Anatomic Alterations in Aging and Age-Related Diseases of the Eye

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Numerous anatomic changes occur in the eye with age. These changes generally include loss and attenuation of cells, such as the corneal endothelium and RPE; degenerative processes, such as vitreous liquefaction; and accumulations of materials, such as drusen. There are research opportunities to image the effects of aging, thus, predicting diseases that are characterized by abnormal or premature aging as well as understanding the effects of aging on therapeutic drug delivery to arrest ocular disease.

**Cornea**

As the eye ages, the cornea flattens. The thickness of Bowman's layer, 8 to 10 μm, remains constant throughout life. There is a tendency for calcific deposition at the periphery of Bowman's layer with aging. Arcus senilis, a deposition of lipid near the limbus, also may occur with aging. The stromal keratocyte density appears higher in children than adults. Arcus senilis appears in the peripheral cornea with aging in some patients. The thickness of Descemet's membrane increases with aging. There is a decrease in corneal endothelial cell density that occurs with aging. The most precipitous decrease in cell density occurs in the first five years of life. In general, the corneal endothelial cell density decreases from approximately 5000 cells/mm² at birth to 3000 cells/mm² in older age. There is a direct correlation between histologic corneal endothelial cell number and specular microscopic endothelial cell density. The corneal endothelial cell density is not uniform, with an increased endothelial cell density in the paracentral and peripheral regions of the cornea, which declines with age at a rate of between 0.2% and 0.6% per year. There is some evidence that endothelial stem cells are present in a regenerative zone near Schwalbe's line which give rise to a paracentral storage zone of cells.

**Trabecular Meshwork**

With age, the trabecular meshwork changes histologically from a long, wedge shape to a shorter, more rhomboidal form. The trabeculae become progressively thickened and ultrastructural examination shows a change in the appearance of extracellular materials. The cellularity of the trabecular meshwork decreases with age. A progressive decrease in trabecular endothelial cellularity (58%) and absolute cell number (47%) was documented in newborns to persons aged 81 years. This change parallels the decrease in corneal endothelial cell density and corresponds with senescence of cultured trabecular meshwork cells. Aqueous outflow spaces in the trabecular meshwork also decreases with age, which may account for an increase in intraocular pressure. This is thought to be due to an accumulation of extracellular sulfated proteoglycans with accompanying changes in collagen/microfibril architec-
turate. Additionally, there is an age-related reduction of giant vacuoles and intracellular pores in Schlemm’s canal. All of these changes may result in a decrease in aqueous outflow facility.

**Ciliary Body**

With advancing age, the stroma of the ciliary processes becomes collagenized, the processes appear to become less vascularized, and they also appear shorter and more blunt. The cellularity of the ciliary body appears to diminish with age and the ciliary body smooth muscle bundles undergo age-related changes in morphology suggestive of an antero-inwards displacement of the muscle mass. Occasionally, age-related hyperplasia of the ciliary body nonpigmented epithelium occurs and forms a Fuchs adenoma. This is a benign lesion that may occur as an incidental finding in eye bank eyes, although occasionally it clinically mimics a malignant neoplasm.

**Lens**

The shape of the crystalline lens in histologic sections changes with age. In infants, the lens assumes a reniform configuration, whereas in adults, it is more oval. The lens increases in weight from approximately 90 mg at birth to 150 mg at age 20 years, 190 mg at age 40 years, and 240 mg at age 80 years. Cataracts are associated with aging and are manifest with color changes in the lens due to oxidation of lens proteins. The most common age-related histologic cataractous changes are equatorial and posterior cortical degeneration. These changes result in inward turning of equatorial cortical fibers, and a difference in staining with hematoxylin and eosin between the lens nucleus and cortex. This may be accompanied by posterior migration of the lens epithelium. These cells may lie along the inner surface of the posterior capsule, and become balloon-like and swollen (Wedl cells). A proliferation of these cells along the posterior capsule results in posterior subcapsular cataract. Eosinophilic fluid may appear between lens cortical cells with age, and when the cells eventually break down with aging, the released protein from the cells results in Morgagnian globules and eventual liquefaction of the cortex, with the lens nucleus floating in a sea of liquefied cortex (Morgagnian cataract).

