# 5
# Angiography of Retinal Vascular Diseases

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The optical properties of the eye make the ocular fundus the only location in the human body where direct noninvasive monitoring of vascular flow is possible. During fluorescein angiography (FA) and indocyanine green videoangiography (ICGV), a rapid sequence of serial photographs taken after the intravenous administration of fluorescein or indocyanine green (ICG) is used to visualize and document choroidal and retinal blood flow. Other than blood flow, FA and ICGV provide information about the integrity of the blood–retinal barriers and the fine details of the retinal pigment epithelium (RPE), and provide a glimpse of associated systemic pathology. Although both technologies reveal important and different aspects of retinal and choroidal diseases, some phases of various diseases are best seen with FA and other aspects are best revealed with ICGV.

This chapter reviews several vascular pathologies of the retina including diabetic retinopathy (DR), retinal vascular occlusions, retinal arterial macroaneurysms, radiation retinopathy, ocular ischemic syndrome, hypertensive retinopathy, Coats' disease, parafoveal telangiectasia, sickle cell retinopathy, and Eales' disease.

## Diabetic Retinopathy

Currently we are facing a worldwide epidemic of diabetes mellitus (DM). In the year 2000, more than 176 million people throughout the world suffered from DM. The World Health Organization has estimated that by the year 2030 there will be 370 million people affected with DM in the world, and every one of them will be at risk of developing retinopathy. The degree and duration of hyperglycemia, as well as hypertension and hyperlipidemia are risk factors that increase the severity and development of diabetic retinopathy (DR).[1–4]

The first report of DR, specifically diabetic macular edema (DME), appeared in 1856.[5,6] Prior to the advent of panretinal photocoagulation, proliferative diabetic retinopathy (PDR) was the main culprit of diabetic blindness. Since the development of laser photocoagulation, DME has become the most common cause of visual loss in diabetic patients in the developed world. It is estimated that in the United States alone there are 500,000 patients with DME, with 95,000 new cases every year.[7–9]

### Pathogenesis

Hyperglycemia, by a poorly understood mechanism, causes leukostasis, which leads to endothelial dysfunction and progressive retinal ischemia.[10] In fact, DR is the prototype for the ischemic retinopathies where ongoing retinal ischemia causes upregulation of vascular endothelial growth factor (VEGF).[11] Diabetic macular edema is characterized by the accumulation of intraretinal fluid, which is modulated by the balance between oncotic and hydrostatic pressures as described by Starling's law.[12] Vascular endothelial growth factor, also known as vascular permeability factor (VPF), plays a central role in the pathogenesis of DME.[13–15] Disruption of the blood–retinal barrier, which results in an increase of vascular permeability, is caused by VEGF. As the intraocular levels of VEGF increase, its angiogenic properties promote retinal neovascularization and its sequelae.[14]

### Classification

Although the modified Airlie House Classification used in the Early Treatment of Diabetic Retinopathy Study (ETDRS) is considered to be the gold standard classification scheme for DR, most ophthalmologists and even retinal specialists shun its use in their daily clinical work. It is an excellent tool in the research setting but its clinical applicability is limited due to its complexity.

At the 2002 joint meeting of the American Academy of Ophthalmology and the Pan-American Association of Ophthalmology, a new classification was unveiled: the International Clinical Diabetic Retinopathy Disease Severity Scale,

which is based on the findings of the Wisconsin Epidemiologic Study of Diabetic Retinopathy and the ETDRS. It consists of five levels: no DR, mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and PDR. In addition, the presence or absence of macular edema should be noted. If edema is present, then one should note if the edema involves the center (severe DME), threatens the center (moderate DME), or is far from the center (mild DME) (Fig. 5.1).[16]

Mild NPDR consists solely of microaneurysms. The findings in moderate NPDR fall in between mild and severe NPDR. The diagnosis of severe NPDR is based on the 4:2:1 rule of the ETDRS. One can easily diagnose severe NPDR by mentally dividing the fundus into four quadrants centered on the optic nerve and examining the four midperipheral quadrants with slit-lamp biomicroscopy. If hemorrhages of at least the magnitude of standard photograph Figure 5.2A are present in all four quadrants, then by definition severe NPDR is present. If two quadrants or more have venous beading of the same magnitude or greater than standard photograph Figure 5.2B, then by definition severe NPDR is present. If one or more quadrant has intraretinal microvascular abnormalities (IRMAs) of the same magnitude or greater than standard photograph Figure 5.2C, then by definition severe NPDR is present (Fig. 5.2).

## Clinical Findings

Diabetic retinopathy represents a spectrum of disease that can be broadly divided into a nonproliferative stage and a proliferative stage. The first clinical sign of NPDR is the appearance of microaneurysms. With increasing severity, intraretinal hemorrhages start to appear. These hemorrhages may be flame shaped or round dot blots. If the retinal ischemia persists, cotton-wool spots, venous beading, tortuosity of the retinal veins, and IRMAs will develop.

As the degree of ischemia increases, PDR develops (Figs. 5.3 and 5.4). It is characterized by all the prior in addition to neovascular and fibrovascular proliferation. It may appear at the disc (neovascularization of the disc [NVD]) or at the junction of perfused and nonperfused retina (neovascularization elsewhere [NVE]). Partial posterior vitreous detachment caused tangential and anteroposterior traction that leads to vitreous hemorrhage, rhegmatogenous, and tractional retinal detachment.

Diabetic macular edema may be present at any stage of DR and may be focal or diffuse. In the focal type, usually there are microaneurysms surrounded by a ring of hard exudates (Fig. 5.5). In the diffuse type, usually there are no hard exudates or microaneurysms. In a small number of eyes, one may observe a glistening, taut, and thickened posterior hyaloid that exerts vitreomacular traction.[17]

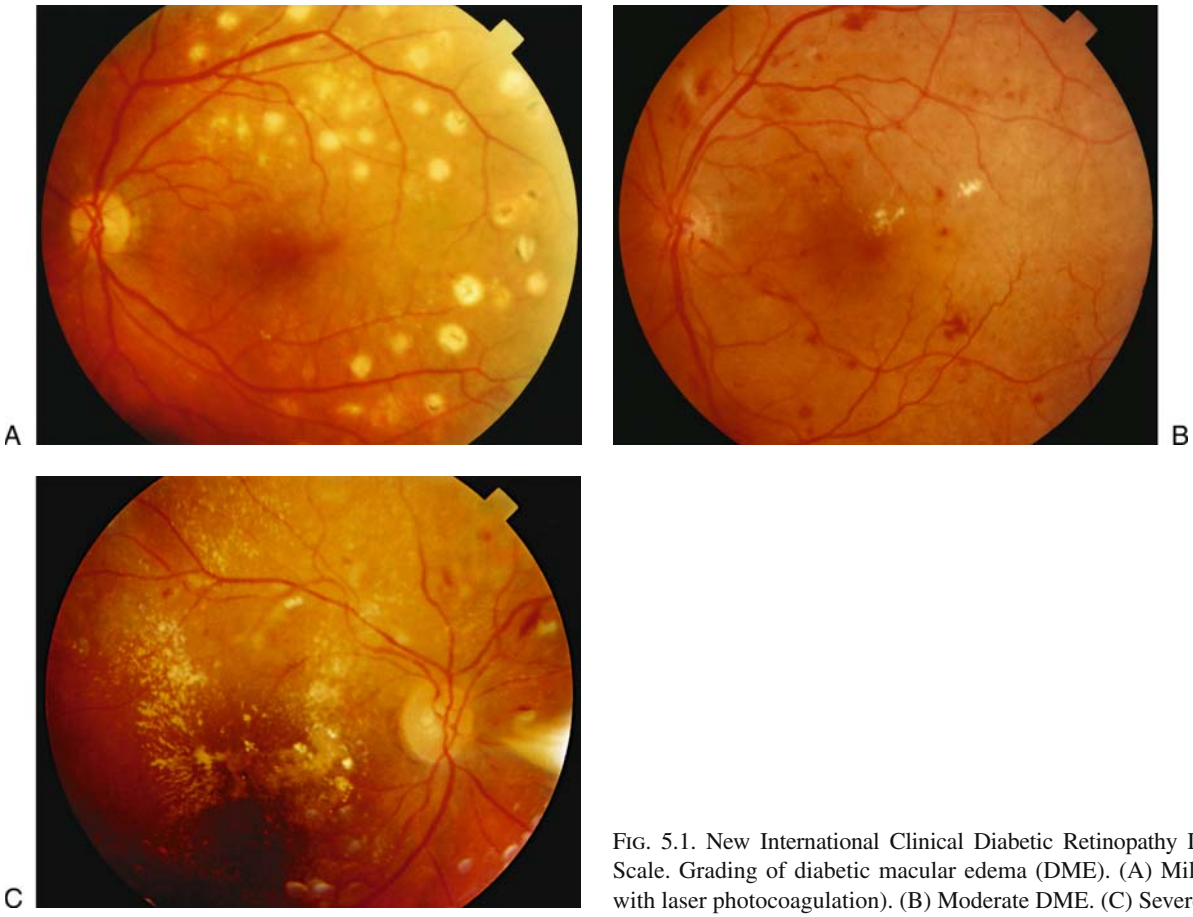


Fig. 5.1. New International Clinical Diabetic Retinopathy Disease Severity Scale. Grading of diabetic macular edema (DME). (A) Mild DME (treated with laser photocoagulation). (B) Moderate DME. (C) Severe DME.

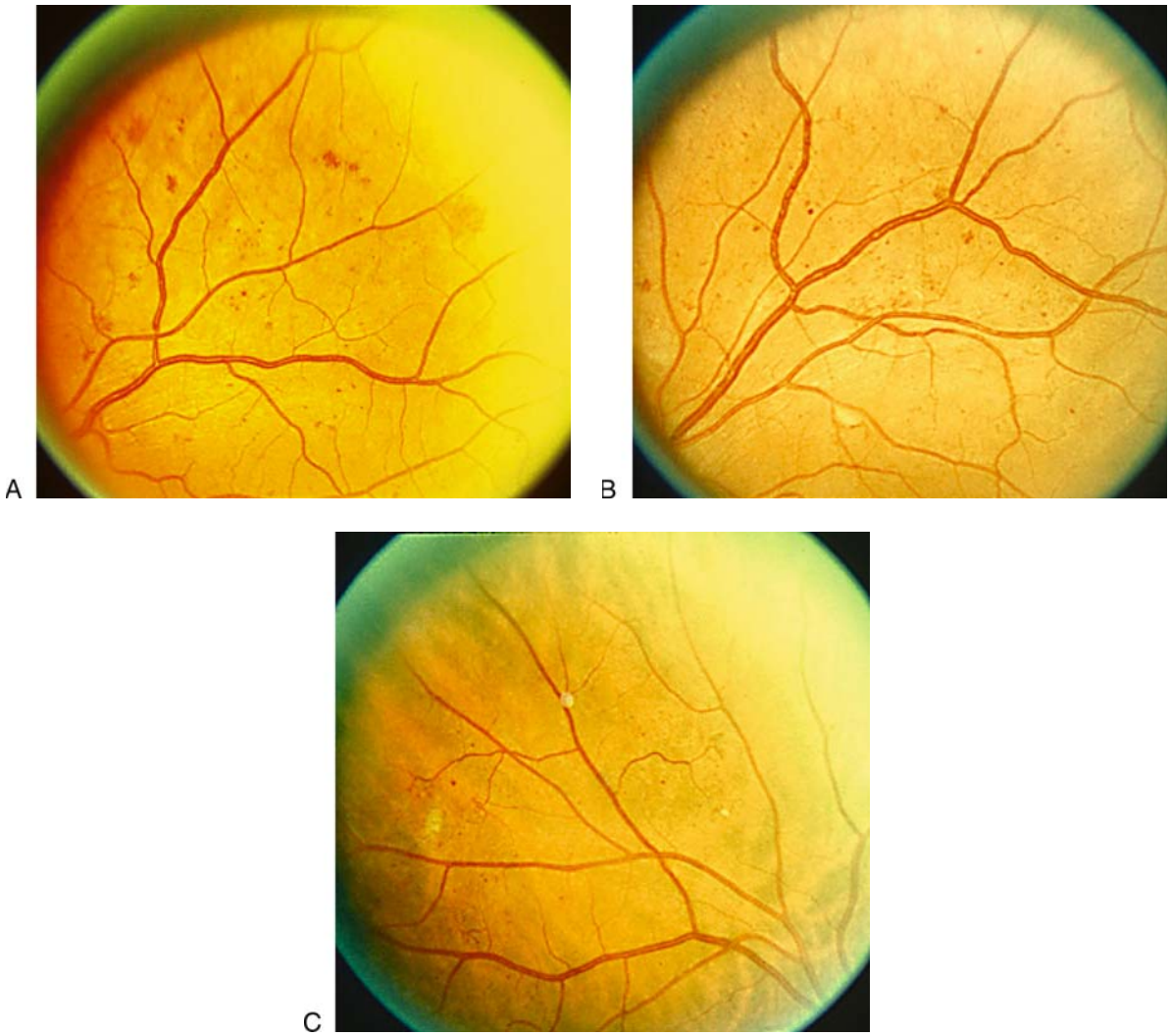


FIG. 5.2. Clinical determination of severe nonproliferative diabetic retinopathy (NPDR). (A) If hemorrhages of at least the magnitude of this standard photograph are present in all four quadrants, then by definition severe NPDR is present. (B) If two quadrants or more have venous beading of the same magnitude or greater than this standard photograph, then by definition severe NPDR is present. (C) If one or more quadrant has intraretinal microvascular abnormality (IRMA) of the same magnitude or greater than this standard photograph, then by definition severe NPDR is present. (Reprinted with permission from the Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison, WI.)

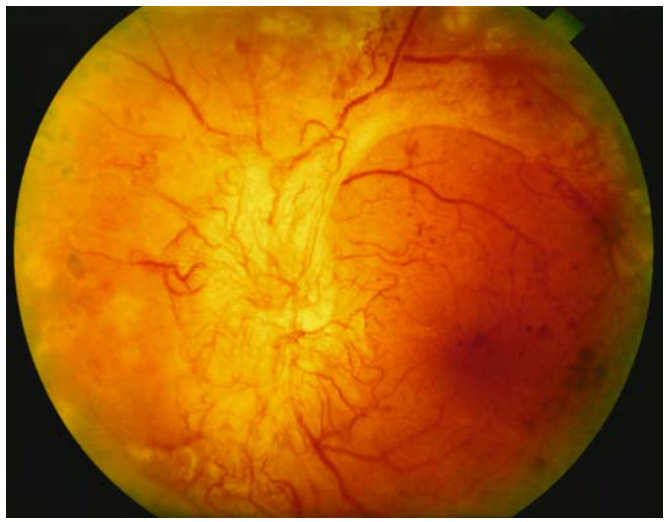

FIG. 5.3. Proliferative diabetic retinopathy. Neovascularization of the disc (NVD).

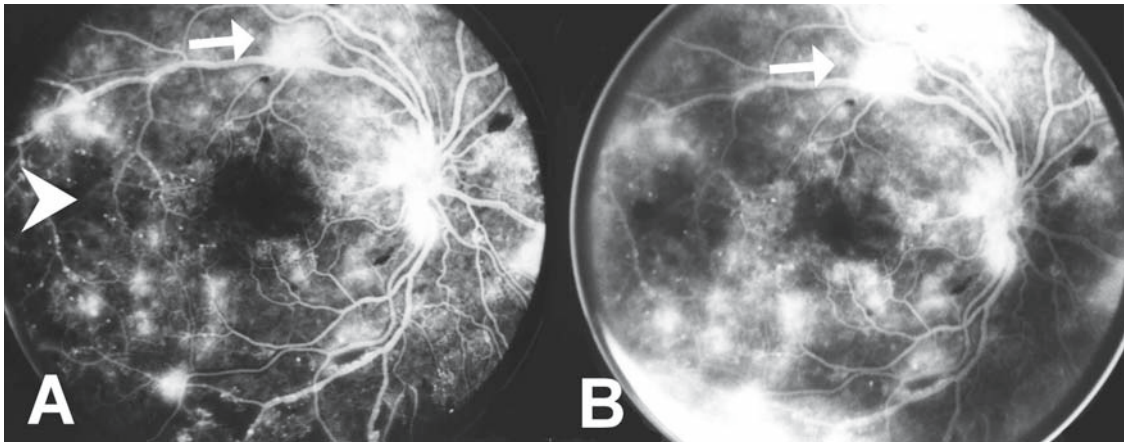


Fig. 5.4. Fluorescein angiography (FA) in proliferative diabetic retinopathy demonstrating neovascularization elsewhere (NVE). (A) Microaneurysms appear as pinpoint hyperfluorescent lesions, and capillary nonperfusion is seen as hypofluorescent zones (arrowhead). (B) Fluorescein angiography shows the sequence of leakage from a patch of neovascularization superior to the optic disc (arrows in A and B).

