Alkaptonuria (ochronosis) is an inherited aminoacidopathy of the phenylalanine/tyrosine metabolism (Figure 1). Phenylalanine is an essential amino acid that is irreversibly hydroxylated to tyrosine by homogentisic acid (HGA) oxidase, which is found in the liver and kidneys. In alkaptonuria, the enzyme is absent, and HGA accumulates in collagenous tissues such as cartilage and tendon, especially in the ear, nose, cheeks, conjunctiva, cornea, and sclera. Although conjunctival involvement in ochronosis is rare, it should be considered in the differential diagnosis of pigmented lesions and deposits of the ocular sur-
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 elastotic 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
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. Others have found necrosis of fibrocytes in the most heavily pigmented areas. Kampik et al 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.

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

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).

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 Slovakian families established HGO as the defective gene in alkaptonuria.8,11 Concurrently, 13 additional mutations were found in unrelated subjects with alkaptonuria from 6 European countries, Algeria, Turkey, and Japan.12,13 The latest published study7 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 α2-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-