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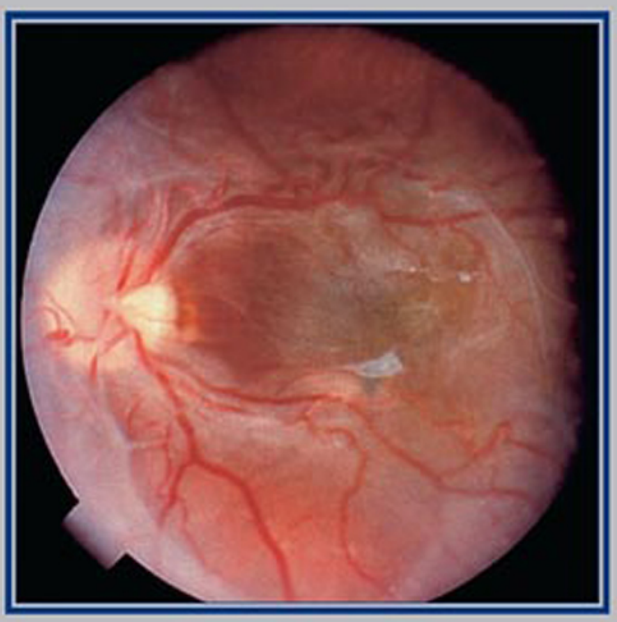
Clinical Pathways in Vitreoretinal Disease

Scott M. Steidl
Mary Elizabeth Hartnett



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Foreword

Clinical pathways define plans of best clinical practice that can be applied to a group of patients with a specific disease to aid in the coordination and delivery of the highest quality care. For a majority of patients with a similar diagnosis, the development of clinical pathways enables the standardization of the diagnosis and care of the disease.

In this text, the editors, Doctors Scott M. Steidl and Mary Elizabeth Hartnett, have successfully assembled a group of accomplished vitreoretinal specialists to write clinical algorithms for the assessment and treatment of vitreoretinal diseases. Each of the authors has expertly discussed topics or answered focused questions in a succinct, and clinically relevant manner.

This book will be most useful to both the resident seeking to expand his knowledge of vitreoretinal diseases and the practicing eye specialist as a quick reference on diagnosis or management of a specific retinal finding. This compendium is a resource for clinical approaches with invaluable pearls that can be used to provide the best outcomes for patients with vitreoretinal diseases.

Stanley Chang, M.D.

Preface

Vitreoretinal disease is the primary cause of severe vision loss in developed countries. This book was designed with this responsibility in mind and is dedicated to making diagnosis of retinal pathology more available to the medical community as a whole. This is a general reference manual and a diagnostic tool requiring a minimal level of understanding for identification of diseases and diagnosis development. The format of this book has some unique characteristics. Readers are urged to spend a few minutes reviewing the table of contents. Chapters are arranged by descriptive findings, which should allow readers to find information quickly and easily.

The text makes use of evidence-based medicine to develop management strategies. Decision trees and descriptions in the text highlight these strategies. The decision trees present a focused, "yes-or-no", approach to a problem. However, they are not meant to stand alone, but to be used as general guidelines. Specialists should be sought to clarify gray areas when they arise.

Although the primary focus of this book is diagnosis, treatment information is generally included. Effort has been made to be comprehensive for most of the diseases described. Specialized texts may be required for complete evaluation of treatment options and methods.

We hope that this book will have a role in aiding current and future eye care specialists in managing the daunting challenges posed by vitreoretinal disease. Owing to the tremendous effort brought forth by the contributing authors, this publication presents a broad glimpse of what's new and current in the field of vitreoretinal disease management. The systematic evidence-based methods as well as the up-to-date information presented here should arm the general eye care provider, student, and specialist with tools to navigate this rapidly changing field and to provide a glimpse of the road that lies ahead.

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I would like to thank Geri Mohler
for her many hours of hard work and dedication.

Scott M. Steidl

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for her expert editorial assistance and hard work.

Mary Elizabeth Hartnett

Dedications

To my loving wife, Mary, for her support, encouragement,
and two wonderful children, Lauren and William

Scott M. Steidl

To Bill

Mary Elizabeth Hartnett

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SECTION I

History, Physical Examination, and Diagnosis

1

Key Questions for a Focused History

DAVID G. MILLER AND LAWRENCE J. SINGERMAN

In all fields of medicine, a focused history is an essential starting point in the care of the patient. The order and method in a well-composed vitreoretinal history are similar to those in any medical history (Table 1–1), and the information obtained helps to develop both the diagnosis and the treatment plan. A comprehensive form (Fig. 1–1, pages 2 to 7) can be most useful in helping the physician to collect the necessary data.

What Is the Chief Complaint?

Simply stated, the chief complaint is usually a single sentence or phrase, from the patient's perspective, stating the reason for seeking medical attention. It is the patient's response to the examiner when asked, "Why did you come to the office today?" As an example, in ophthalmology, the most common chief complaint is, "My vision is blurred."

What Is the History of Present Illness?

The history of present illness (HPI) is a well-constructed paragraph that includes all the salient details evolving from the chief complaint. This will identify the problem in more detail (Table 1–2).

The key questions usually answered in the HPI concern location, timing, duration, severity, context, modifying factors, and associated symptoms. The location in an ophthalmic history identifies which eye is involved and whether both eyes are involved. In addition, if the complaint involves the patient's vision, the history identifies whether it is the central or the peripheral vision that is affected. The timing and duration explain when the complaint began and whether it is permanent, transient, or progressive. The patient often describes the severity of visual loss in relation to some visual task, such as reading small print (newspaper) or recognizing faces. Modifying factors describe alleviating or aggravating associations that affect the complaint, for example, positional changes or time of day. Associated symptoms are those noted to occur with the ocular problem, such as the onset of headache following ocular migraines or nausea associated with papilledema. The patient always should be questioned about the nonsymptomatic eye to elicit any subtle or vague changes that might be important to the underlying condition.

TABLE 1–1. General Patient History Components

Chief complaint
History of present illness
Past medical/surgical history
Medications
Allergies
Family history
Review of systems
Social history

TABLE 1–2. Ocular History of Present Illness

Which eye or part of the vision is involved?
When did the symptom start? How long did it last? Is it progressing?
What is the severity?
What is the context? What initiated the symptoms?
Does anything make it better or worse?
Are any other nonocular symptoms present?

BWD LKWD SW YT AKN WRN MNTR

Tech_____ DATE____/____/____ LJS MAN HZ ZNZ SDP DGM

PATIENT Referring Doctor OPHTH OD INTERNIST

_____ _____ _____ _____
LAST FIRST LAST FIRST
Mr. Mrs. Miss Ms. Dr.

DOB_____ _____ _____ _____
Last seen To see again # times seen

AGE_____ Primary Medical Doctor

_____ _____ MD DO
LAST FIRST

SEX____

PRIMARY DIAGNOSIS

1._____ R L B 6._____ R L B
2._____ R L B 7._____ R L B
3._____ R L B 8._____ R L B
4._____ R L B 9._____ R L B
5._____ R L B 10._____ R L B

Procedures	Dx (# from above)	Treatment
1._____	_____	_____
2._____	_____	_____
3._____	_____	_____
4._____	_____	_____

Tx

OD	OS
TYPE_____	
SIZE_____	
POWER_____	
EXPOSURE_____	
NUMBER_____	

RECOMMENDATIONS

1._____
2._____ R.V. RACI FA R L B
3._____ REF. MD OD Photos R L B
4._____
5._____ DICTATION Y N N/N
Fax Sht/form
TECH _____ MD _____

FIGURE 1–1. Initial evaluation and management documentation form.

Page 2

Patient Name _____ _____ TECH_____ MD_____
LAST FIRST

REASON FOR REFERRAL _____

_____

CHIEF COMPLAINT _____

_____

HISTORY OF PRESENT OCULAR PROBLEMS

SYMPTOMATIC EYE

EYE

R L B _____ *minimum 4*

location
timing
quality
context
severity
modifying factors
duration
assoc. signs

FELLOW EYE

R L B _____

EYE MEDS

	Dose	Date			Dose	Date	
1._____	_____	_____	OD / OS	4._____	_____	_____	OD / OS
2._____	_____	_____	OD / OS	5._____	_____	_____	OD / OS
3._____	_____	_____	OD / OS	6._____	_____	_____	OD / OS

Past Ocular History

		DATE	MD
Cataract Removal	OD	_____	_____
	OS	_____	_____
YAG	OD	_____	_____
	OS	_____	_____
Scleral Buckle	OD	_____	_____
	OS	_____	_____
Vitrectomy	OD	_____	_____
	OS	_____	_____

		# Treatments	Dates	Dx	MD
Laser	OD	_____	_____	_____	_____
		_____	_____	_____	_____
	OS	_____	_____	_____	_____
		_____	_____	_____	_____

FIGURE 1–1. (*Continued*)

Patient Name _____ _____ TECH_____ MD_____
LAST FIRST

PAST OCULAR HISTORY (CONTINUED)

		Date Diagnosed	Others		Date Diagnosed
Age-related Mac. Degen.	OD	_____	_____	OD	_____
	OS	_____	_____	OS	_____
Diabetic Retinopathy	OD	_____	_____	OD	_____
	OS	_____	_____	OS	_____
Glaucoma	OD	_____			
	OS	_____			

PRESENT / PAST MEDICAL HISTORY

Illness 1. Diabetes + - ___yrs. Blood Sugar_____ well controlled Y N Hgb A1C____ 6._____

2. HTN + - ___yrs. 4._____ 7._____

3. Cancer + - ____ yrs. _____type 5._____ 8._____

Injuries _____

Operations _____

_____

Hospitalizations _____

_____

Medications

Insulin Y N Type_____ _____ u am pm

Type_____ _____ u am pm

(Present Medications)

1._____ dose_____ date_____ 5._____ dose_____ date____

2._____ dose_____ date_____ 6._____ dose_____ date____

3._____ dose_____ date_____ 7._____ dose_____ date____

4._____ dose_____ date_____ 8._____ dose_____ date____

Drug Allergies

1._____ 2._____ 3._____ 4_____

Allergic to Fluorescein ? Y N

Allergic to ICG ? Y N

FIGURE 1–1. (*Continued*)

Patient Name _____ _____ TECH_____ MD_____
LAST FIRST

REVIEW OF SYSTEMS (circle condition if positive)

Endocrine	+	-	
General (fever, chills)	+	-	BP_____/_____ Rt / Lt arm
Ear Nose Throat (Sinus)	+	-	
Cardiovascular	+	-	
Respiratory	+	-	
Immunologic	+	-	
Gastrointestinal	+	-	
Genitourinary	+	-	
Skin	+	-	
Musculoskeletal (joints)	+	-	
Neurologic	+	-	
Hematologic	+	-	
Psychiatric	+	-	

FAMILY HISTORY	Mother	Father	Sibling	Other
AMD				
RD				
Blindness				
Glaucoma				
Cancer				
Heart Disease				
Diabetes				
Other				

Social History

Occupation_____

Smoke ?	Y	N	If yes, how long_____	how much_____
Alcohol ?	Y	N	how much_____	
Sexually Transmitted Disease?	Y	N	Diagnosis_____	

FIGURE 1–1. (*Continued*)

Patient Name _____ _____ TECH_____ MD_____
LAST FIRST

Mental Status Exam: Alert and oriented x3 with proper affect ☐YES

EYE EXAM

			PAM		
DV	R	JVR	OD	c + -	
DV	L	JVL	OS	c + -	

Glasses Rx x_____yrs

R _____ add _____

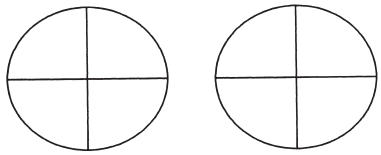
L _____ add _____

Amsler

R NL ABNL ND

L NL ABNL ND

CVF



External Exam NL ABNL _____

EOM Full ABNL _____ ET XT

Pupils

	SIZE	Reaction to LIGHT		APD					
OD	____	Y	N	Y	N	0	+1	+2	+3
OS	____	Y	N	Y	N	0	+1	+2	+3

Dilated with (circle)
Myd 1%
Cyc 1%
Neo 2.5%
Neo 10%

Time_____

IOP APPLANATION OD_____ OS_____
SHIØTZ

SLIT-LAMP EXAM

	OD Normal	OD Abnormal	OD	OS Normal	OS Abnormal	OS
Lids – Lashes	____	____	_____	____	____	_____
Conjunctiva	____	____	_____	____	____	_____
Cornea	____	____	_____	____	____	_____
A/C	____	____	_____	____	____	_____
Iris	____	____	_____	____	____	_____
Lens	____	____	_____	____	____	_____
			ACIOL			ACIOL
			PCIOL			PCIOL
Capsule	____	____	_____	____	____	_____
Ant. Vit.	____	____	_____	____	____	_____

FIGURE 1–1. (*Continued*)