## Fluorescein Angiography

Microaneurysms appear as pinpoint hyperfluorescent lesions that fade in the later phases of the angiogram. The hypofluorescence of dot and blot hemorrhages distinguishes them from the hyperfluorescent microaneurysms. Areas of capillary nonperfusion are seen as homogeneous dark patches.

Neovascularization usually occurs at the border of perfused and nonperfused retina. Prior to the appearance of frank neovascularization, IRMA develops. The angiographic appearance of IRMA is of collateral vessels that do not leak. On the other hand, neovascularization is characterized by hyperfluorescent leaking areas that increase in size and intensity as the study progresses (Figs. 5.4 and 5.6).

The earliest change in diabetics is an increased vascular permeability, which is seen as late hyperfluorescence emanating from the retinal vessels (Fig. 5.7). If the macula is not clinically edematous, this hyperfluorescence should not be interpreted as macular edema.

## Optical Coherence Tomography

Optical coherence tomography (OCT) has come to revolutionize the management of macular diseases because it can objectively measure retinal thickness, which correlates better with visual acuity rather than fluorescein leakage.[18] Normal foveal thickness as measured by OCT has been reported to be 152 ± 21 μm.[19] Diabetic macular edema is imaged as a zone of low reflectivity in the outer retinal layers. The low reflectivity is due to the accumulation of intraretinal fluid.

## Treatment

### *Laser Photocoagulation*

The ETDRS showed that panretinal photocoagulation reduces the risk of severe visual loss in eyes with high-risk characteristics

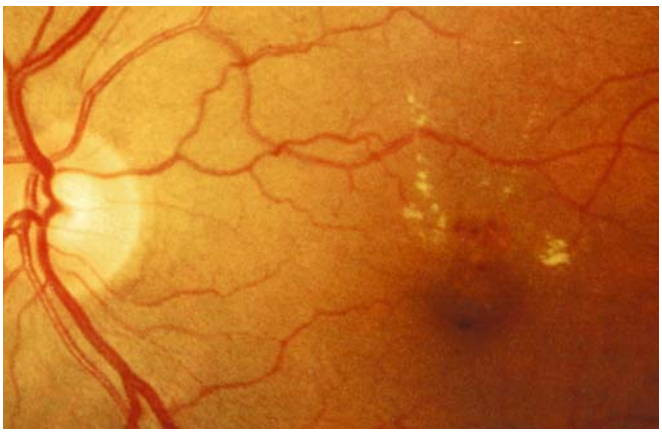

Fig. 5.5. Diabetic macular edema (DME). Focal DME threatening the fovea in an eye with mild NPDR. Notice the hard exudates and the microaneurysms.

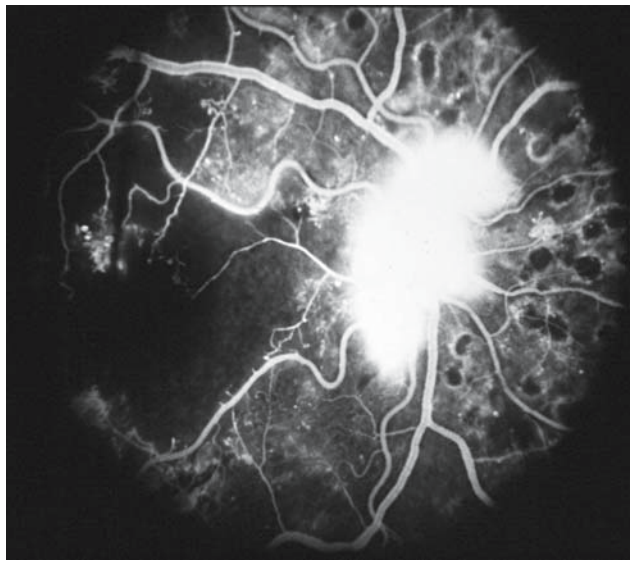

Fig. 5.6. Fluorescein leakage from neovascularization. Late-phase fluorescein angiogram shows leakage from a patch of NVE superior to the optic disc.

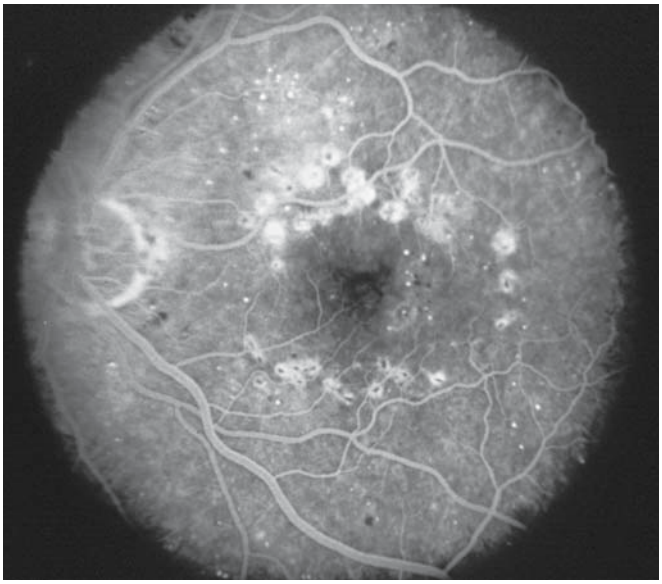

FIG. 5.7. Diabetic macular edema. FA frame shows laser scars in a circular pattern around the fovea.

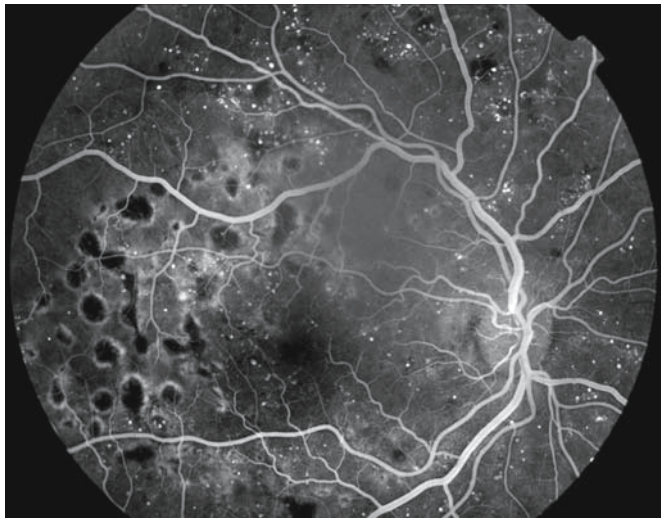

FIG. 5.9. Expansion of the chorioretinal scars with time. Three years prior to this photograph, the patient underwent focal photocoagulation for DME. Notice how some of the laser scars (original laser spot size 75 μm) have expanded and coalesced.

by 50% (Fig. 5.8).[20] The ETDRS has defined cotton-spot macular edema (CSME) as retinal thickening within 500 μm of the foveal center; hard exudates within 500 μm of the foveal center, if they are associated with adjacent retinal thickening; and retinal thickening of at least one disc area in size, with part of this thickening being within one disc area of the foveal center, and should be considered for focal or grid macular photocoagulation. In eyes with severe NPDR, similar results were seen.

Macular photocoagulation is a very safe procedure. Without a doubt, inadvertent foveal photocoagulation is a disaster. To avoid this complication, it is recommended that any eye with DME with distortion of the macular anatomy should be treated in two or more sessions. Iatrogenic breaks of Bruch's membrane secondary to small spot sizes have caused choroidal neovascular membranes. Thermal ablation has been tried with limited success.[21,22] The use of photodynamic therapy with verteporfin and submacular surgery have been described.[23,24] It has been reported that laser scar expansion occurs with time (Fig. 5.9). Thus laser scars can coalesce and lead to paracentral scotomas. Subretinal fibrosis is a fairly uncommon complication in DME. Although it has been reported that subretinal fibrosis is associated with the intensity of the burn and small spot sizes, the ETDRS has shown that the severity of hard exudates is the most common risk factor.[25]

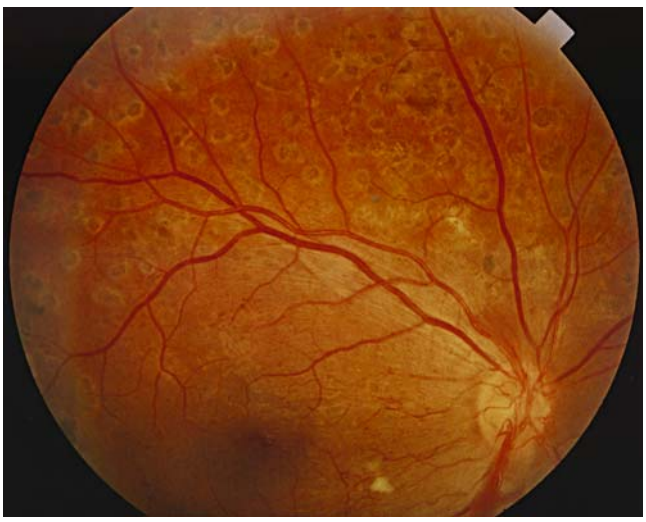

FIG. 5.8. Panphotocoagulation in an eye with neovascularization of the disc (NVD). Notice the chorioretinal scars outside the arcades.

### *Corticosteroids*

Recently it has been shown that triamcinolone through its antipermeability properties secondary to its anti-VEGF effects strengthens the blood–retinal barrier and prevents its disruption.[26] Intravitreal injection of 4 to 25 mg of triamcinolone has been described in the literature. The most common dose is 4 mg since it is easy to aliquot and inject 0.1 cc from the commercially available 40-mg/mL vial.[27,28] Optical coherence tomography has documented reduction in macular thickness and normalization of the macular anatomy following an intravitreal injection of triamcinolone (Fig. 5.10). Many eyes show an improvement in visual acuity. Complications include the progression of nuclear sclerosis, increase of intraocular pressure,[29] retinal detachments, sterile endophthalmitis,[30] and infective endophthalmitis.[31]

### *Anti–Vascular Endothelial Growth Factor Agents*

Since VEGF plays a major role in the pathogenesis of DME, anti-VEGF treatments have been proposed as an alternative treatment. The short-term functional and anatomic results

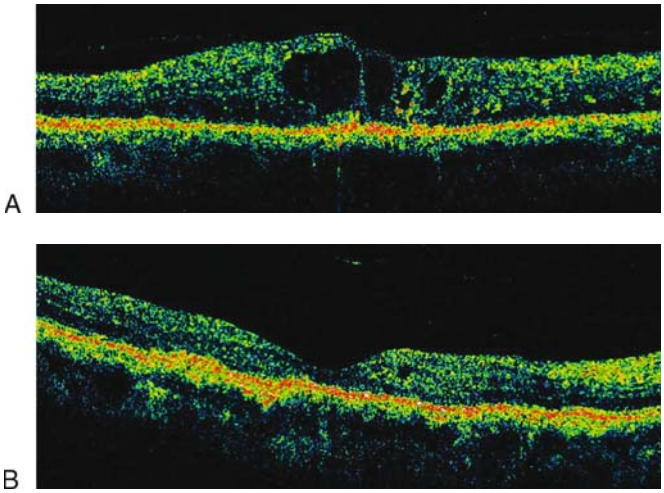


Fig. 5.10. Intravitreal triamcinolone. (A) Eye with DME refractory to laser treatment injected with 4 mg of intravitreal triamcinolone. (B) Optical coherence tomography (OCT) of the same eye 3 weeks following triamcinolone injection.

following an intravitreal injection of bevacizumab are very promising (Fig. 5.11).[32]

### *Vitrectomy*

The development and refinement of vitreous surgery has also been shown to be beneficial in the treatment of eyes with advanced proliferative disease. The indications of vitrectomy in DR include nonclearing vitreous hemorrhage, tractional retinal detachment, combined tractional and rhegmatogenous retinal detachment, severe fibrovascular proliferation, and DME.[33] Optical coherence tomography has documented a subset of eyes with DME secondary to vitreomacular traction and foveal serous detachment. Vitrectomy in these eyes improves visual acuity significantly. Others have reported visual success in eyes with DME without any macular tractional component.[34]

### *Other Treatments*

Several large prospective randomized clinical trials have shown that visual loss from DR can be avoided by macular photocoagulation, scatter photocoagulation, or vitreous surgery.[35] However, despite the findings and recommendations of these major clinical trials over the past few decades, diabetic retinopathy, especially DME remains an important cause of visual loss.

## Central Retinal Vein Occlusion

Much confusion exists in the literature because central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) often are clumped and studied together. But the natural history and complication rate for each entity is quite different. The treatments and their results vary from one condition to the other.

The first description of a CRVO was reported by Liebreich in 1854, but it was not until 1877 that von Michel correctly identified thrombosis as the cause of this condition. Histopathologic studies have shown thrombosis of the central retinal vein at the level of the lamina cribrosa.[36]

A survey from the Wilmer Eye Institute found that retinal vein occlusions (branch and central) were the second most common retinal vascular disorders after diabetic retinopathy. Epidemiologic studies have identified cardiovascular disease, diabetes mellitus, age over 55 years, and hypertension as important associations with CRVO.[37,38]

### Clinical Findings

The most common symptom is a sudden loss of central vision. Some patients may complain of transient obscurations of vision that last from a few seconds to minutes. Patients with neovascular glaucoma (NVG) complain of ocular pain and redness.

Acutely, CRVOs are characterized by some degree of dilation and tortuosity of the retinal veins. Intraretinal hemorrhages are seen in all four quadrants. The severity of these hemorrhages varies from a few scattered superficial hemorrhages to extensive full retinal thickness hemorrhages with breakthrough into the vitreous cavity. Patches of cotton-wool spots may be seen. The optic nerve is usually swollen (Fig. 5.12). Vitreous hemorrhage is occasionally seen.

In the chronic stages, the hemorrhages may have disappeared. Optic nerve head collaterals and macular edema may be the only residual ophthalmoscopic evidence that a prior CRVO had occurred.

One of the two major complications resulting from CRVO is macular edema (Fig. 5.13). Macular edema results from diffuse capillary leakage. Chronic macular edema may lead to epiretinal membrane formation, cystoid degeneration, and pigmentary degeneration.

