Choriocapillaris Degeneration and Related Pathologic Changes in Human Diabetic Eyes

Jingtai Cao, MD, PhD; D. Scott McLeod; Carol A. Merges, MAS; Gerard A. Lutty, PhD

**Objectives:** To measure the extent of choriocapillaris degeneration (CCD) in diabetic choroids and to study the association of CCD with choroidal neovascularization and pathologic changes in Bruch's membrane–like basal laminar deposits.

**Materials and Methods:** Human choroids from 10 postmortem subjects (diabetic, 5 [group 1]; nondiabetic, 5 [group 2]) were incubated for the histochemical demonstration of alkaline phosphatase and nonspecific esterase activities, permitting analysis of the choroidal vasculature and polymorphonuclear leukocytes, respectively. The tissue was then flat embedded and sectioned for structural analysis. Areas of CCD were measured in the flat perspective by computer-assisted image analysis and verified in cross-sections of flat-embedded tissue.

**Results:** The CCD in choroids from subjects with diabetes (group 1) appeared in 2 patterns: diffuse (partial loss of alkaline phosphatase activity in a poorly defined area, ie, degeneration of some capillary segments) and focal (complete degeneration of choriocapillaris or loss of alkaline phosphatase activity in a relatively well-defined area). The mean±SD percentage of the choroid with focal CCD in group 1 was 5.08%±1.13% of the total choroidal area vs 1.16%±0.35% in group 2 (P<.001). Focal CCD in group 1 was more prominent in the posterior pole than in the peripheral choroid. Choroidal neovascularization was associated with some areas of diffuse CCD in group 1. Pathologic changes in Bruch’s membrane–like basal laminar deposits were often associated with CCD; the thickness of the deposits was greater in group 1 than in group 2 and greater in areas with focal CCD than in areas with diffuse or no CCD.

**Conclusion:** The percentage of choroid with focal CCD in group 1 choroids was more than 4-fold greater than that in nondiabetic choroids. The presence of CCD was related to basal laminar deposits and, in some cases, to choroidal neovascularization.


Nonperfusion of retinal capillaries is an early event in diabetic retinopathy. Kohner and Porta suggested that capillary closure, a precursor for neovascularization and all common causes of visual field loss, is the most important lesion in diabetic retinopathy. The mechanisms of vaso-occlusion in the retina remain unknown. Most attention has focused on retinal angiopathy in subjects with diabetes, but recent evidence suggests that choroidal angiopathy may also occur in these subjects. The concept of diabetic choroidopathy was first suggested by Hidayat and Fine, who observed capillary dropout, basement membrane thickening, and choroidal neovascularization (CNV) in 2 of 8 eyes from subjects with advanced diabetes. More recently, McLeod and Lutty reported choriocapillaris dropout in subjects with diabetes that in some cases seemed to be associated with CNV. Although Hidayat and Fine introduced the term diabetic choroidopathy, there is still no universally accepted definition of this microangiopathy. One reason is that few histopathological studies of the diabetic choroid have been performed, and high-resolution clinical visualization of the choriocapillaris is difficult, owing to its posterior location and the presence of pigmented cells.

The observations of McLeod and Lutty on the diabetic choroid, made using alkaline phosphatase activity as a marker for endothelial cells in the choroidal vasculature of postmortem eyes, showed that the loss of alkaline phosphatase activity in the choriocapillaris represented loss of viable endothelial cells and, therefore, CCD. The present study was conducted to measure the extent of choriocapillaris degeneration (CCD) in diabetic choroids and to study the association of CCD with CNV and pathologic changes in Bruch’s membrane. To meet these objectives, we analyzed choroids that...
MATERIALS AND METHODS

Human eyes from 10 subjects ranging in age from 50 to 90 years (diabetic, 5 [group 1]; nondiabetic, 5 [group 2]; Table) were provided by the Maryland Eye Bank (Baltimore) and the National Disease Research Interchange (Philadelphia, Pa). The mean±SD age for group 1 was 65.2±11.8 years and for group 2, 79.6±5.0 years. The mean±SD postmortem time (ie, from death to specimen fixation) for group 2 was 24.8±4.6 hours and for group 1, 20.2±5.4 hours; the mean±SD time from death to enucleation for group 2 was 2.7±1.2 hours and for group 1, 3.1±1.9 hours. The difference in postmortem times and death to enucleation times between diabetics and nondiabetics was not statistically significant. Eyes with photocoagulation, sepsis, or a history of ocular surgery were excluded from the study. The choroid from 1 eye of each subject was prepared for alkaline phosphatase and nonspecific esterase flat embedding, and the fellow eye was cryopreserved for immunohistochemical analysis that will be reported elsewhere.

