9
Angiography in Pharmacologic Retinal Toxicity

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Retinal angiography, specifically fluorescein angiography (FA), is important for the diagnosis and follow-up of pharmacologic retinal toxicity. At this time, there does not appear to be a significant role for indocyanine green (ICG) videoangiography, and even the role of optical coherence tomography (OCT) for these conditions is very limited. Fluorescein angiography appears to be particularly helpful in early cases of possible toxicity where the clinical findings may be mild. Early diagnosis is beneficial, as prompt discontinuation of the offending agent may on occasion reduce the risk of permanent vision loss.

Toxicity with Diffuse Retinal Changes

Toxicity with Pigmentary Degeneration

Quinolines

Chloroquine (Aralen, Sanofi Winthrop Pharmaceuticals, New York, NY) and hydroxychloroquine (Plaquenil, Sanofi Winthrop Pharmaceuticals, New York, NY) are quinoline antimalarials. In the United States, they are primarily used in the management and treatment of various autoimmune diseases, especially rheumatoid arthritis and systemic lupus erythematosus (SLE).

Quinoline toxicity typically follows a well-described course, in which objective clinical changes precede subjective visual disturbance.[1–4] Although FA is not always necessary to make the diagnosis,[5] it remains quite useful for documentation purposes and for clinically borderline situations. In early cases, there is a loss of the foveal light reflex with no definite FA changes. This may progress to nonspecific macular pigmentary alterations, with associated transmission hyperfluorescence (window defects) on FA (Fig. 9.1). The classic bull's-eye lesion develops in fairly advanced cases (Figs. 9.2 and 9.3). In the end stage, a retinitis pigmentosa (RP)-type picture may develop, with diffuse pigmentary changes, vascular attenuation, and optic atrophy (Fig. 9.4). While retinal toxicity is more common with chloroquine, it does occasionally occur with hydroxychloroquine alone (Fig. 9.5).

Additional adjunctive tests include the Amsler grid,[6] automated perimetry,[7] and color vision testing,[8] though the role of these tests in the diagnosis and management of toxicity is limited. There is a yet to be fully defined role for electroretinography (ERG),[9] multifocal ERG (mfERG),[10] and OCT.[11]

Early retinopathy typically stabilizes or resolves upon discontinuation of the agent, although advanced cases oftentimes progress.[12] Because of the unusually long clearance time of these agents,[13] occasional patients develop toxicity years after discontinuation of the medication[13] (Fig. 9.6).

The American Academy of Ophthalmology (AAO) recommended guidelines for monitoring patients on hydroxychloroquine therapy.[14] Suggested at the initiation of quinoline therapy is a baseline ocular examination consisting of a dilated posterior segment examination, along with Amsler grid testing or automated perimetry.[15] Baseline fundus photography and FA are not routinely indicated, but may be useful in patients with preexisting macular pigmentary changes. Patients are classified as being at a higher risk of developing toxicity if they exceed 3 mg/kg/day of chloroquine or 6.5 mg/kg/day of hydroxychloroquine, have been on medication in excess of 5 years, have a high fat level body habitus, have renal or liver disease, or are older than 60 years of age. These patient's need to be monitored more closely; otherwise, patients can be followed as recommended by the AAOs Preferred Practice Pattern.[16] However, obese patients require additional monitoring because quinolines are stored to a greater degree in lean body tissues than in fat. When determining an individual patient's risk of toxicity, the dose should be calculated based on ideal weight rather than actual weight.[17] If signs of toxicity develop, the medication should be discontinued, as toxicity may progress even after the medication has been discontinued.

Quinine

The related compound quinine (Quinamm, Marion Merrell Dow, Inc., Kansas City, MO) is associated with a distinct toxicity. Quinine is prescribed for benign nocturnal muscle cramps, and may cause toxicity with acute overdose. The syndrome is characterized by headache, nausea, vomiting, tremor, hypotension,

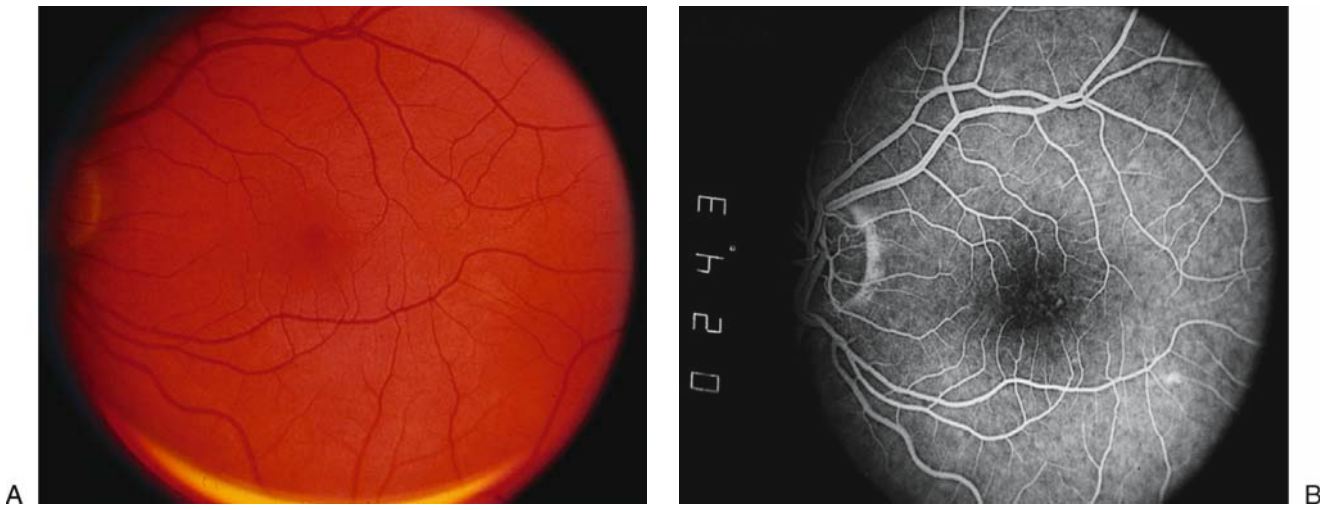


FIG. 9.1. (A) Color photograph of the left eye (OS) shows subtle retinal pigmentary changes along the temporal border of the macula in a patient on chloroquine. (B) Fluorescein angiography (FA) shows transmission defects corresponding to the areas of retinal pigment mottling.

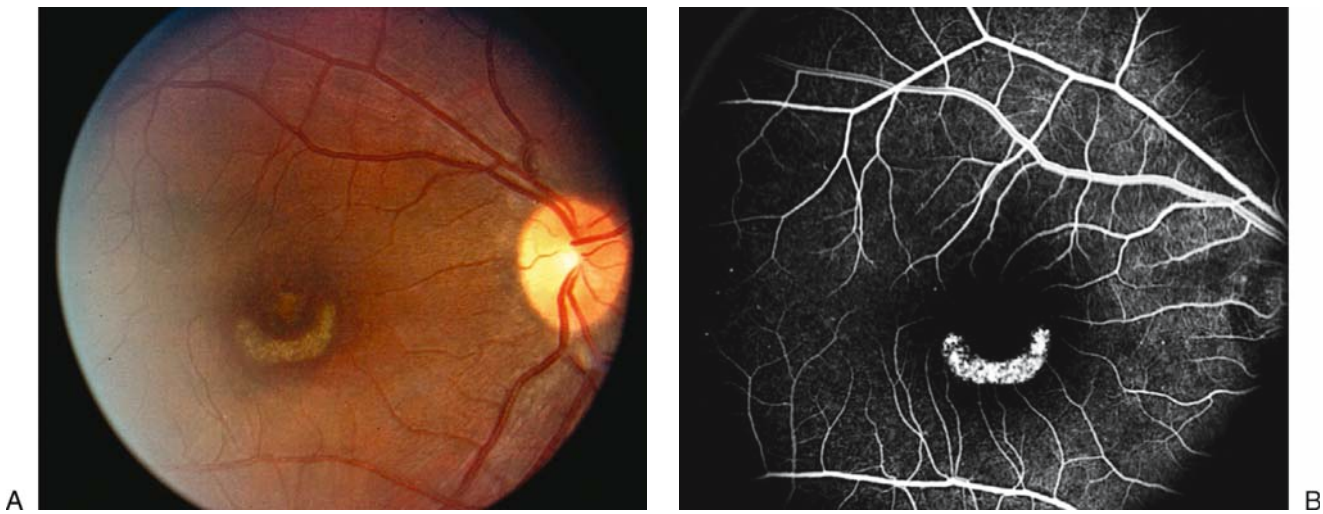


FIG. 9.2. (A) Color photograph of the right eye (OD) shows a partial (inferior) bull's-eye lesion in a patient on chloroquine. (B) Fluorescein angiography reveals a transmission defect corresponding to the area of retinal pigment atrophy.