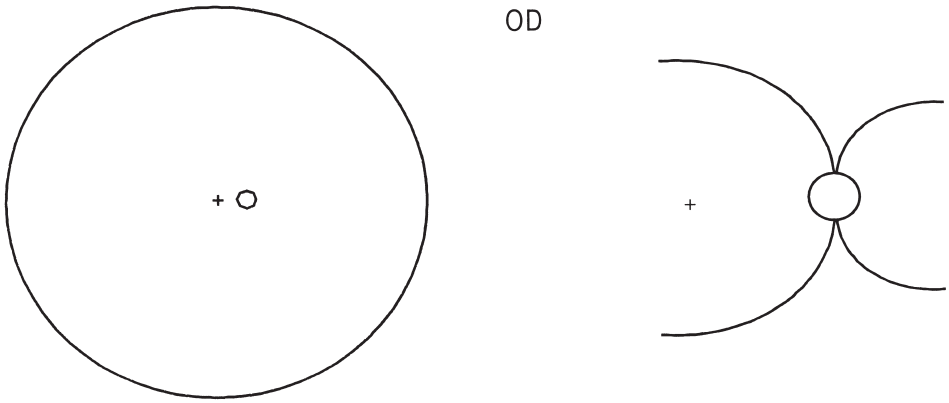
Page 6

Patient Name _____ _____ TECH._____ MD_____
LAST FIRST

Ophthalmoscopy

Ophthalmoscopy CL _____ 78D/90D _____ R L B
Scleral Depression R L B

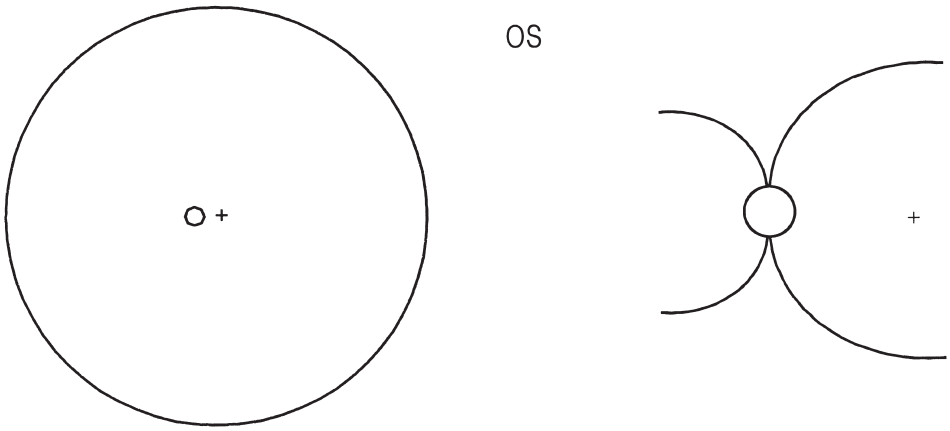
OD



Normal

Disc _____ C/D _____
Macula _____ _____
Vessels _____ _____
Periphery _____ _____
Vitreous _____ + – PVS _____

OS



Normal

Disc _____ C/D _____
Macula _____ _____
Vessels _____ _____
Periphery _____ _____
Vitreous _____ + – PVS _____

FIGURE 1–1. (*Continued*)

TABLE 1–3. Past Ocular History

Natural refractive state
Ocular trauma
Ocular laser procedures
Ocular surgeries
Glaucoma
Macular degeneration

TABLE 1–4. Components of Past Medical History

Previous medical diagnoses or illnesses
Hospitalizations
Surgeries
Injuries
Medications (including over-the-counter)
Drug allergies

What Is the Past Ocular History?

The past ocular history should include a complete summary of any previous eye diagnosis or surgery (Table 1–3). This includes the refractive state of the eye and, if it is pseudophakic, the refractive state prior to cataract surgery. In the case of corrected myopia secondary to lens implant surgery or refractive surgery, the prior myopic status can be estimated as low, medium, or high. This estimation is based on the patient's recollections of how thick his or her glasses were before the surgery or how close he or she had to hold a newspaper to read it clearly without correction. These simple questions often will reveal the "previously" high myope.

The ocular surgery history should include all procedures and specific inquiry about laser surgery; many patients will omit this information because they do not consider it ocular surgery. Any history of ocular trauma is important, including both recent and remote events. Such events include blunt trauma to the eye or head and penetrating trauma with or without a retained foreign body. The history of trauma can be important with regard to management and also to nonmedical issues, such as insurance and litigation.

Previous ocular diagnoses should be listed, including noting which eye was involved. In particular, those diagnoses common to the particular demographic involved should be sought. Examples include macular degeneration in the older white patients and glaucoma in African Americans. Inquiring about any eye medications or eyedrops often reveals an underlying diagnosis that was previously overlooked (e.g., topical aqueous suppressants, artificial tears).

What Is the Past Medical History?

Systemic conditions often influence the development of vitreoretinal disease and can affect their management. A list should be compiled of previous medical diagnoses, surgical procedures, hospitalizations, medications, and allergies (Table 1–4). A patient may forget to mention a particular medical diagnosis that can be inferred from the medications taken or previous surgery performed. An example is the patient who fails to note a history of cardiovascular disease but lists using nitroglycerin or having undergone previous heart surgery.

What Systemic Diseases Are Important in the Diagnosis?

Some medical illnesses, including diabetes mellitus, hypertension, sickle cell anemia, leukemia, and sepsis, have a direct link to vitreoretinal disorders. Among these, diabetes and hypertension are prevalent as well as causative or contributory to many retinal disorders. In fact, diabetes mellitus is the most common systemic condition that causes blindness. In patients with diabetes, the duration of the disease significantly influences the severity of the retinopathy. Also, as shown in the Diabetes Control and Complications Trial, the more well controlled the blood sugar, the lower the incidence of severe retinopathy.[1] Therefore, asking the patient about the duration of the disease (years), the usual range of blood sugars, or even the hemoglobin A1c can provide clues to diagnosis and treatment. In addition, associated diabetic complications, such as nephropathy, neuropathy, and peripheral vascular disease, can provide guidance as to likely ocular involvement from diabetes mellitus.[2]

What Systemic Factors Are Important in Determining Treatment and Anesthesia?

Other systemic conditions are important when considering the treatment plan, especially if surgery is required. Medications to which the patient is allergic are to be avoided, although often a more detailed allergy history will determine that the supposed allergy was more likely a medication side effect or a coincidental happening at the time the medication was used. An example is nausea with intravenous fluorescein injection, which is a side effect, not an allergic reaction. Particular allergies that should be noted include those to fluorescein and indocyanine green (ICG), two dyes commonly used in the diagnosis of retinal disorders. ICG allergic reactions are more likely in people who have shellfish or iodine allergies, and the physician must use clinical judgment in deciding whether ICG angiography should be done in these cases.

In consideration of surgery, especially important systemic conditions to take into account, include recent myocardial infarction, thrombophlebitis, anticoagulation therapy, back or neck pain, arthritis, and pregnancy. Patients who have had a myocardial infarction in the previous 6 months have a higher risk of recurrent infarction under general anesthesia, and local anesthesia is preferred in such cases. Patients with prior thrombophlebitis are at risk for recurrence and pulmonary embolism, especially if prolonged and strict postoperative positioning is used. In these cases, early postoperative ambulation may be helpful. Patients on anticoagulation therapy must be managed to minimize operative complications if they are unable to discontinue the anticoagulation at the time of surgery. Patients commonly overlook aspirin as a medication because it is purchased over the counter, but aspirin is a known platelet inhibitor and can cause increased intraoperative bleeding. The patient with neck and back pain or arthritis may not be able to lie on the operating table for the time required unless general anesthesia is used. Also, such patients may not be able to sustain postoperative positioning, and so a modification of the surgery plan is indicated. The care of pregnant patients should be approached so as to minimize exposure to all medications, including eyedrops. This may require surgery without intravenous sedation at the time of retrobulbar block and a quicker tapering of postoperative eye drops.

Some medical conditions can be exacerbated by systemic absorption of topical eye medications. In particular, the beta-blocking aqueous suppressants can have harmful effects on heart rate and blood pressure as well as on the patient's mood. Even the more common eyedrops, such as atropine, which can cause altered mental status, and phenylephrine, which can raise blood pressure, should be used judiciously in patients who already have these diagnoses. A common method used to avoid these complications of treatment is punctal occlusion, which requires digital pressure at the medial canthal area for several minutes after instillation of the eyedrop. If a patient at risk of complications from systemic absorption of eyedrops is unable to perform punctal occlusion, the choice of topical agents may have to be modified or at least the signs of systemic toxicity closely monitored by patient, family, and physician.

What Is a Review of Systems?

A review of systems is a systematic search for other illnesses through questioning the patient about symptoms unrelated to the chief complaint (Table 1–5). A full medical review of systems can be helpful in patients with undiagnosed systemic conditions that are linked to vitreoretinal disease or with systemic conditions that can affect treatment plans (Table 1–5). One common example is the undiagnosed diabetic patient, who may be having nocturia or paresthesias (Table 1–5). The review of systems may lead the physician to suspect a previously undiagnosed medical condition that affects the risks associated with treatment. For example, shortness of breath or occasional chest pains might indicate possible heart disease. It certainly would be advantageous to know about this condition before undertaking surgery.

TABLE 1–5. Review of Symptoms

General: fever, chills
Endocrine: weight loss or gain, lethargy, polydipsia
Ear, nose, throat: hoarseness, tinnitus, nasal congestion
Cardiovascular: chest pressure, shortness of breath, orthopnea
Respiratory: shortness of breath, cough, mucus production
Immunologic: recurrent infections, high-risk HIV behavior
Gastrointestinal: nausea, diarrhea, heartburn
Genitourinary: nocturia, hematuria, frequency
Dermatologic: changing moles or skin lesions
Musculoskeletal: stiffness of joints, swelling, weakness
Neurologic: paresthesias, weakness
Psychiatric: depression, anxiety

A more specific ocular review of symptoms can be helpful in diagnosing complex or multiple ocular conditions and in planning treatment. A simple way to classify this type of review is by ophthalmic subspecialty: anterior segment, glaucoma, neuroophthalmology, oculoplastics, strabismus, and posterior segment. An example would be the patient with macular degeneration who also has intermittent diplopia or ptosis secondary to undiagnosed myasthenia gravis.

What Is a Relevant Family History?

A relevant family history is used to uncover vitreoretinal diseases in some fully or partially inherited ocular conditions (Table 1–6). An efficient method of identifying severe inherited ocular conditions is to ask whether any extended family members have lost vision, especially at a younger age. Typically, this will

TABLE 1–6. Family Ocular History

Blindness at young or middle age
Retinal detachment
Macular degeneration
Glaucoma
Ocular cancer
Diabetes

reveal families with macular dystrophies, retinal detachments, retinoblastoma, and other such conditions. It is sometimes helpful to examine some of the family members as part of a more thorough family history.

A family history also may detect genetically determined systemic diseases with ocular complications, such as Marfan syndrome, Stickler syndrome, and homocystinuria. Often, a genetic component of the vitreoretinal problem is suspected following the examination. In these cases, the family history may be further investigated following the examination.

What is a Relevant Social History?

A relevant social history includes the patient's occupation, living arrangements, smoking, and alcohol use. Occupational concerns revolve around whether the patient will be able to continue in that line of work. Many vitreoretinal diseases are extremely disabling and can involve both eyes eventually. The patients need to be aware of a realistic prognosis and to be able to make plans regarding time off from work, short-term disability, or long-term disability.

Postoperative living arrangements are more important than ever because vitreoretinal surgery has evolved into an outpatient surgical specialty. Frail patients or those with poor vision in the postoperative period will need assistance with eyedrops, systemic medications, and possibly activities of daily living. These needs may be short-term or long-term, depending on the prognosis. Also, if a patient needs to travel or fly shortly after surgery, the surgical plan may have to avoid the use of intraocular gases.

Summary

A well-constructed history often points the physician in the right direction for diagnosis and treatment. In addition, it can help the astute surgeon lower the risk of some complications and lead to a more satisfactory outcome.

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2

Sorting Out Possible Diagnoses from the History

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What Is the Importance of the Clinical History?

The approach to successful diagnosis and therapy begins with the clinical history. The medical interview should serve to collect information helpful to detect, treat, and prevent illness.

Obtaining the history requires considerable skill that is developed only through extensive experience. As physicians, we should remember to perform thorough but goal-oriented questioning of each patient. Many patients fail to mention details relevant to the history or symptoms that affect them because they forget or think there is no relation to their eye problem. During the dialogue, patients will provide a more accurate testimony if they are comfortable and good rapport has been established between them and the clinician. A careful interrogation of the patient regarding his or her past history and chief complaint can produce a broad clinical picture that leads to the suspicion of different categories of retinal disease (Table 2–1). Information obtained from the history frequently leads us to pay particular attention to subtle aspects of the ocular or physical examination. The patient's history is also used to guide the diagnostic workup that eventually may point in the direction of a particular retinal disease. A fact that is applicable to every patient who has a visual or ocular complaint is that a carefully obtained history makes reaching a correct diagnosis more likely. Although often diagnoses and treatment decisions of retinal pathology rely in large part on a meticulous ocular examination, in a significant percentage of cases, sorting out the proper retinal diagnosis may depend largely on the history.

