MOSBY
An affiliate of Elsevier Inc.

First edition 1989
Second edition 1994
Third edition 2001
Fourth edition 2006

ISBN 0323025986

This book is also available as an E-dition package, including access to online updates:
ISBN 0323040918

An online version of this book, with updates is also available:
ISBN 0323043232

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalog record for this book is available from the Library of Congress

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The Publisher

Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Chapter 108

Drug Toxicity of the Posterior Segment

Robert A. Mittra
William F. Mieler

A variety of systemic medications can generate retinal toxicity. Fortunately, in the majority of cases the loss of visual function is minimal or reversible following discontinuation of the inciting drug. Nevertheless, permanent or progressive visual loss may occur in some instances. We present only those medications known to produce a well-described anomaly and have omitted those that have not been definitively proven to cause retinal abnormalities. The medications are grouped according to the type of retinal toxicity they produce (Box 108-1).

DISRUPTION OF THE RETINA AND RETINAL PIGMENT EPITHELIUM

Phenothiazines

Thioridazine

Blurred vision, dyschromatopsia (reddish or brownish discoloration of vision), and nyctalopia characterize acute toxicity with thioridazine.[1] In the earliest stages the fundus appearance may be normal or display only mild granular pigment stippling (Fig. 108-1). An intermediate stage is characterized by circumscribed nummular areas of retinal pigment epithelial (RPE) loss from the posterior pole to the midperiphery[2] (Fig. 108-2A). Fluorescein angiography (FA) reveals disruption of the choriocapillaris in these zones of pigment rarefaction (Fig. 108-2B). In late stages of thioridazine toxicity, widespread areas of depigmentation alternating with hyperpigmented plaques, vascular attenuation, and optic atrophy are seen[3] (Fig. 108-3).

Retinal toxicity from thioridazine is dependent more on the total daily dose than on the cumulative amount of drug received.[4] With higher daily doses, toxicity can occur rapidly, even within the first 2 weeks of therapy.[5] Toxicity is rare at dosages less than 800 mg/day. Nonetheless, a few cases have been reported with lower doses given over several years.[6–10] As a result, many now suggest that any patient taking thioridazine, regardless of the daily dose, be monitored for the development of visual symptoms or fundus changes.

In the initial stages of toxicity, visual field testing can reveal mild constriction, paracentral scotomas, or ring scotomas. Electroretinography (ERG) is either normal or shows decreased oscillatory potentials. In the later stages, both the rod and cone functions of the ERG, as well as the electro-oculography (EOG), are markedly abnormal.[11] If the drug is stopped early, ERG testing improves over the first year.[12] Histologic studies demonstrate that atrophy and disorganization of photoreceptor outer segments occurs primarily, with a secondary loss of the RPE and choriocapillaris.[3]

The early fundus changes associated with thioridazine often progress despite discontinuation of therapy.[2] It is unclear whether this degeneration represents continued toxicity of the drug or a delayed expansion of chorioretinal scarring to areas of subclinical, pre-existing damage.[12] Visual function, in contrast to fundus appearance, usually improves over the first year after a toxic reaction; this undoubtedly would not occur if thioridazine caused persistent toxicity.

The mechanism of thioridazine-mediated toxicity remains unknown. Many phenothiazines bind melanin granules of the RPE and uveal tissue, but not all commonly instigate retinal toxicity.[13–15] The compound NP-207 (piperidyl-chlorophenothiazine hydrochloride) has a remarkably similar chemical structure to thioridazine, including the same piperidyl side chain. NP-207 was never marketed because of the pronounced pigmentary retinopathy that developed during early clinical trials.[16] This piperidyl side chain is not present in other phenothiazines such as chlorpromazine, which exhibit much less retinal toxicity. Experimental studies demonstrate that phenothiazines both alter enzyme kinetics and inhibit oxidative phosphorylation with subsequent abnormalities in rhodopsin synthesis.[17–19] Other studies postulate that phenothiazine toxicity is due to the drug's effect on the dopamine receptors in the retina. Further study is necessary to determine whether these observed effects are involved in the pathogenesis of thioridazine toxicity.

A review of the daily and cumulative drug dosage is essential in patients taking thioridazine. Baseline fundus photography and possibly ERG testing may be helpful if future toxicity develops. Given the many antipsychotic medications available today, consideration of alternative agents may be discussed with the patient's psychiatrist. At the earliest sign of toxicity, thioridazine should be discontinued.

Chlorpromazine

Chlorpromazine is a piperazine similar to thioridazine but lacks the piperidyl side chain mentioned above. The compound binds strongly to melanin and can cause hyperpigmentation in the skin, conjunctiva, cornea, lens, and retina[20–24] (Fig. 108-4). Other ocular

Box 108-1 Patterns of retinal toxicity

Disruption of the retina and retinal pigment epithelium
Phenothiazines
Quinine sulfate
Thioridazine
Clofazimine
Chlorpromazine
Deferoxamine
Chloroquine derivatives
Corticosteroid preparations
Chloroquine
Cisplatin and BCNU (carmustine)
Hydroxychloroquine

Vascular damage
Quinine sulfate
Aminoglycoside antibiotics
Cisplatin and BCNU (carmustine)
Interferon
Ergot alkaloids
Talc
Phenylpropanolamine
Oral contraceptives

Cystoid macular edema
Epinephrine
Latanoprost
Nicotinic acid

Retinal folds
Sulfa antibiotics
Hydrochlorothiazide
Acetazolamide
Triamterene
Ethoxyzolamide
Metronidazole
Chlorthalidone

Crystalline retinopathy
Tamoxifen
Talc
Canthaxanthine
Nitrofurantoin
Methoxyflurane

Uveitis
Rifabutin
Cidofovir

Miscellaneous
Digoxin
Methanol

effects include oculogyric crisis, miosis, and blurred vision caused by paralysis of accommodation. Usual doses range from 40 to 75 mg/day, but dosages up to 800 mg/day are not uncommon.

Retinal toxicity from chlorpromazine is rare. When massive doses are given (e.g. 2400 mg/day for 12 months), pigmentary changes may occur in the retina with attenuation of retinal vessels and optic nerve pallor[23] (Fig. 108-5). Similar to thioridazine, the development and extent of toxicity are more closely related to daily dosage than total amount of drug taken.

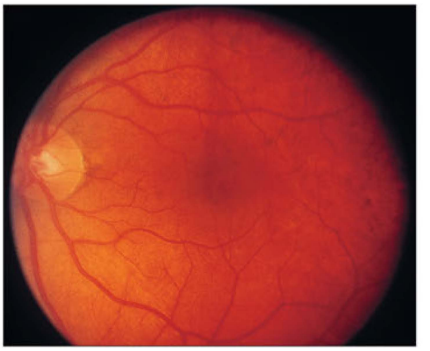

Fig. 108-1 Early thioridazine toxicity. Photograph shows mild granular pigment stippling of the temporal macular region.