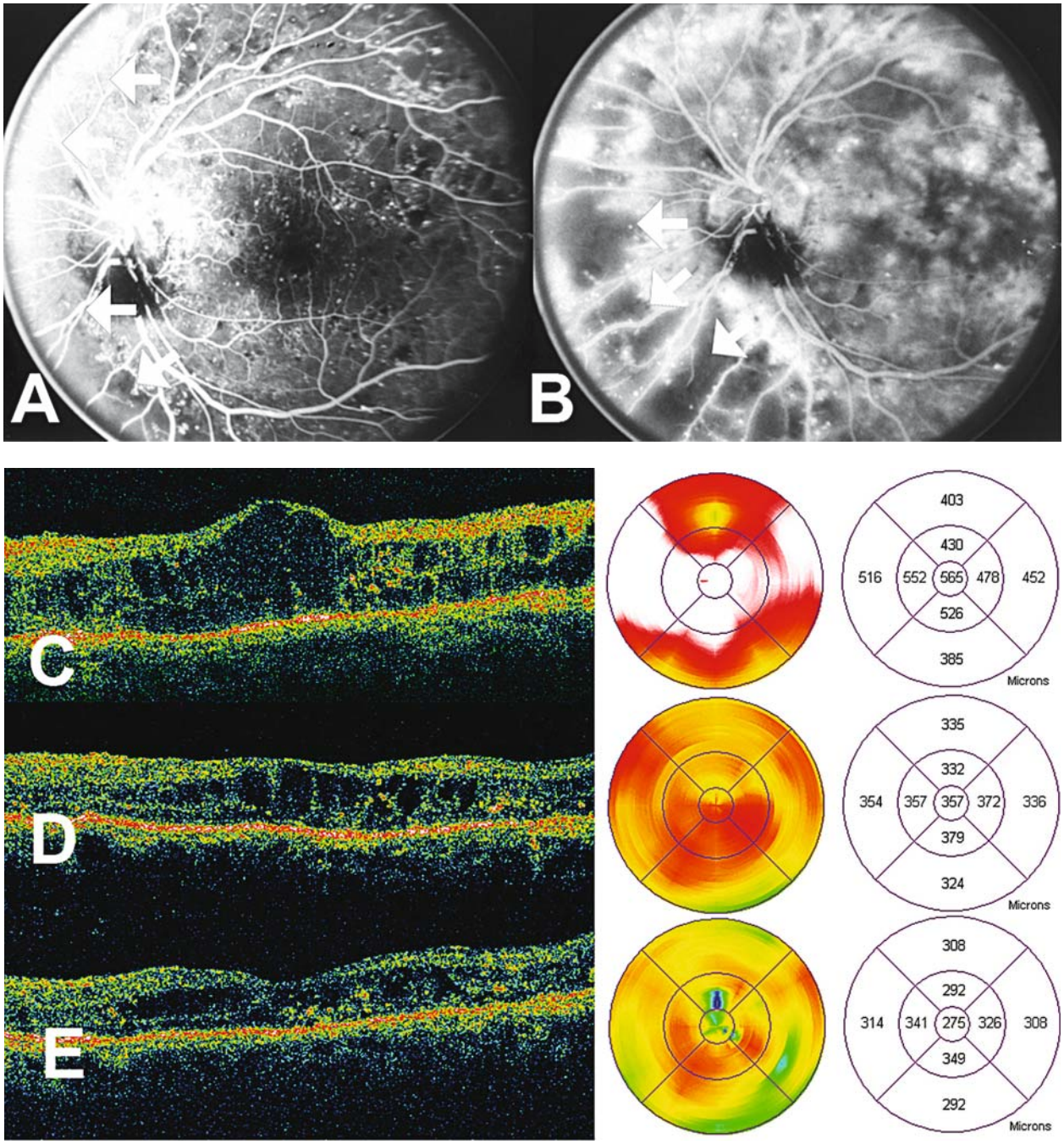


FIG. 5.11. A 78-year-old woman with a history of diabetic retinopathy complained of decreased vision in her left eye. Her visual acuity in this eye was 20/200. Retinal examination showed dot and blot hemorrhages throughout the posterior pole in addition to increased retinal thickness. (A) Early-phase fluorescein angiogram (FA) revealed presence of perifoveal dots of hyperfluorescence consistent with microaneurysms. In addition, nasal nonperfusion is demonstrated (arrows). (B) Late-phase FA showed leakage consistent with macular edema. In addition, nasal nonperfusion is again demonstrated (arrows). (C) A horizontal optical coherence tomography (OCT) scan obtained through the fovea revealed loss of the normal foveal contour, diffuse macular thickening, and areas of low intraretinal reflectivity consistent with intraretinal cysts and fluid accumulation. The retinal map analysis revealed a foveal thickness of 565 μm. The patient underwent an intravitreal injection of bevacizumab at a dose of 2.5 mg in this eye. (D) One week after the injection, an OCT scan showed that the foveal thickness had decreased to 357 μm. (E) One month after the injection the cystic spaces had resolved almost completely and her visual acuity (VA) improved to 20/80. The foveal thickness had decreased to 275 μm.

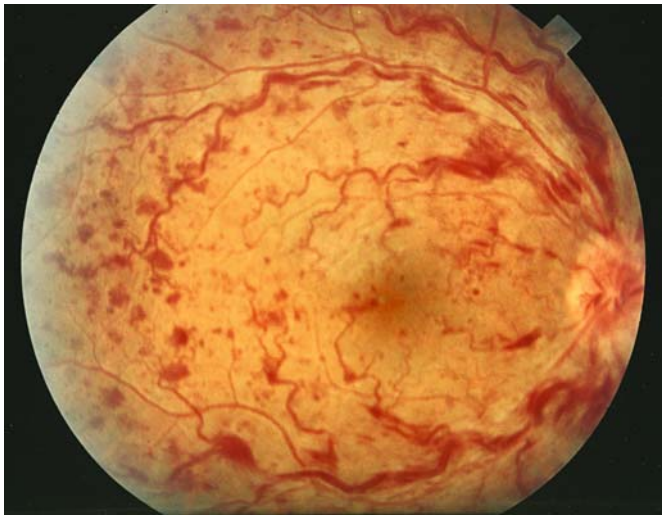

FIG. 5.12. Acute central retinal vein occlusion (CRVO). Notice the venous dilatation, tortuosity, swollen optic nerve, and the scattered intraretinal hemorrhages in all four quadrants.

The other major complication is intraocular neovascularization. It occurs more commonly in the anterior segment. It results from the secretion of angiogenic factors such as VEGF from areas of nonperfused retina.[39] Depending on the degree of capillary nonperfusion, CRVOs have often been classified in the literature as being perfused or nonperfused, incomplete or complete, and nonischemic or ischemic.

In the Central Vein Occlusion Study (CVOS), eyes were arbitrarily classified as nonperfused if the fluorescein angiogram revealed more than 10 disc areas of capillary nonperfusion. This differentiation is important because up to one third of nonperfused eyes in the CVOS developed anterior segment neovascularization. The greatest risk of developing neovascularization occurs in the first 7 months.[40] It is noteworthy that 15% of eyes initially classified as perfused became nonperfused after 4 months of follow-up. An additional 19% progressed to nonperfusion after 3 years of follow-up. The CVOS has recommended a monthly visit for the first 8 months where undilated slit-lamp examination of the pupillary border and gonioscopy are performed to detect early neovascularization in the anterior segment.

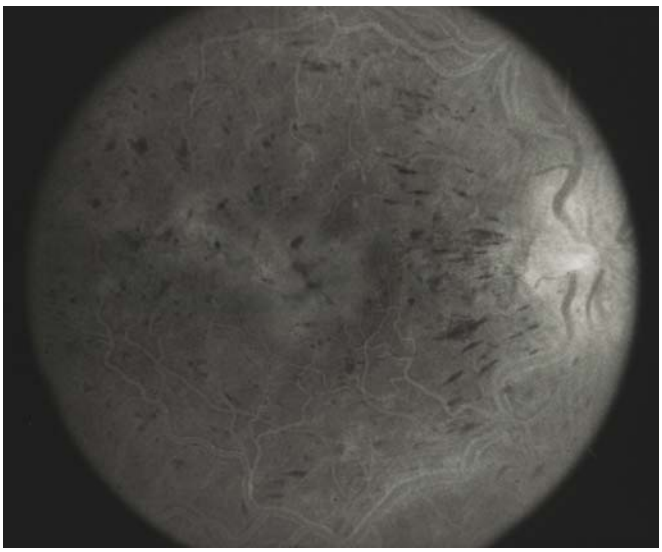

FIG. 5.13. A 66-year-old woman complains of decreased vision in the right eye for the past 6 weeks. Macular edema secondary to CRVO is the cause of her loss in vision. Late-phase fluorescein angiogram shows macular edema and staining of the retinal veins.

## Fluorescein Angiography

The angiographic findings depend in great part on the ophthalmoscopic findings at the time of the FA. In all eyes there is a delay in the filling of the retinal circulation, with relatively normal choroidal filling. Blockage of the underlying retinal circulation and choroidal circulation may occur if extensive intraretinal hemorrhages are present. Invariably there is some degree of capillary nonperfusion. Fluorescein angiography is a useful ancillary test to help determine the perfusion characteristics of the eye (Fig. 5.14). Retinal capillary nonperfusion is an important precursor of intraocular neovascularization. It may range from minimal to extensive and serves as the basis of the classification of CRVO into perfused or nonperfused types. There is also some leakage from the optic nerve head secondary to disc edema.

## Treatment

### *Laser Photocoagulation*

The CVOS demonstrated that grid laser treatment was of no visual benefit in the treatment of macular edema despite the elimination of macular edema in those eyes that were treated. It also showed that the best strategy in nonperfused eyes was to delay panretinal photocoagulation until two clock hours of iris neovascularization or any angle neovascularization was observed.[41] Panretinal photocoagulation is effective in controlling anterior segment neovascularization (Fig. 5.15).

### *Chorioretinal Anastomosis*

In an attempt to restore venous outflow, McAllister and Constable[42,43] have pioneered the creation of a chorioretinal anastomosis in order to bypass the occlusion in eyes with perfused CRVO. To successfully create a chorioretinal anastomosis, Bruch's membrane and the adjacent retinal vein must be ruptured with the argon and yttrium-aluminum-garnet (YAG) laser. Successful rupture of the vein is seen in about a third of cases treated with the argon laser. In those cases where the vein has not ruptured with the argon laser, a YAG laser is used to rupture the vein. Using the above sequential technique, a chorioretinal anastomosis can be created in 67% of cases.[44] Complications arising from this treatment include distal vein closure, fibrovascular proliferation, and vitreous hemorrhage.[45]

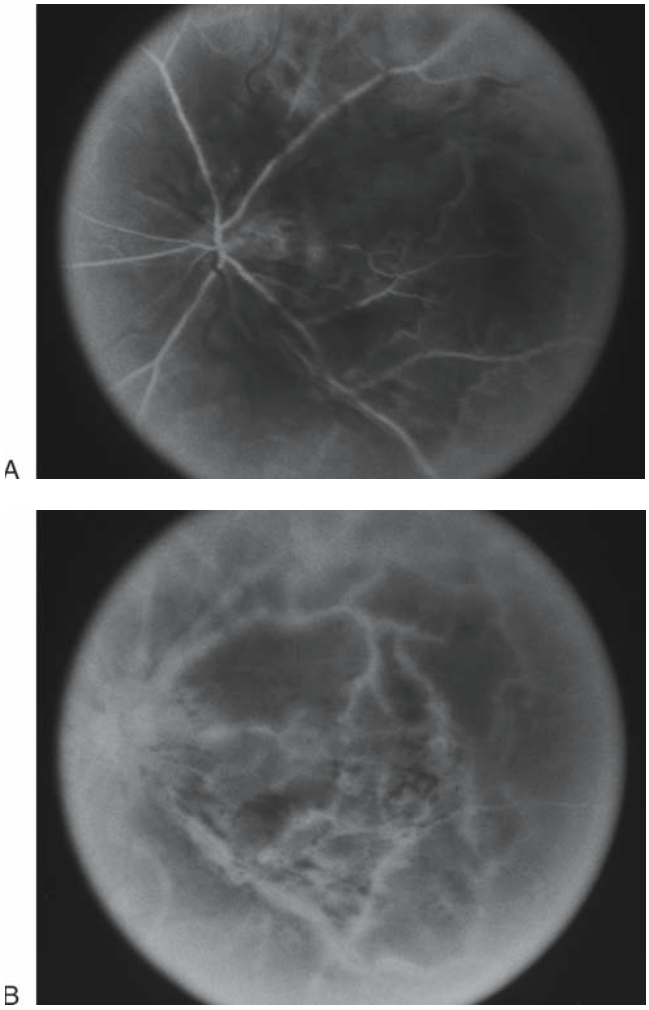


FIG. 5.14. A 76-year-old man complains of decreased vision in his left eye for a month. The visual acuity is 1/200. (A) Early-phase fluorescein angiogram shows delayed filling of the retinal veins. (B) Late-phase fluorescein angiogram shows perivenular leakage and severe capillary nonperfusion.

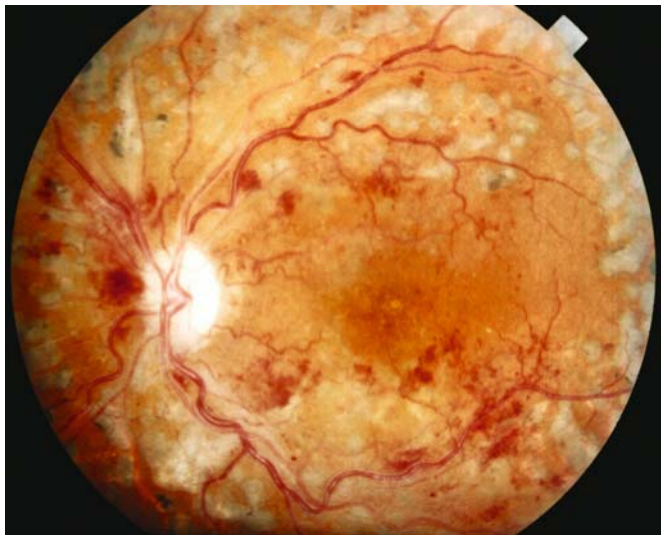

FIG. 5.15. A 55-year-old woman was diagnosed with neovascular glaucoma secondary to a CRVO of her left eye. She underwent prompt panretinal photocoagulation.

### *Intravitreal Triamcinolone*

The combined effects of vascular damage and the secretion of VEGF lead to the formation of macular edema. Corticosteroids have been shown to downregulate VEGF expression and strengthen the blood–retinal barrier. [26] In patients with macular edema secondary to CRVO who have been injected with intravitreal triamcinolone, an increase in visual acuity with a concomitant reduction in macular thickness as measured by OCT has been reported (Fig. 5.16).[46]

### *Radial Optic Neurotomy*

Some investigators have proposed that a CRVO results from a compartment syndrome at the level of the optic nerve. [47,48] They hypothesize that by decompressing the optic nerve, resolution of the CRVO may occur. More recently radial optic neurotomy (RON), which is an internal approach through a pars plana vitrectomy followed by a radial cut into the substance of the optic nerve, has been advocated to relieve this compartment syndrome. Some researchers think that perhaps a radial optic neurotomy works by creating a chorioretinal anastomosis rather than through decompression of a compartment syndrome.[49] RON may improve visual acuity (VA) in some eyes with CRVO but complications are common (Fig. 5.17). A large controlled prospective clinical trial is necessary to determine its role in the management of CRVO.

### *Thrombolytic Therapy*

In an attempt to lyse the venous clot at the lamina cribrosa, systemic thrombolytic therapy with tissue plasminogen activator (t-PA) was used and found to be effective in a pilot study. Unfortunately, the complications from such treatment included a fatal stroke. In order to avoid such systemic complications, some investigators have injected t-PA intravitreally. [50]

FIG. 5.16. A 42-year-old woman with 20/100 vision in her right eye for 2 weeks (same patient as Fig. 5.12). Three months post–intravitreal injection of 4 mg of triamcinolone, macular edema and retinal hemorrhages have resolved. Vision has returned to 20/20.

Others have pursued cannulation of the retinal venous system followed by an injection of t-PA.[51]

## Branch Retinal Vein Occlusion

### Etiology

Anatomic, hypertensive, atherosclerotic, inflammatory, or thrombophilic conditions may lead to retinal endothelial vascular damage with subsequent intravascular thrombus formation. Inflammatory conditions that have been associated with a BRVO include sarcoidosis,[52] Lyme disease, and serpiginous choroiditis.[53] Thrombophilic conditions such as protein S deficiency, protein C deficiency, resistance to activated protein C (factor V Leiden), antithrombin III deficiency,[54] antiphospholipid antibody syndrome,[55] lupus erythematosus, and gammopathies have also been associated with BRVO.

Eyes with arteriovenous crossings appear to be at risk of developing BRVO.[56,57] In these eyes, the thick-walled artery is anterior to the thin-walled vein in most cases. In the presence of systemic vascular disease, the risk of occlusion may be accentuated when arteriolar sclerosis results in an increased rigidity of the crossing artery, which causes compression of the underlying vein. Turbulent flow results, which in turn damages the vascular endothelium, creating a local environment favorable to intravascular thrombus formation.