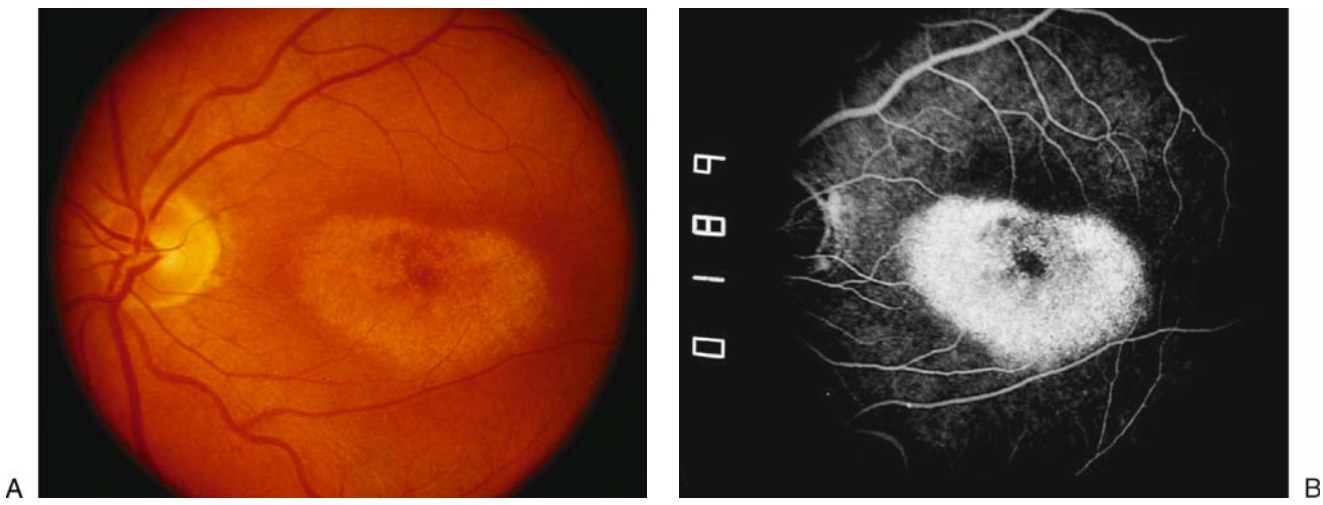


FIG. 9.3. (A) Color photograph OS documents a complete bull's-eye lesion in a patient on chloroquine, who had lost central vision. (B) Fluorescein angiography shows a transmission defect corresponding to the area of central retinal pigment atrophy.

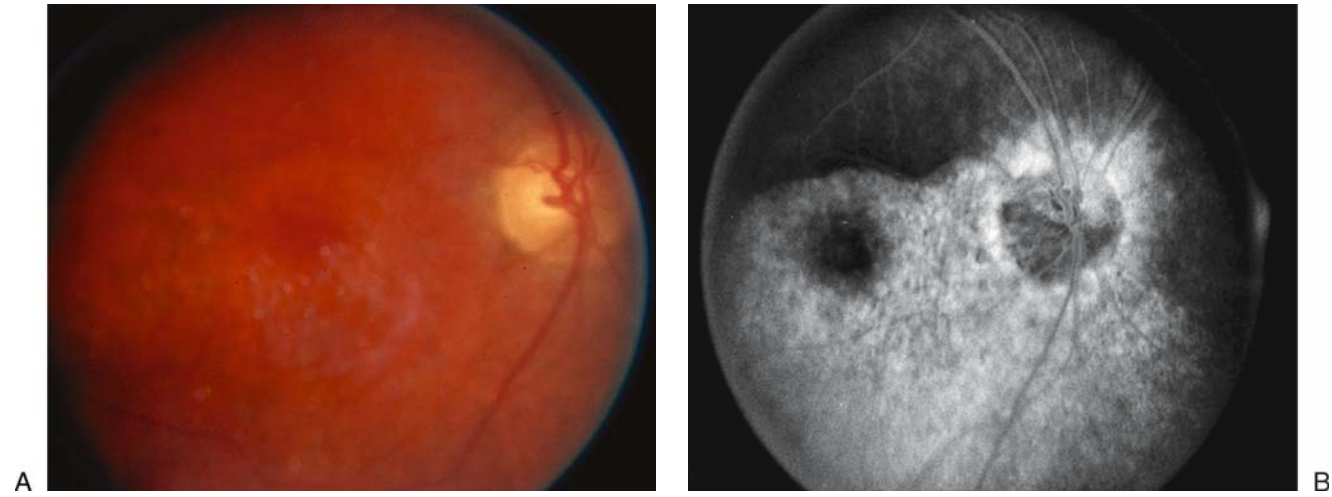


FIG. 9.4. (A) Color photograph OD shows extensive, diffuse retinal pigment atrophy, disc pallor, and vascular attenuation in a patient on long-standing chloroquine therapy. The area of pigment atrophy extends far beyond the area of the macula. (B) Fluorescein angiography documents the extensive transmission defect corresponding to the area of retinal pigment atrophy.

and loss of consciousness associated with profound vision loss, which may be irreversible.[18]

Acutely, there is mild retinal edema with mild venous dilation. Over several weeks, arteriolar attenuation and optic atrophy develop (Fig. 9.7). There may also be a mild degree of diffuse retinal pigment mottling. The FA may show minimal changes or may be normal.[19] More pronounced abnormalities may be documented on perimetry, ERG, mfERG, electro-oculography (EOG), dark adaptometry, and visual evoked potentials (VEPs).[20,21] Acutely, hemodialysis may be beneficial in the treatment of an overdose. Visual outcomes, however, are extremely variable.

Phenothiazines

The phenothiazines are antipsychotic agents whose use in the United States has declined over the years. Of the phenothiazines, the most toxic potential is found in the piperidines, particularly with thioridazine (Mellaril, Sandoz Pharmaceuticals, East Hanover, NJ).

Toxicity manifests as decreased vision, nyctalopia, and dyschromatopsia (red or brown).[22] Mild, nonspecific macular pigmentary changes are seen initially (Fig. 9.8), and may be followed by salt-and-pepper pigmentary loss (Fig. 9.9). This pattern of pigment loss may coalesce into broader zones of

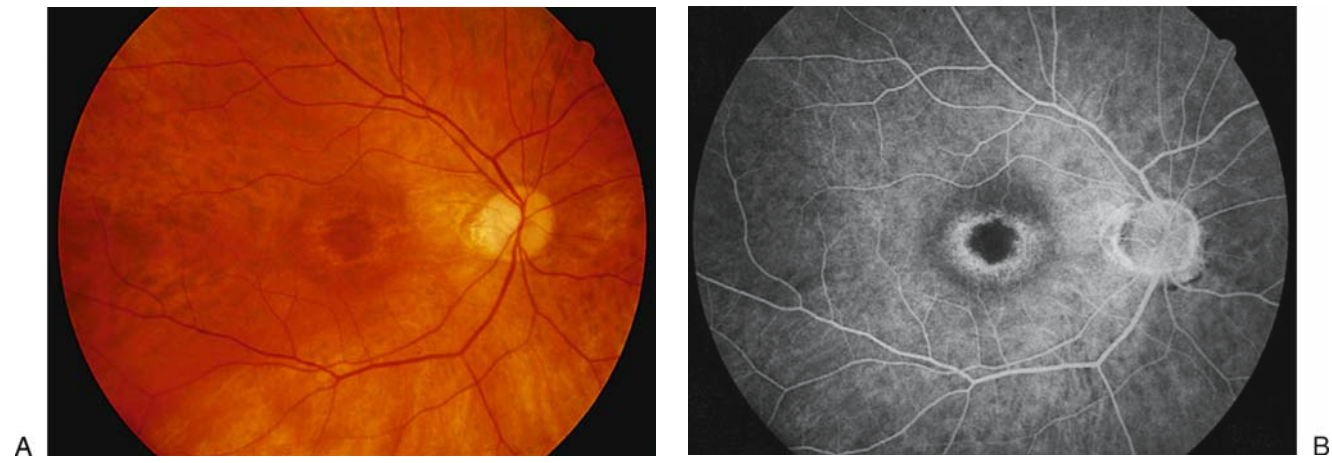


FIG. 9.5. (A) Color photograph OD of a patient on hydroxychloroquine for rheumatoid arthritis. The patient had never been on chloroquine. The patient was frail, weighing only 100 lb, and the dose of hydroxychloroquine exceeded the recommended daily dose. (B) Fluorescein angiography documents a transmission defect corresponding to the zone of retinal pigment atrophy seen on clinical examination.