Chloroquine derivatives

Chloroquine

Chloroquine was first used as an antimalarial drug in World War II. Currently it is prescribed for treatment of amebiasis, rheumatoid arthritis, systemic lupus erythematosus, and for prophylaxis against malaria. Retinal toxicity with degeneration of the RPE and neurosensory retina as a result of long-term daily use of chloroquine has been well described.[25–32] However, most cases of retinopathy have developed when a higher than currently recommended (3 mg/kg/day using lean body weight) dose was used.[33] A daily dose exceeding 250 mg with a total cumulative dose between 100 and 300 g is customarily needed to produce toxicity.[34] One study showed a 19% incidence of chloroquine retinopathy in patients taking a mean daily dose of 329 mg.[35] Conversely, with strict adherence to a low dose per diem, the incidence of retinal abnormalities is minimal even when cumulative doses reach over 1000 g.[36]

A paracentral scotoma may be the earliest manifestation of retinal toxicity and can precede the development of any ophthalmoscopic or ERG abnormality.[37] Subtle macular pigment stippling with a loss of the foveal light reflex (Fig. 108-6) usually appears on fundus examination before the development of a classic bull's-eye maculopathy, in which a ring of depigmentation surrounded by an area of hyperpigmentation is seen centered on the fovea (Fig. 108-7). Visual acuity decreases when the RPE abnormalities involve the center of the fovea. The peripheral retina can display pigment mottling, which may, in severe cases, develop into the appearance of primary tapetoretinal degeneration with narrowed retinal vessels, optic disc pallor, and eventual blindness (Fig. 108-8).

After the cessation of chloroquine treatment, early subtle macular changes can revert to normal. Although far advanced cases may progress despite discontinuation of the drug, most patients remain stable with long-term follow-up.[38,39] Chloroquine,

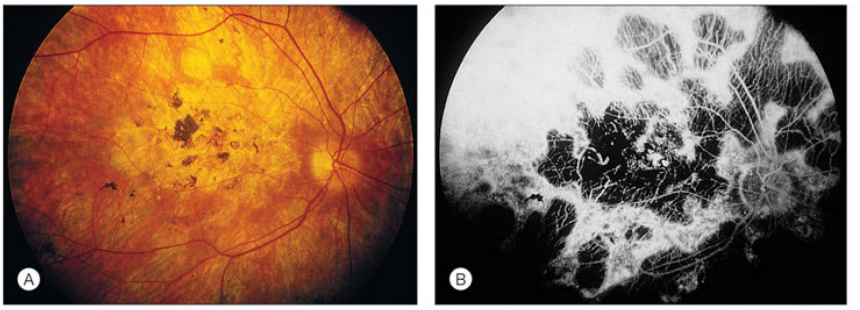

Fig. 108-2 Intermediate thioridazine toxicity. Photograph (A) and fluorescein angiogram (B) show central and peripheral nummular pigmentary changes with corresponding atrophy of the choriocapillaris.

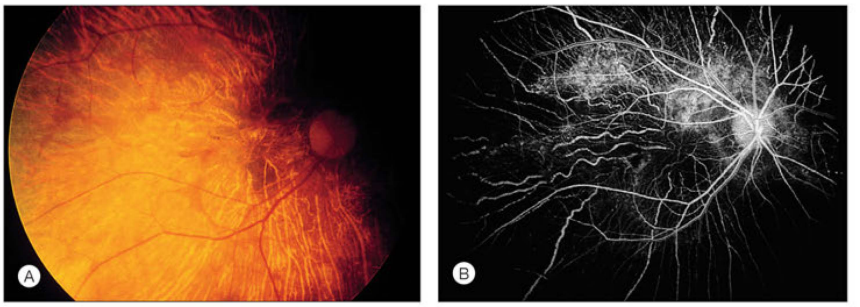

Fig. 108-3 End-stage thioridazine toxicity. Photograph (A) and fluorescein angiogram (B) show diffuse pigmentary and choriocapillaris atrophy, optic atrophy, and vascular attenuation.

however, is very slowly excreted from the body. It has been detected in the plasma, red blood cells, and urine of patients 5 years after their last known ingestion.[40] This prolonged presence may account for the rare cases of delayed onset of chloroquine retinopathy seen up to 7 years or longer after discontinuation.[41,42]

Fluorescein angiography can be helpful in the early demonstration of pigment abnormalities in the macula (see Figs 108-6 and 108-7). There is minimal evidence of damage to the choriocapillaris on FA in the areas of pigment disturbance. The ERG and EOG may be abnormal early, although the EOG is sometimes supernormal initially.[43] Histopathologic sections demonstrate loss of RPE pigmentation with an accumulation of pigment-laden cells in the outer retinal layers with damage and reduction of photoreceptors.[44] Electron microscopic studies reveal more widespread damage to the retina, especially the ganglion cell layer.[45]

The mechanism of chloroquine-mediated retinal toxicity is unknown. Like the phenothiazines, chloroquine is bound by melanin and concentrated in the RPE and uveal tissues.[46] Possible explanations include inhibition of critical enzymes and interference with the metabolic function of the RPE and photoreceptors.[41,47]

Hydroxychloroquine

Given the incidence of toxicity with chloroquine, most rheumatologists prefer hydroxychloroquine for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Although it can produce a retinopathy identical to chloroquine, its occurrence is rare.[48–51] Only a few cases of toxicity have been well documented, involving decreased visual acuity, paracentral scotoma, and a bull's-eye maculopathy (Figs 108-9 and 108-10).[52–57] Many of these patients received above the recommended daily

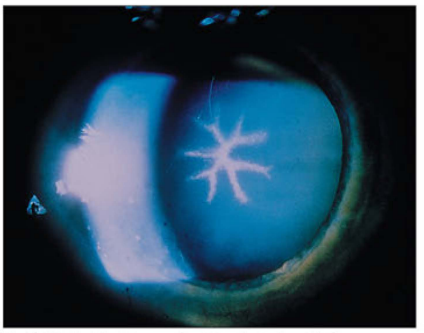

Fig. 108-4 Typical chlorpromazine-induced anterior stellate lens opacities.

dosage of 6.5 mg/kg/day, but the classic fundus findings have been reported at lower doses as well.[58-60]

Several authors have questioned the utility of screening given the low yield, high cost, and the difficulty in diagnosing the condition early enough to prevent damage.[61-64] Nevertheless, toxicity does occur, and if retinal and functional changes are detected early, severe visual impairment can be averted.[65,66] Use of static perimetry through the vertical meridian with a red test object may be the best method to detect an early paracentral scotoma.[37] These changes usually occur before visible retinal abnormalities and therefore should be performed on follow-up examinations. The red Amsler grid is also useful in detecting an early paracentral scotoma and may be substituted for static perimetry.[67] In addition, the grid can be given to patients so that they can monitor their visual function at home. Recent data suggest that multifocal electroretinographic evaluation may detect toxicity at its earliest stages.[68-72]

The American Academy of Ophthalmology guidelines for screening include a baseline examination performed at the commencement of therapy.[73] Screening exams during the first five years of therapy can be performed during routine ophthalmic examination (interval to be determined by age of the patient). If the dosage used is higher than 6.5 mg/kg/day for hydroxychloroquine (3 mg/kg/day for chloroquine), the patient is obese, has renal or liver dysfunction, has concomitant macular disease or is more than 60 years of age, screening should be performed at least annually. After five years of therapy, screening should be performed at least annually.[74] If ocular toxicity occurs,[75-78] and is recognized at an early stage, efforts should be made to communicate this directly to the prescribing physician so that alternatives can be discussed with the patient. In almost all cases, cessation of the drug should be suggested.