### Symptoms

Most patients present complaining of a sudden onset of painless loss of vision. Another common symptom is a paracentral scotoma. Rarely, if the BRVO is located in the nasal half, the patient is asymptomatic.

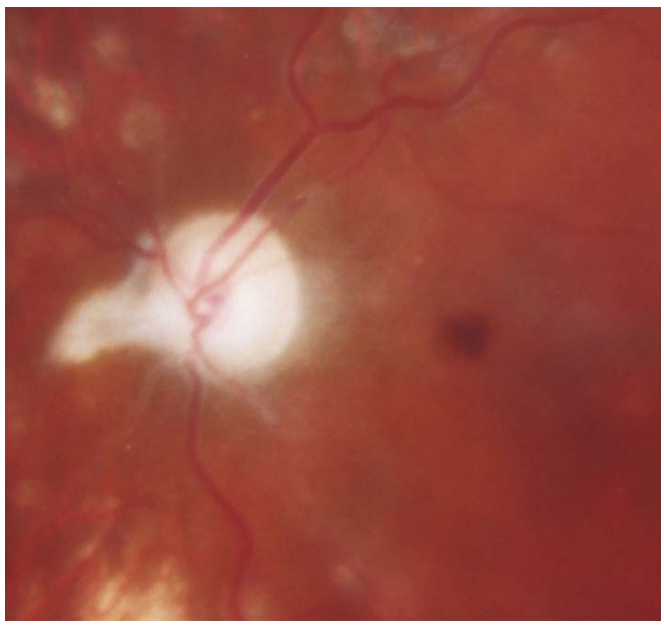

FIG. 5.17. Optic nerve atrophy 3 months after radial optic neurotomy for central retinal vein occlusion.

## Clinical Findings

Leber first described the condition ophthalmoscopically in 1877.[37] Most occlusions occur in the superotemporal quadrant since most arteriovenous crossings occur in this location. During the acute phase, intraretinal hemorrhages (usually flame shaped), retinal edema, and cotton-wool spots are seen in the distribution of a retinal vessel (Fig. 5.18). Serous detachment of the macula may also be seen.[58] During the chronic stage, hemorrhages may be absent. Macular edema may be the only sign present. Telangiectatic vessels may extend across the horizontal raphe. The upstream side of the occlusion may become fibrotic. In certain eyes with large areas of nonperfusion, retinal neovascularization may be seen. Vitreous hemorrhage with tractional retinal detachments may ensue. Further traction may create retinal breaks, creating combined rhegmatogenous and tractional retinal detachments. Both NVG and NVD are rare events with BRVO.

## Angiographic Findings: Fluorescein and Indocyanine Green

In the acute stage of a partial or complete venous occlusion the FA shows venous engorgement upstream of the crossing, resulting in ischemia, hemorrhage, and cotton-wool spot formation. If fluorescein angiography is performed when the intraretinal hemorrhages are still present, a hypofluorescent area corresponding to the blood will block both the retinal and choroidal circulations during the early phases. In the late phases, some leakage that results from the endothelial cell damage and the increased intracapillary pressure may be seen extending beyond the hemorrhages. Typical angiographic findings following clearing of the intraretinal hemorrhages include a prolonged retinal circulation time, perivenous staining in the obstructed area, evidence of capillary leakage, macular leakage consistent with cystoid macular edema (Fig. 5.19), areas of capillary nonperfusion, and in certain cases retinal neovascularization. These collaterals usually support enough flow to maintain some retinal function. It typically takes 6 to 24 months for the collaterals to mature and stabilize. Reduction of leakage and edema often results in an improvement in visual acuity, provided that no irreversible foveal damage has occurred.

Due to its fluorescence in the infrared, ICG penetrates blood much better than fluorescein. Even though ICG may be performed in the acute phase while the intraretinal hemorrhages are still present, [59] no one has been able to show that the information gathered from an ICGA is useful in the management of a BRVO.

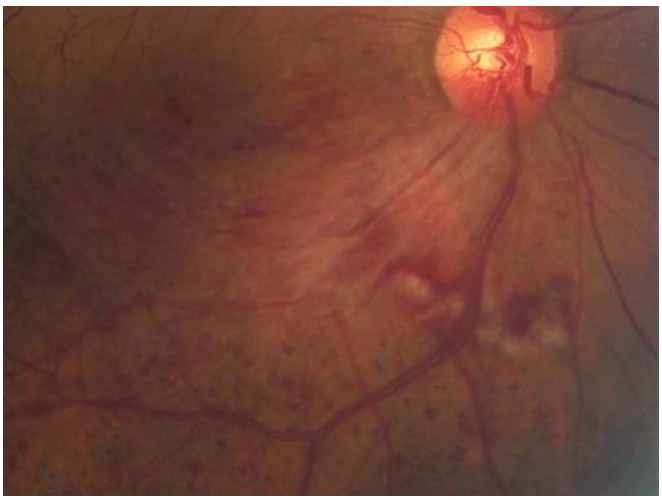

Fig. 5.18. A 55-year-old man with systemic hypertension noticed decreased vision in his right eye. He had a visual acuity of 20/400 and was diagnosed with an inferotemporal branch retinal vein occlusion (BRVO).

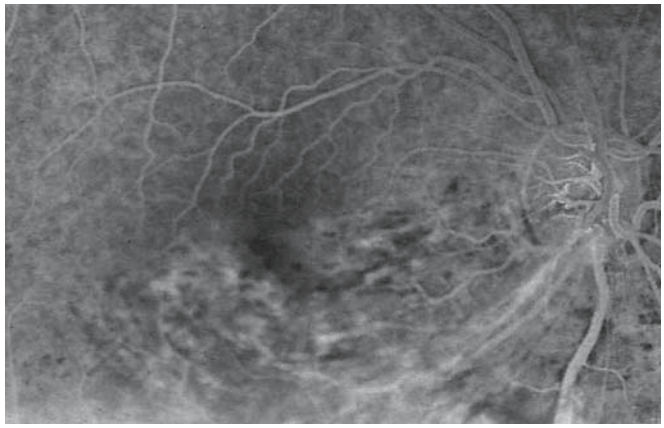

Fig. 5.19. Late-phase FA shows telangiectatic vessels and macular edema in the same patient as in Figure 5.18.

## Optical Coherence Tomography

The benefits of studying macular thickness with regard to visual function as compared to fluorescein leakage has already been discussed and applies to BRVO as well.[60] Optical coherence tomography has been shown to be more sensitive than FA in demonstrating cystoid macular edema in eyes with BRVO. In addition, OCT documented the presence of serous retinal detachment and subretinal hemorrhage in eyes with BRVO where both ophthalmoscopy and FA failed to do so.[58]

## Treatment

Medical treatment has not been shown to be effective in this condition nor in its complications. These complications include macular edema and the sequelae from retinal neovascularization (i.e., vitreous hemorrhage, tractional retinal detachment, epiretinal membrane formation, and NVG).[59]

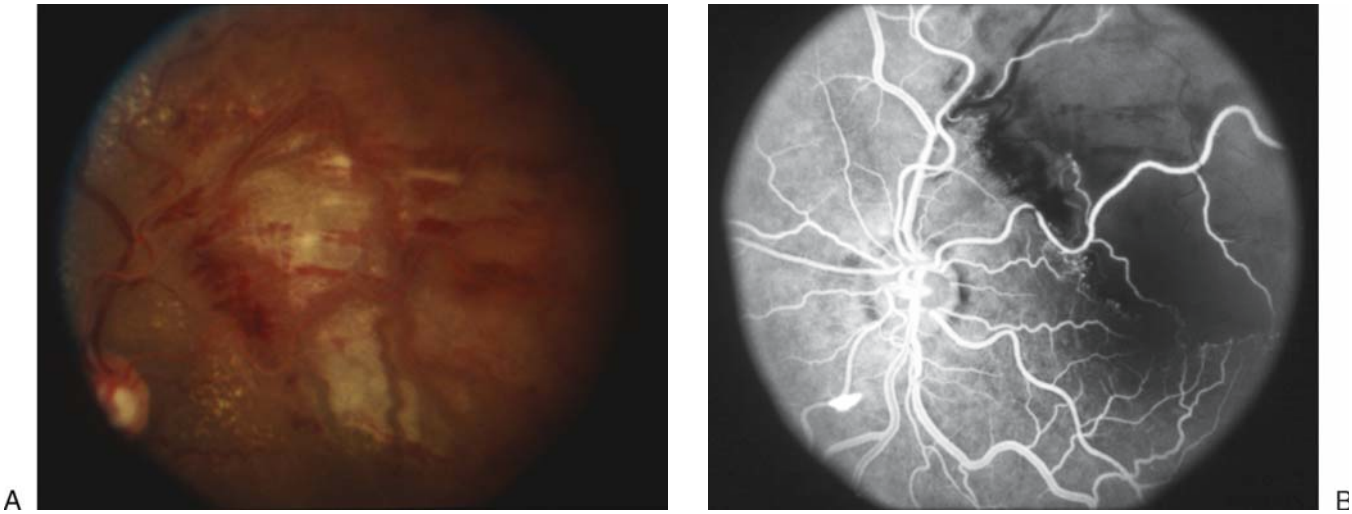


Fig. 5.20. A 60-year-old man with diabetes mellitus (DM) and systemic hypertension complained of decreased vision in his left eye for the past 3 months. He had developed a superotemporal BRVO and visual acuity was 5/200. (A) Color photograph shows involvement of the superotemporal quadrant with retinal edema, lipid exudation, and intraretinal hemorrhages. (B) Early frame of the FA shows large areas of capillary nonperfusion distal to the site of the occlusion.

## Macular Grid Laser Photocoagulation

Macular grid laser photocoagulation has been shown to be effective in the treatment of macular edema in a prospective multicenter randomized clinical trial, the Branch Retinal Vein Occlusion Study (BVOS).[61] The current recommendation is to wait 3 months to see if spontaneous improvement in vision occurs. If no improvement is seen and the hemorrhages have mostly cleared from the macular area, an FA is obtained. Conversely, if macular ischemia is responsible for the loss of vision, laser photocoagulation should not be offered to the patient. If the FA shows leakage in the macular area that is responsible for the decrease in vision, a macular grid laser is recommended. After 3 years of follow-up care, 63% of laser-treated eyes improved two or more lines of vision compared to 36% of control eyes. But on average, eyes gained only 1.3 lines of visual acuity from baseline.[61] If the FA reveals macular nonperfusion, laser is not warranted and observation is recommended (Fig. 5.20).

## Intravitreal Steroid Injection

Due to its potent antipermeability and antiinflammatory properties, intravitreal triamcinolone has recently been used to treat macular edema from different etiologies (Fig. 5.21).[62]

## Scatter Photocoagulation

Neovascularization usually occurs at the border between the ischemic and nonischemic retina. Eyes with NVD are believed to have more extensive ischemia than those without NVD. According to the BVOS, approximately 40% of eyes with large areas of ischemia (more than five disc areas of nonperfusion) are at risk of developing neovascularization (Fig. 5.22).[63] Of the eyes that do develop neovascularization, 60% have a vitreous hemorrhage. The BVOS demonstrated that scatter photocoagulation reduces the prevalence of neovascularization by one half (from 40% to 20%). However, if one were to treat all eyes with nonperfusion, a large percentage of patients (60%) who would never develop neovascularization would be treated with scatter photocoagulation. Therefore, the recommendation is to wait until neovascularization actually develops before considering scatter photocoagulation.

## Laser-Induced Chorioretinal Anastomosis

Bypass of the normal retinal venous drainage channels is attempted by creating a communication between the obstructed vessel and the choroid by literally blasting a hole through the RPE and choriocapillaris with a high-energy argon or YAG laser.[64] Complications from the procedure include tractional retinal detachment and vitreous hemorrhage.

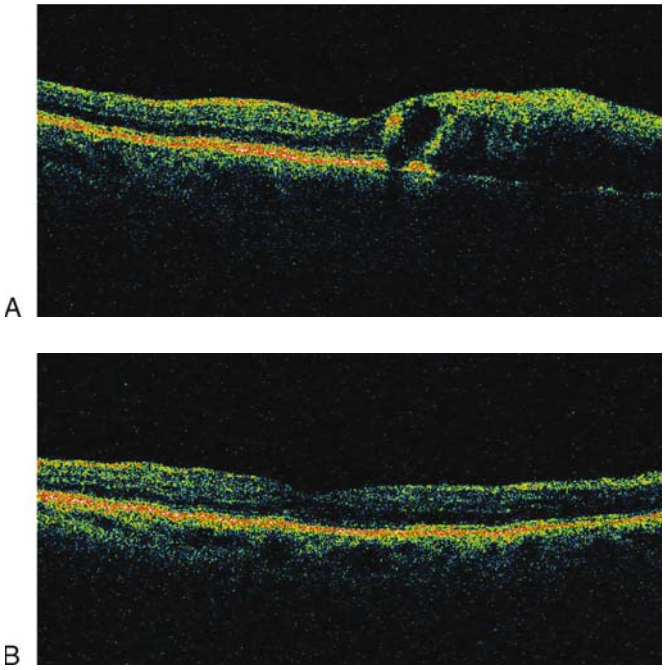


FIG. 5.21. A 55-year-old man with macular edema secondary to BRVO underwent intravitreal triamcinolone injection of 4 mg. (A) Preinjection OCT demonstrates macular edema. (B) Three weeks postinjection OCT shows normalization of the foveal anatomy.

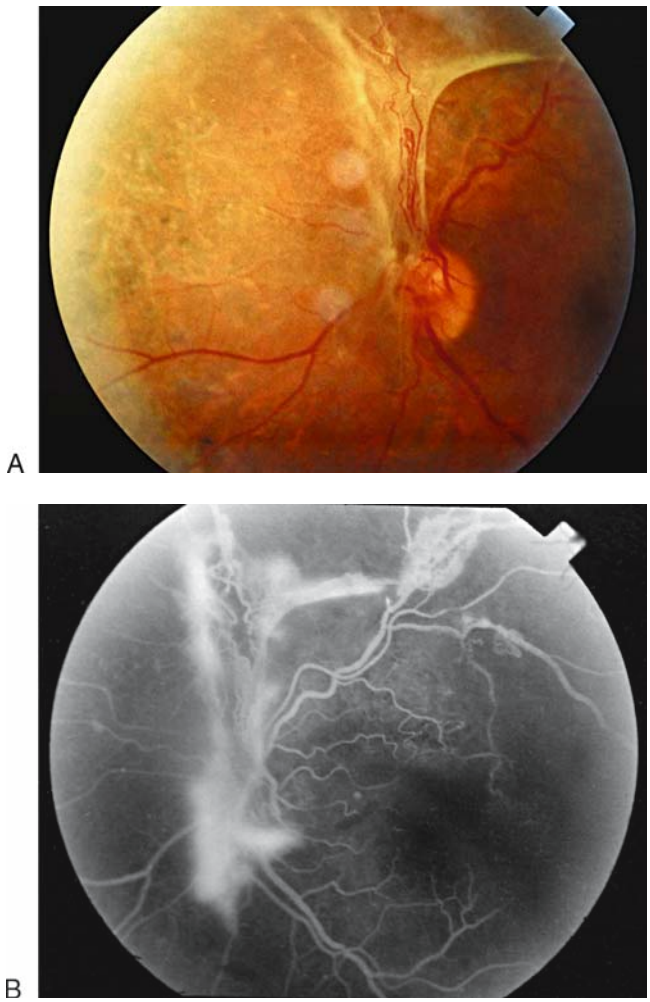


FIG. 5.22. A 65-year-old woman has visual acuity of 20/50 in her left eye. She was diagnosed with a superotemporal BRVO complicated by disc neovascularization and vitreous hemorrhage. She underwent prompt scatter photocoagulation. (A) Clinical photograph shows NVD and vitreoretinal traction. Notice the laser scars nasal to the disc. (B) Fluorescein angiogram shows leakage from the NVD.

## Ocular Ischemic Syndrome

When the ipsilateral carotid artery has more than 90% stenosis,[65] the perfusion of the ipsilateral central retinal artery drops 50%. The ocular changes seen with this condition were initially described by Kearns and Hollenhorst[66] in 1963 with the name of venous stasis retinopathy.