TABLE 2–1. Important Components of a Complete Clinical History

Age
Gender
Race
Place of birth and history of travel and residence
Place and type of employment
Family medical and ocular history
Past medical and ocular history
Medications
Diet and habits
Review of systems
Chief complaint and history of present illness

What Elements in the History Are Useful in Sorting Out the Diagnosis?

Age

This is probably the most important piece of demographic information leading to the inclusion or exclusion of large numbers of probable diagnoses. The retinal diseases that commonly affect the newborn are rare for older children. Retinal disorders frequently encountered in older patients differ from those found in middle-aged patients. There are many reasons for the effect of age on retinal pathology. Genetic defects that affect ocular physiology manifest more commonly in the earlier years of life; susceptibility to infectious insult is higher at the extremes of our life term; and time-related degenerative changes lead to disease in older persons. A clear example of age affecting the selective suspicion for retinal diagnoses is age-related macular degeneration (AMD) of older patients, which contrasts with inherited macular dystrophies, which are much more typical in young and middle-aged persons. Retinoblastoma, leukemia, Coats disease, and familial exudative vitreoretinopathy are

most often retinal diagnoses of childhood. Birdshot and serpiginous chorioretinopathy, in contrast, are more prevalent in persons older than 50 years of age. Masquerade syndromes should be suspected at both ends of the spectrum. Metastatic carcinoma, uveal melanoma, intraocular lymphoma, ocular ischemia, and paraneoplastic retinal syndromes usually occur in older persons.

Gender

Many eye diseases are more common in one gender than the other. Multiple facts explain this, including retinal diseases that may be linked to hormonal factors or those that are linked to a gene defect in a sexual chromosome and other less understood reasons. Central serous chorioretinopathy, for example, affects men much more frequently than women. Incontinentia pigmenti, on the other hand, is found almost exclusively in women.

Race

The ethnic background of a patient is very pertinent information when discerning possible retinal diagnoses because many disorders have marked differences in their incidence among various races. These differences are probably due to certain gene defects and other forms of molecular predisposition to disease being found more commonly in one race than in others. For instance, birdshot retinochoroidopathy in white persons has a strong association with antigen human leukocyte antigen (HLA)-A29. Another example is the case of melanin in uveal tissue, a proposed protector against environmental light irradiation. Its relative abundance or scarcity is believed to predispose for different ocular pathology: Vogt–Koyanagi–Harada disease is an autoimmune affliction against melanin in darker-skinned patients, usually Asians, Hispanics, and Native Americans; uveal melanoma has a correlation with sun exposure in less pigmented persons, such as those of Northern European ancestry. Diseases like sickle cell disease retinopathy or sarcoid uveitis occur much more frequently in African Americans. Other disorders, like white-dot syndromes, inflammatory chorioretinopathies, or AMD, have a much higher prevalence in the white population.

Place of Birth and History of Travel and Residence

A patient's geographic history holds important in the consideration of retinal conditions, particularly those of an inflammatory nature. Ocular infectious agents and environmental factors that affect them often are limited to certain locations and climates. This is the case for presumed ocular histoplasmosis syndrome or fungal and parasitic diseases, including onchocerciasis. Socioeconomic factors, dietary customs, and hygienic practices may vary in different places, again increasing the risk for infectious retinal diseases such as toxoplasmosis, which is associated with poor sanitation and the practice of eating undercooked meat.

Place and Type of Employment

External risk factors for retinal disease may be linked to the type and location of the occupation of a patient. Exposures to potential toxic agents, trauma resulting in a rhegmatogenous retinal detachment, and excessive sun exposure related to uveal melanoma are possible associations between employment and retinal disorders. Patients who work in sewers may be in contact with rodent urine and therefore at risk for leptospirosis, whereas brucellosis is more likely to occur in farmers and veterinarians.

Family Medical and Ocular History

This part of the history is particularly important in considering inheritable retinal diagnoses. Some retinal diseases are autosomal dominant and have a classic mendelian inheritance pattern. A positive family history may orient to conditions such as vitelliform dystrophy or retinitis pigmentosa, for example. Other inheritable retinal disorders are recessively transmitted: The presence of disease in siblings or history of consanguinity may suggest the diagnosis, as it may occur in gyrate atrophy or fundus flavimaculatus.

Past Medical and Ocular History

Of all the mentioned components in the history, prior history of disease, either systemic or ocular, has the highest yield in suggesting the cause of the complaints the patient describes. Complete past medical and surgical history often will unveil systemic illnesses associated with retinal diseases. Many common systemic diseases have a retinal component. The most familiar scenarios are diabetes mellitus, systemic hypertension, and rheumatic diseases. History of previous ocular disease is naturally very relevant to possible retinal complications or new disorders that a person may develop. An example is high myopia in a patient complaining of progressive central loss of vision, in which the suspicion for choroidal neovascularization is very high. Another common situation is endophthalmitis in a patient who recently had intraocular surgery.

Medications

Commonly used systemic medications have been associated with retinal disease. Medications well known for resulting retinal degeneration include chloroquine, hydroxychloroquine, and thioridazine. The in-

terferons need to be monitored for the retinal vascular occlusive disease they often induce. Corticosteroids are an important consideration when central serous chorioretinopathy is suspected.

Diet and Habits

Avitaminosis, particularly among children and older persons, may cause retinal disease. Vitamin A deficiency is an example of producing fundus xerophthalmia and nyctalopia. As mentioned earlier, consumption of raw or partly cooked meat can lead to toxoplasmosis or cysticercosis. Individuals who include unpasteurized milk in their diet are at risk of tuberculosis and brucellosis. Important habits to keep in mind are drug use, such as intravenous injection of heroin, which can result in retinal arterial occlusions if the drug is impure or in endogenous endophthalmitis. Sexual promiscuity and sometimes drug use are important risks for human immunodeficiency, herpes viruses, and syphilitic uveitis. A history of contact with unwormed dogs is significant in children with suspected ocular toxocariasis.

Review of Systems

For many retinal diseases, a meticulous review of systems is necessary to establish the diagnosis. It serves to recognize relevant symptoms previously unrecognized by the patient to be relevant to his or her eye illness. This is particularly true in uveitic, vascular, or neoplastic retinal disorders. An example is HLA-B27-associated uveitis, which frequently coincides with pathology in the skin, mucosae, joints, and gastrointestinal system. Unless directly asked, patients do not realize that there may be a common source with their uveitic disease, which is why they usually fail to mention complaints affecting other organs. Recognition of systemic symptoms is not only extremely helpful in arriving at the retinal diagnosis, but it can be used to prevent serious progression of disease elsewhere in the body.

Chief Complaint and History of Present Illness

These categories of information in the clinical history contain the key facts needed to reach a probable diagnosis. For this reason, the physician seeks these components in the history first in the interrogation. The chief complaint is the main reason the patient has come to the ophthalmologist. Identification of the chief complaint allows the physician to recognize the most relevant symptom of the patient's disease and immediately raises certain categories of retinal disease versus others. In the history of present illness, the severity, time of onset, course, and other characteristics of the patient's retinal symptoms, starting with the chief complaint, must be thoroughly described. Blurred or decreased vision is most commonly the symptom for which patients seek care. Other usual symptoms include scotomata, which suggests focal retinal damage; metamorphopsia, which can result from mechanical distortion of macular topography from conditions such as epiretinal membranes or subretinal or intraretinal fluid; and flashes and floaters, which are common in vitreoretinal traction syndromes. Pain and photophobia, when associated with retinal disease, are symptoms that most commonly reflect anterior intraocular inflammation affecting the iris or ciliary body or elevated intraocular pressure.

How Should the Information Be Included in the Patient's History of Present Illness?

The history of current illness is a chronologic description of the patient's complaints. Each symptom should be distinguished by its type and quality; its intensity; time of onset, and mode of progression; its duration and frequency of recurrence; the existence of precipitating factors, alleviating factors, or aggravating factors; and associated events that precede, occur simultaneously, or follow the symptom described. Retinal diseases typically present with visual and ocular symptoms, which often can be explained on the basis of the underlying pathophysiologic process. One type of information that is particularly revealing in retinal problems is whether the complaint is monocular or binocular and to what extent symptoms may be asymmetric. Important clues to retinal diagnosis, particularly those of an inflammatory nature, also may lie in systemic complaints, including those that affect the neurologic system, the skin and mucosae, the musculoskeletal system, the respiratory and gastrointestinal systems, and others.

The clinical experience and knowledge base of the individual physician affect the process by which that physician classifies and reasons about information obtained in the history. One of the complexities affecting the practice of caring for retinal diseases, much like the rest of medicine, is that patients do not consult the physician while having a known diagnosis but seek alleviation of one or more symptoms. Symptoms in each individual patient are subjective and are modified by the particulars of the disease process itself. Not infrequently, symptoms are forgotten, suppressed, or exaggerated by patients. The ability of patients to report about the retinal disease affecting them is influenced by their age, education level, gender, cultural background, socioeconomic status, and ethnicity. Most patients with a retinal illness present with both specific and nonspecific symptoms. The former are key complaints the patient reports that point to a specific disease. Nonspecific symptoms are those

that will not be decisive in reaching the diagnosis because they do not form part of a cluster of symptoms that we recognize as corresponding to a specific pathological entity. Determining the level of accuracy of reported symptoms in retinal disease is an important task. The precision of the descriptions given by the patient affects our efficiency to sort out a pattern that will lead to suspicion of a particular diagnosis.

What Does the Process of Sorting Out Possible Diagnoses Entail?

Development of a reasonable suspicion for one or more retinal diagnoses requires an analytic process that resembles the scientific method, in which observation leads to a hypothesis that can be tested with experimentation to refute or confirm the hypothesis. Physicians formulate potential diagnoses based on the clinical observations that will guide diagnostic testing, or experimentation, to hold one possible diagnosis over others.

The collection of clinical information, starting with the history, is essential to problem solving in retinal diagnosis. The application of scientific reasoning becomes a repetitive cycle during the process of sorting out one true clinical conclusion. As data are accumulated regarding a retinal illness, new hypotheses are produced and supported, and others are invalidated. The physician must remain alert for clinical clues that do not fit the current hypothesis and that might make it necessary to consider renewal of the assessment of information.

The diagnostic process in the retina, and in other fields of ophthalmology as well, is a dynamic one that begins with the history. This process is carried out not only as linear thinking, but several lines of evidence are considered in a parallel manner to reach one or more suspect diagnoses that will be investigated during the physical examination, laboratory testing, and other special testing.

What Retinal Diagnoses Are Suggested by Reduction in Central Visual Acuity?

Loss of foveal vision, even in small degree, is probably the most commonly reported symptom by patients who consult the ophthalmologist. The impact on the patient varies, depending on the type and degree of vision loss, whether onset is sudden or gradual, and also whether one or both eyes are affected. Many nonretinal causes exist for the loss of central visual acuity, including refractive conditions, diseases of the cornea and lens, glaucoma, and neuroophthalmologic disorders.

Because of the lack of anterior ocular findings, neuroophthalmic diseases often need to be carefully distinguished from retinal conditions. An important question is whether the degree of visual loss is explainable by the retinal findings. For example, a patient with mild epiretinal membrane maculopathy and severe reduction in visual acuity should be further investigated for other possible causes of visual loss. Diseases of the optic nerve, such as optic neuritis, ischemic optic neuropathy, and impinging tumors, are usually unilateral. A characteristically bilateral optic nerve pathological process that may lead to pronounced visual loss is papilledema seen in increased intracranial pressure. Chiasmal lesions can result in a visual loss that exhibits a variety of patterns with bilateral field involvement. Retrochiasmal neurologic disorders affect typically bilateral vision but spare half the macular vision without a decrease in visual acuity.

Numerous retinal causes exist for diminished foveal vision, and these causes may or may not be accompanied by a loss of peripheral vision, including ischemic processes, ocular inflammatory processes, retinal detachment, vitreous hemorrhage, retinal toxic insults, infectious disorders, dystrophic and degenerative diseases, and neoplastic disorders.[1,2] A method for determining the cause of central vision loss is outlined in Figures 2–1, 2–2, and 2–3. Here we discuss central vision loss subdivided by its association with other characteristics and symptoms.

Which Retinal Diseases Are Suspected in Severe Loss of Central Vision?

