomatous rabbits, assuming a sufficiently large stock can be maintained. These studies include the effects of miotics to one eye on the prevention of ocular damage, the ability of long-term secretory inhibition to prevent the development of buphthalmos, and the role of unilocular operations of various types. Studies are planned for the earlier detection of the glaucomatous eye, including water provocative tests, suction cup tests, etc. It is already known that topical steroids have no effect on these eyes when given three to four times daily for as long as 3 months.\(^5\) This is in contrast to their marked effects in adult human chronic simple glaucoma.\(^4\)

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REFERENCES