**Retina**

With aging, there is diffuse thickening of the internal limiting membrane of the retina and diminution of neural elements with gliosis in the peripheral retina. These changes lead to disorganization in the area of the ora serrata, and the RPE may migrate into the sensory retina in this area. There may be a reduction of nuclei in the outer nuclear layer of the retina with age. Corpora amylacea may be observed in the peripapillary region. There may be a migration of the inner limiting membrane to the peripheral capillaries of elderly persons with age.23 Corpora amylacea may be observed in the peripapillary region. There may be a migration of the inner limiting membrane to the peripheral capillaries of elderly persons with age.23

**Retinal Pigment Epithelium and Bruch’s Membrane**

The RPE increases in density from birth to two years of age, when the adult density is achieved. With aging, the RPE becomes more pleomorphic, with the macular RPE becoming narrower with an increased height, and opposite occurring in the periphery. Peripheral RPE cells become broader, lower, vacuolated, and pleomorphic with aging. Lipofuscin accumulates in the cytoplasm with aging and the lipofuscin-associated A2E-epoxides may be toxic to RPE. There is clinical interest in RPE lipofuscin-related fundus autofluorescence patterns with regard to aging and age-related macular degeneration, although the histologic correlations of these findings are unclear. Autofluorescence imaging of the RPE with the adaptive optics scanning laser ophthalmoscope (AOSLO) or a two-photon tunable dye laser may prove to be tools for further evaluation aging changes of the RPE mosaic. Sub-RPE nodular drusen accumulate with age. These drusen are excrescences formed on the inner aspect of Bruch’s membrane, and are composed of granular substance, lipid, protein, crystalline deposits of calcium, and residual bodies. There are several histopathologic types of drusen, including hard, soft, confluent, and large drusen. Hard drusen are nonspecific and age-related. Soft, confluent, and large drusen are associated with age-related macular degeneration. Eosinophilic, brush-like material that accumulates external to the basement membrane of the RPE with age is termed “basal laminar deposit.” This material contains granular material, noncoated and coated vesicles, and wide-spaced collagen. Although the presence of basal laminar deposit may be associated with aging, it becomes very thick in age-related macular degeneration. Basal linear deposit, which accumulates between the basement membrane and plasma membrane of the RPE, may be a specific ultrastructural
marker for AMD.\textsuperscript{45} Bruch's membrane itself becomes thickened and may become calcified with aging. The thickening includes focal and diffuse thickening of the inner aspect of Bruch's membrane.\textsuperscript{22} Lipid, including cholesterol, accumulates in Bruch's membrane with aging.\textsuperscript{46,47} Curcio et al. have noted that Bruch's membrane ages like the arterial intima and other connective tissues for which lipoproteins are the source of extracellular cholesterol.\textsuperscript{47} Some of the lipid in Bruch's membrane appears to arise from esterified cholesterol-rich apolipoprotein B-containing lipoprotein particles produced by the RPE.\textsuperscript{48}

**CHOROID**

There are clinical data using optical coherence tomography (OCT) indicating an inverse relationship between age and choroidal volume.\textsuperscript{49} Histopathologic studies have shown a negative correlation between age and choriocapillaris density.\textsuperscript{50} Although there may be an early increase in choriocapillaris density in age-related macular degeneration,\textsuperscript{51} eventually there is a decrease that is more pronounced than in normal aging.\textsuperscript{50,51}

**VITREOUS**

With aging, vitreous attachments to the retina weaken, thus resulting in posterior vitreous detachment.\textsuperscript{52} The space between the detached vitreous and retina is filled with liquefied vitreous. In one study of 786 eyes examined postmortem, 16% of the eyes from patients aged 45 to 65 years and 41% of eyes from patients aged over 65 years had a posterior vitreous detachment.\textsuperscript{53} A subsequent study showed that posterior vitreous detachment was present in 63% of postmortem eyes from patients aged in their 70s.\textsuperscript{54} Posterior vitreous detachment may result in the formed vitreous contracting forward to the vitreous base, thus causing traction on the peripheral retina and occasionally a retinal tear.\textsuperscript{52,52} As the vitreous liquefies and the formed vitreous collapses with aging, vitreous channels and compartments collapse, thus potentially affecting intravitreal drug delivery to the posterior retina.\textsuperscript{55}

