Cataract-webbed trait in *Peromyscus*

II. Biomicroscopy and histology of eyes

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A longitudinal biomicroscopic study of lenses and fundi of over 2,000 Peromyscus maniculatus *(deer mice) which have cataracts as an autosomal recessive trait has been correlated with histologic development of cataracts. By selective breeding, early-onset cataracts (Type I), which are frequently associated with abnormal closure of the fetal fissure and hyaloid vascular abnormalities, have been separated from later-onset (Type II) cataracts, which are more heterogeneous. Type I cataracts occur in syndactylous deer mice, develop rapidly, and histologically may show backward migration of disrupted lens bow cells before lens opacity is apparent biomicroscopically. Posterior subcapsular cataracts then develop and spread centrally and inferonasally to the equatorial area and then to the entire equator. The nucleus opacifies in either a "shell" pattern or as isolated dots. Anterior cortical opacification progresses to mature cataract. Histologically, abnormal migration and proliferation of lens epithelium and enlargement and vacuolar degeneration of the basal (posterior) processes of cortical lens fibers are early changes in Type I cataracts. Disruption of the lens bow with failure of differentiation and inward turning of lens epithelium to become lens fibers occurs concurrently. Type II cataracts may follow the developmental pattern of Type I but are rarely associated with severe hyaloid vascular abnormalities and progress more slowly. About 6% of animals develop diabetes, which is not associated with the cataract-webbed trait.*

Key words: cataract, coloboma, diabetes, hyaloid, lens, *Peromyscus*, persistent hyperplastic vitreous, retinal dysplasia

Cataracts in the deer mouse, *Peromyscus maniculatus*, were first discovered by Huestis.[1] He established that the cataracts were inherited as an autosomal recessive trait associated with syndactyly or webbed toes on the hind feet; thus the name cataract-webbed *(cw/cw)*.[2, 3] The histologic appearance of some stages of cataract development was described in a preliminary report.[4] This report describes the biomicroscopy and histology of whole eyes of normal and *cw* deer mice. Two subpopulations of deer mice have been separated and characterized: Type I, which has an early onset of cataract and multiple congenital anomalies of the eye, and Type II, which has a later onset of cataract and may not show the congenital abnormalities of the eye or toes.

Materials and methods

Maintenance, selection, and breeding techniques have been described.[3] Eyes were examined with a Bausch and Lomb slit lamp after pupillary dilatation with a 1:1 mixture of 1% atropine sulfate and 10% phenylephrine aqueous solutions. The vitreous cavity and fundus were examined by placing the eye in contact with a Hruby lens through a thin film of saline. Biomicroscopy is difficult but possible shortly after the eyes open at

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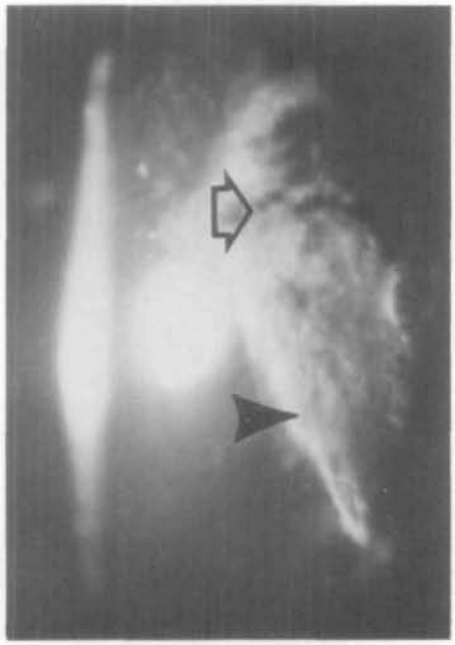

Fig. 1. Slit-lamp photograph of posterior subcapsular cataract with sheetlike opacity *(black arrow)* and plaques *(white arrow)*.

15 to 18 days after birth. Fundus examinations also are difficult until the animal is 5 to 6 weeks old. General anesthesia is not necessary.

In some series, cataract development was studied by biomicroscopy at monthly intervals for 12 months beginning shortly after the eyes opened. Other mice have been examined at irregular intervals for approximately 2½ years. Cataracts were described biomicroscopically according to degree and location within the lens. Abnormalities of the optic nerve, retina, and vitreous were recorded routinely after 6 weeks. Syndactyly was recorded within 1 month after birth. Eyes of heterozygotes (*cw*/+) and wild-type (+/+) *Peromyscus* of various ages were also examined.

At selected intervals eyes were removed for study. Some eyes were fixed in Carnoy's or alcoholic Bouin's fixative, and whole lenses were stained with Feulgen reagent to demonstrate the normal location of cell nuclei and the posterior displacement of nuclei in *cw* lenses. Several methods of fixation and embedding were used for histology: 10% formalin fixation and paraffin embedding (standard histology), buffered 1% paraformaldehyde-2% glutaraldehyde followed by 2% osmic acid fixation and epon-araldite embedding (standard electron microscopy), and various combinations of aldehyde fixation and/or osmic acid fixation with embedment in low-viscosity embedding media, e.g., Spurr, methacrylate, etc. Poor penetration of fixatives and embedding media was always a problem. Cutting the lenses caused herniation of lens tissue and leaching of lens proteins during processing; therefore this was rarely done. Best results were obtained by fixing the lenses for at least 3 days in aldehyde fixative and in osmic acid for at least 30 hr. Infiltration with plastic was never entirely satisfactory even when the lenses were soaked for long periods in dilute solutions of the resin; routinely, 5 days was required for infiltration and embedding.

