INTRODUCTION

In this chapter, we consider a group of glaucomas in which a tissue element lines the anterior chamber angle. The tissue element may be a fibrovascular membrane, an endothelial, epithelial, or fibrous layer, or an inflammatory membrane. In the early stages of these glaucomas, the angle is typically open, and the resistance to aqueous outflow is created by the tissue element lining the inner surface of the trabecular meshwork. In the later stages, however, the tissue element contracts, creating obstruction to outflow by closure of the anterior chamber angle.

NEOVASCULAR GLAUCOMA

This is the most common form of glaucoma within the pretrabecular group of mechanisms. It is characterized by neovascularization on the anterior surface of the iris (rubeosis iridis or NVI) and in the anterior chamber angle (NVA). The natural history of the NVA, that is, if untreated, leads in most cases to the formation of a fibrovascular membrane over the trabecular meshwork, which initially causes the open-angle form of neovascular glaucoma (NVG) and subsequently contracts to cause the closed-angle form of NVG. The initiating factor in the majority of cases, however, is an abnormality in the posterior aspect of the eye, which leads to a hypoxic disorder of the retina and the subsequent neovascularization in the anterior chamber.
**Initiating Factors**

The two most common initiating conditions leading to the retinal hypoxia are diabetic retinopathy and central retinal vein occlusion (CRVO). Approximately, one-third of the cases of rubeosis iridis and subsequent NVG are related to diabetic retinopathy (1,2), and the frequency of this association is increased with pars plana vitrectomy for proliferative retinopathy (3), an unrepaired retinal detachment after vitrectomy (4), and cataract extraction, especially with an open posterior capsule (5). CRVO accounts for approximately another one-third of cases of NVG (1). Predisposing conditions for CRVO include elevated intraocular pressure (IOP) and systemic hypertension. Other retinal vascular occlusive events that less commonly lead to NVG include central retinal artery disease, branch retinal vein occlusion, and branch retinal artery occlusion. The third most common initiating event is carotid artery obstructive disease, with subsequent retinal ischemia, which accounted for 13% of NVG in one series (2). Other conditions that may lead to retinal hypoxia and subsequent rubeosis irides include rhegmatogenous retinal detachment, a choroidal melanoma beneath a retinal detachment, sickle-cell retinopathy, and carotid-cavernous fistula. One initiating event for rubeosis iridis, that is not associated with retinal hypoxia, is chronic anterior uveitis, which was seen in 11% of one series (1) and 1.5% of another series (2) of NVG.

**Theories of Angiogenesis**

In all of the initiating events, with the exception of anterior uveitis, a common feature is the retinal hypoxia. This appears to stimulate the release of the diffusible angiogenic peptides, such as vascular endothelial growth factor (VEGF), which is synthesized by several types of retinal cells although Müller cells appear to be the main source of VEGF under conditions of retinal ischemia (6,7). Evidence supporting the role of VEGF in ocular neovascularization include the observations that elevated levels of VEGF have been identified in the aqueous humor of patients with NVG (8), and neutralizing VEGF antibodies prevented NVI in a nonhuman primate model of retinal vein occlusion (9).

Although VEGF is the most extensively studied proangiogenic factor in the mechanism of NVG, others factors are also released by endothelial cells in response to specific stimuli, such as hypoxia, including basic fibroblast growth factor, tumor necrosis factor-α, insulin-like growth factor, and platelet-derived growth factor.

Physiologically, the vasculature appears to be maintained in a quiescent state through a delicate balance between proangiogenic and antiangiogenic factors. In the eye, this balance is largely between VEGF and the antiangiogenic factor, pigment epithelium-derived growth factor (PEDF) (10). An imbalance of the VEGF–PEDF equilibrium has been documented in the vitreous of eyes with proliferative diabetic retinopathy, that is, increased VEGF and decreased PEDF (11). This process in turn stimulates a cascade that results in the activation, proliferation, and migration of endothelial cells, resulting in the formation of new, leaky, fragile blood vessels. The diffusible nature of the angiogenic peptides may explain the increased risk for rubeosis iridis following removal of the vitreous or lens, that is, elimination of barriers between the posterior and anterior segments. An alternative theory is that vasoinhibitory factors may be released by the vitreous (12) or lens (13).