Sudden and severe loss of vision is a traumatic event that usually prompts the patient to seek immediate medical attention. In older patients, especially if predisposing conditions in the medical history of the patient exist, ischemic processes leading to loss of central vision should be among the first considered. Such retinal diseases include branch retinal artery obstruction, central retinal artery occlusion, ocular ischemic syndrome, branch retinal vein occlusion, central retinal vein occlusion, and hemiretinal vein occlusion. Retinal detachment is a frequent cause of painless monocular loss of visual acuity. Severe loss of vision can occur with the three pathogenic forms of retinal detachment. Rhegmatogenous retinal detachment secondary to a retinal break often is associated with a history of aphakia, pseudophakia, ocular trauma, and high myopia. Tractional retinal detachment can be present in patients with a history of proliferative diabetic retinopathy, retinopathy of prematurity, penetrating trauma, proliferative vitreoretinopathy, angiomatosis retinae, Behçet syndrome, Coats disease, or pars

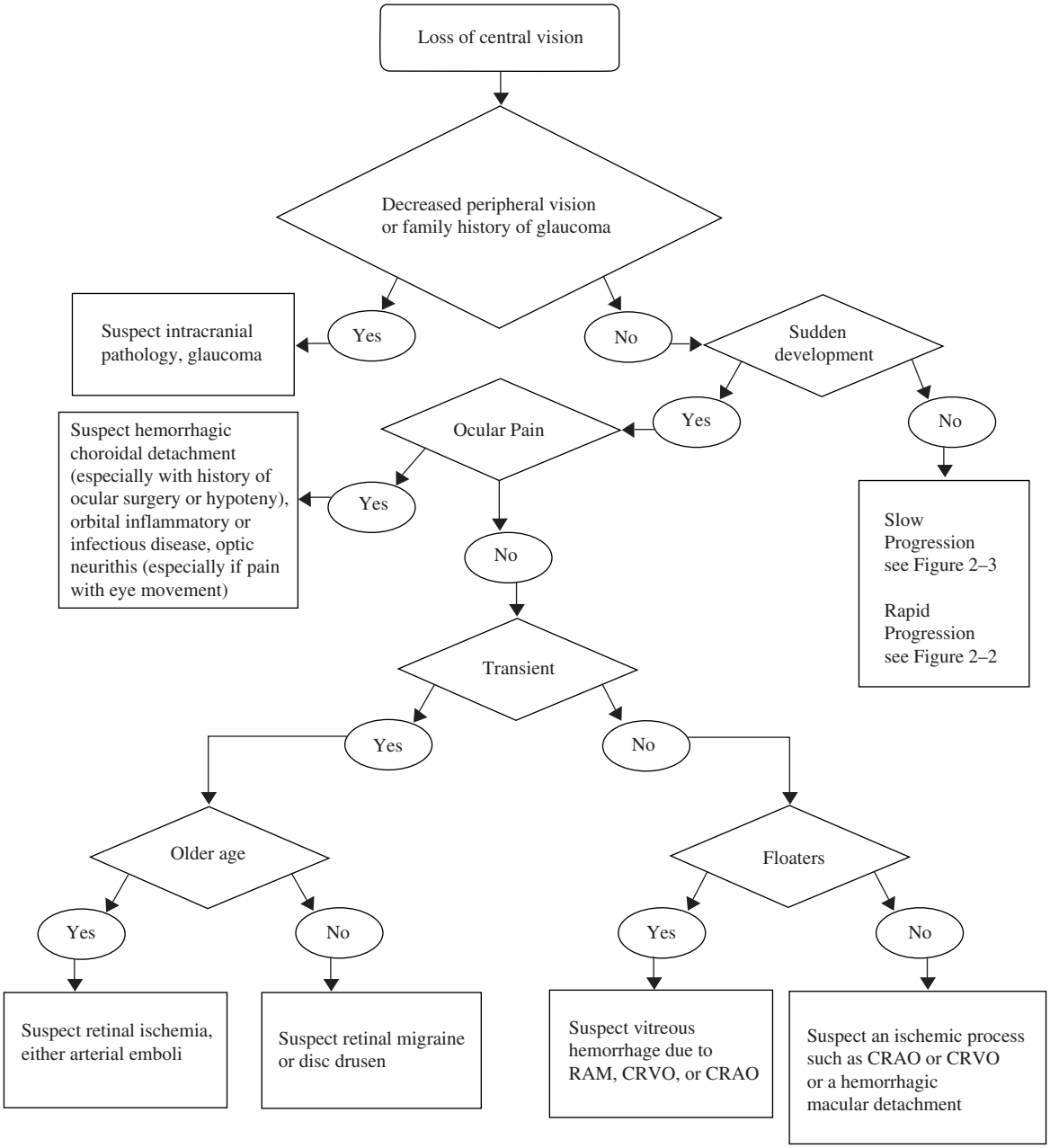

FIGURE 2–1. General clinical pathway for loss of central vision. RAM, retinal arterial macroaneurysm; CRVO, central retinal vein occlusion; CRAO, central retinal artery occlusion.

planitis. Exudative retinal detachments are associated with neoplasms, Harada disease,[3] posterior scleritis, collagen–vascular disease, malignant hypertension, sympathetic ophthalmia, uveal effusion syndrome, postocular surgery,[4] and toxemia of pregnancy. Choroidal neovascular (CNV) membranes bleed and leak, producing painless loss of vision. In most cases, it begins as a monocular complaint. Associated conditions include neovascular AMD, presumed ocular histoplasmosis syndrome (POHS), high myopia, angioid streaks, sarcoidosis, multifocal choroiditis, punctate inner choroidopathy, melanoma, hemangioma, osteoma, and laser photocoagulation. Development of CNV membranes in patients with multiple evanescent white-dot syndrome may occur on rare occasions and also can be idiopathic in some patients.

Other pathology related to retinal disease results in loss of central vision. A common condition with painless monocular loss of visual acuity is vitreous hemorrhage, which has multiple causes.[1,2,5,6] Ocular hy-

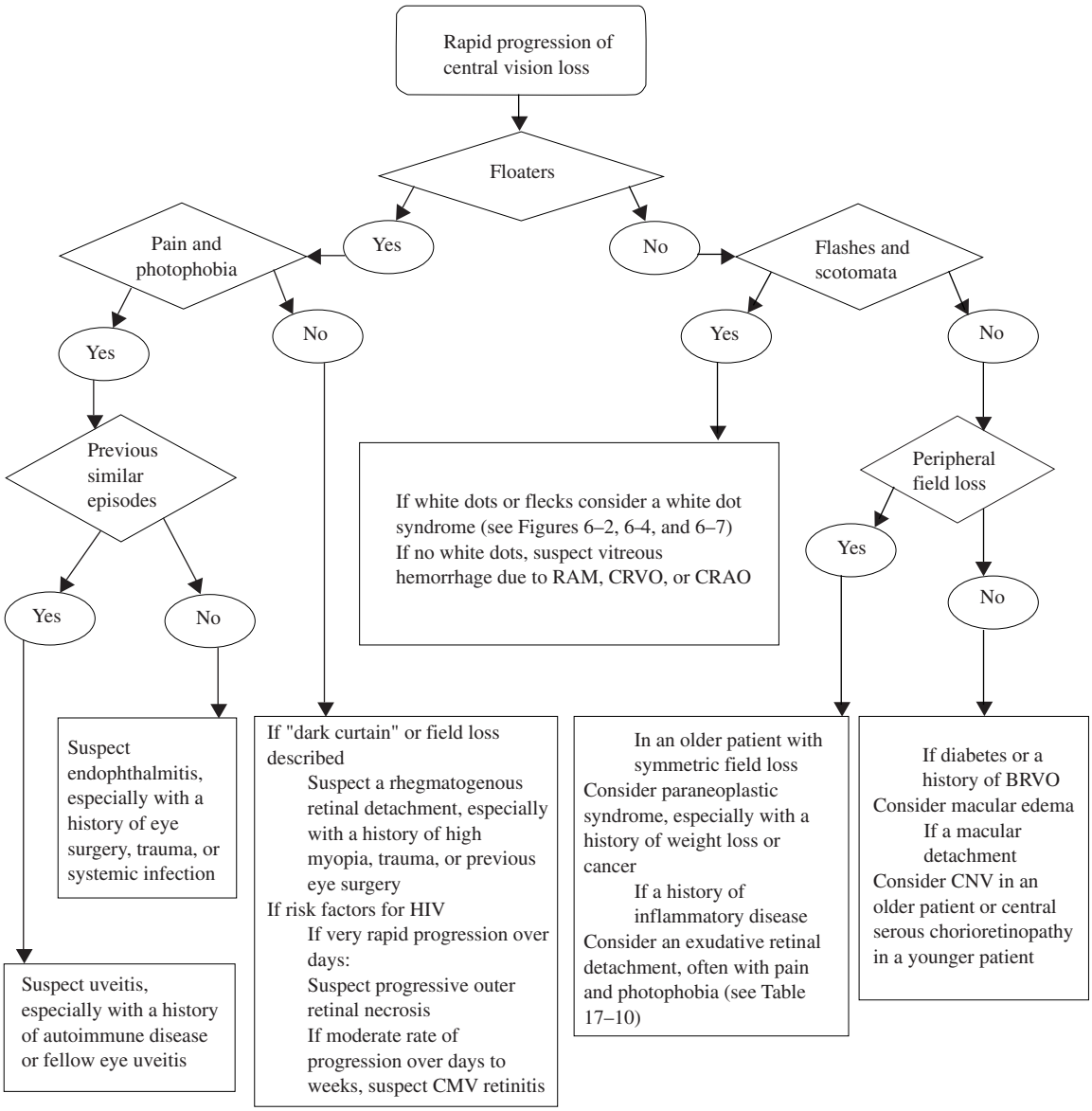

FIGURE 2–2. Rapid progression of central vision loss. BRVO, branch retinal vein occlusion, RAM, retinal artery macroaneurysm; CRVO, central retinal vein occlusion; CRAO, central retinal artery occlusion; BRVO, branch retinal vein occlusion; CNV, choroidal neovascularization; CMV, cytomegalovitus.

potony associated with malfunction of the ciliary body may result in severe reduction of vision associated with pain. Intraretinal hemorrhage, especially when affecting the fovea, can lead to painless monocular loss of visual acuity. It may be suspected in patients with retinal vascular abnormalities, hypertensive retinopathy, retinal macroaneurysm, and idiopathic polypoidal choroidal vasculopathy.

Toxicity to retinal cells is a cause of severe loss of vision. Quinine poisoning should be suspected in patients under quinine treatment. Methyl alcohol poisoning is usually seen in alcoholic persons who have accidentally or intentionally consumed this substance.

In healthy older women complaining of sudden or gradual decrease in vision, macular hole should be suspected. Bilateral involvement is present in 13 to 19% of patients.[7] Middle-aged men exposed to stress or corticosteroid medications are predisposed to central serous chorioretinopathy with consequent painless monocular loss of visual acuity.[8]

In patients who have undergone laser photocoagulation in the past, sudden painless monocular loss of visual acuity may be due to macular edema, foveal

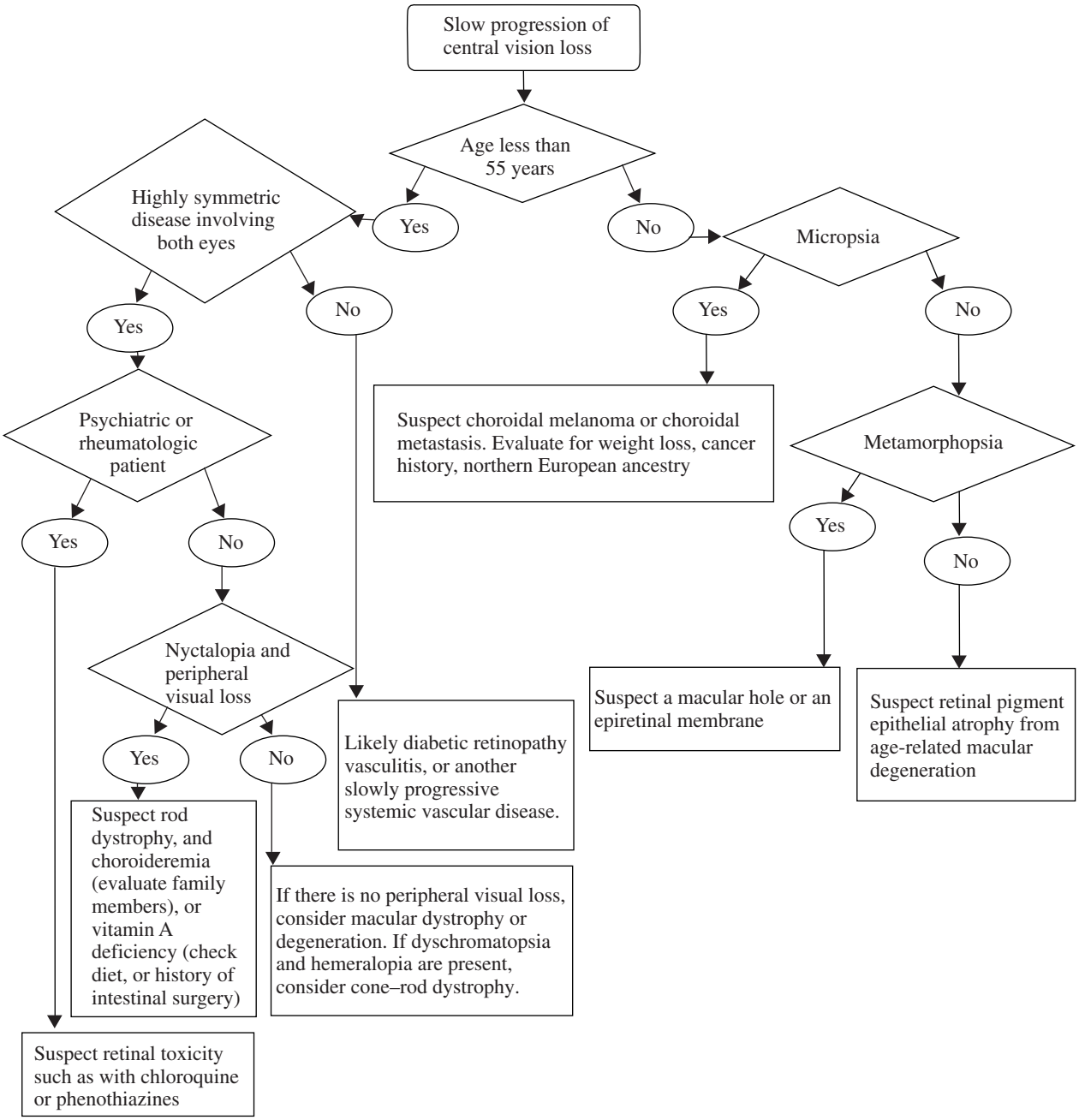

FIGURE 2–3. Slow progression of central vision loss.

traction, or serous or choroidal detachment. Photocoagulation of the foveal avascular zone is a serious complication that may occur.