Paraffin-embedded sections were stained with hematoxylin and eosin or periodic acid-Schiff (PAS). Epoxy-embedded semithin sections were stained with toluidine blue, osmic acid-paraphenylenediamine, or PAS.

Elderly mice were autopsied by removing all of the organs and examining them grossly and microscopically. Blood chemical analyses were done by exsanguinating the animal, separating the serum, and processing it through a multiple channel analyzer.[5]

Results

Systemic findings. The *cw*/*cw* *Peromyscus* appeared healthy, and many lived for over 2 years. Complete autopsy results on eight elderly *cw*/*cw* animals, with histologic examination of all organs, did not disclose any generalized abnormalities.[5] Ovarian cysts and renal fibrosis occurred approximately equally in *cw* and noncataract control mice. Determination of blood chemistries on 10 *cw*/*cw* mice and *cw*/+ mice approximately 1 year old resulted in values generally in the normal range for humans, with the exception of greatly elevated serum lactic dehydrogenase and glutamic oxalacetic transaminase levels in both groups. Of 1,020 animals tested for glycosuria 62 (6.1%) were positive, but only 11 were consistently glycosuric, with blood glucose levels from 332 to 1,140 mg/dl. This diabetes-like syndrome was found in equal proportions of webbed and nonwebbed mice, and thus it is inherited separately from *cw*. Glucosuria was not specifically correlated with Type I or Type II cataracts. Although hereditary spherocytosis was present in a few *Peromyscus*,[6] this was not associated with cataract formation. Thus general examination

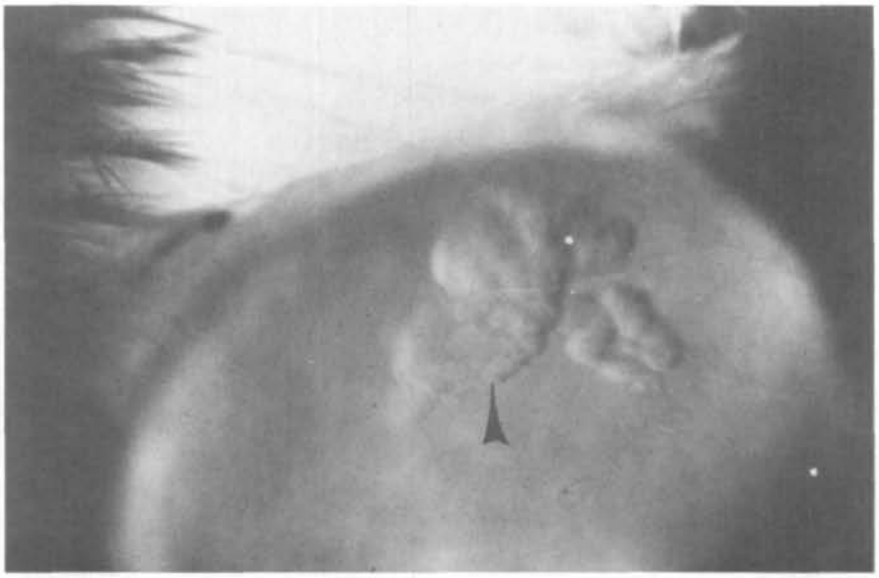

Fig. 2. Slit-lamp photograph of large vacuoles *(arrow)* which appear transiently in dorsotemporal equator of lens with posterior subcapsular opacity extending inferonasally.

of the deer mice did not show consistent systemic abnormalities associated with early cataract development.

Biomicroscopy. Evaluation of the clarity of lens was often difficult in the early stages of cataract formation because of uncertainty in differentiating biomicroscopically the earliest stages of posterior subcapsular cataract occurring within the lens from fibrovascular vitreous remnants behind an apparently normal lens; the vitreous remnants are separated from the lens only by the width of the posterior lens capsule. Posterior subcapsular cataracts were generally first observed at or near the posterior lens pole. They appeared as grayish-white opacities or small empty areas which we termed plaques (Fig. 1). In later stages, iridescent multicolored (blue, red, yellow, and green) "crystals" were seen; these were similar to those seen in human cataracts.[7] At approximately the same time, large vacuoles appeared at the otherwise clear dorsotemporal equatorial cortex (Fig. 2). The posterior subcapsular cataract gradually increased in size and thickness, extending into the posterior lens cortex and spreading toward the nasal ventral periphery of the lens to form an equatorial cataract. Occasionally, sheetlike white opacities were visible at the equator in combination with the vacuoles.

