A blink rate.³ Intubated or sedated patients are at risk for lagophthalmos and exposure-related keratitis. The post-LASIK neurotrophic status of these patients may further predispose them to infectious keratitis.

The first case represents, to our knowledge, the earliest post-LASIK human histopathologic finding (9 days post-LASIK). The neurotrophic cornea would certainly be a risk factor in the immediate post-operative period. The first patient had evidence of probable traumatic displacement of the LASIK flaps, which may have contributed to the development of keratitis (Figures 1A and 3A). Late traumatic displacement of LASIK flaps occurring more than 2 years after the procedure, complicated by diffuse lamellar keratitis, has been reported.⁴ Late post-LASIK fungal keratitis related to trauma has also been reported.⁵ Based on the well-healed scar of the second case, the neurotrophic status of the cornea may predispose the cornea to infection even months after the LASIK procedure. Postmortem microbial contamination of the donor corneas is unlikely given the chronic inflammatory cell response documented by histopathologic examination.

These cases suggest that intensive care unit personnel consider adding a refractive surgery query to the eye history taken from family members of trauma patients and other obtunded patients. Intubated and sedated patients who have had LASIK surgery require close monitoring for exposure keratopathy and prompt diagnosis of keratitis. These patients would probably benefit from aggressive lubrication and prophylactic antibiotic ointment.

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face. Often, ocular pigmentation is the initial manifestation of the disease.

We report a case of bilateral conjunctival pigmentation as the initial manifestation of alkaptonuria and review the literature on ocular ochronosis.

**Report of a Case.** A 49-year-old white man on initial examination reported red eye and foreign body sensation for the last 3 to 6 months in both eyes, but more prominently in the left eye. Ophthalmologic examination revealed corrected visual acuity of 20/20 OU. The intraocular pressure was within normal limits in both eyes, and the fundi were unremarkable. Bilateral conjunctival pigmentation was present ([Figure 2](#)). The pigmentation was described as yellow-tan to dark brown, with a powdery appearance involving the interpalpebral bulbar conjunctiva. Pigmentation was more prominent nasally in the left eye. Bilateral lesions consistent with pinguecula were present. The pigmentation was seen extending beyond the elastotic changes of the pinguecula. A biopsy sample of the lesion from the left eye was obtained to exclude primary acquired melanosis ([Figure 3](#)). Histopathologic examination of the conjunctival tissue showed elastotic degeneration of the collagen fibers admixed with yellowish waxy globules and fiber-like deposits that were slightly refractile, as seen in hematoxylin-eosin–stained slides ([Figure 4](#)). Deposits were found under the epithelium and in the superficial stroma. Melanin stain (Fontana-Masson) and special stains for elastic fibers disclosed that the deposits were negative for melanin and strongly positive for elastic material ([Figure 5](#)). After more clinical history was obtained, we learned that the patient had a history of early-onset osteoarthritis. We suggested measuring urine levels of HGA. The results showed an elevated level of more than 100 mmol of HGA per millimole of creatinine. The collective findings were those of conjunctival ochronosis associated with pinguecula ([Figure 6](#)).

**Comment.** Alkaptonuria has played a paradigmatic role in the history of human and biochemical genetics. It was this rare autosomal recessive disorder that led Garrod to demonstrate the applicability of the rediscovered mendelian laws to *Homo sapiens* in 1902 and to formulate the fundamental concept of “inborn errors of metabolism” in 1908. Half a century later, La Du et al presented the first experimental evidence for a specific enzyme defect in humans: the deficiency of HGA 1,2-dioxygenase activity in the liver of a patient with alkaptonuria. Homogentisic acid oxidase is

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**Figure 1.** Graphic representation of the metabolic cascade of phenylalanine in normal and alkaptonuric conditions. The deficiency of homogentisic acid oxidase causes accumulation of homogentisic acid in the involved tissues.

**Figure 2.** Clinical photograph of the bulbar conjunctiva of the right eye, with light brown pigmentation of the temporal portion (left arrow, temporally located) and changes consistent with pinguecula (right arrow, by the limbus).

**Figure 3.** Clinical photograph of the bulbar conjunctiva of the left eye after biopsy, with pigmentation (arrow) and erythema (asterisk) at the site of biopsy.

**Figure 4.** Deposits were found under the epithelium and in the superficial stroma. Melanin stain (Fontana-Masson) and special stains for elastic fibers disclosed that the deposits were negative for melanin and strongly positive for elastic material (Figure 5). After more clinical history was obtained, we learned that the patient had a history of early-onset osteoarthritis. We suggested measuring urine levels of HGA. The results showed an elevated level of more than 100 mmol of HGA per millimole of creatinine. The collective findings were those of conjunctival ochronosis associated with pinguecula (Figure 6).
Excreted in the urine and sweat. Urine levels above the normal 100 mmol of HGA per millimole of creatinine are considered pathologic. When sodium hydroxide is added to freshly collected urine, the HGA in the urine oxidizes and turns black within minutes. The same effect can be achieved by exposing the urine to room air for more than 12 hours.\textsuperscript{4,5}

The most serious consequences of ochronosis stem from deposits of the pigment in the articular cartilages of joints, nose, ear, and cardiac valves. The deposits of pigment cause the cartilage to lose its normal resiliency and become brittle and fibrillated, especially in the intervertebral discs, knees, shoulders, and hips. Pigment polymer deposits located between and within cells form discrete granules or homogeneous laminated structures with a yellow-tan to dark brown color. The ochronosis deposits are more refractile than melanin. Ultrastructurally, the pigment appears more like melanin, but histochemically resembles elastin.\textsuperscript{5}

Although the metabolic defect is present from birth, pigment deposits and degenerative arthropathy develop slowly and are usually clinically evident by the fourth decade of life. Although alkaptonuria is not life threatening, it may be a crippling disease because severe osteoarthritis in ochronosis occurs at a younger age than degenerative osteoarthritis.