Which Retinal Diseases Are Suspected in Painless Progressive Loss of Central Vision?

The most common conditions leading to progressive loss of vision are age-related diseases. An older patient with progressive visual loss should lead to a suspicion of AMD, which is the most common cause of reduction in visual acuity in patients older than 50 years of age. Patients may have the nonexudative or exudative form of the disease. When choroidal neovascular membranes are present, they may produce new-onset metamorphopsia or a central scotoma involving the area served by the fovea and macula. Patients note a loss of central detail; peripheral acuity remains clear.

Young adults are less likely to develop retinal diseases, but binocular loss of vision may result from

late-onset congenital disorders. Family history of retinal diseases is an important factor to consider in the medical history. Diseases that have a familial component include, for example, high myopia that may be inherited in an autosomal-dominant fashion; Stargardt disease has bilateral gradual visual loss in young patients with an autosomal-recessive inheritance pattern. In retinitis pigmentosa, the mode of inheritance can be autosomal dominant, recessive, or X-linked. Vitelliform dystrophy usually presents as slow decrease in bilateral visual acuity over the course of many years in young adult patients. It is inherited as autosomal dominant with variable penetrance. Angioid streaks may cause visual loss due to pigment degeneration, CNV, or macular edema. It is associated with different systemic diseases and has different modes of inheritance according to the underlying disease. Other retinal diseases that have a familial component include autosomal dominant drusen, X-linked juvenile retinoschisis, or dominant cystoid macular dystrophy where visual acuity decreases with age. Cone dystrophies can be congenital or progressive and typically affect central vision early in life.

A negative family history may orient the physician to suspect macular edema, a common cause of progressive loss of vision. Macular edema most commonly is associated with a history of diabetes. It is important to note the date of diagnosis or initiation of diabetic symptoms because the best predictor of diabetic retinopathy is the duration of the disease. Other causes of macular edema include postsurgical cystoid macular edema, retinal macroaneurysms, radiation retinopathy, uveitis, retinal venous occlusive disease, systemic hypertension, choroidal neovascularization, retinal telangiectasis, and others.[9]

Retinal and choroidal neoplasms, such as capillary hemangiomas, retinoblastomas, retinal hamartomas, ocular lymphoma, choroidal melanoma, and metastatic tumors, also must be considered as occasional causes of monocular loss of central vision, most often affecting very young and older patients.

Which Retinal Diseases Are Suspected in Painful Loss of Central Vision?

Duration, localization, irradiation, and intensity of pain as well as triggering factors are of importance in the differential diagnosis of painful loss of vision. Diseases with ocular pain and loss of vision are most frequently uveitic in nature, such as Vogt–Koyanagi–Harada disease, posterior scleritis, and other conditions causing severe vitreitis. These diseases may be infectious in nature, such as endophthalmitis, which can be suspected if a history of surgery or ocular trauma is present. Immunocompetent healthy patients at any age can suffer from acute retinal necrosis syndrome. The fellow eye becomes affected in one third of these patients. Toxoplasmic papillitis may be suspected in healthy young adults with pain during eye movement. Unilateral painful loss of vision in young patients, presenting as chronic endophthalmitis, a granuloma, or other atypical presentations, may point to the diagnosis of ocular toxocariasis. Young patients are also predisposed to ocular trauma, with loss of vision occurring after penetrating or perforating injury, blunt trauma, or intraocular foreign bodies.[10] Orthostatic ocular pain, in which eye discomfort arises with changes of body position, has been described in patients with ocular ischemic syndrome. In contrast, ocular pain that is elicited with changes of gaze position is more frequently associated with optic neuritis. Older white patients from northern climates are more predisposed to suffer from giant cell arteritis (temporal arteritis), which can cause retinal and optic nerve ischemic events associated with pain in different parts of the head.

What Retinal Diagnoses Are Suggested by Peripheral Loss of Vision or Paracentral Scotomata?

Loss of extrafoveal vision encompasses a reduction in sensitivity of a large part of the peripheral visual field or the presence of smaller paracentral scotomata, sometimes described by patients as “spots in front of my eyes.” These “spots” can be distinguished from floaters by their stationary nature, even with saccadic eye movements. When foveal vision is preserved, loss of vision in the pericentral and peripheral visual field can go unnoticed by patients, especially when it is present only monocularly. In the absence of associated visual symptoms, most persons are able to ignore small scotomata or even more extensive visual depressions. This is exemplified by the lack of perception of the physiologic blind spot during monocular viewing conditions. On occasion, there are recently monocular, perceptive patients who do complain of a scotoma corresponding to the blind spot. Small scotomatous defects are more likely to be detected if they are close to the fovea, or when they are present as part of a scintillating scotoma. Retinal reasons for paracentral scotomata or peripheral field loss must be differentiated from glaucoma and neurologic disease. Distinction of chronic glaucoma from retinal disease usually requires a meticulous fundus examination. Similarly, identification of optic nerve disease as opposed to a retinal etiology can be difficult without the use of ophthalmoscopy. In some cases, there may be

indicators of optic nerve pathology, such as pain or visual changes with different positions of gaze. Retrochiasmal neurologic disease can lead to scotomata and visual field defects, too. In these cases, it is usually bilateral homonymous, and frequently there are associated neurologic complaints.

Multiple retinal conditions can result in a loss of extrafoveal vision. Perhaps the most commonly encountered cause of monocular visual field reduction is rhegmatogenous retinal detachment, which classically progresses centripetally over the course of several hours to a few days, often accompanied by floaters and photopsias. Parafoveal or peripheral exudative retinal detachments from either central serous chorioretinopathy or a choroidal tumor also are known causes for central, paracentral, and peripheral visual loss. Tractional retinal detachments along the vascular arcades, as they typically occur in proliferative retinopathy of diabetes and other microvasculitic processes, are a frequent cause for peripheral visual loss. These latter disorders, together with retinal vein or artery occlusions, cause peripheral field loss through retinal ischemia.[11] Peripheral retinoschisis sometimes can be found in patients with dense loss of visual field, although it is usually eccentric and asymptomatic.

Hereditary retinal degenerations, such as retinitis pigmentosa, gyrate atrophy, Bietti crystalline dystrophy, and choroideremia, are typified by the early preservation of central visual acuity with bilateral loss of peripheral vision. There are multiple patterns of loss of visual field in these disorders. Initially, there may be only a ring scotoma, but with time this scotomatous area extends to the periphery and infringes on the central field until only a small area of vision remains. Macular dystrophies, including central areolar choroidal dystrophy, central areolar pigment epithelial dystrophy, fenestrated sheen macular dystrophy, benign concentric annular dystrophy, and sometimes fundus flavimaculatus and pattern macular dystrophies, may cause paracentral scotomata and may not be symptomatic unless the central macula becomes involved.

Inflammatory retinochoroidal diseases may present monocularly or binocularly with a combination of scotomata preceded or bordered by photopsias, such as occurs in acute zonal outer occult retinopathy (AZOOR), multiple evanescent white-dot syndrome (MEWDS), multifocal choroiditis, acute macular neuroretinopathy, idiopathic blind-spot enlargement, and others. Bilateral scotomata associated with photopsias and nyctalopia is seen in birdshot retinochoroidopathy. Serpiginous choroiditis is characteristically bilateral, although it may begin monocularly. It leads to paracentral scotomata that eventually tend to involve the fovea in middle-aged patients. Inactive ocular toxoplasmosis and presumed ocular histoplasmosis usually leave scotomata produced by atrophic scars; these may be symptomatic if they are located centrally enough. Patients with cytomegalovirus retinitis and other herpesvirus retinitis usually develop a loss of peripheral visual field that progresses toward the center, and they may complain of photopsias and floaters.

Hydroxychloroquine and chloroquine can result in central, paracentral, or peripheral scotomata and abnormal color vision. Solar retinopathy may lead to bilateral central or paracentral scotomata, metamorphopsia, dyschromatopsia, and afterimage. A similar pathological mechanism can be induced postsurgically by retinal light toxicity from the operating microscope or endoillumination.[12] Patients who have undergone laser photocoagulation for macular edema or choroidal neovascularization may also complain of paracentral scotomata.

What Retinal Diagnoses Are Suggested by Floaters?

Floaters are frequent symptoms. Unless they are very pronounced, they most often occur in healthy persons. Floaters, or "spots, flies, or cobwebs before the eyes," happen when opacities suspended in the optically transparent vitreous cavity block and scatter incident light anterior to the retina.[13] Floaters have subtle to frank motility with eye saccades and should be distinguished from small scotomata, which can be identified as stationary.

Most commonly, reported floaters are the result of the condensation of collagen fibrils in the vitreous, casting a shadow on the retina. Floaters may become more visible in a liquefied vitreous, but the sudden onset of markedly evident floaters is usually suggestive of an acute posterior vitreous separation. A single large, central floater is likely to be noticed if there is glial tissue of epipapillary origin adherent to the posterior vitreous cortex. Floaters also may result from cells in the vitreous. If the underlying pathology is vitreous hemorrhage, patients sometimes can identify the reddish or brown coloration of erythrocytes, which, if their origin is fresh, may be perceived to move upwardly, forming "strands." The perception of floaters during vitreous hemorrhage is usually indicative of a small amount of blood. With denser hemorrhage, floaters become homogeneous, and the patient's most prominent symptom is reduced vision. The cause for the vitreous hemorrhage may be any of a long list of retinal diseases, including ischemic disorders that cause neovascularization, retinal and choroidal vascular anomalies, trauma, ocular tumors, infectious and uveitic diseases, and others.

Dark floaters may be seen from retinal pigment epithelial cells that enter the vitreous following an acute retinal tear formation. A large number of inflammatory and infectious ocular disorders can give rise to floaters as a distinct complaint by inducing leukocytic invasion of the vitreous. Neoplastic diseases, such as B-cell ocular lymphoma, leukemia, retinoblastoma, melanoma, and metastatic disease, also can produce vitreous cells and floaters. Vitreous cells in these cases may be malignant in some cases or benign as a result from inflammatory reaction to the neoplasia or from tumor-induced hemorrhage.

Floaters also can indicate vitreous debris, such as amyloid vitreous deposition in systemic amyloidosis, or lenticular material dropped into the vitreous cavity during cataract surgery. Rarely, patients with asteroid hyalosis complain of floaters as well.

What Retinal Diagnoses Are Suggested by Photopsias?

Photopsias are symptoms commonly reported by patients with retinal and nonretinal disease. A photopsia, or "flash," is a false perception of light in the absence of an external source.[14] Patients typically appreciate them best in dim illumination settings or when they close their eyelids. Photopsias may occur sporadically in normal subjects as a brief, small flash of light in the peripheral field. Photopsias also can be part of entoptic phenomena, such as those produced by application of external pressure on the globe, by an abrupt accommodative impulse, or by rapid and sudden movement of the eyes in a very dark environment.[15–17]

Frequent or intense photopsias usually represent disease. Their association with visual or other complaints is further evidence that they are an abnormal event. Photopsias may be part of neurologic illness, such as demyelinating disorders affecting the optic nerve or, if they are binocularly hemianopic, affecting the posterior visual pathways.[18] Additional evidence that they are not retinal in origin is their association with other neurologic symptoms and deficits. In the case of photopsias caused by migraine or epilepsy, they may have intricate shapes and colors and characteristically are not stationary but expand through a hemifield, affecting both eyes.[19]

The most common cause of photopsias in retinal disease is that produced by vitreoretinal traction during or after a posterior vitreous separation. In a significant percentage, this symptom may be indicative of a retinal tear and sometimes a consequent retinal detachment.[20] Typically, these photopsias are noticed in the far peripheral visual field and are stationary. Inflammatory retinochoroidal diseases also give rise to photopsias that may occur in more central locations, monocular or binocular. Of these conditions, photopsias associated with scotomata are most typical in a group of disorders clustered together for their believed common pathophysiology. Included are AZOOR, multiple evanescent white dots syndrome, multifocal choroiditis, acute macular neuroretinopathy, idiopathic blind-spot enlargement syndrome, and others. Photopsias happen, as does birdshot retinochoroidopathy. They are usually bilateral and associated with nyctalopia. During an embolic arterial occlusion, patients frequently report a bright photopsia, sometimes blue, which becomes extinguished as visual loss sets in. Autoimmune retinopathy, which can be part of cancer-associated retinopathy, produces binocular photopsias in the setting of rapidly progressive visual loss. Patients with human immunodeficiency virus retinopathy are known to complain of sporadic bilateral photopsias. Other forms of retinitis may involve photopsias as well.