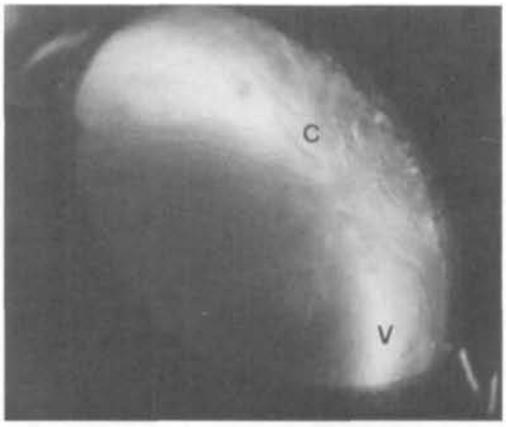

Fig. 3. Anterior cortical opacity which progresses unevenly from equator to center of anterior lens surface. *V*, Vacuoles. *C*, water clefts.

In time the posterior-equatorial cataract usually extended onto the anterior cortex, starting in the inferonasal quadrant. Then the anterior cortex gradually opacified, usually with irregular degrees of opacity and translucency occasionally interspersed with vacuoles and water clefts (Fig. 3). The process even-

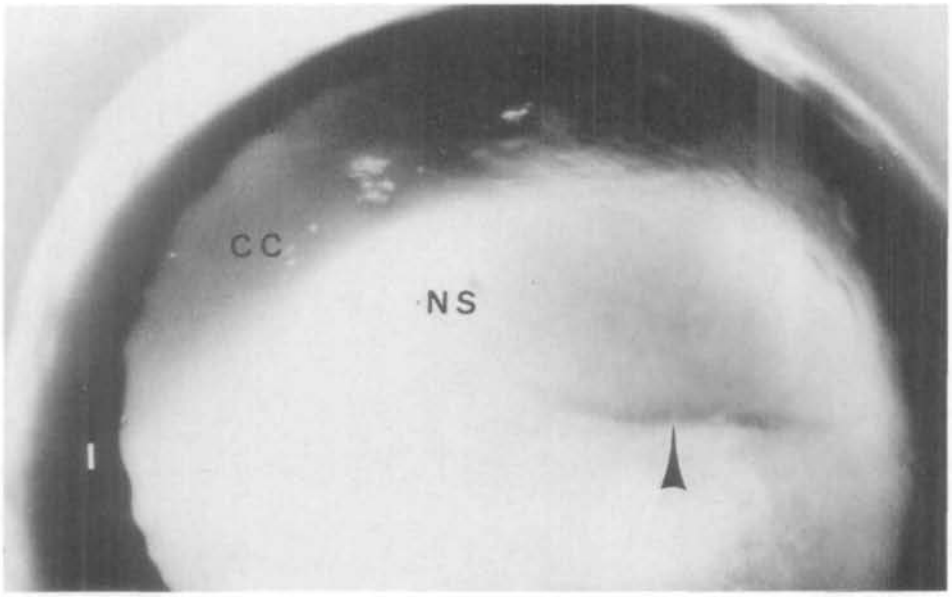

Fig. 4. Nuclear "shell" cataract *(NS)* deep to clear cortex *(CC)* outlines anterior Y-suture *(black arrow)*. The cataract is an even discrete zonular opacity outside a clearer central nucleus. *I*, Iris.

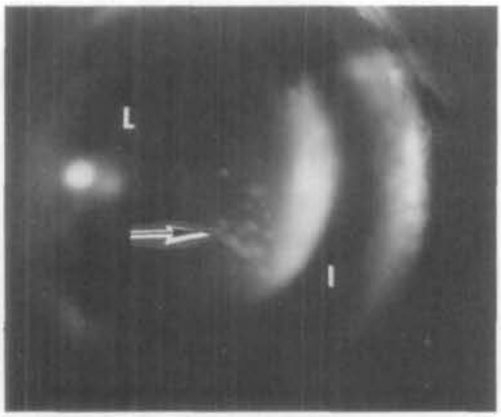

Fig. 5. Nuclear dots *(arrow)* appear as localized translucencies, which become more opaque and enlarge till hidden by anterior cortical or nuclear shell opacities. *L*, Lens. *I*, iris.

tually terminated in a total opacity which prevented further visualization of the interior of the lens.

Nuclear cataract appeared in these lenses at approximately the same time as the cortical cataract began to extend from the inferonasal equator to the anterior cortex. The most common type of nuclear cataract was a rapidly developing white-opaque "shell" at about the junction of the inner two thirds and outer third of the lens, in which the "Y" suture remained transparent (Fig. 4). The shell was not dense enough to prevent a view of the interior of the lens, which remained semitranslucent in appearance. Less frequently, nuclear punctate opacities appeared as a collection of 10 to 40 dots or rods, occupying approximately one-tenth the volume of the nucleus. These dots, translucent at first and later becoming opaque, were grouped in localized areas of the semitranslucent nucleus, while other areas appeared uninvolved (Fig. 5). These nuclear punctate cataracts gradually enlarged until other opacities of the anterior cortex or the nuclear shell cataract prevented visualization biomicroscopically.