### Clinical Findings

The majority of patients complain of a gradual and progressive loss of vision. About 12% suffer a visual loss of sudden onset. Upon presentation 43% of eyes have a visual acuity between 20/20 and 20/50, while 37% have a visual acuity of counting fingers or worse. In up to 40% of cases, ocular pain is present.

Two thirds of eyes have rubeosis iridis at presentation. However, only about 50% of these eyes suffer from NVG. A cataract may develop as the disease progresses. The retinal arteries are narrow and the veins are dilated but do not show tortuosity. NVD is present in 35% of eyes, NVE in 8% of eyes, and vitreous hemorrhage occurs in 4% of eyes. A cherry red spot occurs in 12% of eyes.[65]

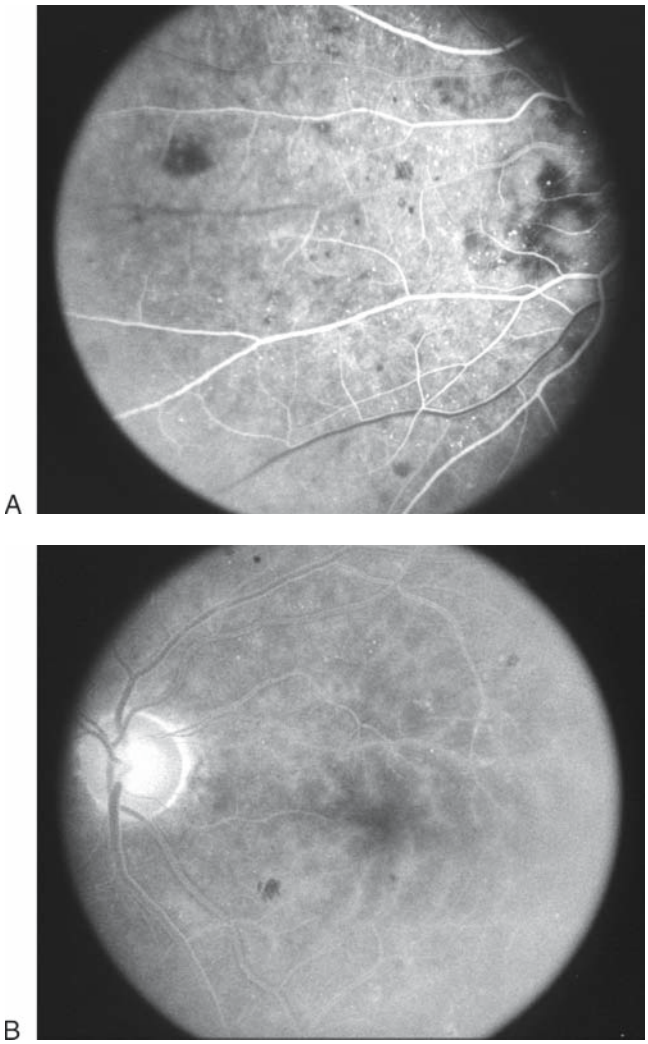


FIG. 5.23. A 61-year-old man with complete occlusion of the left common carotid artery noticed decreased vision for the past 2 weeks. His visual acuity was 20/100. (A) Midphase FA frame shows that the nasal retina also fills slowly. There are hypofluorescent areas consistent with intraretinal hemorrhages. (B) Late-phase FA frame shows the absence of macular edema. But there is staining of the vessels in the posterior pole.

### Fluorescein Angiography

These eyes most often have a marked prolongation or patchy choroidal filling with delayed retinal arteriovenous transit time. Macular edema is seen in 17% of eyes. Other angiographic findings include retinal capillary nonperfusion, optic nerve head hyperfluorescence, intraretinal hemorrhages, and microaneurysmal hyperfluorescence (Fig. 5.23).

### Treatment

Most eyes with rubeosis iridis end up with legal blindness after a year of follow-up. Carotid endarterectomy has been recommended in symptomatic patients with a high-grade stenosis (70% to 99%) and asymptomatic patients with a hemodynamically significant stenosis (≥60%).[67,68] Although the studies did not specifically address ocular ischemic syndrome, carotid endarterectomy should be considered in these eyes if the carotid stenosis is of high grade.

Scatter photocoagulation is indicated when rubeosis iridis or retinal neovascularization are present. However, only about 36% of eyes show regression of the neovascularization following laser treatment.

## Retinal Arterial Obstruction

In 1859, von Graefe[69] described a patient with endocarditis and multiple systemic emboli who suffered an embolic central retinal artery obstruction. Based on the location of the obstruction, retinal artery obstructions can be classified as follows:

1. Central retinal artery obstruction (57% of cases)
2. Branch retinal artery obstruction (38% of cases)
3. Cilioretinal artery obstruction (5% of cases)
4. Combined central retinal artery and vein obstruction

### Systemic Associations

Once a retinal artery obstruction is diagnosed, a complete systemic workup is necessary. Up to 90% of patients have an associated systemic condition.[70,71] In patients older than 30 years of age, carotid atherosclerosis and cardiac disease are the usual culprits. Carotid stenosis or ipsilateral plaque is seen in 45% of eyes with retinal artery obstruction. If the stenosis is 60% or greater, it is considered to be hemodynamically signifi-

cant. Almost 50% of patients with a retinal artery obstruction suffer from cardiac disease. Nevertheless, cardiac pathology is severe enough in only 10% of these people to warrant cardiac surgery or systemic anticoagulation.[72] Giant cell arteritis must be ruled out in patients older than 50 years of age.[73] The etiology of retinal arterial obstructions of patients younger than 30 years of age is somewhat different and includes conditions such as migraine, cardiac disease, trauma, hemoglobinopathies, optic nerve drusen, and prepapillary arterial loops (Fig. 5.24).

## Clinical Presentation

Patients with central retinal artery obstruction complain of a painless loss of vision. The visual acuity ranges between counting fingers and light perception in 90% of eyes. An afferent pupillary defect is usually present. The funduscopic appearance may be completely normal if the obstruction is very recent. In the acute stage, the retina in the posterior pole loses its transparency and acquires a whitish appearance. A cherry red spot is present in the region of the foveola (Fig. 5.25). Segmentation of the blood column, also called "boxcarring," is seen in the retinal arterioles. In most cases the retina assumes its normal color over a period of 4 to 6 weeks, leaving a pale optic disc, narrowed retinal vessels, and visible absence of the nerve fiber layer in the region of the optic disc. Neovascularization of the disc has also been noted to occur, and develops in about 2% of eyes.[74] The incidence of rubeosis iridis is approximately 20%; it develops 4 to 5 weeks after the event. If rubeosis iridis is present at the time of the obstruction, the presence of a concomitant carotid artery obstruction should be considered. The incidence of neovascularization of the iris and subsequent NVG following acute central retinal artery occlusion (CRAO) is reported to be between 1% and 5%. Approximately 25% of eyes with an acute central retinal artery obstruction have a patent cilioretinal artery that supplies part or all of the papillomacular bundle (Fig. 5.26).[75] Emboli are visible within the arterial system in about 20% of eyes. The most common variant is the glistening yellow crystal cholesterol embolus that is called the Hollenhorst plaque. It is often seen at the bifurcation of the vessels. It most commonly arises from atherosclerotic plaques in the carotid arteries. Other types of emboli include fibrin-platelet thrombi and calcium emboli.

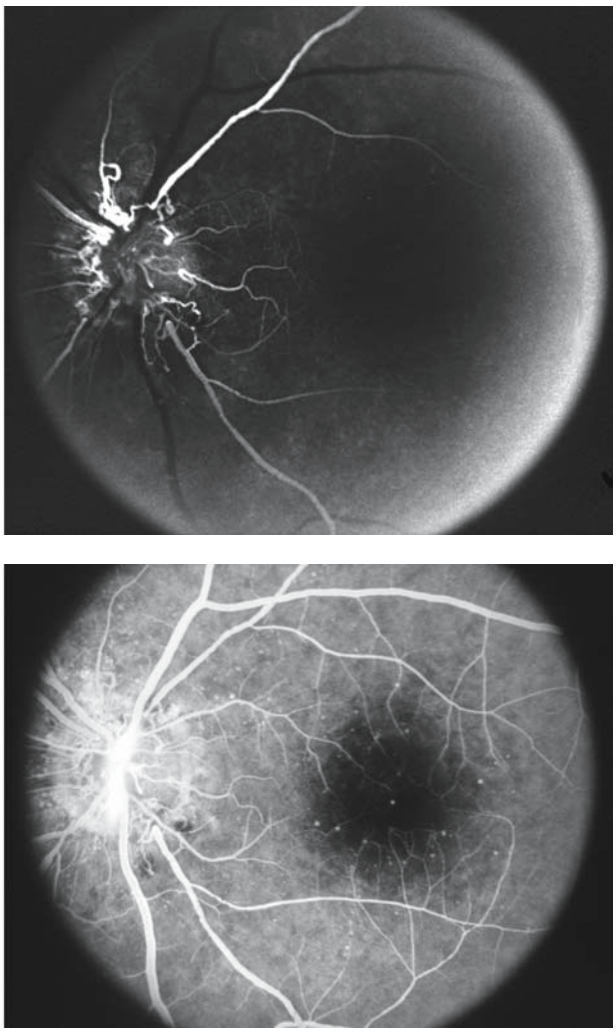


Fig. 5.24. A 56-year-old woman noted decreased vision in her left eye of 9 months, duration. Her current visual acuity was 20/200. (A) Early FA frame shows the dye circulating in the vascular loop, vessels in the disc, and the four branches of the central retinal artery. (B) Mid-FA frame demonstrating obliteration of the perifoveal capillary bed.

Patients with a branch retinal artery obstruction complain of a scotoma that is unilateral, painless, and sudden in onset. Over 90% of branch retinal artery obstructions involve the temporal retinal vessels (Fig. 5.27). Ophthalmoscopic findings include retinal whitening corresponding to the distribution of the affected retinal artery. The involved artery is narrowed and "boxcarring" may be seen. Artery-to-artery collateral vessels may develop in the retina and are pathognomonic for branch artery obstruction. Ocular neovascularization after a branch retinal artery obstruction is a rare event.[76] The visual prognosis in eyes with branch retinal artery obstruction is usually quite good, unless the fovea is completely surrounded by retinal edema and ischemia.

Cilioretinal arteries are clinically and angiographically present in 20% and 32% of eyes, respectively. Cilioretinal artery occlusion presents itself as retinal whitening along the course of the vessel. They may occur as isolated events, in combination with a central retinal vein occlusion or in conjunction with anterior ischemic optic neuropathy. The visual outcome is very good for eyes with isolated cilioretinal artery obstruction. Eyes with combined anterior ischemic optic neuropathy and cilioretinal artery obstruction have a poor visual outcome.

A combined central retinal artery obstruction and central retinal vein occlusion is a rare occurrence. Most patients complain of a sudden decrease of vision. Ophthalmoscopic examination reveals retinal whitening, a cherry red spot, dilated and tortuous veins, retinal hemorrhages, macular edema, and a swollen optic disc. Rubeosis and NVG eventually occur in 80% of these eyes.[77]

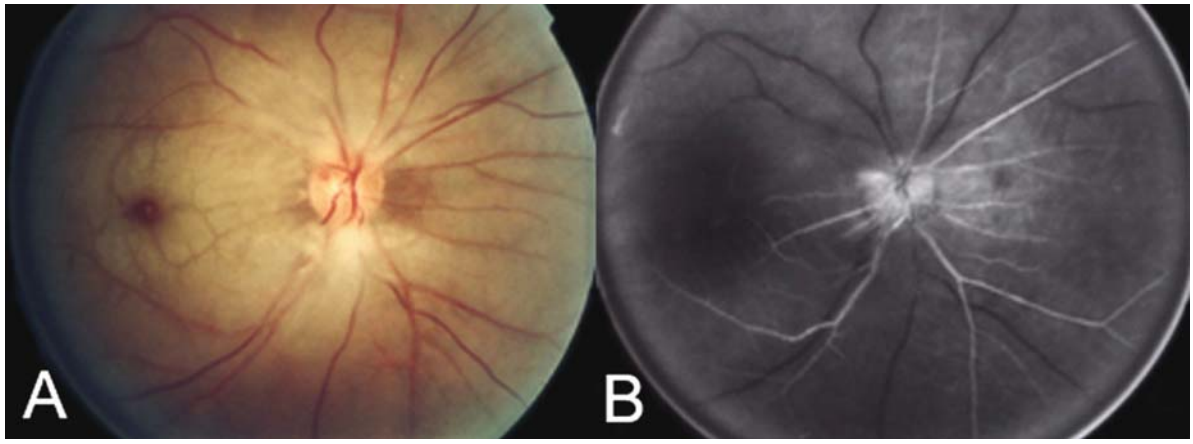


Fig. 5.25. Central retinal artery occlusion (CRAO) demonstrates a cherry red spot in the region of the foveola. (A) Color photograph. (B) Fluorescein angiogram.

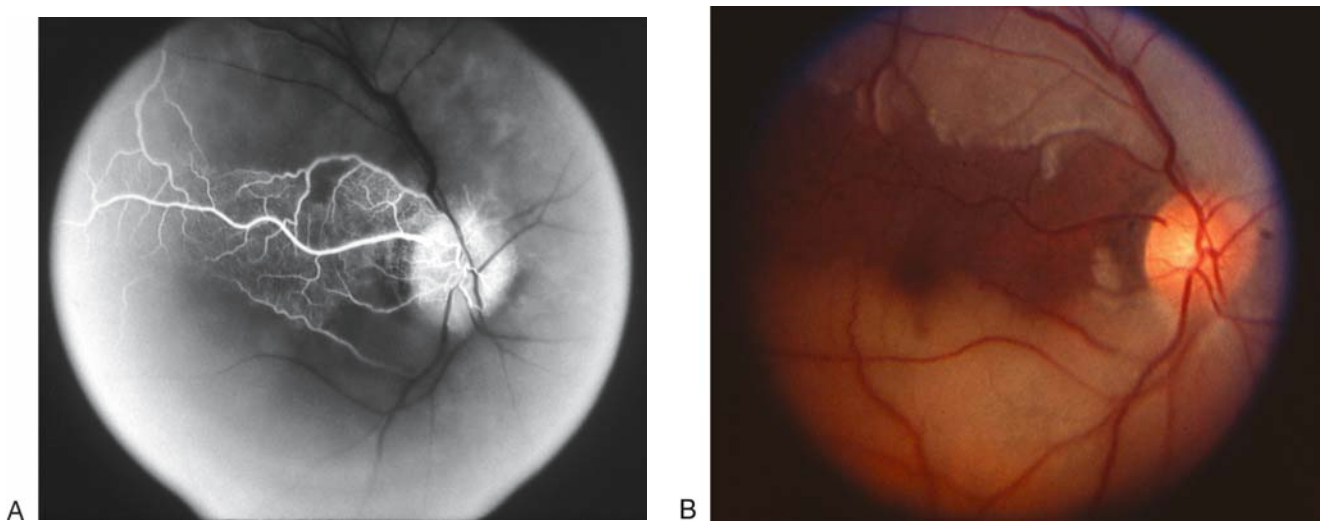


Fig. 5.26. A 58-year-old healthy woman developed sudden loss of vision in her right eye 2 days prior to presentation. Her vision was 5/200. (A) Clinical photograph shows whitening of the inner retina in the posterior pole sparing the inferocentral and nasal macula. No visible emboli are seen. (B) Early FA frame shows prompt filling of a cilioretinal artery with filling of the superior macular area.

## Fluorescein Angiography

In central retinal artery obstructions the choroidal circulation fills normally. In a normal eye, the choroid fills 1 to 2 seconds prior to filling of the retinal arteries and is completely filled within 5 seconds of the appearance of the dye. When the central retinal artery is obstructed, a delay in retinal arterial filling or a delay in the retinal arteriovenous transit time is commonly seen. Irregular and sluggish filling of the retinal arteries is the hallmark of the disease (Fig. 5.25). Late staining of the optic disc is variable.