What Retinal Diagnoses Are Suggested by Metamorphopsia and Diplopia?

Metamorphopsia is the most common abnormality in which retinal disease affects the perception of the spatial pattern that is seen. Patients usually complain of distortion in the shape of things they observe in their central and paracentral visual field. In addition to metamorphopsia, other forms of dysmetropsia include *micropsia*, the illusion that objects are smaller than in reality, and *macropsia*, in which objects appear larger than they really are. Dysmetropsia can be caused by neurologic and psychiatric illness. In these cases, complaints are almost always binocular, may be associated with other neurologic symptoms, and sometimes affect only a hemifield. Dysmetropsia may be part of migraine, epilepsy, and vascular or neoplastic disease affecting the occipitotemporal and parietal cerebral cortex.[21] Micropsia also may be a rare side effect of some medications, such as zolpidem. Causes of nonretinal monocular dysmetropsia include abnormalities in the refractive apparatus of the eye, such as anisometropia and irregular astigmatism.

Despite numerous plausible nonretinal etiologies, metamorphopsia is most often a symptom of retinal disease. Patients suffering from macular disorders that produce an increased or irregular separation between foveal photoreceptors sometimes report retinal micropsia or metamorphopsia.[22] Visual acuity is often reduced as well, and it is frequently a monocular complaint. If binocular, it is usually asymmetric. Retinal diseases that may simultaneously produce both micropsia and metamorphopsia include macular edema of any cause, central serous retinopathy, severe papilledema, macular detachment, and cystoid macular edema, all of which produce an accumulation of subretinal or intraretinal fluid.[23] The chief complaint of

patients with epiretinal macular membranes is usually metamorphopsia, which results from the distortion provoked by traction on the retina and alteration of photoreceptor orientation.[24] Choroidal neovascularization from AMD, presumed ocular histoplasmosis syndrome, pathological myopia, choroidal rupture, multifocal choroiditis, and various other causes often first manifest through complaints of metamorphopsia.

In the case of AMD, mild metamorphopsia sometimes is seen from drusen, in the absence of neovascularization. Macular angioid streaks, birdshot retinochoroidopathy, serpiginous choroiditis, acute retinal pigment epithelitis, cytomegalovirus retinitis, and many other inflammatory retinochoroidal diseases cause metamorphopsia as well as other visual symptoms. Visual distortion has been seen with segmental buckling and also subsequent to any other procedure where reattachment of the macula may result in some misalignment. Orbital and choroidal tumors also may lead to dysmetropsia through compressive distortion of the retinal plane.

Retinal macropsia is an uncommon complaint. It may be the primary misperception when photoreceptors are compacted together by fibrosis and scarring subsequent to acute macular inflammation or other causes. Monocular diplopia, or sometimes "ghost images," can be the symptom described by patients suffering distortion of their foveas by central chorioretinal scars or any of the diseases that can give rise to dysmetropsia. Retinal diplopia must be distinguished from that caused by nonretinal pathology, such as cerebral diplopia and polyopia (usually accompanied by major field defects and other signs of parietal dysfunction), and optical aberrations of the refractive media, including high astigmatism, multirefractile cataracts, oil droplets in the tear film, and excessive tearing.

What Retinal Diagnoses Are Suggested by Dyschromatopsia?

Dyschromatopsia refers to the inability to distinguish some colors and their different tonalities from others. Complete loss of color perception is called *achromatopsia*. Color vision deficiency can be congenital or acquired. Prior military history may be useful information to distinguish an acquired dyschromatopsia because military recruits usually have their color vision checked. Retinal causes of dyschromatopsia must be distinguished from optic nerve and cerebral causes. Patients with optic neuritis, syphilitic optic atrophy, Leber hereditary optic neuropathy, and other optic neuropathies usually have monocular or binocular red– green dyschromatopsia with a mild blue-–yellow loss of discrimination, which occasionally is more prominent than the decreased visual acuity. Cerebral dyschromatopsia and achromatopsia can occur with lesions of various causes in the inferior occipital cortex. They are differentiated from retinal color anomalies in that they often are restricted to one hemifield in both eyes and frequently are accompanied by a superior quadrantanopsia and other neurologic deficits. Other nonretinal causes that should be considered in the differential diagnosis of dyschromatopsia include pseudophakia, hysteria, jaundice, and glaucoma.

If symmetric depression of color vision in both eyes is longstanding, but visual acuity is normal, a hereditary color deficit involving an abnormality of the cone photoreceptor pigments should be suspected. The most common form, usually affecting men, is deuteranomalous hereditary color deficiency. It disturbs red–green sensitivity. Several other varieties exist for each of the visual pigments. Blue-cone monochromatism with only normal blue-cone pigment present in the retina is much more rare and is accompanied by photoaversion, congenital poor visual acuity, and consequent nystagmus. A similar clinical picture is seen with complete congenital achromatopsia or rod monochromatism with no functioning cone pigment. In contrast to congenital retinal causes of dyschromatopsia, blue–yellow deficiency is usually the color vision defect observed in acquired retinal diseases such as retinitis pigmentosa, diabetic retinopathy, and others. Nevertheless, patients with cone dystrophy and macular dystrophies, such as fundus flavimaculatus and Stargardt disease, may report an acquired red–green dyschromatopsia caused by a loss of cone photoreceptors in the macula. X-linked juvenile retinoschisis may have a mild dyschromatopsia, too. In acute retinal necrosis, when optic nerve involvement occurs, an acquired dyschromatopsia is often present.

Many drugs have been associated with dyschromatopsia, including alcohol, amodiaquine, amphetamine, chloramphenicol, chloroquine, digitalis, lanatoside C, ouabain, atropine, ergotamine, sulfacetamide, acetaminophen, marijuana, thiopental, sildenafil, vitamin A, and hashish. Poisons like picric acid, methyl salicylate, aconite, chromic acid, and carbon disulfide also can produce dyschromatopsia.

What Retinal Diagnoses Are Suggested by Nyctalopia?

Nyctalopia, or night blindness, refers to reduced visual sensitivity in conditions of dim illumination. It is a classic symptom of retinitis pigmentosa but is not pathognomonic. Nyctalopia typically is a binocular complaint and usually indicates the presence of an ocular rather than intracranial disorder. Nonretinal causes of nyctalopia that need to be identified include anemia, carbon monoxide poisoning, psychosis, malingering,

optic atrophy, glaucoma, bilateral corneal edema, and dense bilateral cataracts. Probably the most frequent cause of mild nyctalopia is myopia. Patients using topical pilocarpine may suffer from relative nyctalopia, which is produced by inhibited iris dilation and consequent reduction in retinal illumination.

Nyctalopia may be one of the earliest complaints of patients with retinal degenerations, such as rod–cone dystrophies, choroideremia, Goldmann–Favre syndrome, and gyrate atrophy. Patients with these diseases report a progressive deterioration of their night vision over time, in addition to peripheral visual field loss that may or may not start early in life. In progressive cone–rod dystrophies, nyctalopia tends to occur subsequent to a noticeable reduction in visual acuity. Nearly all patients with Refsum syndrome (heredopathia atactica polyneuritiformis), a potentially treatable condition of abnormal lipid metabolism, suffer from nyctalopia as the most common initial ocular symptom, usually occurring before the third decade of life and associated with chronic polyneuritis. Other retinal diseases that can be suggested by progressive nyctalopia include familial drusen, fundus flavimaculatus, birdshot retinochoroidopathy, ocular siderosis, and paraneoplastic retinopathy. Of importance because of its potential response to treatment is prompt recognition of the latter, typified by cancer-associated retinopathy. This condition is characterized by progressive photoreceptor degeneration, with subsequent insidious visual loss over several months in patients who have distant cancer, usually small cell carcinoma of the lung. The presenting symptoms include nyctalopia, diminished visual acuity, visual-field defects, visual obscurations, photopsias, and scotomata. Perhaps the most readily treatable retinal condition resulting in nyctalopia is fundus xerophthalmicus due to vitamin A deficiency, which occurs in malnutritional states, liver dysfunction, and malabsorption disorders.[25,26] Patients who have been treated with panretinal laser photocoagulation occasionally complain of nyctalopia as well; its severity depends on the intensity of treatment.

In contrast to the aforementioned diseases, complaints of stable or nonprogressive nyctalopia are associated with fundus albipunctatus, fleck retina, Oguchi disease, and congenital stationary night blindness.[27] Patients with vitreous opacities, such as hemorrhage, sometimes complain of nyctalopia.

Several drugs have been associated with nyctalopia, including alcohol, amiodarone, carbon dioxide, chloroquine, colloidal silver, deferoxamine, dronabinol, ergonovine, ergotamine, etretinate, hashish, hydroxychloroquine, isotretinoin, lysergide, marijuana, mescaline, methylergonovine, methysergide, oxygen, psilocybin, silver nitrate, silver protein, tetrahydrocannabinol, vinblastine, and vincristine.

What Retinal Diagnoses Are Suggested by Hemeralopia?

Hemeralopia, or "day blindness" consists of decreased visual acuity in the presence of bright light. If the hemeralopia is severe enough, patients will display an avoidance of intensely illuminated settings, a behavior known as *photoaversion*. Hemeralopia and photoaversion must be distinguished from *photophobia*, in which light exposure does not necessarily cause diminished visual sensitivity but rather physical discomfort. Hemeralopia is an uncommon but important symptom. Nonretinal conditions that should be included in the differential diagnosis include posterior subcapsular and nuclear cataracts, Adie pupil, albinism, and aniridia.

Retinal diseases that may induce patients to report hemeralopia include progressive cone degenerations, hereditary X-linked retinoschisis, choroideremia, blue-cone monochromatism, and rod monochromatism (hereditary total color blindness). Hemeralopia may be present after partial occlusion of the central retinal artery and other retinal ischemic disorders and from ocular siderosis, consequent to retinal toxicity from a retained iron intraocular foreign body. Timely recognition of the latter may prevent progressive loss of retinal function. Children with Leber amaurosis are usually blind early in life and may complain of both severe night blindness and occasionally photoaversion.[28,29]

What Retinal Diagnoses Are Suggested by Ocular Pain and Photophobia?

Ocular pain and photophobia are two common symptoms encountered in ophthalmology. Because the retina itself is devoid of pain sensitivity, disorders of this tissue can produce eye nociception only when other ocular structures become affected. Pain receptors are found in the choroid, ciliary body and iris, sclera and optic nerve sheath, cornea, extraocular muscles, and conjunctiva. Ocular pain may be reported when inflammation affects the eye adnexa and orbit and by neurologic conditions affecting the sensory systems. Pain originating from pathology in other facial structures may be referred to the eye as well.

Photophobia and eye pain are important elements in the history that lead us to suspect a group of selected retinal and uveal illnesses. Whereas most forms of anterior and posterior uveitis carry pain and photophobia, often accompanied by floaters, intermediate uveitis can be differentiated usually by a lack of pain. Posterior uveitis that causes pain and retinal involvement includes Behçet syndrome, Vogt–Koyanagi–Harada disease, posterior scleritis, sarcoid and syphilitic uveitis, among others. Retinal vasculitis and ocular pain can be associated with any connective tis-

sue disease, such as giant cell arteritis, systemic lupus erythematosus, dermatomyositis, Wegener granulomatosis, polyarteritis nodosa, and rheumatoid arthritis. Pain and photophobia, and their modes of progression, are probably the most crucial symptoms when considering the diagnosis of bacterial or fungal endophthalmitis.[30] Acute retinal necrosis frequently is accompanied by eye pain. Vascular disorders affecting the retina are usually not painful except in unusual circumstances, such as hypoperfusion retinopathy and anterior segment ischemia or combined central retinal artery and vein occlusion. More often, development of pain in the setting of retinal ischemia leads us to suspect neovascular glaucoma and consequent high intraocular pressure. Other causes of glaucoma-mediated pain that involve the retina are choroidal metastasis or melanomas interfering with aqueous drainage. These diseases also can cause pain independent of eye pressure when they impinge directly on a long posterior ciliary nerve. The contrary abnormality of intraocular pressure, hypotony, frequently results in soreness of the eye and retinal malfunction. Ocular pain is also an important symptom to follow in postsurgical retina patients because it may signal the development of suprachoroidal hemorrhage, orbital cellulitis, or endophthalmitis.[31]

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3

How to Use the Instruments for Examination of the Posterior Segment

ALLEN C. HO

Examination of the posterior segment of the eye is a technically demanding and challenging task. To examine these structures—the vitreous, retina, subretinal layers, pars plana, and optic nerve—one must combine excellent observational skills, clinical experience, and a facility with the instruments and lenses used to illuminate and magnify the posterior structures of the eye. The basic principle of ophthalmoscopy is focusing light rays from the patient's fundus onto the examiner's fundus (Fig. 3–1). This chapter reviews the various methods of ophthalmoscopy as well as the many types of tools used to examine the posterior ocular structures. Diagnostic imaging techniques of the posterior segment of the eye, such as ultrasonography, optical coherence tomography, and angiography, are discussed in Chapter 4.