When the anterior cortex became so white that subjacent structures of the lens were no longer visible, the cataract was classified as mature, and at this stage the lens appeared to bulge anterior to the iris. When the anterior capsule became wrinkled from dissolution of some of the lens cortex, the lens shrank in size, and the cataract was termed hypermature. Dislocation of the lens often oc-

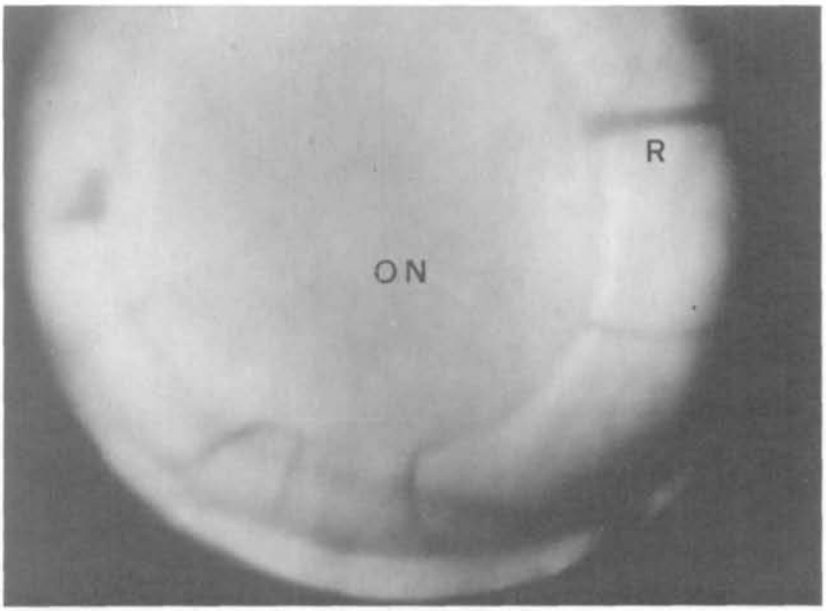

Fig. 6. Coloboma in *cw Peromyscus* optic nerve *(ON)* has deep central cup with retinal *(R)* vessels dipping in at periphery.

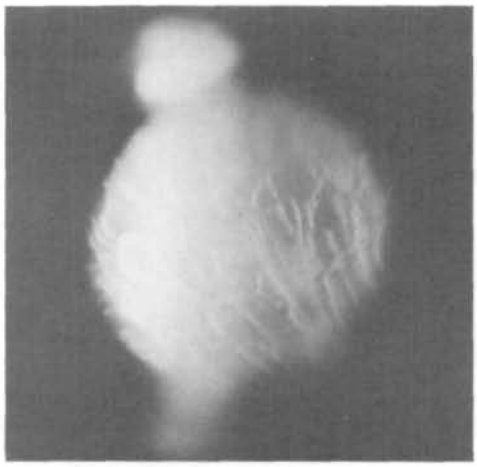

Fig. 7. Biomicroscopic photograph of network of blood-filled persistent hyperplastic vitreous vessels on back of lens.

Fig. 8. Feulgen stain of whole *cw* lens in vitro, showing displacement of lens cell nuclei posterior to the equator *(arrow)*.

curred after extensive atrophy. Iritis, with iris atrophy, vascularization, and posterior synechiae, sometimes ensued. In those deer mice genetically determined to develop early cataracts (Type I), the rate of progression to maturity was much more rapid than in *Peromyscus* destined to develop late cataracts (Type II).[3] Type I animals had onset of cataract in 77% of lenses by 3 months, and 92% by 6 months. Subsequent selective breeding has increased this frequency.

In approximately 5% of animals, both webbed and nonwebbed, we have observed several other types of lens opacities resembling clinical syndromes of human cataracts.[8] These include zonular cataract, anterior polar cataract, and central pulverulent cataract. In-

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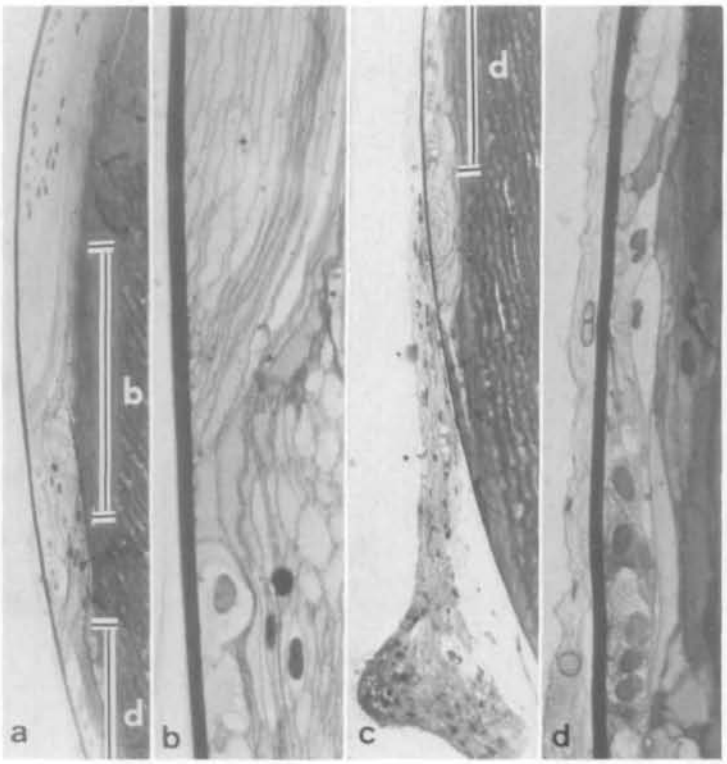

Fig. 9. Early histologic changes in biomicroscopically clear lens. **a**, Low-magnification view of nasal ventral equator showing relatively normal fiber differentiation but abnormally displaced cells posteriorly. (×115.) **b**, Enlargement of bracketed area of **a** showing basal processes of normal looking fiber cells anterior to "bladder cells." (×470.) **c**, Continuation of **b** showing more displaced cells and heavy hyaloid network at posterior pole. (×115.) **d**, Enlargement of bracketed areas of **a** and **c**. (×470.)

crease in optical density of the lens nucleus with increasing age was observed in both webbed and nonwebbed mice; this was considered to be a normal aging change. Lens weight and volume have not been determined.