**SCLERA**

The sclera becomes more rigid as a person ages.\textsuperscript{56} There may be relative dehydration, especially anterior to the insertion of recti muscles, resulting in calcium salt deposition.\textsuperscript{56} The midportion of the involved sclera in this area contains a calcified plaque.\textsuperscript{57} A similar age-related process may occur posteriorly, thus resulting in posterior scleral calcification.

**OPTIC NERVE**

Connective tissue within the fibrovascular pial septae becomes more abundant with age.\textsuperscript{58} Such thickening may result in impairment of exchange of nutrients and other metabolites between the capillaries and nerve fibers.\textsuperscript{58} Cellular and extracellular material may accumulate in the meninges and optic nerve fiber bundles with age. These include arachnoid cell nests and corpora arenacea (psammoma bodies) in the meninges, and corpora amylacea, which were described previously in the retina section. Schnabel cavernous degeneration of the optic nerve has been determined to be an age-related phenomenon related to chronic vascular occlusive disease.\textsuperscript{59} Histopathologic findings include loss of nerve fiber bundles and proteoglycan accumulation within the optic nerve.

**FUTURE DIRECTIONS FOR RESEARCH**

The anatomic alterations in the eye associated with aging offer potential areas of research and therapeutic intervention. Studies may be directed toward decreasing corneal endothelial cell loss with age. Research regarding trabecular meshwork aging changes, including extracellular matrix modulation, may prevent the decrease in outflow facility that occurs with age. Ciliary body dynamics may be studied with regard to aging changes to lessen the severity of presbyopia. Pharmacologic intervention for the prevention of cataracts may be investigated. Aging changes occur in the retinal and choroidal vasculature. These changes are related to retinal vascular disease, such as branch retinal vein occlusion and hypertensive retinopathy, as well as outer retinal ischemia secondary to choroidal vascular insufficiency. Potential areas of research related to these findings include real-time retinal and choroidal blood flow studies, such as may be determined using laser Doppler, and therapeutic interventions that result in normalization of these blood flows.\textsuperscript{60} Neuroprotection may be investigated as a way to lessen age-related loss of photoreceptors and retinal ganglion cells. Another potential area of research based on anatomic considerations of aging is in vivo imaging aging changes in the retina and RPE over time for early prediction of disease and early therapeutic intervention. An example of this is AOSLO imaging of the RPE mosaic as a method to predict age-related macular degeneration before there are fundus and vision changes.\textsuperscript{39,44,61} The AOSLO has been developed and may image the RPE mosaic.\textsuperscript{39,41} There are early histologic signs of AMD involving the RPE/Bruch's membrane complex that do not result in visible fundus changes.\textsuperscript{54} Imaging the RPE with predictive modeling may result in early detection of AMD and allow for early pharmacologic intervention. Analysis of RPE morphometry has been useful in identifying murine phenotype and age (Jiang Y, Chrenek MA, Gardner C, Boatright JH, Grossniklaus HE, Nickerson JM, unpublished observations, 2013).\textsuperscript{62} Comparison of in vivo fundus images of the RPE mosaic with ex vivo flat mounts including the underlying anatomic changes (Fig. 1) may be used to model and predict AMD progression. Investigations may be directed toward maintenance of Bruch's membrane. Another area of research is drug delivery to the
posterior ocular compartment. Vitreous changes with age result in a dynamic change in vitreous compartments, which may impact diffusion of intravitreally injected drugs to the macula (Fig. 2). There are areas of opportunity to study these vitreous compartmentalization changes with age and develop drugs or techniques of drug delivery that overcome barriers to drug perfusion to the macula. Finally, optic nerve neuroprotection and biomechanics may be investigated with regard to glaucoma damage and other optic neuropathies.

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