Quinine sulfate

Quinine sulfate was first used for the treatment of malaria in World War II, but it currently is prescribed for the management of nocturnal muscle cramps or "restless leg syndrome." The recommended daily dose is less than 2 g. Signs of systemic toxicity occur with doses greater than 4 g, and the fatal oral dose is 8 g. Ocular toxicity with quinine develops after an overdose, either by accidental ingestion or by attempted abortion or suicide. Rarely, chronic ingestion at low levels can result in ocular toxicity as well.[79] With an overdose, a syndrome known as *cinchonism* is rapidly produced, consisting of nausea, vomiting, headache, tremor, and sometimes hypotension and loss of consciousness. When patients awake they often are completely blind and have dilated, unreactive pupils.[80] In the acute stages of toxicity, fundus examination reveals mild venous dilation with minimal retinal edema and normal arterial caliber. The FA

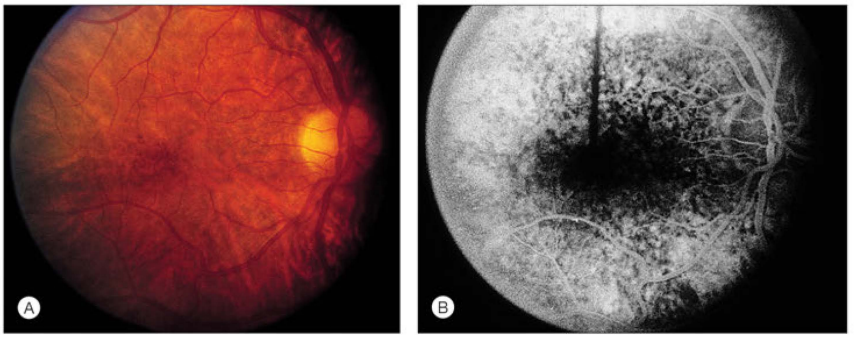

Fig. 108-5 Chlorpromazine toxicity. Photograph (A) and fluorescein angiogram (B) show granular pigment changes less severe than those seen with thioridazine.

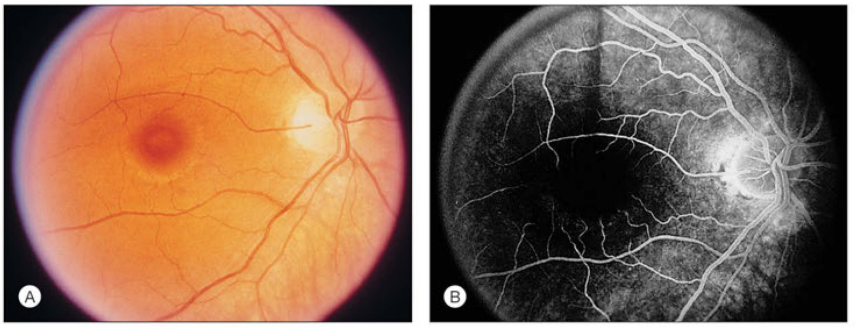

Fig. 108-6 Early chloroquine toxicity. Photograph (A) and fluorescein angiogram (B) show early perifoveal pigmentary changes. From Mieler WF. Focal points. American Academy of Ophthalmology, Dec 1997.

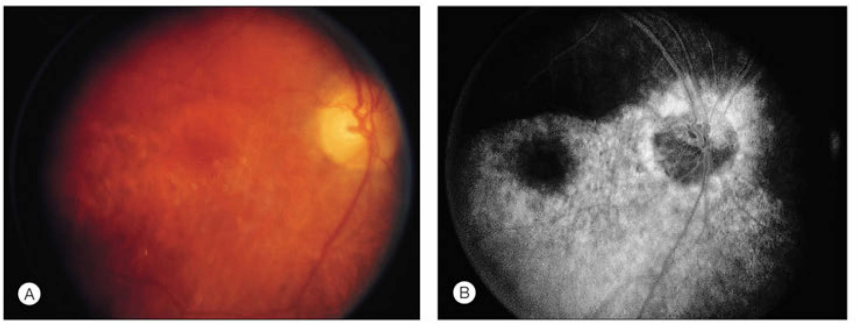

Fig. 108-7 Advanced chloroquine toxicity. Later photograph (A) and fluorescein angiogram (B) from the patient in Fig. 107-6 show marked progression with advanced widespread pigmentary changes. From Mieler WF. Focal points. American Academy of Ophthalmology, Dec 1997.

displays minimal abnormalities. ERG testing shows an acute slowing of the a-wave with increased depth, loss of oscillatory potentials, and a decreased b-wave. EOG and visual evoked potential (VEP) testing are also abnormal.

Over the next few days visual acuity returns, but the patient is left with a small central island of vision. There is a progressive attenuation of the retinal arterioles with the development of optic disc pallor over the next few weeks to months (Fig. 108-11). Early investigators believed the mechanism of quinine toxicity to be vascular in origin. This was based primarily on the fundus appearance several weeks after ingestion, which showed marked arteriolar attenuation and optic disc pallor.[80,81] More recent experimental and clinical studies have demonstrated minimal involvement of the retinal vasculature in the early stages of quinine toxicity.[80-82] Furthermore, ERG and histologic studies show that the site of toxicity is likely the retinal ganglion, bipolar, and photoreceptor cells.[80,82] The exact mechanism of quinine toxicity is unidentified, but some have suggested that it may act as an acetylcholine antagonist and disrupt cholinergic transmission in the retina.[83]

Clofazimine

Clofazimine is a red phenazine dye that has been used to treat dapsone-resistant leprosy, psoriasis, pyoderma gangrenosum, discoid lupus, and more recently, *Mycobacterium avium*-complex infections in AIDS patients. With treatment over several months,

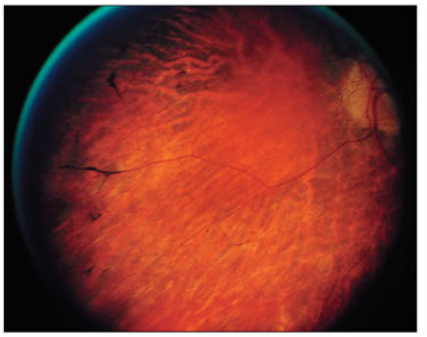

Fig. 108-8 Chloroquine retinopathy. Photograph shows bone-spicule pigmentary changes that can develop in advanced cases. The appearance is similar to end-stage retinitis pigmentosa.