Fundus examinations of noncataractous, nonwebbed (+/+ or +/*cw*) mice showed a pink to orange, round or oval optic nerve with retinal vessels branching on the disc. The pattern of retinal vessels was easily recognized as normal. The pigmentation of the fundus varied from pink in the albino mutant to dark brown in the melanotic mutants. The various eye color mutations did not appear to influence cataract incidence. In *cw* mice, colobomas of the optic nerve were noted as pale excavations of the optic disc with the blood vessels dipping in at the edges of the optic nerve (Fig. 6). Colobomas of the retina and choroid were frequently seen adjacent to the coloboma of the optic nerve in the inferior nasal quadrant of the eye and appeared as a gap in the fundus with pigment remnants or bare sclera showing, or as an elevated whitish mass where dysplastic retinal tissue piled up. This tissue often extended a short way from the disc and occasionally beyond the area visible with Hruby lens. Myelinated nerve fibers, appearing exactly as their counterpart in humans, were often contiguous with this. Retinal dysplasia and myelinated nerve fibers often occurred together and joined with hyperplastic vitreous.

In the normal deer mouse the tunica vasculosa lentis and central vitreous hyaloid vessels are visible at the time the eyes open but atrophy rapidly thereafter. By 6 weeks, these

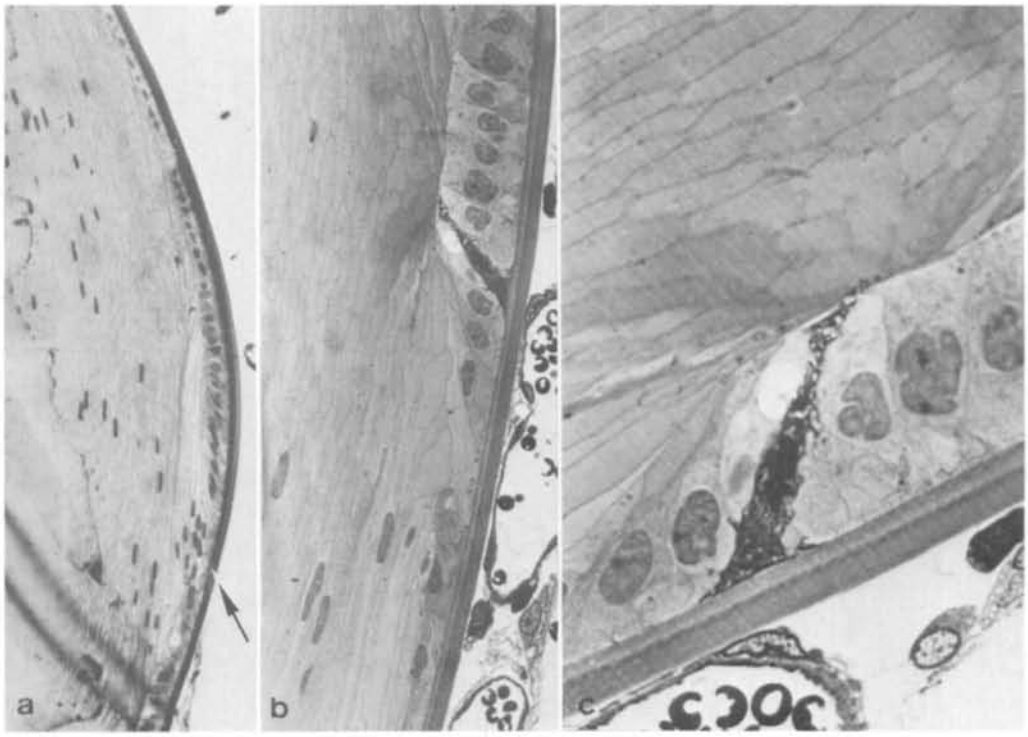

Fig. 10. Abnormal epithelium-fiber differentiation. a, Low-magnification view showing equatorial region of nasal ventral quadrant of *cw* lens. Note failure of epithelial cells to "drop into" the cortex; nuclei have continued backward *(arrow)*. Lens bow is disorganized. (×180.) b, Serial section of a showing degenerating epithelial cell in zone of differentiation. (×470.) c, Higher magnification of b. (×1150.)

had largely disappeared in non-*cw* mice, although sometimes a remnant was left either as small white dots on the central posterior pole of the lens (Mittendorf dots), or occasionally as a small tuft of connective tissue on the disc (Bergmeister's papilla). The tunica vasculosa lentis was occasionally seen on the front of the lens in *cw* mice, but occurred more commonly only on the back of the lens. In *cw* mice, the hyaloid artery was often larger and contained blood much longer than normal. This persistent hyaloid vascular system had multiple branches which formed a network of fibrous tissue and vascular channels over the back of the lens (Fig. 7).[9] Thus the coloboma of the optic nerve, retinal dysplasia, myelinated nerve fibers, and persistent hyaloid vascular system sometimes formed an interlacing, contiguous, or separate network of connective, vascular, and retinal tissue. Although the degree of fundus and vitreous abnormalities was variable, it was rarely absent in *cw/cw* mice.