In eyes with a branch retinal artery obstruction, the fluorescein dye does not perfuse into the branch of the artery (Fig. 5.27). The involved sector of the retina has a ground-glass appearance due to tissue swelling from ischemia. The veins in the area of the retina fed by the blocked portion of the artery do not contain fluorescein, Sometimes a retrograde flow of dye into the branches of the artery or veins in the area of occlusion is seen. When the branch artery is only partially occluded, filling in the area will be delayed.

Eyes with a cilioretinal artery obstruction demonstrate poor filling of the obstructed vessel and retinal capillary nonperfusion in the area of distribution of the vessel. Eyes with a combined artery and vein obstruction have a delayed arterial filling phase, a prolonged arteriovenous transit time, severe retinal capillary nonperfusion, and a sudden termination of the midsized retinal vessels.

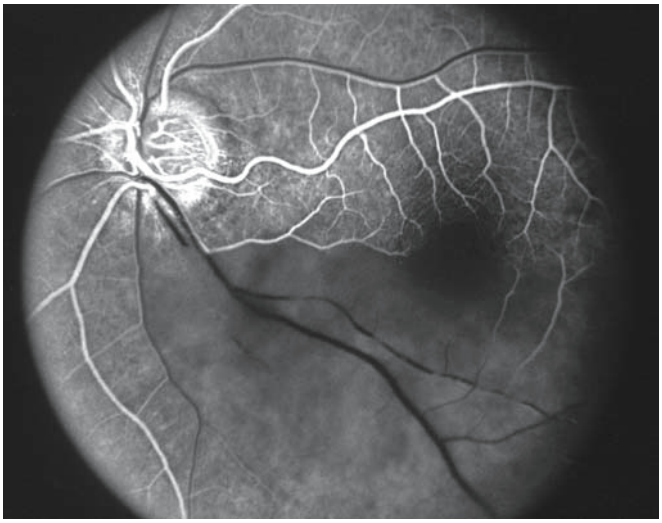

FIG. 5.27. A 72-year-old man complained of a sudden loss of vision in his left eye for 2 days. The visual acuity was 1/200 and a superior altitudinal defect was noted. Early FA frame shows lack of flow in the inferotemporal branch of the central retinal artery. There is marked capillary nonperfusion in the inferotemporal quadrant.

### Treatment

Several treatment modalities including carbogen administration, anterior chamber paracentesis, and ocular massage have been described in the literature. More recently intraarterial fibrinolysis, YAG laser arteriotomy, and embolectomy has been reported.[78,79] However, none has been proven to be effective at all.

## Hypertensive Retinopathy

Systemic hypertension is one of the most widespread diseases in the world today. It is a major public health challenge because of the morbidity and mortality that it causes. According to the Seventh Report of the Joint National Committee of Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII),[80] the classification of blood pressure (expressed in mm Hg) for adults aged 18 years or older is as follows:

1. Normal: systolic <120 mm Hg, diastolic <80 mm Hg
2. Prehypertension: systolic 120–139 mm Hg, diastolic 80–99 mm Hg
3. Stage 1: systolic 140–159 mm Hg or diastolic 90–99 mm Hg
4. Stage 2: systolic ≥160 mm Hg or diastolic ≥100 mm Hg

Sustained elevation of arterial blood pressure leads to vascular lesions in the heart, central nervous system, kidneys, and eyes.

### Clinical Findings

Most patients are asymptomatic unless accelerated hypertension is present. Depending on the vascular bed affected, hypertension can give rise to retinopathy, choroidopathy, and optic neuropathy.

The hallmark of hypertensive retinopathy is diffuse arteriolar narrowing. Hypertension induces a progressive increase in the thickness of the arteriolar wall called arteriolosclerosis. Normally, the arteriolar wall is invisible during ophthalmoscopy, and one solely sees the red blood column of the arteriole. As the arteriolar wall becomes thicker and the lumen narrower, the arterioles manifest a reddish-brown color known as copper wiring. If the thickening continues, the column of blood can no longer be visualized in the arteriole. This gives rise to a whitish color or silver wiring. Usually the arteriole is anterior to the venule. With increasing arteriolosclerosis, compression of the underlying venule by the arteriole occurs. This is seen as a nick in the arteriovenous crossing.

If the blood pressure is very elevated, there is a breakdown of the inner blood–retinal barrier. Retinal hemorrhages, microaneurysms, cotton-wool spots, and lipid exudation may be seen. A macular star, papilledema, and shutdown of the retinal capillaries may occur if the elevation in blood pressure is very severe (Fig. 5.28).

Localized bullous detachments of the neurosensory retina and retinal pigment epithelium can occur secondary to this ischemia. The subretinal fluid is usually turbid because of the protein-rich exudate.[81] Focal chorioretinal atrophy known as Elschnig's spots may also be seen. Siegrist's streaks are linear hyperpigmentation lesions that overly the choroidal arteries.

Optic neuropathy is manifested as optic disc edema with retinal hemorrhages and capillary dilation (Fig. 5.29).

### Fluorescein Angiography

Hypertensive choroidopathy is manifested as patchy nonperfusion of the choriocapillaris. Acutely, Elschnig's spots (Fig. 5.30)

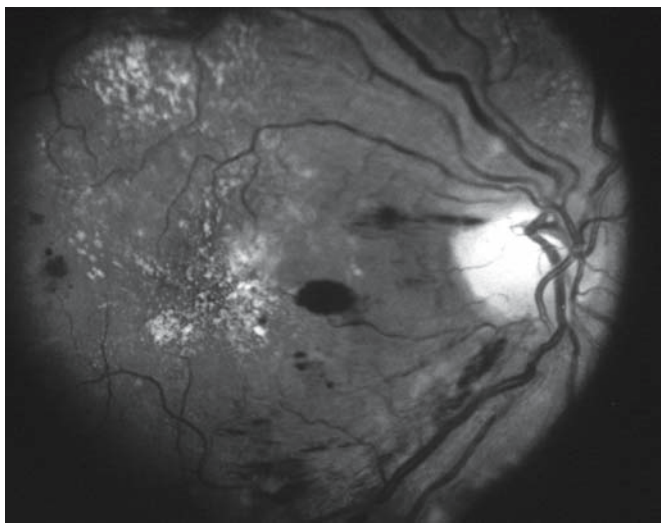

FIG. 5.28. Red-free photograph of the right eye of a 55-year-old man shows splinter hemorrhages on the disc, lipid deposition in the macula, and intraretinal hemorrhages.

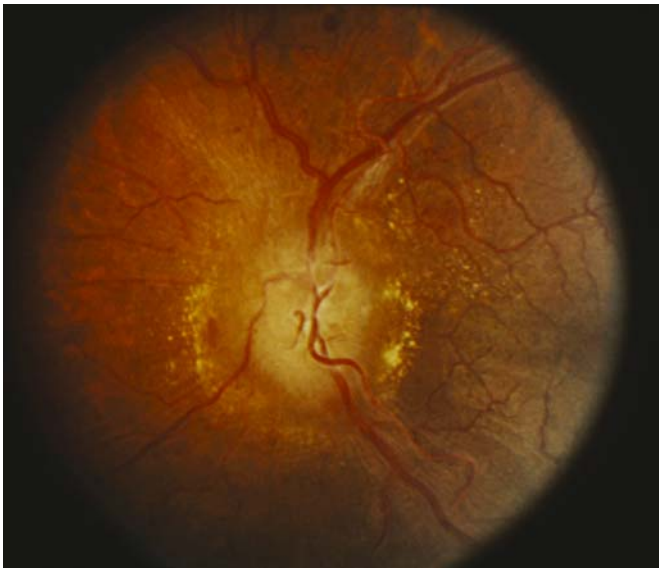

FIG. 5.29. A 45-year-old man complaining of headaches and blurry vision for 2 weeks was seen in the emergency room and diagnosed with acute systemic hypertension. He had a blood pressure of 200/120 mm Hg. Photo of the optic disc also shows edema and lipid exudation.

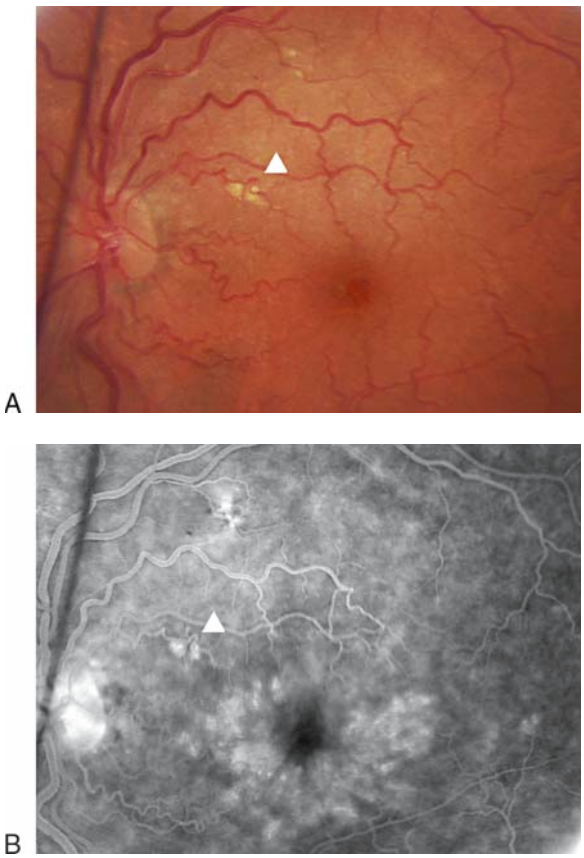


FIG. 5.30. Hypertensive choroidopathy is manifested as patchy nonperfusion of the choriocapillaris. Acutely, Elschnig's spots can be seen. (A) Elschnig's spots (arrowhead) in color photograph. (B) Elschnig's spots (arrowhead) in late-phase fluorescein angiogram on a patient with concomitant pseudophakic cystoid macular edema.

profusely leak fluorescein. Once they heal, Elschnig's spots no longer leak fluorescein. Instead window defects are seen.

Cotton wool spots give a ground-glass appearance to the involved retina. Staining of the vessel walls occur in areas of vascular damage. If hypertensive optic neuropathy is present, leakage or staining of the nerve may be seen.

### Treatment

Patients with hypertensive retinopathy should be referred to an internist for appropriate treatment.

## Retinal Arterial Macroaneurysms

In 1880 Loring described an asymptomatic 25-year-old man who had bulging of the inferotemporal retinal artery. In 1920 Fernandez associated retinal artery macroaneurysms with systemic hypertension. Finally in 1973, Robertson[82] defined retinal arterial macroaneurysm as a distinct clinical entity.

### Clinical Findings

Retinal arterial macroaneurysms are more commonly seen in women in their 50s and 60s who suffer from hypertension and arteriosclerotic vascular changes. They are usually unilateral, but up to 10% may be bilateral. Retinal arterial macroaneurysms are usually single but may be multiple in up to 20% of cases (Fig. 5.31).[83]

The most common presenting symptom is an acute visual loss secondary to hemorrhage, exudation, or macular edema, although many may be asymptomatic and picked up on routine examination. The classic description is of a round or fusiform dilatation of the arterial wall of the retinal arterioles within the first three orders of arterial bifurcation. Close to 50% of eyes have an associated retinal hemorrhage that surrounds the macroaneurysms. This hemorrhage may be preretinal, intraretinal, or subretinal. If the hemorrhage occurs in all layers, it is called an hourglass hemorrhage. Breakthrough vitreous hemorrhage occurs in about 10% of cases.[84] Intraretinal lipid deposition manifested as hard exudates surrounding the macroaneurysms in a circinate ring or as a distal effect on the macula is commonly seen (Fig. 5.31). A detachment of the neurosensory retina may on occasion surrounds the macroaneurysm.

### Fluorescein Angiography

The macroaneurysm typically fills uniformly in the early phase of the angiogram.[85] If the filling is delayed or incomplete, an involuted macroaneurysm may be present. The artery is usually narrowed just distal and proximal to the macroaneurysm. However, sometimes if a large and thick hemorrhage is present, fluorescein angiography may be unable to image the macroaneurysm because of the blockage caused by the hem-

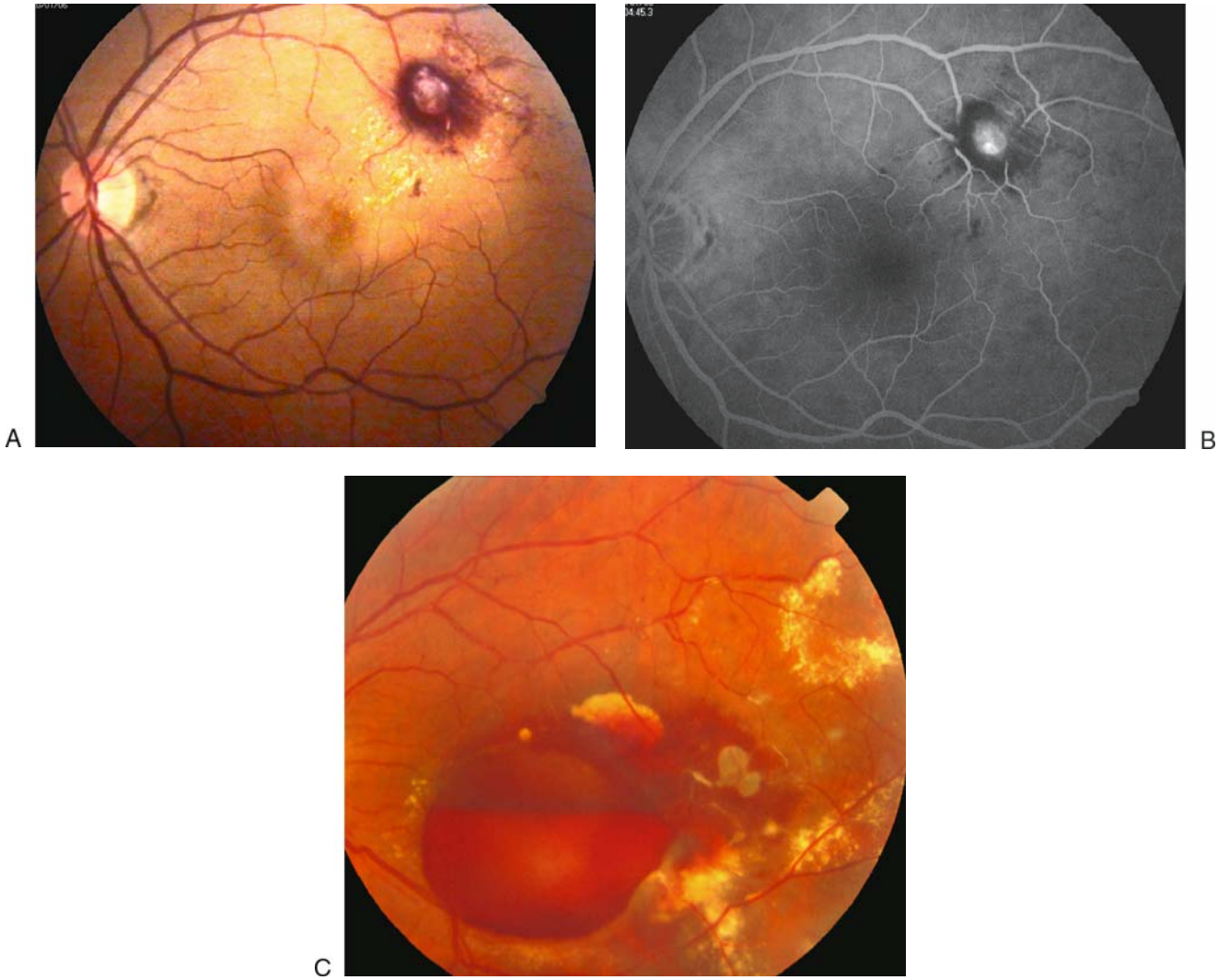


FIG. 5.31. Retinal arterial macroaneurysm along the superotemporal artery. (A) Color photograph demonstrates a retinal arterial macroaneurysm surrounded by hemorrhage and lipid exudation. (B) Late-phase FA frame shows hyperfluorescent arterial macroaneurysm. (C) Another ruptured arterial macroaneurysm with subhyaloidal hemorrhage and lipid exudation. (Courtesy of Dr. Juan Verdaguer.)

orrhage. Depending on the damage caused by the macroaneurysm to the vessel wall, the late phases may show little or no staining of the vessel wall or marked leakage (Fig. 5.31). Small areas of capillary nonperfusion or microaneurysms may surround the macroaneurysm.