Examination of the entire posterior segment requires pupillary dilation. Dilation of the pupil permits adequate illumination of the vitreous and retina and allows one to examine the peripheral retina. Standard pupillary dilating drops are 1% tropicamide (Mydriacyl) and 2.5% Neo-Synephrine (or Mydfrin) drops, which are instilled into an eye anesthetized with topical proparacaine hydrochloride 0.5% (Ophthetic) (Table 3–1). Dilation is generally achieved within 15 or 20 minutes and is often more rapid in eyes with light-colored irides. Darker irides may require a second set of dilating drops.

Methods of Ophthalmoscopy

There are three main methods of ophthalmoscopy: direct ophthalmoscopy, indirect ophthalmoscopy, and slit-lamp contact or noncontact lens biomicroscopic ophthalmoscopy.

What Are the Advantages of Direct Ophthalmoscopy?

Historically, direct ophthalmoscopy was performed using candlelight. The examiner viewed the fundus monocularly through a small peephole. Purkinje first described the technique of ophthalmoscopy in 1823. Subsequently, in 1850, Von Helmholtz first introduced the direct ophthalmoscope. Since that time, illuminating sources for direct ophthalmoscopy have evolved from candlelight to gaslight to external and finally built-in electric light.

Direct ophthalmoscopy is the simplest way to examine the fundus and is the method most commonly used by nonophthalmologists. It is the least technically demanding form of ophthalmoscopy, although it does require practice. Modern direct ophthalmoscopes are often portable and afford various levels of illumination along with green, red, blue, or other filters. The light source illuminates the patient's fundus through the pupillary axis, and an upright and virtual image of the retina is produced with approximately 15 times magnification for the emmetropic eye. If a patient is myopic, the eye has effective plus power and the ophthalmoscope requires a minus neutralizing lens. This resultant lens system is a Galilean telescope that thus increases the magnification of fundus details. The opposite is true for hyperopic eyes whereby the size of the image of the fundus structures may be reduced. The observer creates a crisp image by using neutralizing lenses that are present on the headpiece of the instrument.

Although the direct ophthalmoscope is relatively inexpensive and portable and can be used without pupillary dilation, indirect and slit-lamp biomicroscopic ophthalmoscopy are generally favored by oph-

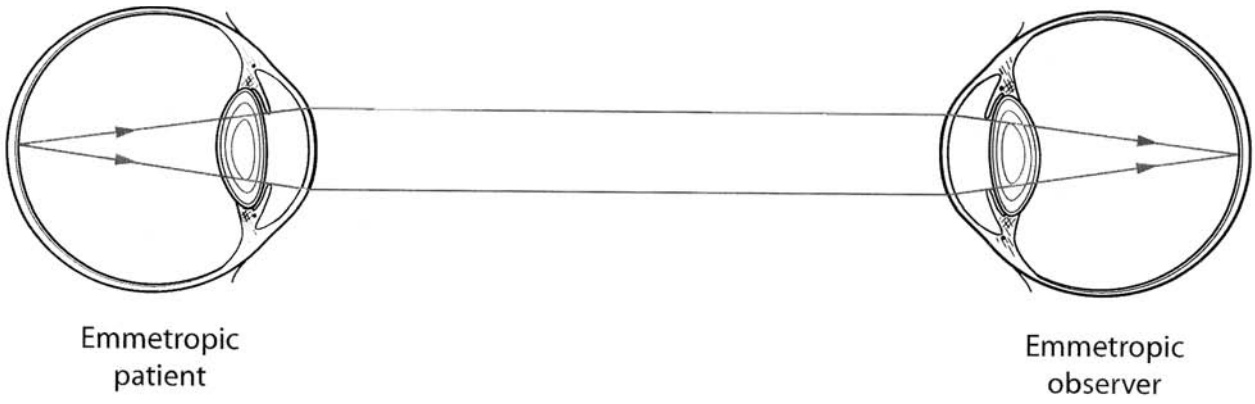

FIGURE 3–1. Conjugate retinal points are shown with an emmetropic observer and emmetropic patient, but inadequate illumination precludes visualization of posterior segment detail.

thalmologists because they offer a wider field of view and superior resolution of posterior segment details.

What Are the Limitations of Direct Ophthalmoscopy?

One major limitation of direct ophthalmoscopy is that only a small field of view is produced. It is important to position the direct ophthalmoscope very close to the patient's eye to maximize the limited field of view. It is analogous to peering into a room through a keyhole: The closer one gets to the aperture or keyhole, the wider the field of view. As in most forms of ophthalmoscopy, it is helpful to have the patient use the opposite eye to fixate on an object to reduce wandering-eye motion. The peripheral retina is not well visualized because of the restricted field of view. Another limitation of direct ophthalmoscopy is that only a monocular image is produced. In contrast, indirect ophthalmoscopy and slit-lamp biomicroscopic ophthalmoscopy permit stereoscopic viewing of the retina, which is very important in the examination of the retina and subretinal layers. Finally, significant

TABLE 3–1. Mydriatics and Cycloplegics

Generic Name	*Trade Names*	*Concentration (%)*	*Onset/Duration Action*
Phenylephrine HCl	AK-Dilate	Soln, 2.5%, 10%	30–60 min/3–5 h
	Mydfrin	Soln, 2.5%	
	Neo-Synephrine	Soln, 2.5%, 10%	
	Generic	Soln, 2.5%, 10%	
Atropine sulfate	Atropisol	Soln, 1%	45–120 min/7–14 d
	Atropine-Care	Soln, 1%	
	Isopto Atropine	Soln, 0.5%, 1%	
	Generic	Soln, 1%	
		Ointment, 1%	
Cyclopentolate HCl	AK-Pentolate	Soln, 1%	30–60 min/ 6–24 h
	Cyclogyl	Soln, 0.5%, 1%, 2%	
	Pentolair	Soln, 1%	
	Generic	Soln, 1%	
Homatropine hydrobromide	Isopto Homatropine	Soln, 2%, 5%	30–60 min/3 d
	Generic	Soln, 2%, 5%	
Scopolamine Hydrobromide	Isopto Hyoscine	Soln, 0.25%	30–60 min/4–7 d
Tropicamide	Mydriacyl	Soln, 0.5%, 1%	20–40 min/4–6 h
	AK-Tropicacyl	Soln, 0.5%, 1%	
	Generic	Soln, 0.5%, 1%	

Soln, solution.

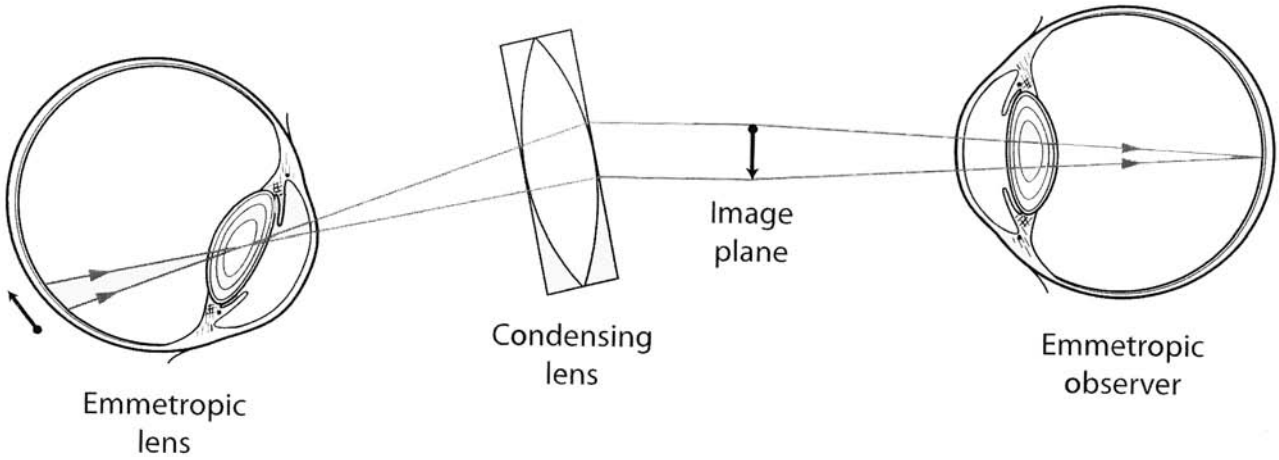

FIGURE 3–2. Indirect ophthalmoscopy is performed with a handheld condensing lens, which produces a real and inverted 30-degree image on the observer's side of the condensing lens.

media opacities, such as cataract, will limit resolution of the image with this instrument.

What Are the Unique Aspects of Indirect Ophthalmoscopy?

Schepens first introduced his binocular indirect ophthalmoscope in 1947, and since then the binocular indirect ophthalmoscope has become a standard ophthalmic instrument for examining the posterior structures of the eye.

The binocular indirect ophthalmoscope is portable, particularly with a mobile energy source, although it is not as small as the direct ophthalmoscope. Traditionally, it has comprised an illuminating headpiece and modified oculars, although recently more portable eyeglass-style indirect ophthalmoscopes have become available. Examination of posterior segment structures requires a handheld condensing lens, most commonly 20 diopters in power, placed in front of the dilated eye (Fig. 3–2). The traditional headpiece incorporates an illuminating light source as well as condensing optics, which effectively narrow the interpupillary distance, thereby affording binocular images of the posterior segment (Fig. 3–3). This also permits stereoscopic viewing of the fundus through a dilated pupil with a typical field of view of 30 degrees or more, depending on the type of condensing lens placed in front of the eye.

Indirect ophthalmoscopy adheres to Gullstrand's principle, whereby illuminating and viewing beams must be totally separated through the cornea, pupillary aperture, and lens (to avoid reflections) but must coincide on the retina to permit viewing. The viewing

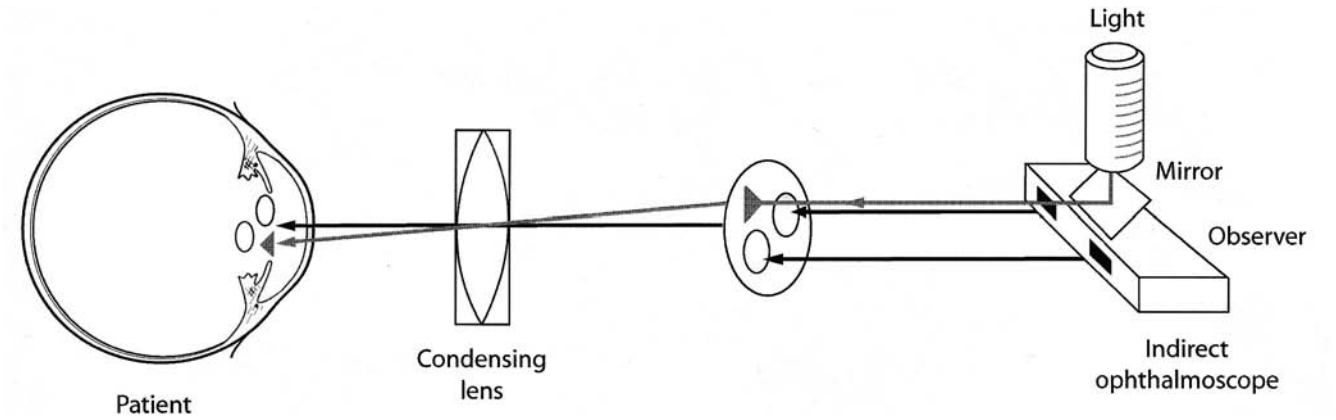

FIGURE 3–3. A binocular indirect ophthalmoscope effectively narrows the observer's interpupillary distance, thus permitting placement of the illuminating and viewing beams within the patient's pupillary aperture.

oculars of an indirect ophthalmoscope reduce the effective interpupillary distance, thereby permitting illuminating light and binocular stereoscopic views through a dilated pupil. An indirect ophthalmoscope permits adjustments in the position of the illuminating light beam as well as the effective interpupillary distance.