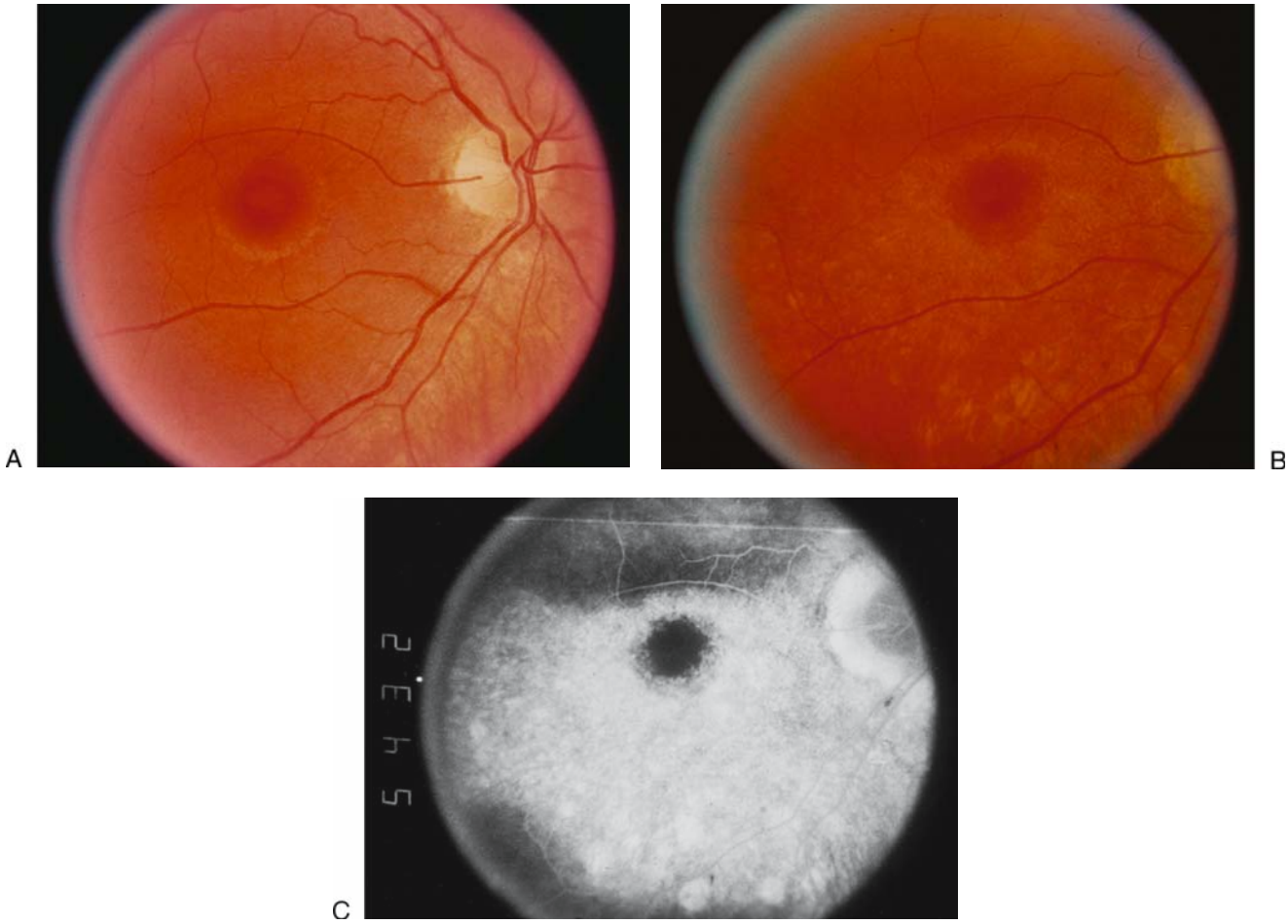


FIG. 9.6. (A) Color photograph OD showing a bull's-eye lesion in a patient on chloroquine. The medication was discontinued, and there was no further exposure to quinoline medications. (B) Two years later, the patient returned, describing loss of central vision. There had been progressive loss of retinal pigmentation extending far beyond the macular region. (C) Fluorescein angiography reveals a prominent transmission defect corresponding to the area of retinal pigment atrophy.

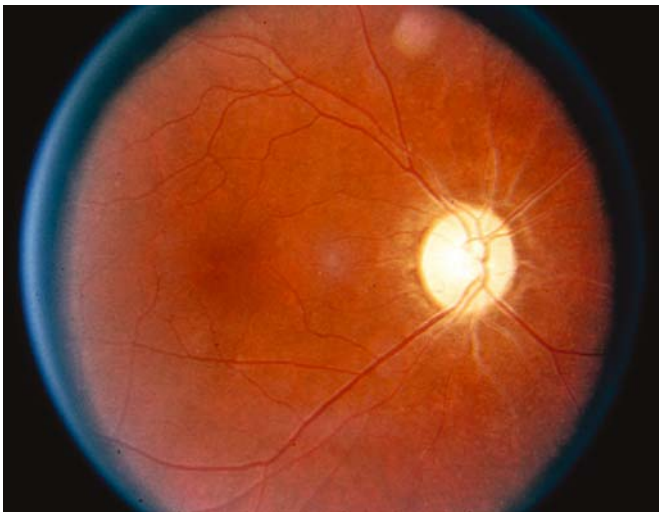
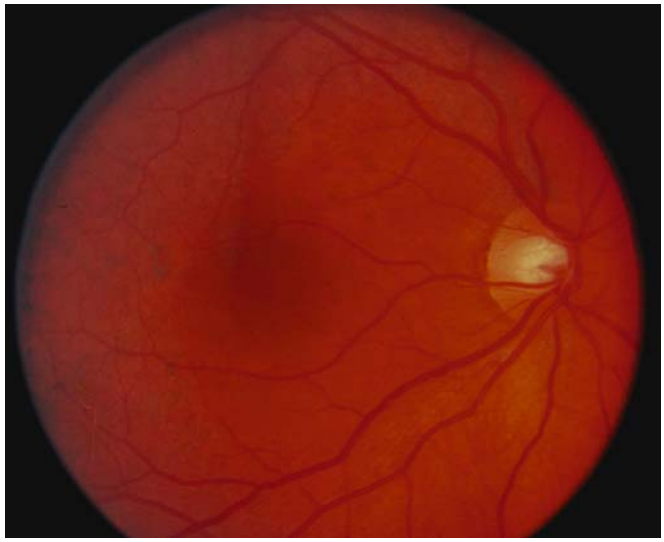


FIG. 9.7. Color photograph of a patient 2 months following quinine ingestion in an attempted suicide. Note the profound optic atrophy, along with the vascular attenuation and very slight retinal pigment mottling. Minimal vision returned, as the patient was left with light perception acuity.

FIG. 9.8. Color photograph OD shows mild retinal pigment clumping temporal to the macula in a patient on thioridazine.



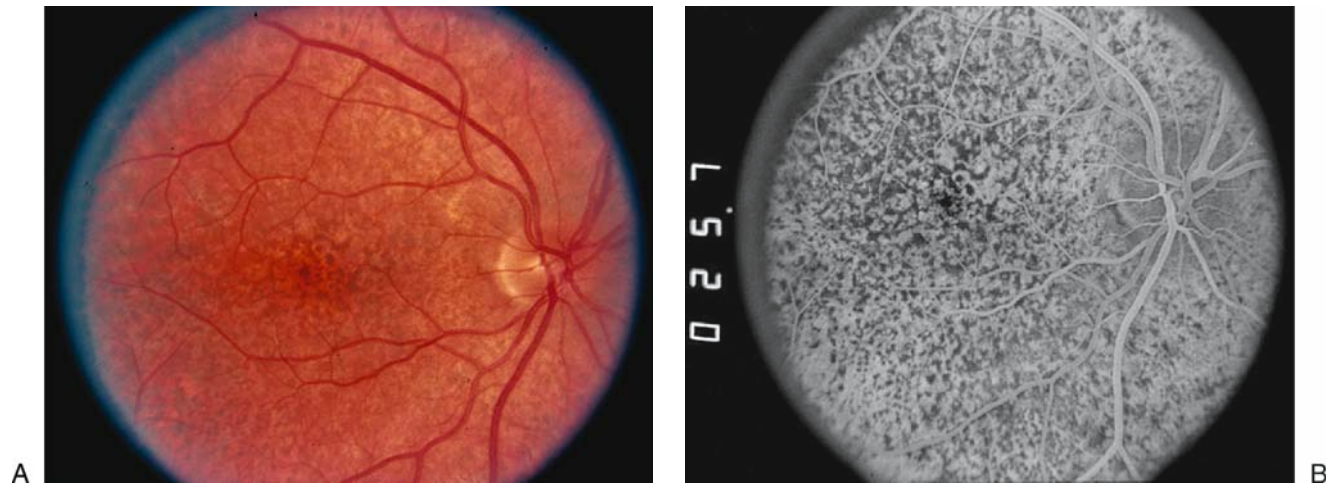


FIG. 9.9. (A) Color photograph OD reveals a salt-and-pepper pattern of pigmentary change in a patient on long-term thioridazine therapy. (B) Fluorescein angiography documents the very prominent pattern of transmission defects interspersed with areas of blocked fluorescence due to pigment clumping (salt-and-pepper pattern).

atrophy (Fig. 9.10) and eventually be followed by nummular areas of loss of the retinal pigment epithelium and choriocapillaris[23] (Fig. 9.11). In severe cases, generalized changes may occur, including vascular attenuation, optic atrophy, and diffuse pigmentary alterations, with virtually a complete loss of the choriocapillaris and retinal pigment epithelium[24] (Fig. 9.12). This end result may appear similar to the condition of choroideremia. The pigmentary disturbance is even more apparent with FA. Adjunctive tests include perimetry, ERG, dark adaptometry, and EOG,[25] although they are of limited value in establishing the diagnosis or in monitoring disease progression.