Histology. Since biomicroscopy is possible only after the eyelids have opened, and we want to correlate the in vivo findings with the histologic appearance of the eye, this histologic study is confined to animals over 17 days old.

The normal deer mouse lens resembles that of other rodents, and we will not describe it further except to report that even in lenses of wild-type *Peromyscus* an occasional atypical (more or less dense than normal) fiber cell was seen. Also, small vacuoles in the superficial cortical fibers were sometimes found in normal lenses; this appeared to be dependent on the rapidity of penetration of fixative into the anterior chamber and vitreous cavity.

Early changes visible in posterior subcapsular cataracts were either enlargement and

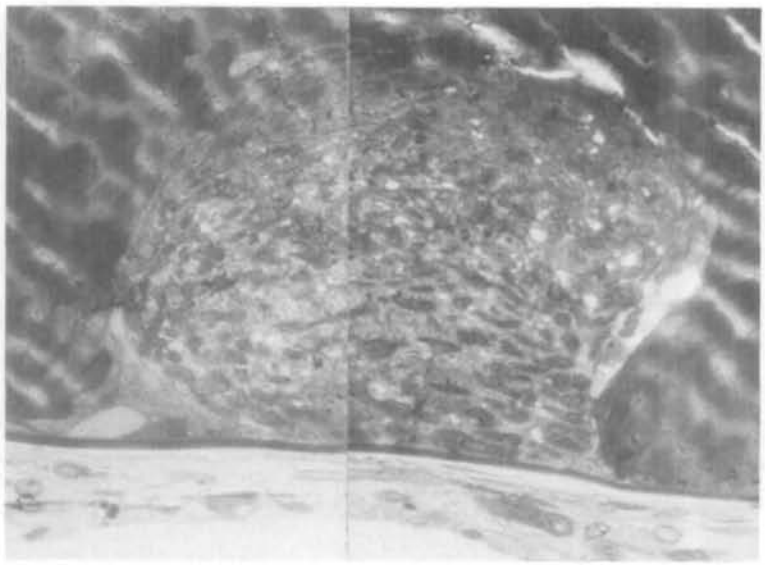

Fig. 11. Nest of displaced cells at posterior pole of lens, organized as layers of spindle shaped cells. (×470.)

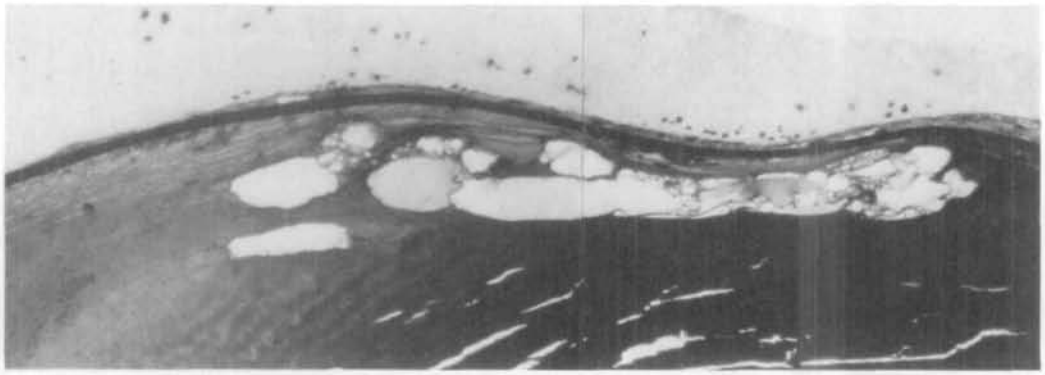

Fig. 12. Subcapsular cortical spaces visible with the slit-lamp (Fig. 2). These intercellular and intracellular vacuoles may contain varying amounts of homogeneous staining substance or may be optically empty. (×180.)

distortion of the subcapsular lens fibers or presence of single or multiple layers of cells posterior to the equator as far as the center of the lens. The relocated cells were demonstrated best by Feulgen stains of whole lenses (Fig. 8). The normal straight margin of lens nuclei at the equator was not seen; rather, an arc of stained nuclei dipped backward as a continuous sheet or as columns of cells. Sometimes islands, rather than a continuous sheet of cells, were seen posterior to the equator of the lens. Occasionally this cellular dislocation was found on histopathologic examination of lenses that had been classified as clear (noncataractous) on biomicroscopic examination (Fig. 9).