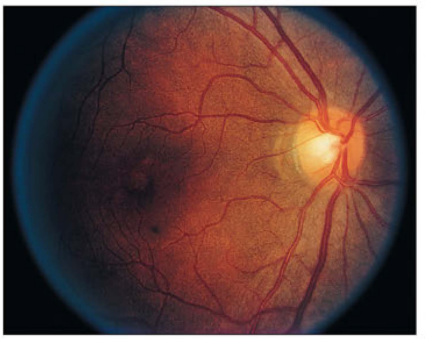

Fig. 108-9 Hydroxychloroquine toxicity. Photograph displays pigmentary changes in the central macula.

clofazimine crystals may accumulate in the cornea. Two cases of bull's-eye maculopathy with pigmentary retinopathy (Fig. 108-12) have been reported in AIDS patients with doses of 200 to 300 mg/day (total dose, 40 to 48 g).[84,85] Visual acuity was mildly affected, with reduced scotopic, photopic, and flicker ERG amplitudes. Cessation of treatment may result in the clearance of the corneal deposits but does not appear to affect the retinopathy.

DDI

A midperipheral pigmentary retinopathy has been noted in three children with AIDS receiving high dose therapy with the antiviral 2′,3′-dideoxyinosine.[86] The cases were associated with ERG and EOG changes. The retinal toxicity stabilized after discontinuation of the medication.

Deferoxamine

Intravenous (IV) and subcutaneous (SQ) administration of deferoxamine has been used to treat patients who require repeated blood transfusions and subsequently develop complications of iron overload. High-dose IV and SQ therapy has produced visual loss, nyctalopia, peripheral and central field loss, and reduced ERG amplitudes and EOG ratios.[87,88] Fundi can be normal initially, or there may be a faint graying of the macula.[89] Pigmentary changes in the macula and periphery develop within a few weeks and are particularly highlighted by fluorescein angiography (Fig. 108-13).[90] Macular changes can resemble vitelliform maculopathy.[91] Return of visual function occurs with cessation of therapy. Deferoxamine chelates many metals other than iron, and it is possible that the mechanism of toxicity may involve the removal of copper from the RPE.[87] Histopathologic changes occur primarily in the RPE and include loss of microvilli from the apical surface, patchy depigmentation, vacuolation of the cytoplasm, swelling and calcification of mitochondria, and disorganization of the plasma membrane.[92]

Corticosteroid preparations

The vehicles of several common corticosteroid preparations have been shown to cause retinal necrosis when inadvertently injected into the eye[93,94] (Fig. 108-14). The corticosteroids themselves probably have a minimal toxic effect on the retina.[95] Celestone Soluspan, with its vehicle benzalkonium chloride, and Depo-Medrol, with myristyl gamma-picolinium chloride, caused the most extensive retinal damage in an experimental study comparing several depot steroids.[96] If one of these agents is inadvertently injected, immediate surgical removal should be instituted.

Cisplatin and BCNU (carmustine)

Cisplatin and BCNU are used for the treatment of malignant gliomas and metastatic breast cancer. Three different types of retinal toxicity have been reported with these agents. One type of change consists of a pigmentary retinopathy of the macula with markedly decreased visual acuity and frequently abnormal electrophysiologic testing. This pigmentary change has been reported after administration of combined intraarterial cisplatin and BCNU and with cisplatin alone for malignant glioma.[97,98] These findings probably are the result of platinum toxicity of the retina. Severe bilateral visual loss was reported after intravenous cisplatin in a patient that received four times the intended dose for treatment of lymphoma.[99] Later histology showed a splitting of the outer plexiform layer.

A second type of retinopathy has been described and consists of cotton-wool spots, intraretinal hemorrhages, macular exudate, and optic neuropathy with disc swelling. This was reported in the setting of high-dose chemotherapy with cisplatin, cyclophosphamide, carmustine, and autologous bone marrow transplantation for metastatic breast cancer.[100] The third type of change

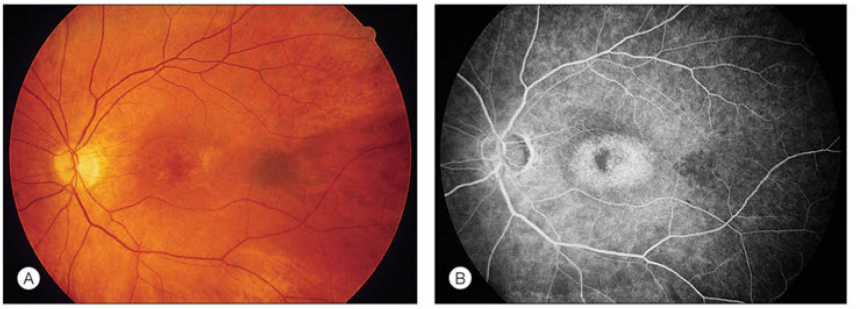

Fig. 108-10 Hydroxychloroquine toxicity. Photograph (A) and fluorescein angiogram (B) show a marked bull's-eye maculopathy.

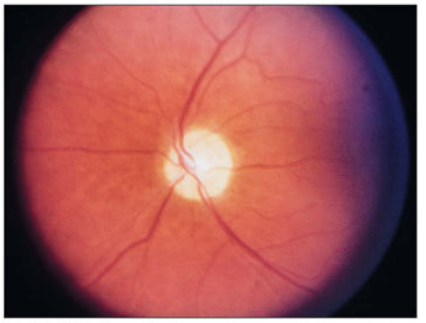

Fig. 108-11 Quinine toxicity. Photograph illustrates the characteristic optic nerve head pallor with diffuse arteriolar attenuation approximately 2 months after ingestion.

involves a vascular retinopathy or optic neuropathy, which can include arterial occlusion, vasculitis, and papillitis. This has been seen in approximately 65% of patients receiving intraarterial BCNU alone or combined with cisplatin for malignant glioma.[98] These fundus changes are associated with a profound visual loss that begins about 6 weeks after the start of therapy. Other ocular effects may include orbital pain, chemosis, secondary glaucoma, internal ophthalmoplegia, and cavernous sinus syndrome. Injection of medication above the ophthalmic artery can still result in toxicity.[101] The visual loss usually is progressive, and no treatment is known.

Potassium iodate

Overdose of potassium iodate, an iodized salt used for iodine supplementation in areas endemic for goiter, has been shown to cause profound visual loss and extensive fundus pigmentary abnormalities.[102] Fluorescein angiography reveals RPE window defects and ERG and VEP testing shows marked impairment of retinal function. Visual acuity may improve slowly over several months.

VASCULAR DAMAGE

Quinine sulfate

See Disruption of the retina and retinal pigment epithelium, p. 1839.

Cisplatin and BCNU (carmustine)

See Disruption of the retina and retinal pigment epithelium, p. 1839.