## Indocyanine Green Angiography

Indocyanine green angiography is useful in elucidating the diagnosis if preretinal, intraretinal, or subretinal blood is too dense to allow a clinical or fluorescein diagnosis.[86] Round focal hot spots adjacent to the retinal arterioles are indicative of an retinal arterial macroaneurysm.

## Treatment

Some retina specialists feel that the visual outcome of retinal arterial macroaneurysms is very good because they can undergo spontaneous thrombosis, fibrosis, and involution. However, it must be kept in mind that even though most macroaneurysms involute, some do not. Preretinal hemorrhages may be complicated by epiretinal membrane formation (Fig. 5.31). Subretinal hemorrhages pose a different problem. Blood in the subretinal space is toxic to the photoreceptors. Pars plana vitrectomy with intraoperative fibrinolysis of these hemorrhages should be considered.[87]

Macular edema and its sequelae is the most common cause of poor vision following a retinal arterial macroaneurysm. Permanent structural damage to the macula may result from

the chronic lipid exudation. Laser photocoagulation may be directed toward the macroaneurysm itself or around it.[88]

## Radiation Retinopathy

Radiation therapy has been used to treat tumors for many years. Radiation retinopathy was first recognized by Stallard[89] in 1933, who described retinal exudation and hemorrhages as a consequence of radon treatment for retinoblastoma.

### Clinical Findings

Injury to the eye may result from direct radiation of intraocular tumors or when the ocular structures are within the treatment beam for extraocular tumors. If the eye receives a total radiation dose of 3000 rad or more; if the daily fractionation dose is in excess of 200 rad; if concurrent adjunctive chemotherapy or bone marrow transplantation is performed; and if simultaneous treatment with external beam radiotherapy and hyperbaric oxygen are given, a higher risk of developing retinopathy is reported. Systemic conditions that are associated with a higher risk of developing radiation retinopathy include diabetes mellitus, collagen vascular diseases, pregnancy, and hypertension.[90]

Symptoms range from metamorphopsia, blurred central vision, and scotomas, to abrupt complete loss of vision. It is uncommon for it to occur within 6 months of the ocular irradiation or more than 3 years after treatment.

Radiation retinopathy is a slowly progressive occlusive microangiopathy where the primary damage is at the level of the retinal capillary endothelium. The microvascular changes include microaneurysms, retinal telangiectasias, dot and blot intraretinal hemorrhages, cotton-wool spots, macular exudates, macular edema, perivascular sheathing, and intraretinal microvascular abnormalities (Figs. 5.32 and 5.33). The severity of the retinopathy is dependent on the extent of the resultant capillary nonperfusion and retinal ischemia. As the retinopathy progresses, extensive retinal vascular occlusion, NVD, NVE, and iris neovascularization occur. This may lead to vitreous hemorrhage, NVG, and traction retinal detachment.

Radiation retinopathy is commonly associated with optic neuropathy, which can present in either of two forms: anterior ischemic optic neuropathy or retrobulbar ischemic optic neuropathy. Both are due to vascular occlusion.

### Fluorescein Angiography

The principal fluorescein angiographic finding is capillary nonperfusion. In addition, capillary leakage, microaneurysmal leakage, and neovascularization are commonly seen (Fig. 5.33).[91] Transmission hyperfluorescence corresponding to the areas of retinal pigment epithelial atrophy may be seen. Ophthalmoscopy may reveal hypopigmented patches, which appear as hypofluorescent area. When radiation optic neuropathy is present, ischemia of the optic nerve head with superficial areas of nonperfusion and leakage can be seen.

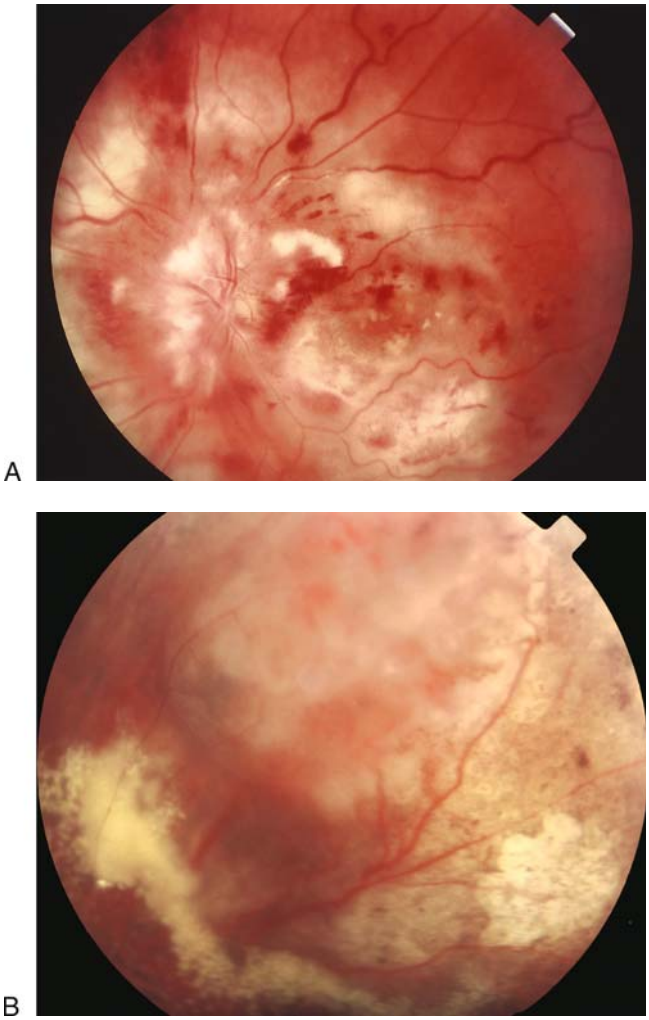


Fig. 5.32. Microvascular changes in radiation retinopathy include microaneurysms, retinal telangiectasias, dot and blot intraretinal hemorrhages, cotton-wool spots, macular exudates, macular edema, perivascular sheathing, and intraretinal microvascular abnormalities. (A) Radiation retinopathy and papillopathy after brachytherapy for retinoblastoma. (B) Radiation retinopathy and papillopathy after brachytherapy for choroidal melanoma. (Courtesy of Drs. Carol and Jerry Shields.)

### Indocyanine Green Angiography

Indocyanine green angiography has demonstrated that ocular and periocular radiation treatment can also cause a radiation-induced choroidopathy.[92] This is characterized by widespread progressive vaso-occlusion of the choriocapillaries and small choroidal vessels. The ICG shows capillary dropout, and small discrete diffuse perfusion defects of the choriocapillaries in the midperipheral zones. Late ICG choroidal staining in the area where radiation retinopathy developed may be observed. Interestingly, many of the areas of choriocapillaris

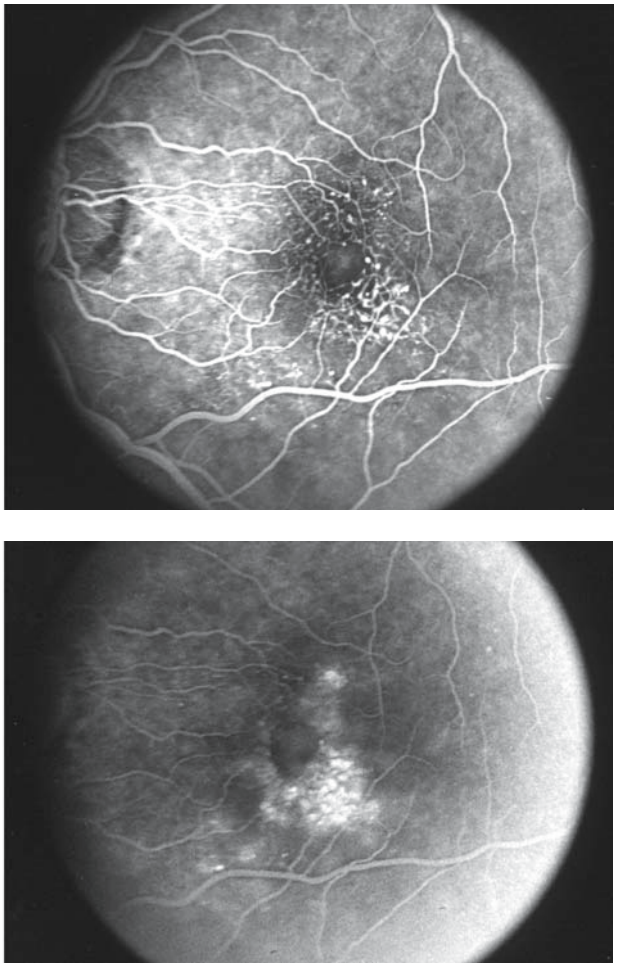


FIG. 5.33. A 49-year-old woman had a left-sided brain tumor removed. She subsequently underwent 20 sessions of radiation therapy. Three years later she complained of blurry vision in her left eye. (A) Early FA frame shows telangiectatic parafoveal capillaries. (B) Mid-FA frame delineating the parafoveal telangiectasia even better.

nonperfusion are distinct from those of retinal ischemia, indicating the widespread nature of the choroidal vascular insult. For the most part, the large choroidal vessels remain normal. At the border of nonperfused and perfused choroid, saccular dilatations and areas of choroidal neovascularization may appear. Choroidal veins can undergo remodeling through the formation of venovenous anastomoses.

### Treatment

Focal and diffuse macular edema can be treated with focal or grid laser photocoagulation. Alternatively, one may consider the use of intravitreal triamcinolone. Repeated injections seem to be needed to maintain the initial effect.[93] Severe nonproliferative and proliferative radiation retinopathy should be treated with scatter retinal photocoagulation, which has been shown to be effective in decreasing and obliterating the proliferative new vessels.[94] Despite laser photocoagulation, some treated eyes may continue to lose vision, due to optic neuropathy and macular ischemia. Tractional retinal detachment, fibrovascular proliferation, and nonclearing vitreous hemorrhage may require standard pars plana vitrectomy techniques.[90]

## Coats' Disease

In 1908, George Coats[95] described an idiopathic entity characterized by unilateral retinal vascular abnormalities with intraretinal and subretinal exudation. He further classified this entity into three groups. Group I had massive subretinal exudates but no visible retinal vascular abnormalities. Group II had massive subretinal exudates with retinal vascular abnormalities. Group III had massive exudates with arteriovenous malformations. von Hippel later characterized this group III as a distinct entity: angiomatosis retinae. In 1912 Theodor Leber described a similar condition characterized by retinal aneurysms, hemorrhages, and telangiectasia, but without the massive subretinal exudates. This condition was named Leber's multiple miliary aneurysm disease. However, in 1915, Leber himself recognized that his disease was the earlier stage of the same entity as the one described by Coats. Reese in 1956 confirmed this concept by describing an eye that had Leber's multiple miliary aneurysms that developed the classic picture of Coats' disease with time.

### Clinical Findings

Coats' disease affects males more commonly than females in a 3:1 ratio. Up to 80% of cases are unilateral. There is no known racial or ethnic predilection.[96] A juvenile and an adult form of the disease are recognized. The juvenile cases usually present with leukocoria, strabismus, or loss of vision. About two thirds of these cases present before the age of 10. The adult form is virtually indistinguishable from the juvenile form, with the exception that the adult form has been associated with hypercholesterolemia and seldom presents with strabismus.

Several case reports have been reported in the literature where Coats' disease has been diagnosed in conjunction with other diseases such as retinitis pigmentosa, Senior-Loken syndrome, Turner's syndrome, and Hallermann-Streiff syndrome.

The underlying problem of Coats' disease is the peripheral retinal vascular abnormality, which causes the breakdown of the blood–retinal barrier. Affected retinal vessels may show sheathing, saccular aneurysmal dilatations, anomalous vascular communications, telangiectasia, and tortuosity. The majority of these abnormalities are located in the inferior and temporal quadrants between the equator and the ora serrata. Leakage of plasma constituents lead to the typical funduscopic findings of yellow intraretinal and subretinal exudates, which find their way to the macular area even if the vascular abnormalities are located in the retinal periphery (Fig. 5.34). The subretinal fluid accumulates inferiorly, causing a bullous retinal detachment.

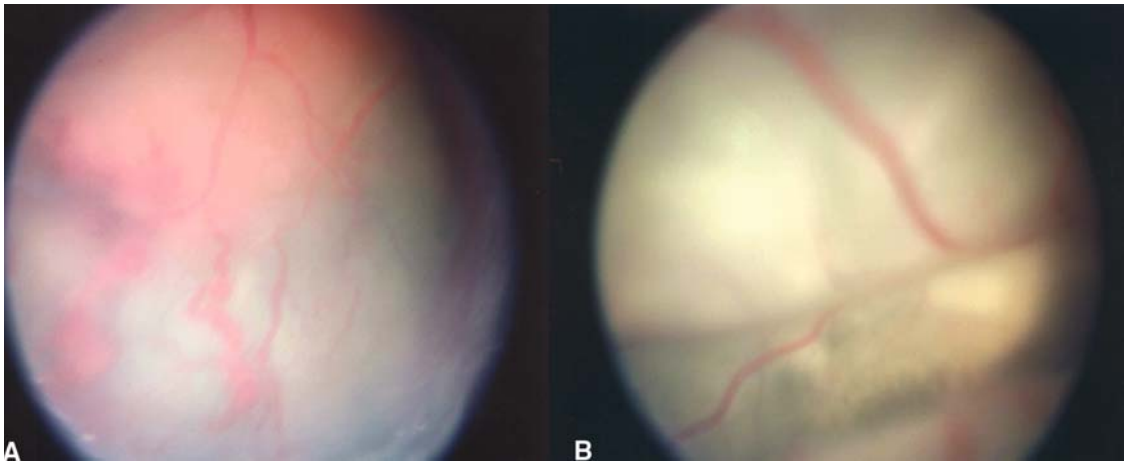


Fig. 5.34. (A,B) Affected retinal vessels show sheathing, saccular aneurysmal dilatations, anomalous vascular communications, telangiectasia, and tortuosity. Leakage of plasma constituents lead to the typical funduscopic findings of yellow intraretinal and subretinal exudates, which find their way to the macular area even if the vascular abnormalities are located in the retinal periphery. The subretinal fluid accumulates inferiorly causing a bullous retinal detachment.

Fibrovascular tissue formation and choroidal neovascularization may follow. Larger zones of capillary nonperfusion can be associated with neovascularization and vitreous hemorrhage.

Complications associated with long-standing retinal detachment include hemorrhagic retinal macrocysts, secondary vasoproliferative tumors, cataract, iridocyclitis, corneal edema, iris neovascularization, anterior chamber cholesterolosis, NVG, and phthisis bulbi.

## Fluorescein Angiography

Fluorescein angiography is a useful adjunct in the diagnosis and management of Coats' disease. The angiogram shows early hyperfluorescence secondary to increased vasopermeability in the area of the affected vessels. If the lipid exudation is extensive, hypofluorescence may be seen. Areas of capillary dropout may be seen in the region of telangiectasia, but retinal neovascularization is rare. In the late phases, mild hyperfluorescence secondary to pooling of the dye in the subretinal fluid may be seen. Hyperfluorescence secondary to leakage from macular edema may also be seen.

## Classification

Shields et al.[97] have proposed the following classification scheme:

Stage 1: Retinal telangiectasia only
Stage 2: Telangiectasia and exudation

A. Extrafoveal exudation
B. Foveal exudation

Stage 3: Exudative retinal detachment

A. Subtotal detachment

1. Extrafoveal
2. Foveal

B. Total retinal detachment

Stage 4: Total retinal detachment and glaucoma
Stage 5: Advanced end-stage disease

## Treatment

The main goal of treatment is to avoid visual loss if possible. If the patient presents early on when there are only retinal vascular abnormalities and extrafoveal exudation or no exudation at all, the ophthalmologist is presented with an opportunity to prevent visual loss by aggressive scatter laser photocoagulation of the involved areas. Once foveal exudation develops, visual loss is common despite treatment. Cryotherapy is the preferred initial method when there are peripheral telangiectasias associated with extensive exudation or subtotal retinal detachment.