Discontinuation of the agent may allow for spontaneous improvement on rare occasion, though more commonly visual loss remains or even progresses. This is felt to be secondary to a continued decline in function of the previously damaged cells, rather than a prolonged effect of the medication.[26] Therefore, if a patient is found to have retinal pigmentary disturbance due to thioridazine, the medication should be discontinued.

Deferoxamine

Deferoxamine (desferrioxamine, Desferal, Novartis, East Hanover, NJ) is a chelator of iron and aluminum. The drug prevents toxicity from these elements in patients receiving repeated blood transfusions. Toxicity consists of decreased vision, nyctalopia, and visual field loss. The most common presenting sign is a gray discoloration of the macula, which progresses to diffuse pigmentary changes (Fig. 9.13). In some patients, however, FA abnormalities (early blocked fluorescence, late staining) may precede ophthalmoscopic findings.[27]

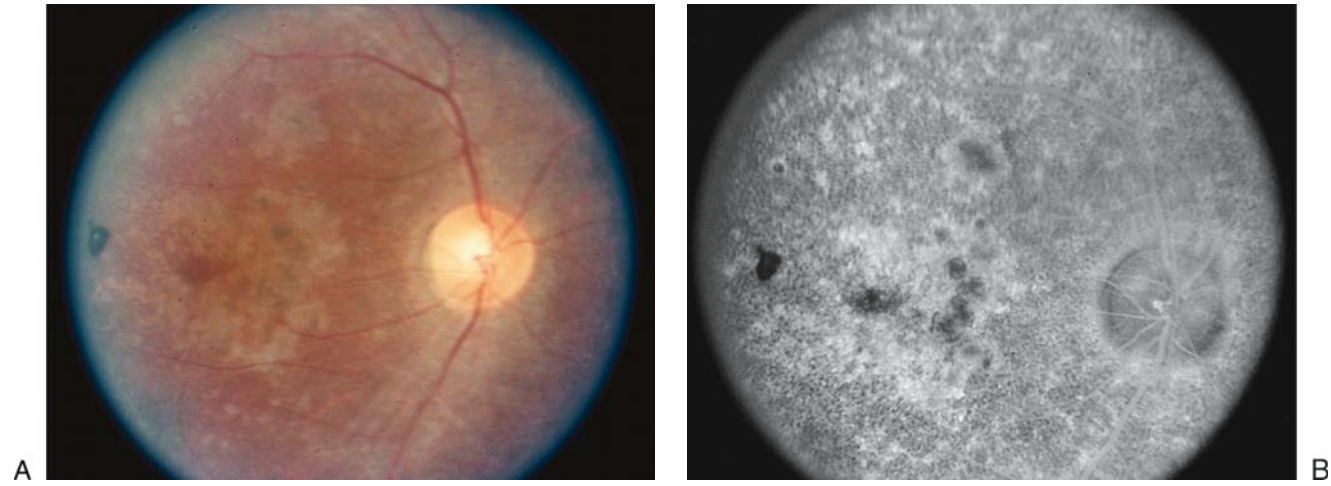


FIG. 9.10. (A) Color photograph OD from a patient on long-term thioridazine shows coalesced areas of retinal pigment atrophy, interspersed with areas of pigment clumping. (B) Fluorescein angiography reveals prominent transmission defects, along with areas of blocked fluorescence corresponding to the appearance of the retinal pigment epithelium.

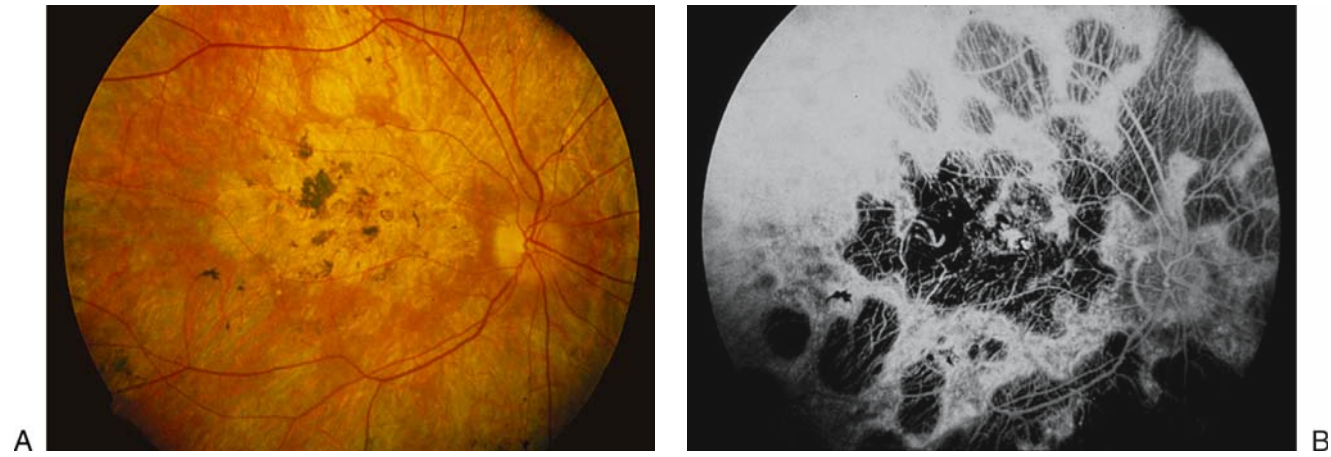


FIG. 9.11. (A) Color photograph OD reveals widespread loss of the retinal pigment in a nummular pattern. (B) Fluorescein angiography documents zones of absent fluorescence, indicative of loss of the underlying choriocapillaris in the areas where the retinal pigment epithelium was also absent.

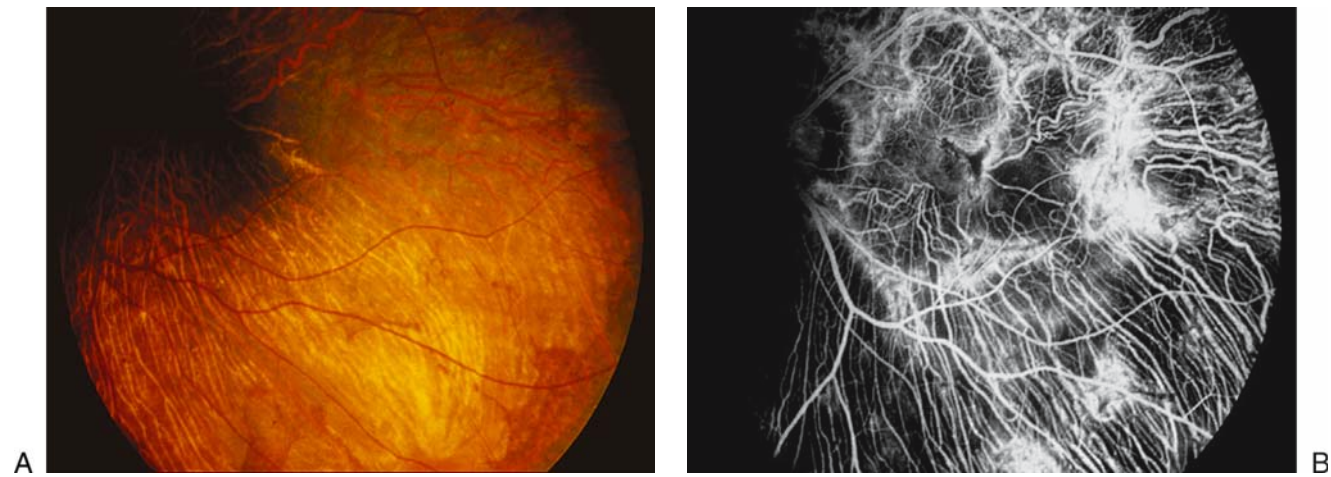


FIG. 9.12. (A) Color photograph OS shows complete loss of the retinal pigment, allowing visualization of the underlying choroidal vessels. (B) Fluorescein angiography documents loss of choriocapillaris. Large choroidal vessels are very readily seen.