Talc

A characteristic retinopathy consisting of small, white, glistening crystals concentrated in the end arterioles of the posterior pole has been described in intravenous (IV) drug abusers[103–105] (Fig. 108-15). These addicts crush oral medications such as methylphenidate hydrochloride (Ritalin) or methadone HCl and then create an aqueous suspension by adding water and heating the mixture. The solution is subsequently drawn up into a syringe, with occasional attempts at filtering the mixture with cotton fibers, gauze, or cigarette filters. These oral medications contain talc (hydrous magnesium silicate) as inert filler material; after IV administration, talc particles embolize to the pulmonary vasculature, where the larger particles are trapped. After repeated injections over months to years, collateral vasculature develops, allowing the particles to enter the systemic circulation and embolize to other organs, including the eye. Even before shunt development, particles smaller than 7 μm can traverse the pulmonary capillary bed and enter the retinal circulation.[106]

Once a large number of talc particles lodge in the small arterioles of the retinal vasculature, a characteristic picture of an ischemic retinopathy begins to develop. Capillary nonperfusion,

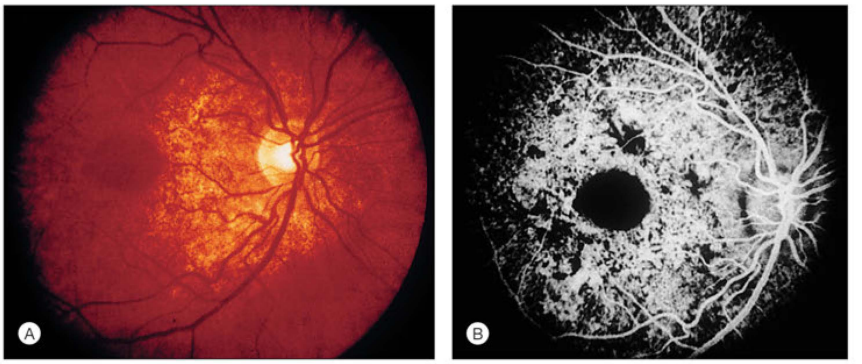

Fig. 108-12 Clofazimine toxicity. Photograph (A) and fluorescein angiogram (B) show moderate macular pigmentary changes in a bull's-eye pattern.

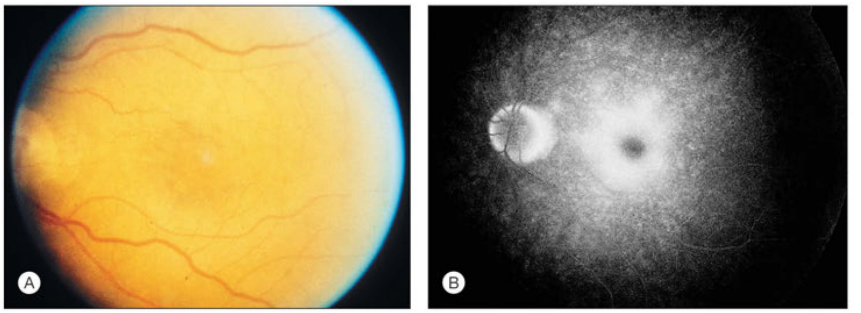

Fig. 108-13 Deferoxamine toxicity. Photograph (A) and fluorescein angiogram (B) show a diffuse pigmentary retinopathy with macular and retinal edema.

microaneurysm formation, cotton-wool spots, and venous loops can all be seen.[107] In severe cases optic disc and peripheral neovascularization and vitreous hemorrhage can develop[108,109] (Fig. 108-16). An experimental model of talc retinopathy in monkeys has demonstrated with light and electron microscopic techniques that the vascular abnormalities induced are very similar to other ischemic retinopathies seen in humans, such as sickle cell and hypertensive retinopathy.[110-112]

Once talc retinopathy is diagnosed, an attempt at educating the patient as to the cause of the disorder is indicated. Treatment of neovascularization and vitreous hemorrhage should be undertaken using laser photocoagulation and pars plana vitrectomy if necessary in a manner similar to that used for sickle cell or proliferative diabetic retinopathy.

Oral contraceptives

Oral contraceptives have been implicated in some cases of central retinal vein occlusion, retinal and cilioretinal artery obstruction, and retinal edema occurring in young women.[113-119] The synthetic estrogen and progesterone contained in contraceptive pills are thought to adversely effect coagulation factors and induce a hypercoagulable state leading to thromboembolic complications. Most of the studies reporting ocular complications are from the 1960s and 1970s, when the estrogen concentrations used in "the

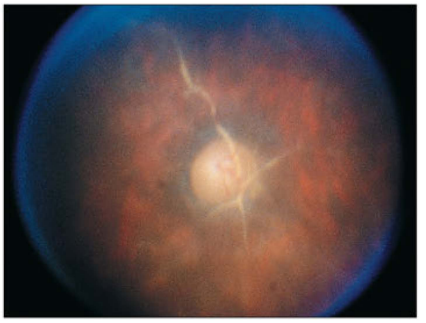

Fig. 108-14 Intraocular corticosteroid injection. Photograph shows end-stage retinopathy, with sclerotic vessels and diffuse pigmentary changes, after an inadvertent intraocular injection of corticosteroid.

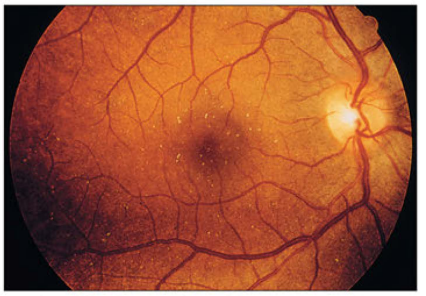

Fig. 108-15 Talc retinopathy. Characteristic perifoveal yellow-white glistening crystals.

pill" were much higher. More recent prospective studies have failed to show an increased incidence of ocular complications with the drug.[120,121]

Aminoglycoside antibiotics

Retinal toxicity from aminoglycoside antibiotics has been reported after inadvertent intraocular injection of massive doses, intravitreal injection for bacterial endophthalmitis, prophylactic intravitreal injection after pars plana vitrectomy, prophylactic subconjunctival injections after routine ocular surgery, and with the use of small amounts in the infusion fluid during cataract extraction.[122-126] Gentamicin is the most toxic antibiotic in the aminoglycoside family, followed by tobramycin and amikacin.[127] Massive doses result in early superficial and intraretinal hemorrhages, retinal edema, cotton-wool patches, arteriolar narrowing, and venous beading (Fig. 108-17).[125] Fluorescein angiography reveals severe vascular nonperfusion in the acute stages. Visual loss is profound, and late rubeosis iridis, neovascular glaucoma, pigmentary retinopathy, and optic atrophy are common. Intra-vitreal injection of smaller doses thought to be safe for the eye (100 to 400 μg) can still cause toxicity with less severe fundus changes.[123-125] The major preservatives found in injectable gentamicin (methylparaben, propylparaben, sodium bisulfite, and edetate disodium) likely play an additive role in its ocular toxicity.

A number of factors appear to affect the extent of toxicity observed with similar doses of these medications. Peyman found that retinal toxicity could be enhanced with an intra-vitreal injection directed at the posterior pole with the bevel of the needle pointed toward the retina, and Zachary and Forster demonstrated that an increased rate of injection during intraocular administration could also increase the retinal toxicity observed.[128,129] One investigator stated that eyes that have undergone a previous pars plana vitrectomy are at greater risk for gentamicin toxicity, but an experimental model has shown no difference between eyes that had cataract extraction alone compared with those that underwent lensectomy and vitrectomy.[126,130] Finally, increased ocular pigmentation protects the rabbit retina from aminoglycoside toxicity and may explain some of the wide variability seen with intraocular exposure in humans.[131,132]

Although clinical aminoglycoside toxicity appears to affect the retinal vasculature primarily, pathologic studies have revealed that gentamicin in small doses causes the formation of abnormal lamellar lysosomal inclusions in the RPE, and larger doses cause increasing amounts of retinal necrosis, first of the outer then inner segments.[133-136] Histologically, vessel closure appears to result from granulocytic plugging.