ALKALINE PHOSPHATASE AND NONSPECIFIC ESTERASE

After removal of the retina and retinal pigment epithelial (RPE) cells, the choroids were dissected and processed for the demonstration of alkaline phosphatase activity as described previously. Briefly, the choroids were fixed in 2% paraformaldehyde in a 0.1-mol/L concentration of cacodylate buffer, pH 7.4, for 1 hour at 4°C and then washed. The choroids were then incubated for nonspecific esterase activity using naphthol AS-D chloroacetate as the substrate. This method stains granulocytes and mast cells red. Choroids were incubated for 1 hour in the dark at 37°C in the following solution prepared as recommended by the manufacturer (kit 91c; Sigma Chemical Company, St Louis, Mo): 1 mL of sodium nitrate solution, 1 mL of fast red violet LB base solution, 1 mL of naphthol AS-D chloroacetate, 5 mL of TRIZMAL 6.3 buffer concentrate, and 40 mL of deionized water. The choroids were fixed again and then bleached in 30% hydrogen peroxide at 4°C. When bleaching was complete, the choroids were quenched in 1% catalase (bovine liver, Sigma) in a 0.1-mol/L concentration of sodium cacodylate for 2 hours at 4°C, washed in a 0.1-mol/L concentration of cacodylate buffer, pH 7.4, for 1 hour at 4°C and then washed.

The choroids were then incubated for 60 minutes at 37°C for alkaline phosphatase activity in an incubation solution consisting of the following: 2 mg of naphthol AS-MX phosphate dissolved, 0.1 mL of dimethyl sulfoxide with 10 mg of fast blue RR salt, and 20 mL of a 0.1-mol/L TRIS buffer, pH 9.2.

The choroids were then incubated for nonspecific esterase activity using naphthol AS-D chloroacetate as the substrate. This method stains granulocytes and mast cells red. Choroids were incubated for 1 hour in the dark at 37°C in the following solution prepared as recommended by the manufacturer (kit 91c; Sigma Chemical Company, St Louis, Mo): 1 mL of sodium nitrate solution, 1 mL of fast red violet LB base solution, 1 mL of naphthol AS-D chloroacetate, 5 mL of TRIZMAL 6.3 buffer concentrate, and 40 mL of deionized water. The choroids were fixed again and then bleached in 30% hydrogen peroxide at 4°C. When bleaching was complete, the choroids were quenched in 1% catalase (bovine liver, Sigma) in a 0.1-mol/L concentration of sodium cacodylate for 2 hours at 4°C, washed in a 0.1-mol/L concentration of cacodylate buffer, and fixed again in 2% paraformaldehyde.

MORPHOMETRIC ANALYSIS

Whole choroids were imaged using a macroscopic system consisting of a Hamamatsu video camera, a 50-mm lens, and a 5-mm extension tube using transmitted light (Hamamatsu City, Japan). Images were digitized and analysis performed on a Macintosh IIci computer (Apple Computer Inc, Cupertino, Calif) with NIH Image software program.

were double-labeled for alkaline phosphatase activity and nonspecific esterase (naphthol AS-D chloroacetate esterase) activity. The choroids had been used previously to study the relationship of polymorphonuclear leukocytes (PMNs) with CCD. Computer-assisted image analysis was used to measure the area of CCD and to correlate the association of CCD with pathologic changes in Bruch’s membrane. We demonstrated a greater than 4-fold increase in CCD in diabetic choroids compared with nondiabetic choroids and a positive association between CCD and basal laminar deposits (BLDs; one form of Bruch’s membrane degeneration).