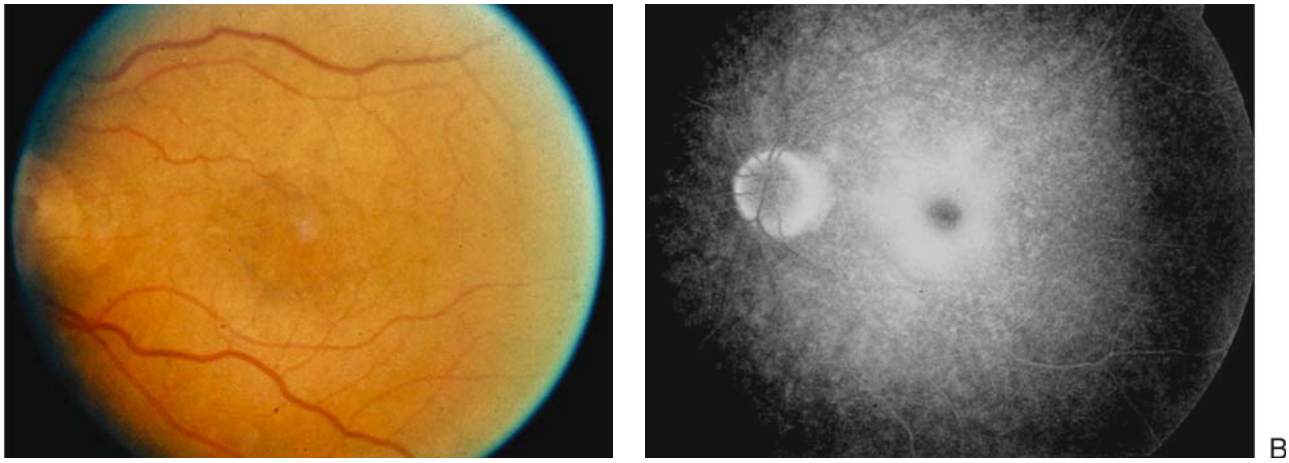


FIG. 9.13. (A) Color photograph OS shows macular pigment mottling in a patient being treated with deferoxamine. (B) Fluorescein angiography documents a transmission defect, along with mild macular leakage.

Abnormalities also may be noted with color vision testing, perimetry, ERG, EOG, and dark adaptometry.[28] Vision loss may persist despite discontinuation of the medication,[29] and toxicity may occur from a single dose.[30]

Toxicity with Crystalline Deposits

Tamoxifen

Tamoxifen (Nolvadex, AstraZeneca, Wilmington, DE), an estrogen antagonist, is primarily used in the management of metastatic breast adenocarcinoma. Toxicity in the form of retinal crystals may be asymptomatic, or may cause mild central visual impairment along with dyschromatopsia.[31] These latter two visual symptoms generally occur secondary to development of cystoid macular edema (CME).

White refractile deposits (crystals) are noted in the posterior pole generally in a circular pattern surrounding the macular region (Fig. 9.14), and may be associated with mild pigmentary changes. In advanced cases, CME may also develop. Fluorescein angiography or OCT are utilized to confirm the presence of CME, though the crystals are not seen on FA.

Asymptomatic patients with retinal crystals may be monitored. Most patients may be continued on the medication, as it is needed in the treatment of their metastatic breast adenocarcinoma. Patients with documented vision loss or CME, however, should discontinue the agent to limit or prevent permanent visual compromise.[32] It is estimated that approximately 2% to 3% of patients on the recommended therapeutic dose of tamoxifen develop retinal crystals.

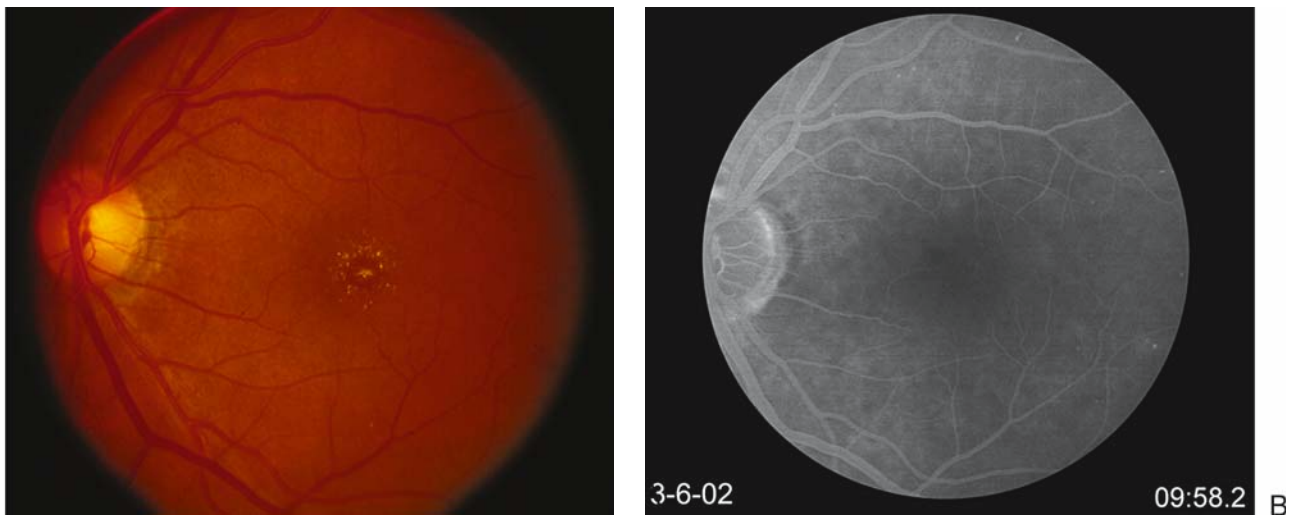


FIG. 9.14. (A) Color photograph shows a small ring of retinal crystals surrounding the macular region in a patient being treated with tamoxifen. The patient was visually asymptomatic. (B) Fluorescein angiography shows no macular abnormality. (Courtesy of Eric R. Holz, MD, Houston, TX.)

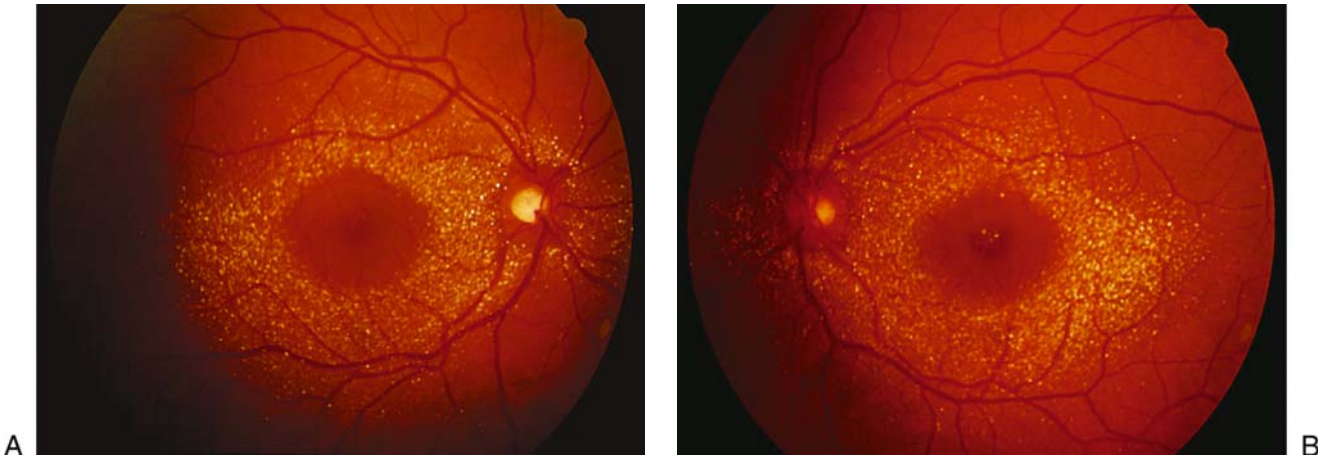


Fig. 9.15. Color photographs OD (A) and OS (B) from a patient who consumed canthaxanthine for sun-tanning purposes. The patient was visually asymptomatic with visual acuity of 20/20 in both eyes. The patient was encouraged to discontinue the medication. (Courtesy of Scott R. Sneed, MD, Traverse City, MI.)