Eyes with extensive bullous retinal detachment may benefit from retinal reattachment surgical techniques such as scleral buckle, vitrectomy, and subretinal fluid drainage in combination with photocoagulation and cryotherapy.[98,99] Advanced cases with secondary glaucoma often require enucleation.

# Parafoveal Telangiectasia

In 1956, Reese coined the term *retinal telangiectasia* to describe a developmental retinal vascular disorder characterized by retinal capillary ectasia. If the abnormalities are limited to the parafoveal area, then the condition is known as parafoveal or juxtafoveal telangiectasia. Gass has classified this entity into three major groups with the following subdivisions[100]:

1. Unilateral parafoveal telangiectasia

a. Congenital
b. Acquired

2. Bilateral acquired parafoveal telangiectasia
3. Bilateral idiopathic perifoveal telangiectasia and capillary obliteration

## Clinical Findings

Patients in group 1 are males in their 40s with unilateral involvement of the perifoveal capillary network. The perifoveal area involved differs between groups 1A and 1B. The eyes in group 1A patients have the temporal area affected one to two disc diameters. Group 1B eyes have only one clock hour involved.

Patients in group 2 have no gender predilection and both eyes are involved. Other findings include right-angle draining venules, retinal pigment epithelial hyperplasia, macular edema, and exudation (Fig. 5.35). Chorioretinal anastomosis and retinal pigment epithelial plaques precede the development of choroidal neovascularization.[100]

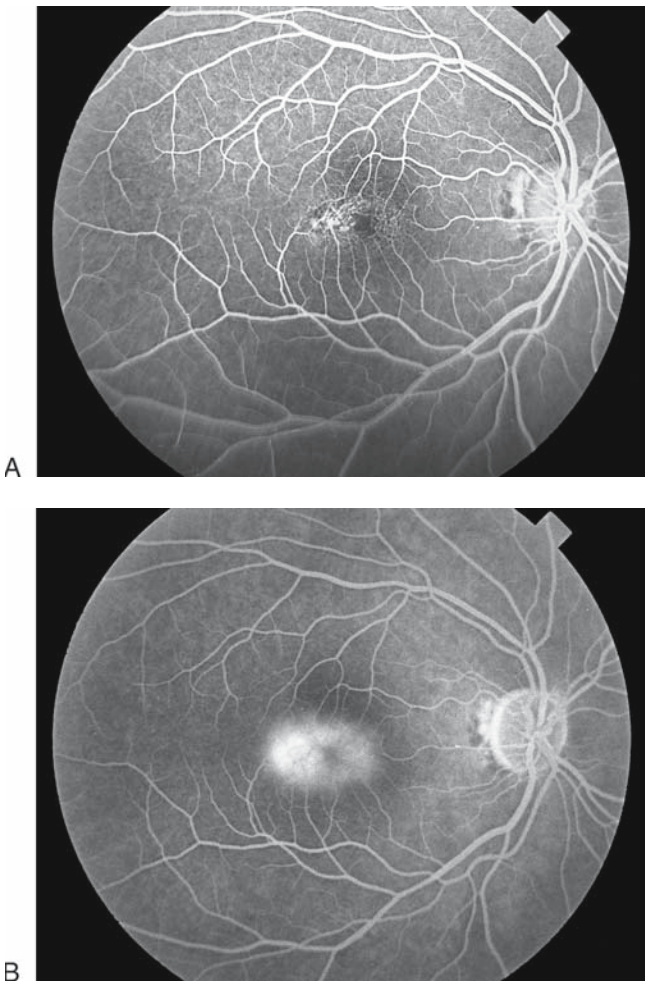


Fig. 5.35. A 42-year-old woman complained of a gradual loss of vision in right eye. Her visual acuity is 20/60 in both eyes. A diagnosis of idiopathic parafoveal telangiectasis was made. (A) Early FA frame of the right eye shows telangiectatic changes in the foveal capillary bed. (B) Late FA frame of the right eye also shows a ring of fluorescein leakage surrounding the fovea.

## Pathogenesis

Histopathologic studies have demonstrated changes very similar to those of diabetic retinopathy in these eyes.[101] These abnormal capillaries are dilated and incompetent like the ones seen in diabetic retinopathy.

## Fluorescein Angiography

During the arteriovenous phase, the abnormal capillaries are seen as dilations especially on the parafoveal temporal side. The abnormalities do not respect the horizontal raphe. If they do, a branch retinal vein occlusion should be strongly suspected. In the late phases leakage occurs secondary to macular edema (Fig. 5.35). Fluorescein angiography has documented that eyes with parafoveal telangiectasia have a small foveal avascular zone.[102]

## Treatment

A small case series reported no benefit from laser photocoagulation. A poor outcome has been reported following submacular surgery in cases of choroidal neovascular membranes. These membranes appear to be very adherent to the neurosensory retina, making their extraction technically difficult and hazardous.[103] Photodynamic therapy with verteporfin has been reported to stop leakage from the choroidal neovascular membrane, but leakage from the telangiectasia persists. Intravitreal triamcinolone has been reported to be useful in a single case report.[104]

# Sickle Cell Retinopathy

Sickle cell disease is a hemoglobinopathy where a point mutation causes a single amino acid substitution in the β-globin chain. This abnormal hemoglobin can occur in combination with normal hemoglobin A or abnormal hemoglobin S or C, leading to various hemoglobinopathies. This results in increased cell hemolysis, blood viscosity, and vaso-occlusion.

## Clinical Findings

Most patients are usually asymptomatic. Retinopathy has been classified as nonproliferative or proliferative depending on the retinal findings.

The precapillary arterioles of the optic disc may undergo repetitive occlusive insults. Angioid streaks may also be seen radiating from the optic nerve.[105] In the posterior pole, an increased vascular tortuosity, arterial occlusion, and nonperfusion lead to an enlargement of the foveal avascular zone and microaneurysms. The macula may become thinned and atrophic, giving rise to a concavity in the area of thinning. This is called the macular depression sign.

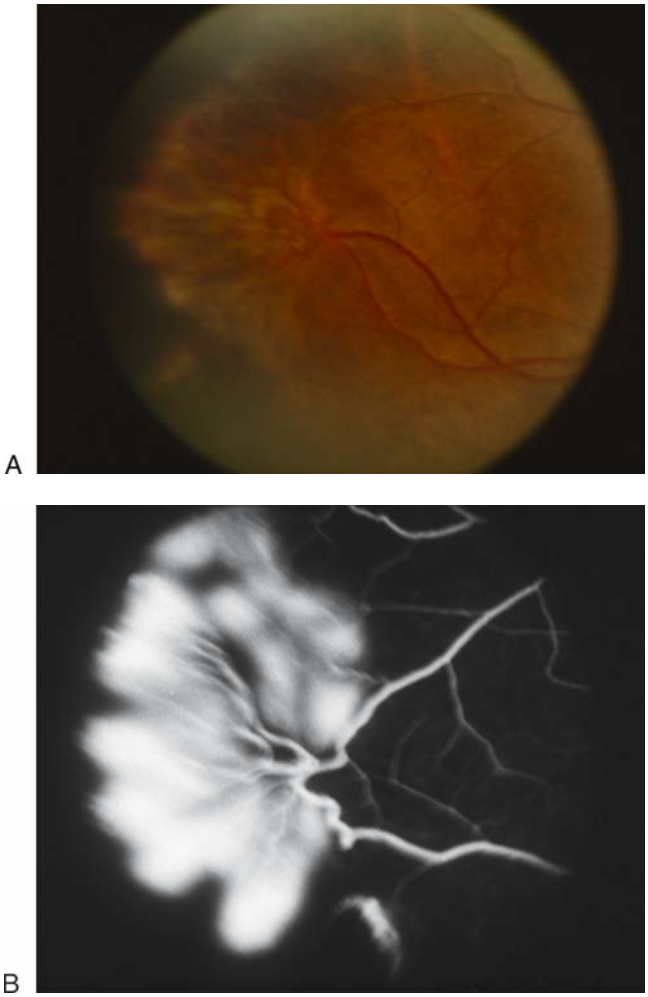


Fig. 5.36. Clinical findings in sickle cell retinopathy. (A) Retinal neovascularization in a sea-fan configuration. (B) The FA frame shows leakage from the sea fan.

In the midperiphery, repetitive episodes of occlusion and ischemia end up weakening the vascular walls. Preretinal or superficial retinal hemorrhages that are oval or round in shape with well-defined borders may occur. The hemorrhage is flat or elevated in a dome-like fashion. With time the red color of the hemorrhage turns into red-orange and then to salmon color. The blood may dissect anteriorly into the vitreous cavity or posteriorly into the subretinal space. These lesions are referred to as salmon patches.[106] Once the hemorrhage of the salmon patch is absorbed, thinning of the underlying retina occurs. A schisis cavity with multiple glistering yellow deposits may develop. These deposits consist of hemosiderin-laden macrophages. These lesions are called iridescent spots. If blood happens to dissect posteriorly, the RPE can undergo a migratory hyperplastic response to it. The result is a round or oval flat black lesion called a black sunburst.

The onset of clinically detectable proliferative sickle cell retinopathy may begin in the first decade of life, but more commonly occurs between 15 and 30 years of age. Proliferative sickle retinopathy is a peripheral retinal vascular disease.[107] The initial event is a peripheral arteriolar occlusion that Goldberg has classified as stage 1. The capillary bed and venules that drain the affected retina become nonperfused. Stage 2 describes the formation of peripheral arteriovenous anastomoses at the border of the perfused and nonperfused retina. Stage 3 is characterized by definite retinal neovascularization that assumes a sea-fan configuration. The sea fan arises from the venous side of the arteriovenous anastomoses and grows from perfused retina toward the peripheral nonperfused retina. Stage 4 refers to vitreous hemorrhage secondary to ongoing vitreoretinal traction. Finally, stage 5 describes tractional or rhegmatogenous retinal detachment.

### Fluorescein Angiography

The hallmark of sickle cell retinopathy is the repetitive nature of the arterial occlusions in the different vascular beds. The angiographic findings demonstrate hypofluorescent areas and nonperfused vessels. The sea fans demonstrate fluorescein leakage (Fig. 5.36).

### Treatment

Up to 60% of eyes with sea fans undergo autoinfarction. Therefore, not all eyes with a sea fan have to be treated. The goal of management is early treatment of lesions in stage 3. Feeder vessel photocoagulation has been shown to be effective in achieving infarction of 88% of eyes with peripheral neovascularization.[108] Scatter photocoagulation is also effective in reducing the risk of developing vitreous hemorrhage. Cryotherapy is reserved for those cases with media opacities.[109] Pars plana vitrectomy carries a high risk of intraoperative and postoperative complications, so it should be reserved for eyes with retinal detachment and nonclearing vitreous hemorrhage.

## Eales' Disease

In 1880 Henry Eales[110] described in seven young patients, who had no evidence of primary retinal or systemic disease, recurrent vitreous hemorrhages associated with distended tortuous retinal veins and epistaxis. He thought that constipation and the ensuing elevated venous pressure caused this condition. Although the etiology of this condition is currently unknown, it has been linked to tuberculous infection. An immune mechanism has been postulated to play a role in the pathogenesis of retinal perivasculitis in patients with tuberculin hypersensitivity.[111] Once the vasculitis subsides, the retinal vascular walls begin to atrophy, remodel, and become ensheathed by glial tissue. This idiopathic peripheral obliterative vasculopathy produces retinal ischemia, neovascularization, and vitreous hemorrhage. Currently, Eales' disease remains a diagnosis of exclusion.

## Clinical Findings

Eales' disease affects mostly healthy young Indian, Pakistani, and Afghan males, usually between 20 and 30 years of age. It is bilateral in up to 90% of patients.

The symptoms that most patients complain of are those secondary to vitreous hemorrhage including floaters, blurring of vision, and gross diminution of vision.

The first stage of the disease is the inflammatory stage. The patients present with a retinal perivasculitis affecting the peripheral retina. This is followed by the second stage, which is characterized by sclerosis of the retinal vessels, which leads to ischemia, The final stage is the proliferative stage where NVE, NVD, and recurrent vitreous hemorrhages with or without retinal detachment occur (Fig. 5.37). Peripheral NVE is reported in 36% to 84% of cases, and NVD in only 9%. Recurrent vitreous hemorrhage is the hallmark of the disease, which affects 37% of the patients. If the hemorrhage remains unresolved, it can lead to organization and retinal detachment.

Macular changes are seen in 18% of the eyes. The findings include macular edema, exudates, epiretinal membrane, subhyaloid hemorrhage, macular hole, and submacular fibrosis.[112]

## Fluorescein Angiography

In cases of active retinal vasculitis, staining of vessels is seen during the early venous phase with extravasation in the late phase. In the healed stage only staining of the vessel wall occurs. Areas of capillary closure, engorged tortuous capillaries and venovenous shunts can be seen in the ischemic stage. Neovascularization is seen with a characteristic sea-fan pattern that hyperfluoresces intensely in the early arteriovenous phase, and leaks profusely in the late venous phase.

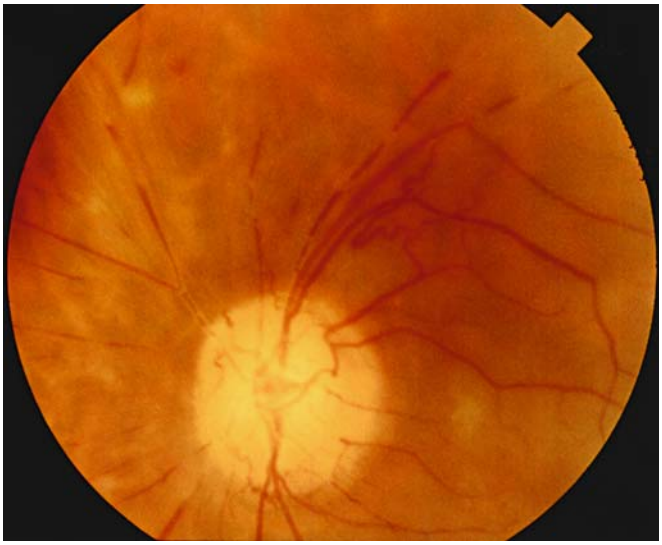

Fig. 5.37. Eales' disease. The patient complained of a sudden decrease in vision of her left eye. She had an afferent pupillary defect and rubeosis iridis. The left optic disc shows pallor, prominent shunt vessels, sheathing, and attenuation of the retinal vessels.

## Treatment

The treatment of Eales' disease depends on the stage of the disease. During the acute inflammatory stage, oral steroids are the mainstay of treatment. Oral prednisolone on the order of 1 mg/kg of body weight is recommended. It is tapered to 10 mg per week over 6 to 8 weeks. In patients who do not respond to systemic steroids or have unacceptable side effects, immunosuppressive agents can be used. Patients with the regressed stage of perivasculitis are observed periodically every 6 months to 1 year. Patients with fresh vitreous hemorrhage are observed at intervals of 4 to 6 weeks, since most of these hemorrhages clear in 6 to 8 weeks. Scatter laser photocoagulation is performed in cases of capillary nonperfusion, NVE, or NVD.[113] Vitreoretinal surgery is required in cases of nonclearing vitreous hemorrhage, especially if retinal detachment is present. The results from such interventions are usually satisfactory.

# Conclusion

Indocyanine green angiography is a highly specialized technique for imaging choroidal vasculature. Fluorescein angiography is highly specialized in the identification of morphologic and dynamic changes of the retinal circulation and RPE. Although retinal fluorescein and ICGV have many physical and chemical differences, the technologies complement each other in the evaluation of a variety of retinal diseases, revealing important and different aspects of retinal or choroidal diseases. Additionally, some stages of various diseases are best seen with FA while other aspects are best revealed with ICGV.

Fluorescein angiography and ICGV have both become very important tools in the evaluation and diagnosis of vascular retinal diseases.

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