Prevention of aminoglycoside toxicity can be accomplished by abandoning the use of these medications as routine prophylaxis following intraocular surgery, eliminating them from intraocular infusion fluids used in vitrectomy and cataract surgery, and using alternative medications for the treatment of bacterial endophthalmitis. Animal studies have demonstrated that thinned sclera alone without perforation can result in markedly elevated intraocular gentamicin levels after subconjuctival injection.[137] If inadvertent intraocular injection does occur, immediate pars plana vitrectomy with posterior segment lavage should be performed.[138,139] Since there is some evidence that gravity plays a role in the predilection of gentamicin-induced toxicity for the macula, the patient should be placed upright as soon as possible after surgery.[140]

Interferon

Interferon-α is used to treat Kaposi's sarcoma, hemangiomas of infancy, chronic hepatitis C, melanoma, renal cell carcinoma, in chemotherapy protocols for leukemia, lymphoma and hemangiomatosis, and experimentally for the treatment of choroidal neovascular membranes. Interferon therapy has been associated with the development of multiple cotton-wool spots associated with retinal hemorrhages[141-143] (Fig. 108-18). Optic disc edema, branch arterial and venous occlusion, central retinal venous obstruction and CME have been reported with the more severe

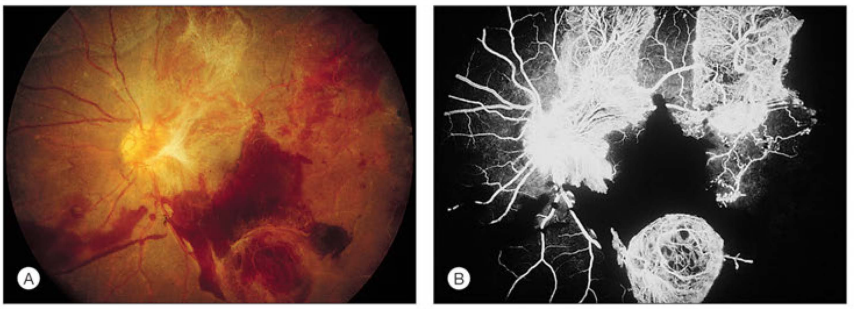

Fig. 108-16 Ischemic talc retinopathy. Photograph (A) and fluorescein angiogram (B) show widespread capillary dropout, neovascularization, and preretinal hemorrhage.

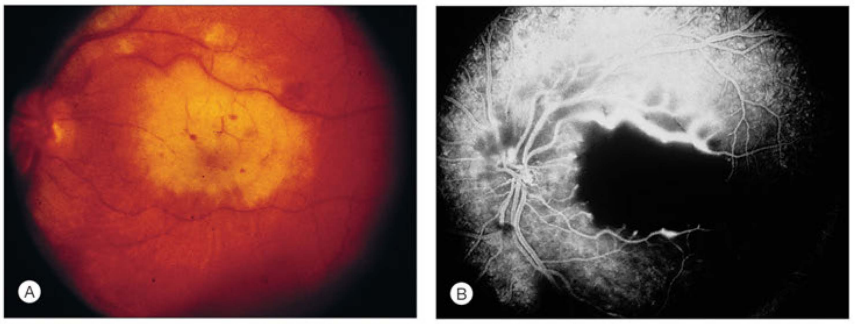

Fig. 108-17 Intraocular gentamicin injection. Photograph (A) and fluorescein angiogram (B) show acute macular necrosis.

findings observed in patients receiving high dose therapy.[144–146] Visual acuity usually is not affected if the fundus findings are limited to cotton-wool spots and intraretinal hemorrhage. Changes are noted within the first 4 to 8 weeks of therapy and are seen more frequently in diabetic and hypertensive patients.[147] Intravitreal injection of interferon-α-2b is well tolerated in the rabbit eye up to dosages of 1 million units; 2 million units causes a vitreous haze and intraretinal hemorrhages.[148] Interferon toxicity may be caused by an increase in immune complex deposition and activated complement C5a with leukocyte infiltration.

Miscellaneous agents

Ergot alkaloids in higher than recommended doses have been reported to cause retinal vasoconstriction,[149,150] and over-the-counter phenylpropanolamine used in appetite suppressants and decongestants has been implicated in one case of central retinal vein occlusion.[151]

CYSTOID MACULAR EDEMA

Epinephrine

The use of epinephrine compounds in glaucoma has decreased with the advent of newer, more efficacious agents. Topical epinephrine can cause macular edema in aphakic eyes, indistinguishable clinically and angiographically from postoperative aphakic cystoid macular edema (CME). In the largest controlled study, 28% of aphakic eyes treated with epinephrine and 13% of untreated aphakic eyes had macular edema, a difference that was statistically significant.[152] Most cases of CME resolve with cessation of epinephrine usage. This medication should be avoided in the treatment of the glaucomatous aphakic and pseudophakic eyes.

Nicotinic acid

High doses of niacin have been used to reduce serum lipid and cholesterol levels. Better-tolerated HMG-CoA reductase

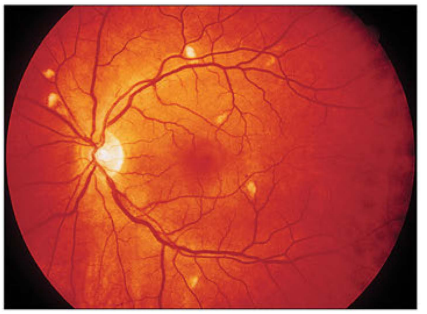

Fig. 108-18 Interferon microangiopathy. Multiple cotton-wool spots dispersed throughout the posterior pole.

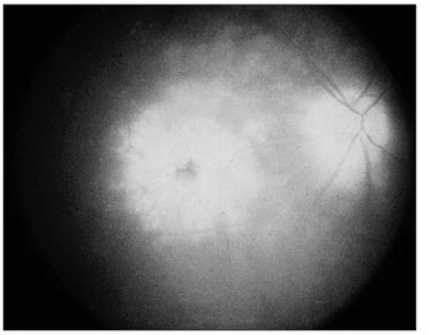

Fig. 108-19 Latanaprost-associated cystoid macular edema. Angiogram shows characteristic fluorescein filling of the cystic spaces.

inhibitor agents have largely curtailed its use. At doses greater than 1.5 g/day, a minority of patients will report blurred central vision, sometimes associated with a paracentral scotoma or metamorphopsia.[153] Fluorescein angiography fails to demonstrate vascular leakage despite the typical clinical appearance of CME.[154,155] This has led to speculation of a direct toxic effect on Müller cells, resulting in intracellular edema.[156] Optical coherence tomography reveals cystoid spaces in the inner nuclear and outer plexiform layers.[157] With cessation of treatment, the CME resolves, and vision generally returns to normal. Given the rarity of this condition, only patients who are taking high-dose niacin and who have visual symptoms should be evaluated.