Canthaxanthine

Canthaxanthine (Orobronze, Dewitte, Greenville, SC) is a carotenoid pigment prescribed for vitiligo and photosensitivity disorders. Ocular abnormalities are rarely seen when canthaxanthine is utilized in the treatment of these conditions. In some countries, the drug is marketed as an over-the-counter oral sun-tanning agent. Toxicity is characterized by an asymptomatic ring of yellow-orange crystals in the macular region[33] (Fig. 9.15). The FA is usually normal, but abnormalities may occur on perimetry, ERG, EOG, or dark adaptometry.[34]

When retinal crystals are seen on clinical examination, it is recommended that the patient discontinue the medication, as it is generally not being employed for a true medical indication. Upon discontinuation of the agent, the crystals generally resorb slowly, with corresponding improvement in electrophysiologic parameters.[35]

Methoxyflurane

The inhalational anesthetic methoxyflurane (Penthrane) is rarely used today in the United States, because of associated potential renal toxicity, which can lead to a form of secondary hyperoxaluria. This is mediated by deposition of calcium oxalate crystals in the renal tubules.[36] In a similar fashion, yellow-white punctate crystals may be found in the macular region or filling the retinal arterioles (Fig. 9.16). The deposits do not show hyperfluorescence on FA.[37,38]

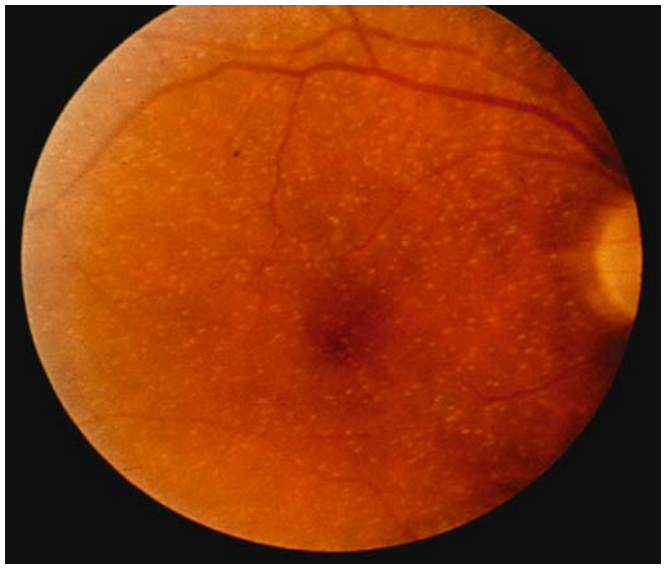


Fig. 9.16. Color photograph OD of a patient who underwent a prolonged surgical procedure in which methoxyflurane was used as one of the anesthetic agents. Renal failure ensued, and methoxyflurane-induced retinal crystals were seen dispersed throughout the posterior pole of both eyes.

Toxicity Without Fundus Changes

Cardiac Glycosides

Xanthopsia from foxglove (*Digitalis purpurea*) has been noted for almost 300 years.[39] Modern cardiac glycosides, including digoxin (Lanoxin, GlaxoSmithKline, Research Triangle Park, NC), are structurally similar and may cause the same toxicity. Visual acuity may be reduced, and color vision is usually diminished. Fundus examination, FA, and EOG are typically normal, although the ERG may show characteristic depressions during toxic episodes.[40]

Sildenafil

The widely used erectile dysfunction agent sildenafil (Viagra, Pfizer, New York, NY) is an inhibitor of phosphodiesterase 5 (PDE-5) in the penile corpora cavernosa, but demonstrates cross-activity with the PDE-6 in the photoreceptors.[41]

A single dose may cause transient and reversible dyschromatopsia,[42,43] though symptoms are generally dose-related. Typically, the funduscopic examination and FA are normal, but rare reported complications include retinal hemorrhages, retinal vascular occlusion,[44] nonarteritic anterior ischemic optic neuropathy,[45] acceleration of proliferative diabetic retinopathy,[46] and central serous chorioretinopathy.[47] Changes commensurate with the above noted diagnoses may be seen on FA or OCT.

More reproducible abnormalities, even in asymptomatic subjects, include transient depressions in ERG and mfERG.[48]

In most cases, sildenafil appears to cause no apparent long-term retinal damage,[49] although individuals with preexisting retinal disease may be at increased risk.[50]

Toxicity with Retinal Edema

Methanol

Methanol, while not prescribed for consumption, is occasionally accidentally ingested, or used in an attempt to commit suicide. Significant vision loss is typical, with development of acute retinal and optic disc edema (Fig. 9.17), leading to eventual optic atrophy, with corresponding FA changes.[51,52] The visual prognosis as well as prognosis for life correlates quite closely with the extent of systemic acidosis. Abnormalities of perimetry, ERG, and VEP may be noted.[53]

Toxicity with Retinal Necrosis

Corticosteroid Preparations

Although most preparations of corticosteroids are quite safe for intravitreal use,[54] the vehicles of some preparations may induce retinal necrosis with formation of retinal breaks and rhegmatogenous retinal detachment. Two particularly toxic compounds are betamethasone acetate/betamethasone sodium phosphate (Celestone Soluspan, Schering-Plough, Kenilworth, NJ) and methylprednisolone acetate (Depo-Medrol, Pfizer, New York, NY).[55,56]

Toxicity with Retinal Vascular Changes

Aminoglycosides

Aminoglycosides may cause ocular toxicity by almost any route of delivery,[57,58] though toxicity is most commonly seen when the medication is injected intravitreally for the treatment of endophthalmitis. Gentamicin appears more toxic than tobramycin or amikacin.[59] The medication is employed less commonly today, as most cases of endophthalmitis are treated with ceftazidime and vancomycin.

With gentamicin toxicity, severe vision loss is characteristic, with vascular changes including retinal edema, cotton-wool spots, intraretinal hemorrhages, arteriolar attenuation, and venous beading (Fig. 9.18). Fluorescein angiography is oftentimes quite striking, as it demonstrates profound macular capillary nonperfusion.[60] Late manifestations include widespread pigmentary retinopathy, optic atrophy, and anterior segment neovascularization.

Talc

Magnesium silicate (talc) is found as a vehicle in many oral medications. Talc may gain access to the systemic vascular

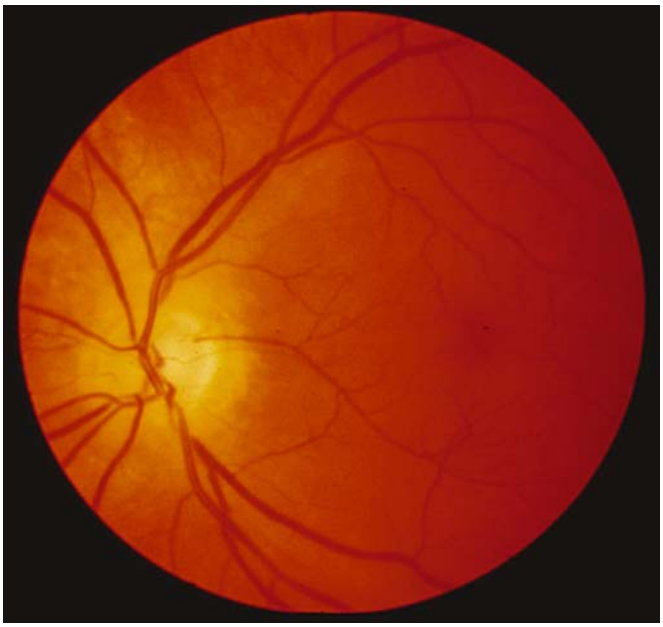


Fig. 9.17. Color photograph OS of a patient following accidental ingestion of methanol. Note the mild diffuse retinal edema. The patient recovered from the incident with vision of 20/60 in both eyes.

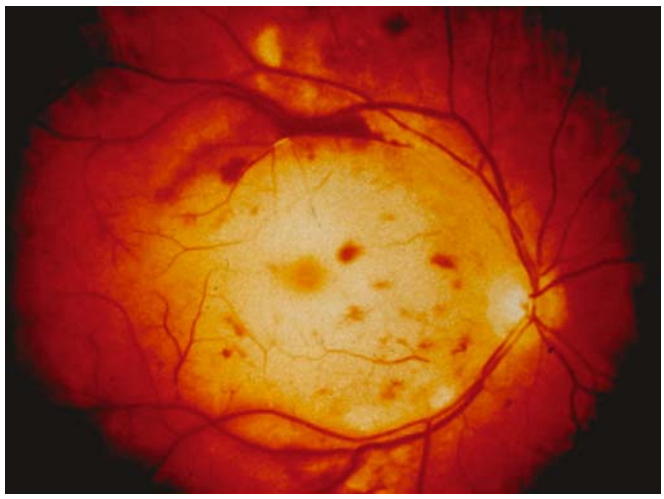


Fig. 9.18. Color photograph OD of a patient 1 day following treatment for endophthalmitis, which included an intravitreal injection of gentamicin 200 μg. The patient exhibited macular infarction, along with scattered retinal hemorrhages. Vision never recovered beyond hand motions.

system when individuals abuse these medications by dissolving them and injecting them intravenously. [61] Small talc particles clear the pulmonary capillary network and enter the arterial system. Chronic injection of talc may cause arteriovenous shunt formation, with access to the central retinal artery possible even for larger particles.[62]

Initially, talc emboli are asymptomatic,[63] but may lead to an ischemic retinopathy. Clinical examination and FA oftentimes demonstrate the intraarteriole talc particles (Fig. 9.19), along with capillary nonperfusion, microaneurysms, cotton-wool spots, and later with retinal neovascularization[64–66] (Fig. 9.20).