Examination of lenses in semithin sections showed that in some lenses the equatorial epithelial cells did not differentiate normally. The normal inward tilt of the apical process of the cell, which is the prelude to differentiation of lens fibers into anteroposteriorly oriented cells, appeared to have failed, and the epithelial cells had continued backward in-

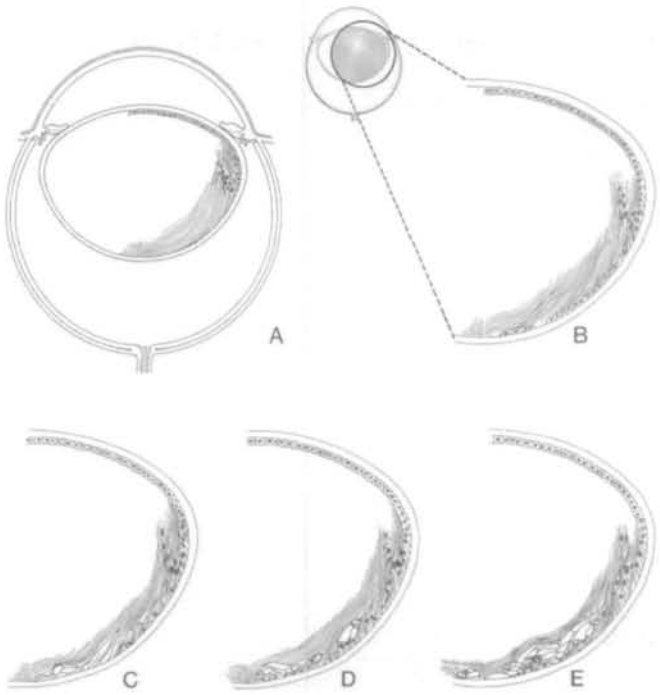

Fig. 13. Diagram depicting early morphologic changes in development of posterior subcapsular cataract of *cw* deer mice. a, Normal. b, Clinical diagnosis of clear lens despite presence of epithelioid cells at posterior pole, inferonasal quadrant. c, Swollen basal ends of superficial fiber cells and posterior migration of equatorial cells. d, Intercellular clefts, swollen fiber cells. e, Involvement of both sides of sutures, formation of ball of fusiform cells.

stead of becoming buried as lens fibers (Fig. 10). As a result, fewer nuclei made up the lens bow of these lenses. Occasionally a degenerated cell was seen at the site of epithelial-fiber cell differentiation (Fig. 10, *b* and *c*). In other cases normal-appearing new lens fibers lay between the bow and the posteriorly displaced cells (Fig. 9, *a* and *b*). In these lenses, nuclei were missing from the deep anterior curve of the lens bow, and thus it appeared that the source of the displaced cells could be either epithelial cells or fiber cells. The cellular migration sometimes preceded the swelling of the lens fibers at the posterior pole; in other specimens cellular migration appeared to be a secondary phenomenon. Some cells in the posterior location were rounded as individual "bladder cells" (Fig. 9), whereas others were flattened and piled up in discrete clusters (Fig. 11). Some migrated cells appeared to wall-off areas of disrupted lens fiber substance and lay down new basement membrane around pockets of debris and between fusiform cells. At this time, vacuoles developed either inside or between lens fibers (Fig. 12); these corresponded to the plaques noted biomicroscopically (Figs. 1 to 3). The early histologic findings in these lenses are shown diagrammatically in Fig. 13.

As the frank cataractous process spread anteriorly, the equatorial cells became involved. Cells became piled up in multiple layers, and eventually extensive vacuolar and globular degeneration occurred. Anterior cortical cataracts at times showed a decrease in number of normal lens epithelial cells, and at other times, multiplication of cells of either epithelioid or spindle-shaped types, with reduplication of capsule. Degeneration of cortical fibers into vacuoles, either intracellular or intercellular, and globule formation were frequently seen. These changes were described earlier.[4]

Nuclear cataracts were studied with difficulty because of problems in obtaining good

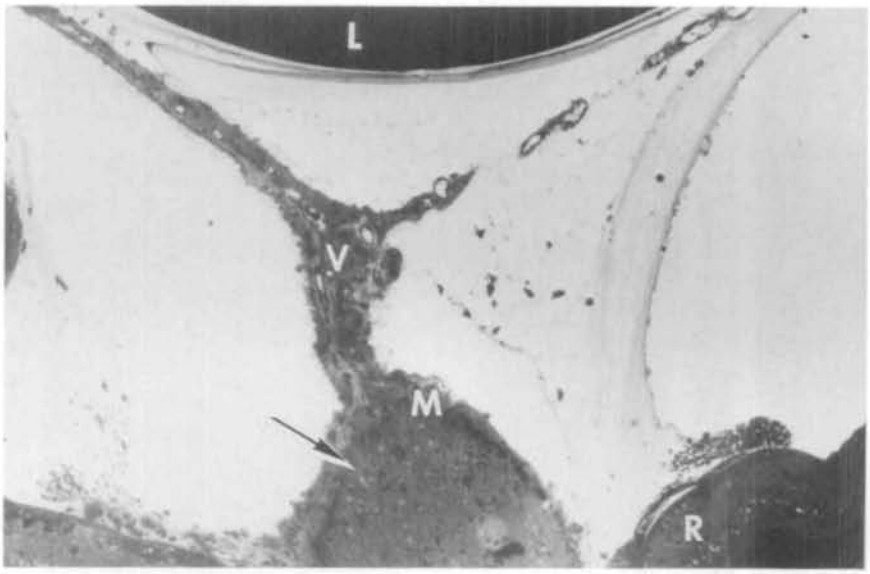

Fig. 14. Fusion of retina *(R)* in coloboma area with hyperplastic undifferentiated retinal cells *(arrow)*, myelinated nerve fibers *(M)*, and fibrovascular remnants of persistent hyperplastic primary vitreous *(V)*, which extends forward to lens *(L)*. (×130.)