RESULTS

The double-label technique resulted in blue alkaline phosphatase reaction product in viable choriocapillaris endothelial cells and red nonspecific esterase reaction product in PMNs and mast cells. Areas of choroid with complete loss of choriocapillaris alkaline phosphatase reaction activity were called local CCD, and these well-defined areas were accurately traced and measured using image analysis. There were small areas of focal CCD in group 2 choroids (Figure 1, case 3), which ranged from 0.09 to 0.42 mm² (0.18±0.06 mm²). We found 2 patterns of CCD in group 1: focal (Figure 2, case 9) and diffuse (Figure 3, case 7). Areas of the choriocapillaris with some loss of alkaline phosphatase activity with poorly defined borders were termed diffuse or mild CCD. As mentioned in the “Materials and Methods” section, areas of diffuse CCD could not be measured accurately with image analysis and, therefore, were not included in the quantitative analysis. In our opinion, diffuse CCD was more common in group 1 than in group 2, and diffuse CCD areas, in general,

<table>
<thead>
<tr>
<th>Case No./Age, y</th>
<th>Type and Duration of Diabetes</th>
<th>Cause of Death</th>
<th>PMT/DET, h*</th>
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<tr>
<td>1/68</td>
<td>None</td>
<td>Cardiac arrest</td>
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</tr>
<tr>
<td>2/73</td>
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<td>3/79</td>
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<td>Cardiac arrest, congestive heart failure, and pneumonia</td>
<td>29.0/3.5</td>
</tr>
<tr>
<td>4/88</td>
<td>None</td>
<td>Hypertension and cardiopulmonary arrest</td>
<td>27.0/2.0</td>
</tr>
<tr>
<td>5/90</td>
<td>None</td>
<td>Cardiac arrest</td>
<td>24.0/1.0</td>
</tr>
<tr>
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<td>27.0/3.0</td>
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<td>1; 26 y</td>
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</tr>
<tr>
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<td>2; 15 y</td>
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<td>21.5/1.0</td>
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<tr>
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<td>Renal failure</td>
<td>17.0/6.0</td>
</tr>
<tr>
<td>10/81</td>
<td>2; 16 y</td>
<td>Myocardial infarction</td>
<td>13.0/3.5</td>
</tr>
</tbody>
</table>

* PMT indicates postmortem time (death to fixation); DET, death to enucleation time.
were larger than focal areas. In group 1, the areas with focal CCD ranged from 0.09 to 4.40 mm² (0.39±0.14 mm²).

All eyes in group 1 had a greater percentage of choroid with focal CCD than eyes in group 2 (Figure 4). The percentage of choroid with focal CCD in group 2 was unrelated to the age of the subject, the duration of insulin dependence, the type of diabetes (type 1 vs 2; Table 1), the severity of retinopathy (data not shown) as judged by adenosine diphosphatase staining (case 6), and the severity of retinopathy (data not shown) as judged by adenosine diphosphatase staining (case 7) had focal CCD that was equivalent to that of the subject with the least severe retinopathy (case 6). The area of focal CCD was 5.08%±1.13% of the total choroidal area in group 1 vs 1.16%±0.35% in group 2 (P<.001). The area of focal CCD in the submacular choroid was more than 4.9-fold greater in group 1 vs group 2 (6.04%±2.62% vs 1.23%±0.64% of the submacular choroid with CCD, P<.001). Focal CCD was more prominent in the posterior pole than in the equatorial or peripheral choroid in group 1 (P<.001, Figure 5). The equatorial region was defined as the area of choroid 4 mm posterior and 4 mm anterior to the geographic equator.

In cross-sections through areas with CCD, some capillary lumens appeared blocked by PMNs, and many of the lumens had few if any viable-appearing endothelial cells (Figure 3). Lutty et al reported an increased number of PMNs within diabetic choriocapillaris that was positively correlated with the size of the areas of CCD, but there was no correlation in non-diabetic subjects.