Oral Contraceptives

Oral contraceptive preparations are linked to systemic thromboembolic events, including retinal vascular occlusions, with corresponding FA abnormalities.[67–69] These complications were more common with older formulas of the contraceptives, which contained higher concentrations of synthetic agents,[70,71] and estrogen in particular. When vascular occlusive disease is seen today, it generally occurs in patients who are in the older age range for oral contraceptive usage, and there is generally a history of underlying systemic vascular disease.

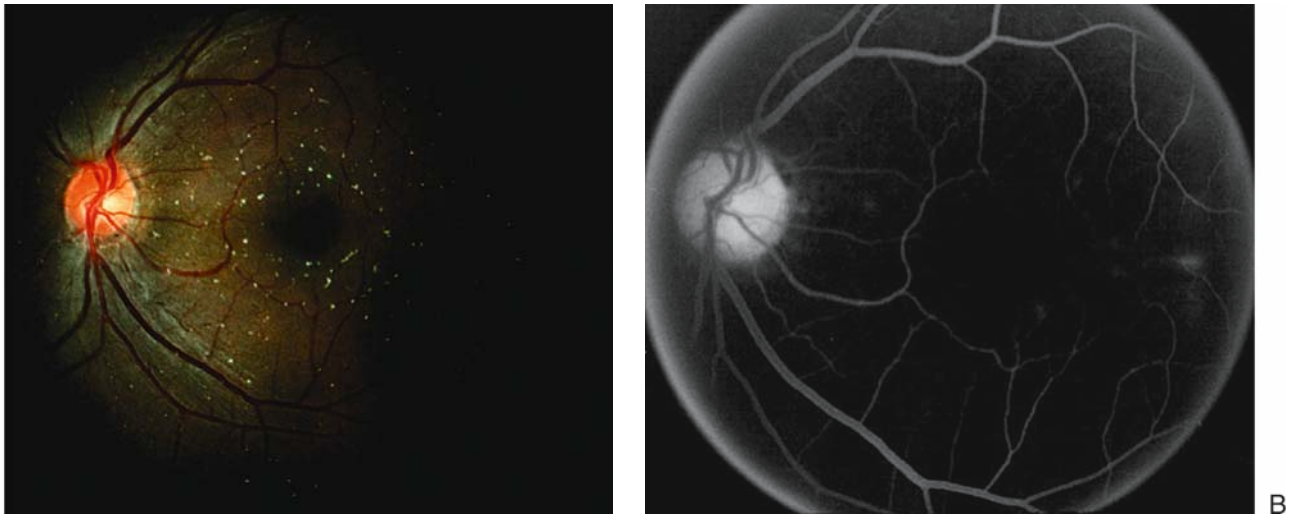


Fig. 9.19. (A) Color photograph OS of a patient who intravenously abused illicit drugs. Numerous talc particles are seen dispersed through the retinal arterioles. (B) The FA demonstrates significant retinal ischemia.

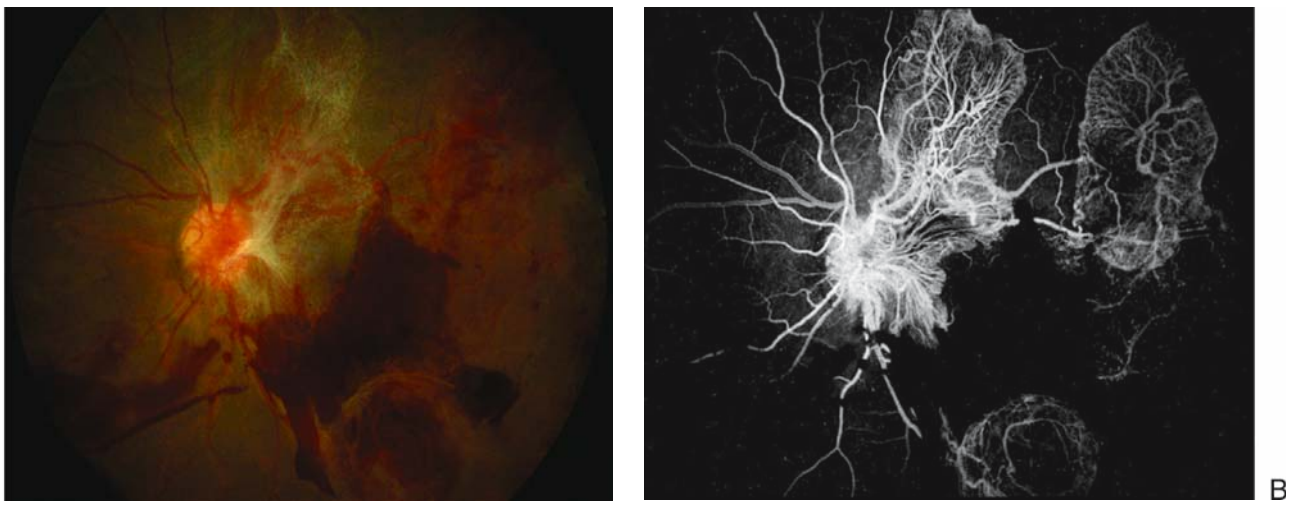


Fig. 9.20. (A) Color photograph OS of a patient with a long-standing history of intravenous drug abuse. Previous ocular examinations demonstrated arteriolar emboli from talc. The patient subsequently developed profound retinal ischemia with development of prominent neovascularization. (B) Fluorescein angiography documents the extensive whorl-like retinal neovascularization with distal retinal ischemia.

Interferon-Alpha

Interferon (IFN) alpha-2a (Roche Pharmaceuticals, Nutley, NY) and alpha-2b (Schering, Kenilworth, NJ) are antiviral agents used to treat chronic hepatitis and various malignancies.

In most patients, visual acuity is normal, with varying degrees of cotton-wool spots and intraretinal hemorrhages[72] (Fig. 9.21). Vision loss may occur secondary to retinal vascular occlusions[73] and cystoid macular edema,[74] with corresponding FA findings. Systemic vascular disease (e.g., diabetes mellitus) is a risk factor for retinal toxicity.[75]

Toxicity with Maculopathy

Toxicity with Cystoid Macular Edema (CME)

Epinephrine and Dipivefrin

The related compounds epinephrine (Epifrin, Allergan, Irvine, CA) and dipivefrin (Propine, Allergan, Irvine, CA) are no longer commonly used to treat glaucoma in the United States. They were previously associated with well-described cystoid macular edema, particularly in aphakic eyes.[76,77]

Latanoprost

Latanoprost (Xalatan, Pfizer, New York, NY) and other prostaglandin agents may cause reversible cystoid macular edema with or without iridocyclitis.[78,79] Risk factors include intraocular surgery, dipivefrin, epiretinal membrane, branch retinal vein occlusion, iridocyclitis, and diabetes mellitus.[80,81]

Toxicity with Other Maculopathies

Niacin

Niacin (nicotinic acid, vitamin B_3) is used to treat hyperlipidemia and hypertriglyceridemia. It causes an unusual toxicity that clinically resembles CME but lacks late fluorescein angiographic leakage.[82,83] Because of the lack of findings on FA, OCT may be particularly helpful to make the diagnosis and for documentation purposes.[84] This pseudo-CME is probably caused by intracellular fluid accumulation, as opposed to true edema, which is in the extracellular space.[85] Treatment is discontinuation of the medication, which generally allows for rapid resolution of the pseudo-CME, and restoration of visual function (Fig. 9.22).

Sympathomimetics

Intravenous sympathomimetics, including epinephrine, may cause a unique macular toxicity with loss of vision or paracentral scotoma formation, similar to acute macular neuroretinopathy, an idiopathic condition.[86] Concomitant elevation of the blood pressure is not necessary to cause this toxicity.[87] Reddish-brown wedge-shaped lesions develop in the outer retina, associated with faint hyperfluorescence on FA (Fig. 9.23). When exposure to the sympathomimetics is discontinued, the ocular findings generally resolve spontaneously.

Toxicity with Retinal Folds

Sulfanilamide-Like Medications

Several related medications (generally containing sulfa), may induce a syndrome including ciliary body swelling, choroidal effusion, and anterior displacement of the lens–iris diaphragm. Anterior segment complications include nonpupillary block angle closure, and posterior segment complications include induced-myopia and retinal folds (Fig. 9.24). The FA generally shows no vascular leakage, supporting the concept that the folds are most likely caused by mild vitreous traction on the macula during axial elongation of the eye. Drugs associated with this syndrome include sulfanilamide,[88] acetazolamide (Diamox, Lederle Pharmaceuticals, Inc., Pearl River, NJ),[89] metronidazole,[90] hydrochlorothiazide,[91] and topiramate (Topamax, Ortho-McNeil, Raritan, NJ).[92] When the offending medication is identified and discontinued, the retinal abnormalities generally return to normal.