Latanoprost

Latanoprost is a prostaglandin analog that is used for the control of a variety of forms of glaucoma. Although initial human and animal studies did not show an association between latanoprost and CME, recent case reports and studies have documented that approximately 2–5% of susceptible patients with glaucoma may develop CME and anterior uveitis, which resolves after discontinuation of the drug[158-166] (Fig. 108-19). This may be caused by the preservative used in the drug formulation.[167] Patients with CME who are taking latanoprost should undergo a trial off the medication before initiating further therapy for the edema. High-risk CME patients, such as those with a history of recent surgery or uveitis, should be managed with other agents.

RETINAL FOLDS

Sulfa antibiotics, acetazolamide, ethoxyzolamide, chlorthalidone, hydrochlorothiazide, triamterene, metronidazole

Several medications, most with a structure similar to sulfanilamide, as those above, can cause a syndrome of transient acute myopia and anterior chamber shallowing. This is thought to occur as a result of ciliary body swelling or choroidal effusion, or both, with subsequent forward rotation of the lens-iris diaphragm.[168-170] Retinal folds in the macula are seen in young patients with this syndrome, but FA does not reveal retinal leakage (Fig. 108-20). The folds presumably develop as a result of vitreous traction on the macula that is caused by the forward shift of the lens and iris.

CRYSTALLINE RETINOPATHY

Tamoxifen

Tamoxifen is an antiestrogen agent used in the treatment of advanced breast carcinoma and as adjuvant therapy after surgical resection of early disease. Retinal toxicity consisting of decreased visual acuity and color vision with white intraretinal crystalline deposits, macular edema, and punctate retinal pigmentary changes can occur.[171] The intraretinal deposits appear to reside in the inner retina and are most numerous in paramacular areas (Fig. 108-21). Early reports involved patients who had received high doses (60 to 100 mg/day, total dosage >100 g) of the drug over 1 year.[172] More recent studies have demonstrated that chronic low-dose administration (10 to 20 mg/day) with as little as 7.7 g total, also can cause ocular toxicity.[173-176] Even asymptomatic patients may exhibit intraretinal crystalline formation.[177] Visual function and edema improve after discontinuation of the drug, but the refractile deposits remain.

Fluorescein angiography demonstrates late focal staining in the macula consistent with CME. Decreased photopic and scotopic a- and b-wave amplitude is noted on ERG testing.[178] Light microscopy reveals lesions confined to the nerve fiber and inner plexiform layers, which stain positive for glycosaminoglycans. Small (3 to 10 μ) intracellular and large (30 to 35 μ) extracellular lesions within axons are noted on electron microscopy.[179] The lesions appear to represent products of axonal degeneration similar to corpora amylacea.

Decreased vision with bilateral optic disc swelling and retinal hemorrhages has been reported in a patient just 3 weeks after

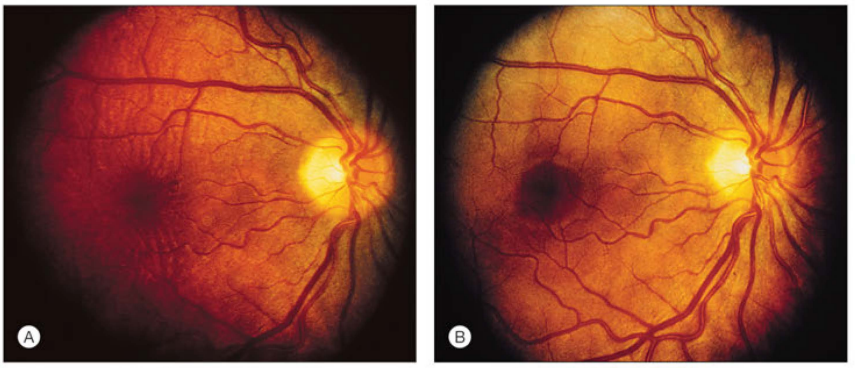

Fig. 108-20 Chlorthalidone-induced retinal folds. Photograph (A) shows perifoveal retinal folds associated with chlorthalidone therapy, which resolve after discontinuation of the drug (B).

commencement of therapy with tamoxifen. These findings resolved completely after the drug was stopped.[180] It is unclear whether the findings in this patient were related to the more commonly seen toxic effects. With current low-dose therapy (10 to 20 mg/day), retinal lesions are rare, and routine examination of asymptomatic patients is not indicated.[180,181] If a patient taking tamoxifen is noted to have intraretinal crystals, FA should be performed, primarily to rule out juxtafoveal telangiectasis, which can have similar-appearing lesions.[182] With confirmed evidence of toxicity causing a visual disturbance, the medication should be stopped.

Canthaxanthine

Canthaxanthine is a naturally occurring carotenoid. It is used as a food-coloring agent, for skin pigmentation in the treatment of vitiligo, and for the treatment of photosensitivity disorders such as erythropoietic protoporphyria, psoriasis, and photosensitive eczema. It also has been used over-the-counter in high doses as an oral tanning agent. Many reports have described a characteristic ring-shaped deposition of yellow-orange crystals in the superficial retina with high doses (usually a total dose greater than 19 g over 2 years)[183–185] (Fig. 108-22). The crystals appear more prominently in eyes with pre-existing retinal disease and with concurrent use of beta-carotene.[183,186]

Patients usually are asymptomatic, and FA usually is normal. There have been published reports of both normal and abnormal ERG, EOG, dark adaptation, and static threshold perimetry.[187–190] Although only clinically evident in the macula, the lipid-soluble crystals are found pathologically in the entire inner retina and ciliary body.[191] The crystals are, as would be expected, larger and more numerous surrounding the fovea. Canthaxanthine crystals are localized to the spongy degeneration of the inner neuropil and are associated with atrophy of the Müller cells. An experimental model of canthaxanthine-induced retinopathy also has demonstrated RPE cell vacuolization and disruption of phagolysosomes.[192]

With discontinuation of treatment, deposits may slowly clear over many years.[193,194] This slow reversal correlates with the detection of high plasma levels of canthaxanthine many months after discontinuation of the drug. Rarely, a fundus picture identical to canthaxanthine maculopathy can be seen in patients who have no known history of extradietary canthaxanthine.[195] A high dietary intake concurrent with pre-existing retinal disease is thought to partially explain this phenomenon.

Methoxyflurane

Methoxyflurane is an inhalational anesthetic, which, if used for extended periods, especially in patients with renal insufficiency, causes irreversible renal failure as a result of deposition of calcium oxalate crystals in the kidney. These crystals are also deposited elsewhere throughout the body. Fundus examination of these patients reveals numerous yellow-white punctate lesions in the posterior pole and periarterially[196,197] (Fig. 108-23). The deposits are located histologically in both the RPE and inner retina.[198,199]

Talc

See Vascular damage, p. 1845.