fixation and embedding of the deep lens fibers. A cleft in the tissues at about the junction of the outer third and inner two thirds was frequently seen, corresponding to the shell-like nuclear opacity. Exact correlation of the nuclear shell-like and punctate opacities with their histologic counterpart has not yet been made.

Mature cataracts showed a combination of all of the above features, and hypermature cataracts were different only in that capsular thickening and wrinkling were present. These features were described previously.[4]

Colobomas of the optic nerve were characterized by depression of the optic nerve below the normal level of the retina in cw mice. In non-*cw Peromyscus* the optic nerve was flat. The coloboma of the optic nerve often merged with abnormal areas of retina. Some areas of retina were atrophic and had cystic dilatations, whereas other areas were thickened by distorted retina formed into rosettes or entirely replaced by masses of abnormal embryonic cells (Fig. 14). Throughout the dysplastic areas, myelinated nerve fibers could be seen, not only on the surface of the retina, but also in deep retinal layers. The ciliary body and iris were colobomatous in a few animals, usually in the lower nasal quadrant.

The normal deer mouse has an embryonic hyaloid vascular system and tunica vasculosa lentis until 3 to 4 weeks after birth. This system is composed of small blood vessels and densely staining vitreous fibrils which gradually atrophy to fibrous strands and isolated cells and then disappear. In the mice that had persistence of the primary vitreous vascular system, an extremely heavy network of vitreous vessels covered the back of the lens in many cases and contained a large number of erythrocytes.[9] Fusion of these vitreous vessels with the optic nerve coloboma and the dysplastic retina was very common, so that a vascularized mass extended from the optic nerve to the posterior pole of the lens (Fig. 14).

Discussion

Based on genetic studies, we have divided cw *Peromyscus* cataracts into Type I (early onset) and Type II (late onset) cataracts.[3, 9] Type I are a relatively homogeneous group with a high degree of reproducibility and rapidity of progression.[3] There is also a close relationship between abnormal hyaloid hy-

perplasia and development of Type I *cw* cataracts.[9] Type I cataracts resemble the cataracts seen in humans with a persistent hyperplastic primary vitreous.[8]

By contrast, animals that develop Type II cataracts have clear lenses for many months prior to gradual onset of opacities. It is not possible to estimate frequency of Type II cataracts at this time because of the late age of development (2 to 3 years). These cataracts resemble senile cataracts in man because three different areas of the lens, posterior subcapsular, nuclear, and cortical, are sequentially involved.

The backward migration of epithelioid cells, which is the hallmark of early cataractogenesis in this animal model, is a feature of senile and steroid-associated human posterior subcapsular cataracts.[10, 11] A recent morphologic study of steroid associated cataractous human lenses, however, did not show a layer of epithelioid cells in the posterior subcapsular zone, although shrunken cells were seen intermittently.[12] The unexpected absence of this morphologic feature in older human lenses may reflect age differences in the cataractogenic response of epithelial cells; in *Peromyscus* lenses, epithelial migration is an early manifestation of the cataractous process. In Type I *cw* lenses, histologic evidence suggests that abnormalities in the differentiation of the equatorial epithelial cells into lens fiber cells may account for the subsequent posterior migration of cells. The underlying cause of this abnormality remains to be determined. This early cellular change is followed by globular and vacuolar degeneration of posterior cortical lens fibers, features that are also seen in human cataracts.[13] Thus, in the *Peromyscus* model of cataract, many of the pathologic features of human cataracts are duplicated. The ultrastructure of the early cataractous changes is under investigation.

The effect of abnormal development of one tissue on another is clearly demonstrated in this animal model. In *Peromyscus* the fetal fissure closes early in intrauterine life (approximately 12 to 14 days in *P. polionotus*[14]). Failure of the fissure to close causes colobomas of the optic nerve, retina-choroid, and ciliary body-iris in the lower nasal quadrant. Reparative or compensatory phenomena such as retinal dysplasia and abnormal persistence of the hyaloid vascular system are associated consequences.[15, 16] Thus poorly differentiating optic cup cells, which come from the forebrain, appear to induce abnormalities of lens cells which originate from surface ectoderm; this interaction has been noted by others.[16, 17] Concurrently, in the same inferior nasal quadrant of the eye in which the colobomas occur, the lens bow is disrupted, and the lens epithelium differentiates abnormally. This is followed by migration of cells to the posterior pole of the lens and cataract development.

The reproducibility of this cataractogenic sequence in different sectors of the *Peromyscus* lens, together with known differences in metabolic activity in different zones of the lens, makes this animal model an excellent one to study the interrelated pathophysiologic changes that lead to the final common disorder known as cataract.

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