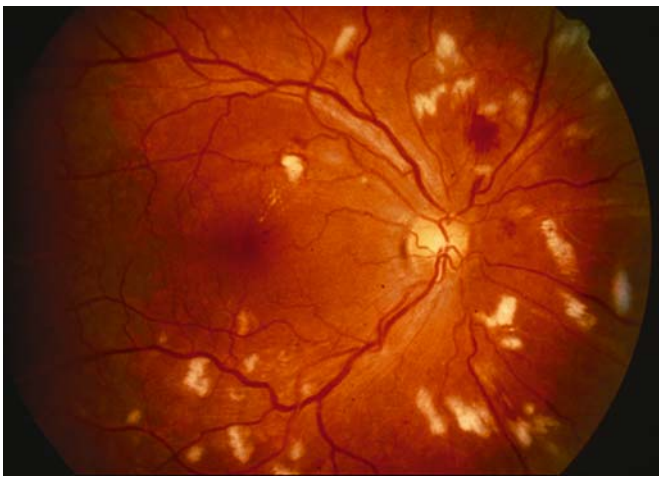


Fig. 9.21. Color photograph OD of a patient being treated with interferon for chronic hepatitis C. Multiple cotton-wool spots developed along with several intraretinal hemorrhages, though the cotton-wool spots gradually dissipated. The patient remained on the interferon therapy.

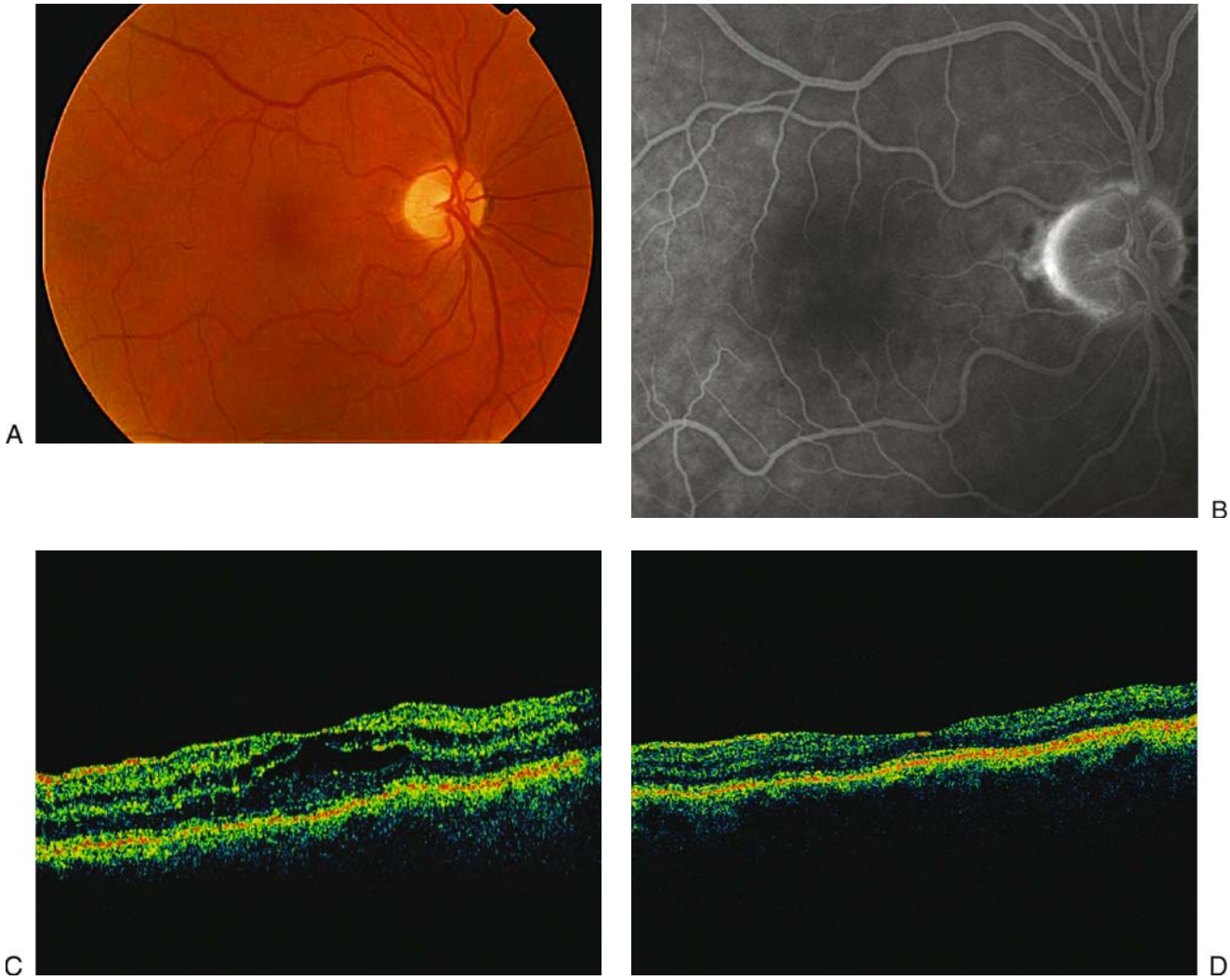


FIG. 9.22. (A) Color photograph OD of a patient taking systemic niacin. The visual acuity is 20/40 and there is blunting of the foveal reflex. (B) Fluorescein angiography shows no appreciable late leakage. (C) Optical coherence tomography (OCT) while on niacin demonstrates the presence of macular thickening. (D) Optical coherence tomography taken 2 weeks following cessation of the niacin therapy has returned to normal, and the vision recovered back to 20/20 as well. (Courtesy of Lawrence A. Yannuzzi, MD, New York, NY.)

Conclusion

In view of the thousands of medications on the market, pharmacologic retinal toxicity remains a limited yet important cause of visual morbidity. Retinal changes may occur when agents are employed at therapeutic dosages, or when the agent is abused. It is important to recognize patterns of toxicity, as there rarely are confirmatory diagnostic tests, short of pattern recognition on clinical examination. In select situations, the fluorescein angiogram is essential for the correct diagnosis, while in most cases it is mainly supportive of the diagnosis.

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FIG. 9.23. (A) Color photograph OS demonstrating reddish wedge-shaped lesions in the macular region compatible with sympathomimetic-induced macular neuroretinopathy. (B) Fluorescein angiography documents no appreciable late macular leakage.

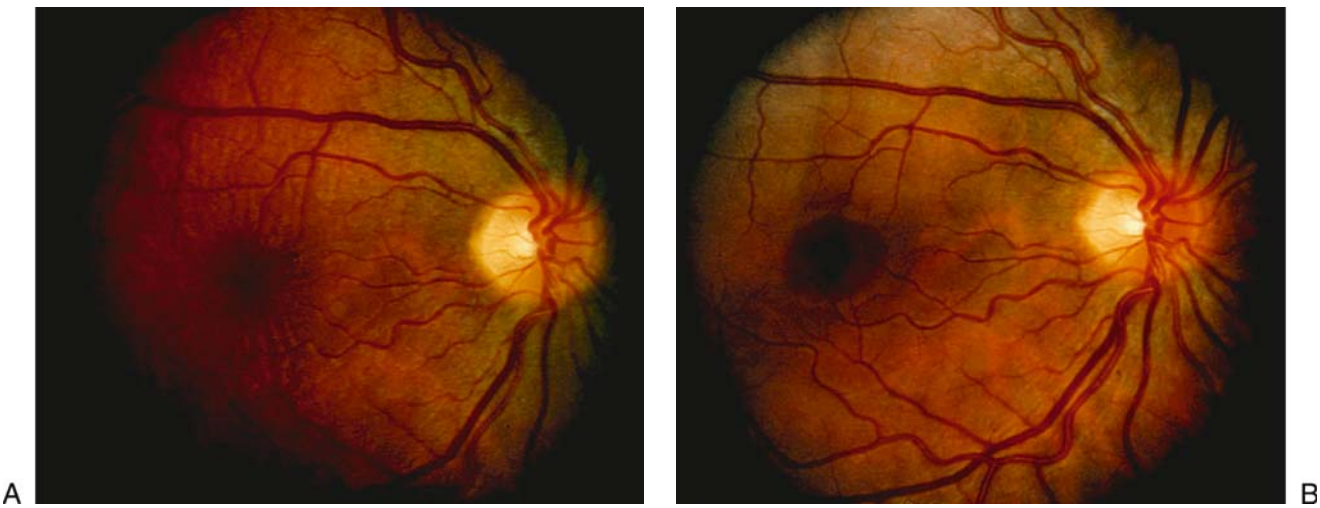

FIG. 9.24. (A) Color photograph OD documenting retinal folds in a patient recently started on topiramate. The patient actually presented with angle-closure glaucoma. (B) Color photograph OD taken 2 weeks after the topiramate was discontinued documents the spontaneous resolution of the retinal folds.

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