Nitrofurantoin

A single case of crystalline retinopathy following 19 years of nitrofurantoin (Macrodantin) use has been reported.[200]

UVEITIS

Rifabutin

Rifabutin is a semisynthetic rifamycin antibiotic that is used for the treatment and prevention of disseminated *Mycobacterium avium*-complex (MAC) infection in patients with AIDS.[201–210] A

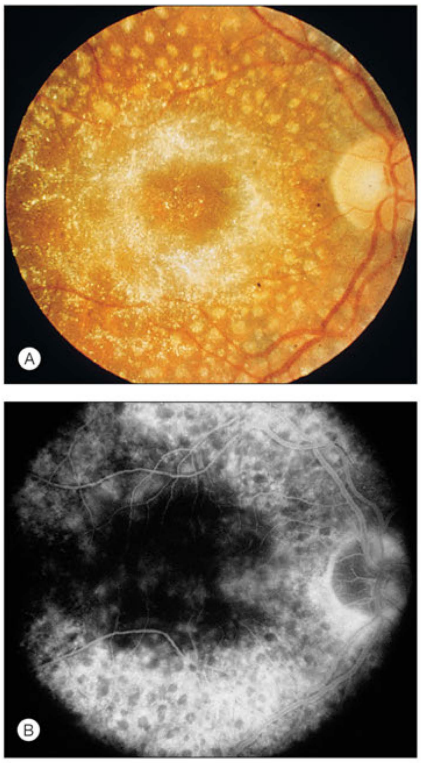

Fig. 108-21 Tamoxifen retinopathy. Characteristic yellow-white macular crystals.

small percentage of patients treated with higher doses of rifabutin (>450 mg/day) for systemic MAC infection, or lower doses (300 mg/day) for prophylaxis against MAC, can develop uveitis. The uveitis usually is bilateral and can be severe enough to cause a hypopyon that simulates infectious endophthalmitis. It can occur from 2 weeks to 14 months after initiation of the drug.[211] Concomitant use of clarithromycin and/or fluconazole, especially when lower doses of rifabutin are used, greatly increases the chance of a uveitic episode. Both systemic fluconazole and clarithromycin elevate rifabutin levels by inhibiting metabolism of the drug via the hepatic microsomal cytochrome P-450.[212] Although most cases have reported mainly an anterior uveitis, posterior vitreitis and retinal vasculitis have been described as well.[213,214]

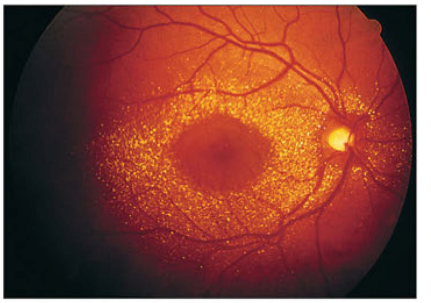

Fig. 108-22 Canthaxanthine retinopathy. Prominent perifoveal punctate yellow deposits in a doughnut-shaped ring surrounding the macula.

Rifabutin-associated uveitis can be treated successfully with topical corticosteroids or by decreasing or discontinuing the medication. Long-term use may result in ERG abnormalities.[215] Patients without systemic MAC infection who are taking rifabutin for prophylaxis and also are taking fluconazole or clarithromycin should be warned about the potential for uveitis and counseled as to its signs and symptoms.

Cidofovir

Cidofovir, also known as HPMPC, is a nucleotide analogue that inhibits viral DNA polymerase and is used for the treatment of cytomegalovirus (CMV) retinitis.[32,216–224] Cidofovir therapy, with both intravenous and intravitreous (20 μg) routes of administration, has been associated with an anterior uveitis, hypotony, and visual loss. These complications can be treated and sometimes prevented with the use of topical corticosteroids, cycloplegics, and oral probenecid. Cidofovir has been shown experimentally and clinically to cause a direct toxic effect to the ciliary body, with a resulting iritis and intraocular pressure decrease.[225,226] Although a 10 μg intravitreous dose had fewer side effects, it is also much less effective against CMV retinitis.[227] Investigations continue to try to determine the optimal dose and route of administration of cidofovir.

Latanoprost

See the drugs listed under Cystoid macular edema, p. 1848.

MISCELLANEOUS

Cardiac glycosides

Cardiac glycosides such as digoxin are used in the treatment of chronic heart failure and as antiarrhythmic agents. Although these drugs do not cause a characteristic fundus abnormality, ocular symptoms including blurred vision, scintillating scotomas, and xanthopsia (yellowing of vision) are common.[228,229] These changes probably are caused by direct toxicity to the photoreceptors. The visual symptoms are reversible with discontinuation of the drug.

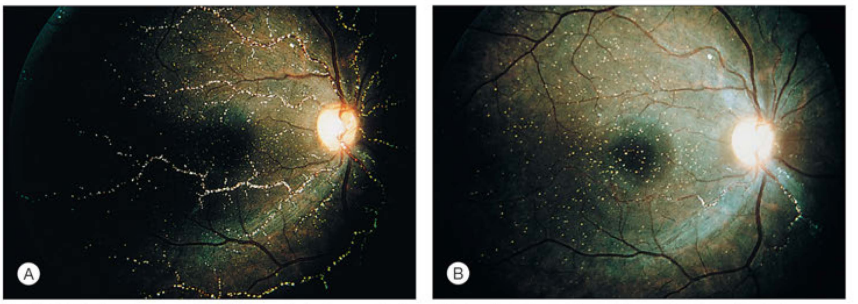

Fig. 108-23 Methoxyflurane crystals. A, Photograph displays periarterial crystals throughout the posterior pole in a patient chronically abusing methoxyflurane. B, Photograph of the same patient several months later demonstrates greater dispersion of the crystals. From Novak MA, Roth AS, Levine MR. Retina 1988; 8:230–236.

Methanol

Methanol occasionally is ingested by alcoholics. Visual blurring and field deficits are seen within 18 hours. Early fundus findings include optic nerve hyperemia and retinal edema, and late findings include optic atrophy[230–242] (Fig. 108-24). Nerve toxicity is mediated by formic acid, a breakdown product of methanol, which directly affects the inner retina and optic nerve.[230] The degree of systemic acidosis correlates well with the extent of visual dysfunction. Early hemodialysis is effective in removing methanol from the body, but if visual recovery is not evident by 6 days, it often remains permanently decreased.

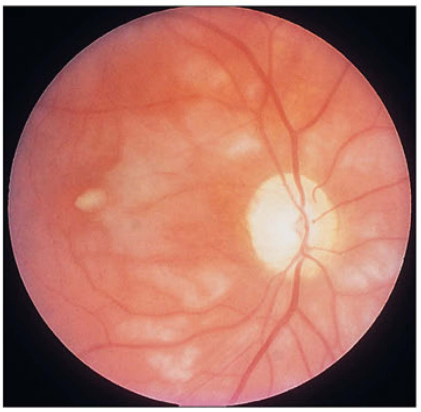

Fig. 108-24 Methanol poisoning. Acute changes revealing peripapillary retinal whitening and edema.

Vigabatrin

Vigabatrin is used for treatment of epilepsy, and has been associated with optic atrophy and visual field defects.[233,235]

SUMMARY

Although there are thousands of systemic medications, only a small number of these agents produce retinal changes. Retinal toxicity can occur when agents are used at standard therapeutic levels, and when they are used for nonapproved indications. The mechanism by which toxicity develops is unknown in many cases. With several new drugs reaching the market annually, ophthalmologists need to maintain a high index of suspicion that patients' symptoms and clinical findings may be related to one or more of their medications.

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