The BLDs were recognized in some specimens in the flat perspective by their yellow translucent appearance (Figure 3, B) and in cross-sections by the characteristic brush border–like appearance and affinity for the PAS stain. In group 2 choroids, the thickness of the BLDs ranged from 0.46 to 1.86 µm (0.80±0.18 µm), and the thickness was greater in areas with CCD. In group 1, the thickness of the BLDs varied within fields that were measured (eg, as in Figure 3, C) and varied by the region of choroid (Figure 6). The thickest BLDs in group 1 were in equatorial regions with CCD; peripheral and posterior regions with CCD had comparable BLD thicknesses (Figure 6). The thickness of BLDs in group 2 was greater in areas of diffuse CCD than in areas without CCD (P<.001), but was greatest in areas with focal CCD (P=.015; Figure 7). The range of thickness in group 1 was 0.8 to 12.0 µm (1.61±0.57 µm) in areas without CCD, so the thickness of BLDs was greater in areas in the group 1 eyes without CCD than it was in areas in the group 2 eyes with focal CCD (P<.001; Figure 7). The thickness of BLDs in group 1 was greatest (5.28±1.26 µm), however, in areas with focal CCD, compared with areas with diffuse CCD or without CCD (1.61±0.40 µm; P<.001; Figure 7). Therefore, the thickness of BLDs was related to the severity of the CCD in group 1 eyes.
OTHER PATHOLOGIC CHANGES IN GROUP 1 CHOROIDS

We confirmed a previous finding that CNV develops in diabetic eyes. In the group 1 choroids analyzed in the present study, CNV was found only within areas of diffuse CCD, not within areas of focal CCD (Figure 8). However, we observed CNV near the border of focal CCD areas (Figure 9). The origin of CNV in the diffuse areas of CCD was usually capillaries with relatively intense alkaline phosphatase activity. All CNV formations were beneath the RPE cells, and most were located in the peripheral choroid. Of the 12 CNV formations we observed in group 1, 50% were atrophic, ie, they lacked endothelial cells and, therefore, alkaline phosphatase activity. Although the areas of focal CCD usually had more substantial BLDs, the thickest BLD formation we observed was associated with peripheral CNV in a diffuse area of CCD from a case in group 1 (Figure 6). In our limited series, we found no CNV in group 2 eyes.

Figure 1. A, Montage flat view of a region in the superior peripheral choroid obtained from a 79-year-old nondiabetic subject (case 3) showing normal alkaline phosphatase activity in choroidal capillaries, arteries (a), and veins (v). There is a small focal area of capillary dropout (arrow) that lacks alkaline phosphatase activity (alkaline phosphatase and nonspecific esterase [NSE] reaction product, original magnification ×45). B, Section of choroid obtained from the same subject that demonstrates normal alkaline phosphatase activity in the choriocapillaris (alkaline phosphatase and NSE reaction product with periodic acid-Schiff and hematoxylin, original magnification ×780).

Figure 2. Montage flat view of peripheral choroid obtained from a 69-year-old diabetic subject (case 9) demonstrates a large area (4.4 mm²) of focal choriocapillaris degeneration (CCD), ie, there is complete loss of alkaline phosphatase staining. There are many nonspecific esterase (NSE)-positive polymorphonuclear leukocytes present in this area of focal CCD, and some are queued within atrophic vessels (arrows) (alkaline phosphatase and NSE reaction product; original magnification ×45).
We found other morphologic changes unique to diabetic choroid and Bruch’s membrane. Periodic acid–Schiff reagent–positive wartlike structures, which appeared to compress capillary lumens (Figure 10), were present most often in areas with diffuse CCD. Another degenerative change associated with Bruch’s membrane in group 1 was increased PAS-positive material within the intercapillary spaces, which closely embraced the capillaries (Figure 10, C). Because the wartlike structures and the material in the intercapillary spaces were PAS-positive and seemed contiguous with Bruch’s membrane, the 2 structures may be composed of similar material that is deposited in different places (Figure 10).

**COMMENT**

The ability to distinguish viable and nonviable choriocapillaris by using the alkaline phosphatase flat-embedding technique permitted us to measure the areas of focal CCD in diabetic and nondiabetic eyes. Labeling with nonspecific esterase permitted determination of the

