changes in the glomerular mesangium. This discussion focuses on the retinal microangiopathy associated with diabetes mellitus, a prototype for the consideration of other retinal microangiopathies.

MORPHOLOGY

The retinal vasculopathy of diabetes mellitus can be classified into **nonproliferative** and **proliferative diabetic retinopathy**.

Nonproliferative diabetic retinopathy includes a spectrum of changes resulting from structural and functional abnormalities of retinal vessels (i.e., confined beneath the internal limiting membrane of the retina). As with diabetic microangiopathy in general, the **basement membrane of retinal blood vessels is thickened**. In addition, the number of pericytes relative to endothelial cells diminishes. **Microaneurysms** are an important manifestation of diabetic microangiopathy. They are typically smaller than the resolution of direct ophthalmoscopes, and findings customarily described as microaneurysms by ophthalmoscopy may in fact be retinal microhemorrhages. Structural changes in the retinal microcirculation have been associated with a physiologic breakdown in the blood-retinal barrier. Recall that VEGF was initially called vascular permeability factor. Thus, the retinal microcirculation in diabetics may be exceptionally leaky, giving rise to **macular edema**, a common cause of visual loss in these patients. The vascular changes may also produce **exudates** that accumulate in the outer plexiform layer. Although the retinal microcirculation is often hyperpermeable, it is also subject to the effects of micro-occlusion. Both vascular incompetence and vascular micro-occlusions can be visualized clinically after intravenous injection of fluorescein. Nonperfusion of the retina due to the microcirculatory change described earlier is associated with up-regulation of VEGF and intra-retinal angiogenesis (located beneath the internal limiting membrane of the retina).

Proliferative diabetic retinopathy is defined by the appearance of new vessels sprouting on the surface of either the optic nerve head (termed "neovascularization of the disc") or the surface of the retina ("designated by the nebulous term neovascularization elsewhere") (Fig. 24-42*C*). The term "retinal neovascularization" is only applied when the newly formed vessels breach the internal limiting membrane of the retina. The quantity and location of retinal neovascularization guide the ophthalmologist in the treatment of proliferative diabetic retinopathy. The web of newly formed vessels is referred to as a neovascular membrane. It is composed of angiogenic vessels with or without a substantial supportive fibrous or glial stroma (Fig. 29-21*B*).

If the vitreous humor has not detached and the posterior hyaloid is intact, neovascular membranes extend along the potential plane between the retinal internal limiting membrane and the posterior hyaloid. If vitreous humor later separates from the internal limiting membrane of the retina **(posterior vitreous detachment)** there may be massive hemorrhage from the disrupted neovascular membrane. In addition, scarring associated with the organization of the retinal neovascular membrane may wrinkle the retina, disrupting the orientation of retinal photoreceptors and producing visual distortion, and may exert traction on the retina, separating it from the RPE (retinal detachment). **Traction retinal detachment** may begin as a non-rhegmatogenous detachment, but severe traction may tear the retina, producing a traction rhegmatogenous detachment.

Retinal neovascularization may be accompanied by the development of a neovascular membrane on the iris surface, presumably secondary to increased levels of VEGF in the aqueous humor. Contraction of the iris neovascular membrane may lead to adhesions between the iris and trabecular meshwork (anterior synechiae), thus occluding a major pathway for aqueous outflow and thereby contributing to elevation of the intraocular pressure **(neovascular glaucoma)**.

Ablating nonperfused retina by laser photocoagulation or cryopexy triggers regression of both retinal and iris neovascularization, emphasizing the central role that retinal hypoxia has in these disorders. More recently, the injection of VEGF inhibitors into the vitreous has been used to treat diabetic macular edema and retinal neovascularization, a successful example of how knowledge of the molecular pathogenesis of a condition may evolve into a successful therapeutic strategy.

Retinopathy of Prematurity (Retrolental Fibroplasia)

At term, the temporal (lateral) aspect of the retinal periphery is incompletely vascularized whereas the medial aspect is vascularized. In premature or low-birth-weight infants treated with oxygen, immature retinal vessels in the temporal retinal periphery constrict, rendering the retinal tissue distal to this zone ischemic. Retinal ischemia may result in up-regulation of proangiogenic factors such as VEGF and lead to retinal angiogenesis. Contraction of the resulting peripheral retinal neovascular membrane may "drag" the temporal aspect of the retina toward the peripheral zone, displacing the macula (situated temporal to the optic nerve) laterally. Neovascular membrane contraction may create sufficient force to cause retinal detachment. The use of VEGF inhibition in this condition is under investigation.

Sickle Retinopathy, Retinal Vasculitis, Radiation Retinopathy

Retinopathy affecting individuals with sickle hemoglobinopathies (Chapter 14) has been divided into two types that roughly parallel those used for diabetic retinopathy: nonproliferative (intraretinal angiopathic changes) and proliferative (retinal neovascularization). The final common pathway in both types is vascular occlusion. Low oxygen tension within the blood vessels in the retinal periphery results in red cell sickling and microvascular occlusions. In the nonproliferative form (which occurs in individuals with hemoglobin SS and SC genotypes), *vascular occlusions* are thought to contribute to preretinal, intraretinal, and subretinal hemorrhages. The resolution of these hemorrhages may give rise to several ophthalmoscopically visible changes, known as *salmon patches, iridescent spots,* and *black sunburst lesions*. Organization of pre-retinal hemorrhage may result in retinal traction and *retinal detachment*. Vascular occlusions may also contribute to angiogenesis secondary to up-regulation of both VEGF and basic fibroblast growth factor. This can give rise to