Ocular ochronosis more frequently involves sclera and episclera near the insertion of the recti muscle (interpalpebral areas) than in the cornea and conjunctiva. Corneal pigmentation is usually bilateral and present in the peripheral stroma as discrete pinhead-sized deposits of light brown to black color. Histopathologic examination shows globules or curled, light yellow, curvilinear structures of varying size in the superficial stroma and surrounding tissues. Melanin stains usually do not distinguish these deposits from those of melanin. However, the ochronotic pigment appears somewhat more refractile than melanin and is more variable in color, ranging from yellow-tan to dark brown. Special stains for elastic tissue stain positive. Some authors have noted that areas of intense scleral pigmentation are devoid of cells, suggesting a probable toxic effect of the pigment.\textsuperscript{5}

Others have found necrosis of fibrocytes in the most heavily pigmented areas.\textsuperscript{6} Kamplik et al\textsuperscript{5} proposed that the localization of the pigment, as seen by electron microscopy, might be interpreted as different stages in the development of the intensity of the coloration of the collagenous tissues of the eye. These authors propose a sequence in which deposition of HGA polymers occurs in a fine granular form around collagen fibrils, altering and obscuring this structure. The granules later coalesce to form plaques, globules, and fiber-like structures, followed by necrosis of the fibrocytes.\textsuperscript{5}

Recent research describes the existence of up to 18 known homogentisate 1,2-dioxygenase (HGO) gene mutations.\textsuperscript{7} The alkaptonuria (AKU) gene locus was mapped to human chromosome 3q21-q23,\textsuperscript{8} and an animal model for alkaptonuria, the \textit{aku} mouse, was described.\textsuperscript{9} Subsequently, the first gene encoding an HGO enzyme was cloned from the fungus \textit{Aspergillus nidulans}.\textsuperscript{10} In 1996 and 1997, the human HGO gene was cloned and

\textbf{Figure 4.} Histologic section of the conjunctival biopsy sample shows slightly acanthotic epithelium. The underlying stroma contains wavy yellowish waxy deposits (hematoxylin-eosin, original magnification ×64).\textsuperscript{64}

\textbf{Figure 5.} At high magnification, the yellowish homogeneous ochronotic pigment (on the right) differs from the elastotic degeneration of the stroma (on the left) (hematoxylin-eosin, original magnification ×100).
characterized. Two missense mutations cosegregating with alkaptonuria in 2 Spanish pedigrees and a third missense and a frameshift mutation in a Slovakian family established HGO as the defective gene in alkaptonuria.\(^{6,11}\) Concurrently, 13 additional mutations were found in unrelated subjects with alkaptonuria from 6 European countries, Algeria, Turkey, and Japan.\(^{12,13}\) The latest published study in 1999 describes the identification of 2 homozygous missense mutations in 2 unrelated German patients who were first diagnosed with this congenital disorder after their referral to ophthalmologists. The importance of recognizing this entity, which enters in the differential diagnosis of pigmentation and deposits of the conjunctiva, is emphasized in our report, in which the recognition of this systemic disease was the initial ocular manifestation of the disease.

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**Anterior Uveitis and Concurrent Allergic Conjunctivitis Associated With Long-term Use of Topical 0.2% Brimonidine Tartrate**

Brimonidine tartrate is a relatively selective \(\alpha_2\)-agonist that lowers intraocular pressure by reducing aqueous humor production and by increasing uveoscleral aqueous humor outflow. Ocular side effects associated with brimonidine use include pruritus, as well as follicular conjunctivitis. Recently, 2 reports have described the development of anterior uveitis in 5 patients treated with brimonidine.\(^{1,2}\) Herein we report 4 additional cases of uveitis and concurrent allergic conjunctivitis associated with the use of 0.2% brimonidine tartrate. The 4 cases are summarized in the Table.

**Report of Cases. Case 1.** An 82-year-old woman sought care from her general ophthalmologist because of redness, blurred vision, and photophobia in her right eye. The patient had a history of glaucoma and had been treated with 0.2% brimonidine tartrate in the right eye during the previous 16 months. Anterior uveitis was diagnosed in the right eye and resolved after a 5-week course of topical 1% prednisolone acetate. The uveitis recurred after the corticosteroids were discontinued, and it failed to improve after 3 weeks of treatment with topical corticosteroids.

The patient was referred to a uveitis specialist, and examination disclosed conjunctival injection in the right eye with mutton-fat keratic precipitates, +2 anterior chamber cells and flare, posterior syn-

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**References**


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**Image**

Figure 6. The large masses of ochronotic pigment (under the epithelium) and the marked actinic elastosis of the stroma stain black with the stain for elastic fibers (Movat pentachrome, original magnification \(\times 64\)).