Figure 3. A, Flat view of an area with diffuse choriocapillaris degeneration (CCD) obtained from a 58-year-old subject with type 1 diabetes (case 7). Some vessels in this area show reduced alkaline phosphatase reaction, while others show normal levels of reaction product. There are queues of polymorphonuclear leukocytes (PMNs) within some vascular segments (alkaline phosphatase and nonspecific esterase (NSE) reaction product, original magnification ×55). B, Higher magnification of the area outlined in Figure 3, A, in which PMNs are queued in capillaries (straight arrows) that have reduced alkaline phosphatase activity in this diffuse area of CCD. The dark structure (curved arrow) was gold-brown in the preparation and represents a thick basal laminar deposit (BLD) (alkaline phosphatase and NSE reaction product, original magnification ×225). C, Section through the area outlined in Figure 3, A, and Figure 3, B, demonstrates PMNs (arrows) within 4 consecutive choriocapillaris lumens (arrows in Figure 3, B). This area is similar in appearance to an area of complete or focal CCD because all capillaries lack alkaline phosphatase activity. The PMNs were associated with the endothelial cells (arrowheads) of the capillaries that lacked alkaline phosphatase activity. A BLD (curved arrow) is present above Bruch’s membrane in this area. The thickest portion of the BLD (curved arrow) represents the dark area in Figure 3, B (alkaline phosphatase and NSE reaction product with periodic acid–Schiff and hematoxylin, original magnification ×395).

Figure 4. The percentage (±SD) of choroid with choriocapillaris degeneration (CCD). The data for the subjects were paired so that diabetic subjects and nondiabetic subjects of similar ages could be directly compared. The mean±SD age of diabetic subjects (group 1) was 65.2±11.8 years and for nondiabetic subjects (group 2), 79.6±5.0 years. For all comparisons shown, the difference between the diabetic subject and the nondiabetic subject was statistically significant (P<.001). NA indicates not available.
relationships of PMNs and mast cells to the degenerative capillaries. Kohner and Henkind demonstrated in retinal tissue that vascular perfusion was associated only with blood vessels containing an intact endothelial cell lining, so we speculate that areas with CCD were nonperfused. Although we observed small focal areas of CCD in group 2, the percentage of choroid with focal CCD was 4-fold greater in group 1 than in group 2. As the number of degenerative capillaries increased (diffuse CCD compared with focal CCD), the thickness of BLDs increased, suggesting that deposition of this material at Bruch's membrane was related to the atrophy of the choriocapillaris. The CNV we observed was most often associated with areas exhibiting diffuse CCD rather than peripheral chorioretinal atrophy ("paving stone" areas with complete or focal CCD).

Peripheral CCD has been documented in subjects with peripheral chorioretinal atrophy ("paving stone" degeneration), and the incidence increases with age.10,11 One might argue that the CCD we observed in group 1 was due to diabetes-related acceleration of the aging process. However, the mean age of the nondiabetic subjects was 14 years more than the mean age of the diabetic subjects, and the CCD we observed in the diabetic choroid was more than 4-fold greater than that in the nondiabetic choroid. In addition, the CCD we report in group 1 was greater in the posterior pole than in the periphery. It has been hypothesized that choroidal nonperfusion was associated with BLDs and CNV in age-related macular degeneration.12 Our study of diabetic choroids lends credence to both hypotheses. The thickness of BLDs increased as CCD became more severe, ie, focal CCD areas had the greatest mean thickness of BLDs.

As in the retina, the cause of vaso-occlusion in the diabetic choroid is unknown. A previous study and the current study suggest several contributing factors. Lutty et al reported increased numbers of PMNs in the human diabetic choriocapillaris vasculature compared with the choriocapillaris vasculature in nondiabetics. The PMNs were often associated with CCD (loss in alkaline phosphatase activity) in the diabetic choroids and often were queued in atrophic alkaline phosphatase–negative capillary segments.7 McLeod et al observed elevated levels of P-selectin and intracellular adhesion molecule 1 in diabetic choroids compared with control nondiabetic choroids; these substances stimulate PMN rolling and adhesion to endothelial cells, respectively. The diabetic PMN produces a greater oxidative burst,14 which could contribute to the endothelial cell loss we observed in CCD areas. The PMNs also release proteolytic enzymes that could further damage endothelial cells.15,16

A structurally and functionally normal choroidal vasculature is essential for normal function of the retina. Compromised choroidal blood flow can result in photoreceptor dysfunction and death. The CCD we observed in group 1 may be responsible for the reduced visual function observed in subjects with diabetes before the onset of retinopathy.17,18 Compromised choriocapillaris can result in insufficient removal of waste generated by the RPE cells, causing an accumulation of such waste at Bruch’s membrane.18,19-21 Our study demonstrated that BLDs increased in thickness with increasing severity of choriocapillaris degeneration, ie, with increased loss in viable capillary segments. In addition, the thickness of the BLDs was greater in diabetics in our se-
ries than in nondiabetics. Other Bruch’s membrane–related deposits associated with CCD were wartlike structures that seemed to impinge on capillary lumens and PAS-positive material within the intercapillary spaces. Whether this material was related to debris from RPE cells or was simply modification of the tissue by the vascular cells in the capillaries cannot be determined from our study. This material may contribute to the decreased capillary diameters we observed in subjects with diabetes (J.C. and G.A.L., unpublished data, 1997).

We observed CNV that was mostly beneath the RPE cells and within Bruch’s membrane. McLeod and Lutty⁶ made the same observation. The importance of these formations is unknown, and they have rarely been reported in the clinical literature. One reason that CNV in subjects with diabetes may have escaped clinical detection is that CNV seems to have a high rate of autoinfarction in diabetes. Fifty percent of the formations we observed in this study and many observed by McLeod and Lutty⁶ were atrophic. In addition, they may not threaten...
vision, owing to rapid autoinfarction or their peripheral location. It is noteworthy that CNV formations were most often associated with diffuse CCD and not complete focal loss. The areas of focal CCD may be atrophic, while the areas of diffuse loss may actually represent ischemic areas that Michaelson and others suggested would elicit production of neovascularization at least in the retina. Ischemia resulting from choroidal nonperfusion might also stimulate the RPE cells to produce angiogenic growth factors.

Although the term diabetic choroidopathy was coined by Hidayat and Fine in 1985, a definitive description of the choroidopathy and its progression has not been defined. The eyes in which Hidayat and Fine observed diabetic choroidopathy were removed from patients with end-stage disease because of blindness and pain. None of the eyes in our study had proliferative retinopathy, and the changes we observed in the choroid seemed to represent earlier stages in the disease process than the changes observed by Hidayat and Fine. If the data from these and other studies are considered together, diabetic choroidopathy could be defined as follows: PAS-positive material is deposited in the intracapillary stroma, often impinging on the capillary lumens (wartlike material). The PAS-positive thickened basilar laminar deposits that Hidayat and Fine reported may occur at a later stage. Choriocapillaris compromise occurs in small segments of lumens (diffuse CCD) or in
areas in which a complete loss of vasculature is present (focal CCD). Fryczkowski et al also observed choroidal compromise by using a vascular cast preparation technique. In areas of choroidal compromise, BLDs may be found. The thickness of the BLDs seems dependent on the severity of CCD, suggesting that compromise or choroidal ischemia may be related to the deposition of the material in BLDs. In areas of diffuse loss, CNV may occur. Hidayat and Fine observed CNV in 2 of 8 eyes they studied. Fukushima et al also observed intrachoroidal neovascularization in subjects with diabetes. The only aneurysms we observed in the diabetic choroid were associated with these intrachoroidal neovascular formations.

The changes that we and others have observed suggest that vaso-oclusions and resultant nonperfusion occur in the diabetic choroid, as well as in the retina. The cause of choroidal nonperfusion is unknown, as it is in the diabetic retina, but PMNs may contribute to occlusive processes. As in the retina, when ischemic conditions exist, CNV may form. The result of diabetic choroidopathy may be the unexplained loss of visual function that occurs in diabetic subjects without retinopathy.

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REFERENCES


Error in “Conclusions” Section of Abstract. In the article titled “Aqueous Humor Uric Acid and Ascorbic Acid Concentrations and Outcome of Trabeculectomy,” in the March issue of the ARCHIVES (Arch Ophthalmol. 1998;116:281-285), extraneous copy was accidentally included in the “Conclusions” section of the structured abstract. The correctly worded “Conclusions” section is printed here. The journal regrets the error.

Conclusions: Uric acid levels were higher at the time of surgery in eyes that had unsuccessful outcomes than in those with successful outcomes. No significant difference in ascorbic acid levels was detectable. A higher uric acid level in the aqueous humor is a risk factor for trabeculectomy failure and might be tested as a prognostic indicator.