Further narrowing of the effective interpupillary distance on the headpiece of an indirect ophthalmoscope allows the examiner to perform funduscopy through a smaller pupil; however, the proximity of the illuminating and viewing beams increases distracting reflections. Increasing the effective interpupillary distance improves stereopsis, whereas decreasing this distance has the opposite effect. A pinhole light diaphragm can produce a narrower beam of light, which can reduce reflections.

What Is the Most Effective Way to Use the Indirect Ophthalmoscope?

Neutralization of a patient's refractive error is achieved by moving the condensing lens toward or away from the examined eye or accommodation by the examiner's eyes. The indirect ophthalmoscope produces a real inverted image for the observer, which can be disorienting for the novice because the field of view is upside down and backward. To use this instrument properly requires considerable practice and experience. Simulating model eyes are available to practice the examining adjustments required to use the indirect ophthalmoscope properly.

To use the indirect ophthalmoscope properly, the headpiece and the eyepieces first must be adjusted. The knob that adjusts the location of the illumination should be set such that the light fills the superior part of the field of view. The examiner checks the alignment of each ocular by closing one eye at a time. The condensing lens should be held 2 to 3 inches from the patient's eye, with its most convex side facing the examiner (white line on the lens toward the patient) between the thumb and the first finger. The examiner's other hand may be used to hold open the patient's eyelids because the intense illuminating light elicits a natural response to close the eyelids.

The observer then systematically examines the retinal periphery and finally the posterior pole. The examiner orients his or her eyes with the condensing lens and the patient's retina in each field of gaze such that an imaginary straight line could be placed between the point midway between the eyepieces, center of the condensing lens, center of the pupil, and area of the retina to be examined. This alignment then allows one to view the retinal area of interest. For example, to examine the superior nasal quadrant of the right eye, the physician first should tell the patient to look up and to the left. The observer then should orient his or her eyes with the lens and the patient's retina to obtain a clear image of this region by moving the condensing lens slowly toward or away from the patient's eye to allow the entire retinal image to fill the lens. The examiner also may change the distance between the headpiece and the condensing lens to achieve the same effect. Because the bright illuminating light is disorienting, it may be helpful to give the patient an object of regard to look at with the eye not being examined, even the patient's own outstretched hand, to help the patient maintain the direction of gaze.

A major advantage of the binocular indirect ophthalmoscope is that it allows one to view the peripheral retina. To increase the field of view of the peripheral retina, it is often helpful to pivot the base of the condensing lens slightly in the direction of the patient's gaze as well as to turn one's head so that the axis between the examiner's eyes is aligned with the patient's direction of gaze. Turning the head results in the image being monocular and not stereoscopic, but it permits illumination and viewing of peripheral structures (Fig. 3–4). In this way, one can often observe the ora serrata without further manipulation of the well-dilated eye. If the peripheral retina is not visualized using this lens and head-tilt technique, one can perform scleral depression to evaluate completely the peripheral retina.

What Are the Key Points to Know for Scleral Depression?

Traditionally, scleral depression is performed using a handheld metal instrument with a dilated end. The scleral depressor indents the eye to bring the peripheral retina into view while performing indirect ophthalmoscopy. Other objects, such as cotton-tipped applicators or wire paper clips, are also often used as scleral depressors. It is helpful to apply topical anesthesia, although this is not essential. A depressor may be placed on the eyelid to indent the globe or may be used directly on the surface of the globe when topical anesthesia is administered. The external aspect of the globe corresponding to the peripheral retinal area of interest is gently depressed inward by using the scleral depressor. Excessive pressure is not necessary and should be avoided to avoid patient discomfort. The examiner should move the depressor around the eye for 360 degrees and observe each area using indirect ophthalmoscopy. This is done with the patient in the supine position, and the examiner often moves around the patient to perform ophthalmoscopy with

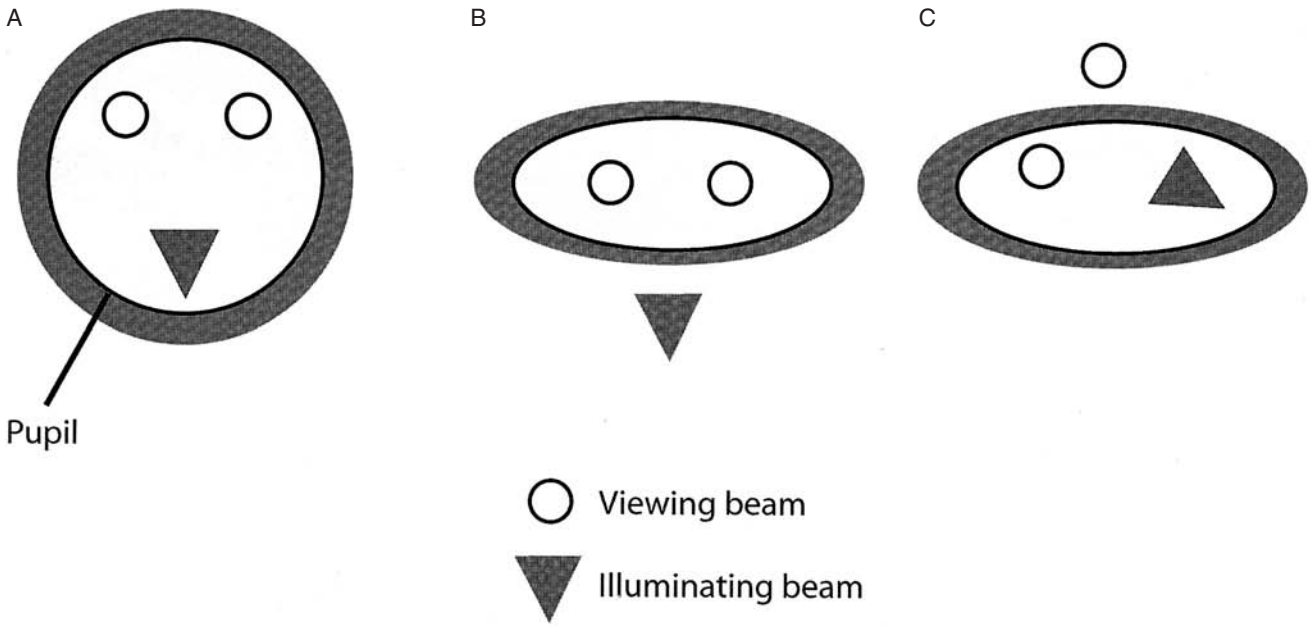

FIGURE 3–4. The principal of head tilt to examine the fundus through an elliptical pupil. An effectively elliptical pupil is created when the patient fixates in extreme gaze to permit visualization of peripheral retina. (A). Both viewing beams and illuminating beam are well accommodated to provide a view of the posterior fundus with the patient looking directly at the observer. (B). The examiner has not adopted a head tilt to accommodate the elliptical pupil; thus, there is no view because the illuminating beam is blocked by the iris. (C). The examiner has tilted his or her head, which permits entry of the illuminating beam and only one viewing beam (nonstereoscopic image).

scleral depression. Scleral depression requires considerable skill and practice.

Scleral depression is a dynamic process, and movement of the scleral depressor underneath a lesion of interest is often helpful in determining, for example, whether a retinal lesion is truly a retinal break or not. Dynamic scleral depression beneath a true retinal tear or hole will elevate the edges of the retinal defect. Dynamic scleral depression also allows the process to be more efficient because sweeps of peripheral retina with the scleral depressor allow the examiner to cover areas more efficiently than individual placement and adjustment of the scleral depressor tip.

What is the Correct Lens Choice for Indirect Ophthalmoscopy?

There are different condensing lenses that can be used with the indirect ophthalmoscope. Although the 20-diopter condensing lens is the most common, other lenses may be used to broaden the field of view, to examine through a small pupil, or to examine the posterior segment when there is intraocular gas. For difficult views, for example, because of a small pupil or intraocular gas, a 28- or 30-diopter lens can be used, but the compromise will be a loss of magnification. The 28- or 30-diopter lenses also increase the field of view. Examination of the posterior segment in the presence of intraocular gas is difficult because of increased reflections at different interfaces of fluid, gas, and tissue. The 28- or 30-diopter lenses can be helpful in this situation. It is also helpful to increase the distance between the patient's eye and the condensing lens as well as the distance between the condensing lens and the examiner's eyes when examining an eye containing intraocular gas.

What Are the Best Color Choices for Ophthalmoscopy?

Finally, some ophthalmoscopes as well as slit-lamps have colored filters that can be useful in certain circumstances. A red filter absorbs red light, and therefore red objects appear black. This can be helpful when examining retinal vascular abnormalities and retinal hemorrhages. Nerve-fiber layer loss and retinal thickening are also highlighted by red-free light because a greater proportion of shorter visible wave-

lengths is scattered by superficial retinal layers. Blue filters highlight fluorescein during fluorescein angiography and can enhance autofluorescence of optic nerve head drusen.

How Does the Surgeon Approach the Retinal Drawing?

Many retinal surgeons have been trained to create formal retinal drawings of the fundus, although this practice is waning with improved diagnostic imaging techniques and fundus photography. The process of a retinal drawing can be a powerful way to improve observational skills of retinal lesions. Standard retinal drawing paper is used, and various lesions are drawn with colored pencils in relation to the optic nerve, retinal vessels, and the three-dimensional boundaries of the fundus depicted on the retinal drawing paper. Some observers place the retinal drawing paper upside down (12 o'clock position toward the feet) on the supine patient's chest so that the drawing can represent what is visualized in the indirect ophthalmoscopic condensing lens and can be sketched during the examination process. Standard left and right retinal drawings are marked by meridional clock hours and concentric circles. The inner circle marks the equator of the globe, and the two outermost circles delimit the pars plana. The middle circle thus represents the ora serrata. Retinal drawings on two-dimensional paper are hampered by problems similar to those that cartographers encounter; lesions in the retinal periphery are larger as a result of peripheral cartesian distortion.

Colors on a conventional retinal drawing are standardized, with red representing attached retina or retinal hemorrhages, blue representing detached retina or subretinal fluid, green representing vitreous opacities, brown representing pigmented lesions or choroidal elevations, and yellow representing lipid exudation or fibrovascular scars.

How Should Retinal Slit-Lamp Biomicroscopic Ophthalmoscopy Be Used in Practice?

Retinal slit-lamp biomicroscopic ophthalmoscopy affords the high magnification and illumination necessary to evaluate in detail the vitreous, optic nerve, and macula as well as small peripheral retinal lesions, such as retinal tears. The slit lamp is used with either a noncontact- or a contact-examining lens in this technique. The image is highly magnified and stereoscopic. The biomicroscopic capabilities of the slit lamp can be applied to examination of preretinal, intraretinal, and subretinal lesions. Furthermore, a detailed examination of the vitreous can be performed to look for features such as pigmented cells or inflammatory cells in the anterior or posterior vitreous. The status of the posterior vitreous attachment also can be assessed, although various cleavage planes within the vitreous body itself can mimic a true posterior vitreous detachment.

What Is the Best Use for Noncontact Lens Slit-Lamp Biomicroscopy?

A noncontact lens biomicroscopic evaluation of the retina can be performed with a Hruby lens, which is present on many slit-lamp ophthalmoscopes. This lens is a planoconcave lens of high negative power that produces an upright vertical image. The lens is swung into place on the slit-lamp stage, and a magnified image of vitreous, retina, or optic nerve can be obtained. A focused image is achieved by manipulating a lever attached to the lens, which moves the lens toward or away from the patient's eye. This lens is useful for studying the optic nerve in detail and also for examining the posterior vitreous for inflammatory cells. To observe the posterior vitreous, it is helpful to narrow the slit-lamp light beam as well as to turn the incident light slightly off axis to retroilluminate the posterior vitreous cells, which then will appear black against the illuminated fundus background.

Noncontact lens biomicroscopic evaluation is performed more commonly using aspherical 60-diopter, 78-diopter, and 90-diopter lenses (Fig. 3–5). These noncontact lenses produce a real inverted, high-quality image for the examiner. The ophthalmologist holds the lens in one hand and places it a few centimeters in front of the patient's eye. The physician also may hold open the patient's eyelids with the same hand. The slit lamp then is used to create a vertical beam to illuminate and examine the retina. A 90-diopter lens produces the widest field of view at the expense of magnification. A 78-diopter lens affords a nice compromise between the field of view and the magnification. The 60-diopter lens provides the greatest magnification. These lenses often are used to examine the optic nerve and posterior pole. The noncontact lens technique is especially useful when done before angiography because these lenses do not disturb the cornea. When using handheld lenses in conjunction with the slit lamp, the examiner often encounters distracting light reflections. It is useful to angle the incident light of the slit lamp slightly off center through the vertical axis or the horizontal axis of the slit-lamp apparatus so that

FIGURE 3–5. For indirect ophthalmoscopy (back), 28- and 20-diopter condensing lenses; for noncontact biomicroscopy (front), 90-diopter and 78-diopter lenses.

reflected light passes obliquely rather than directly back to the examiner.

When and How Should Contact Lens Slit-Lamp Biomicroscopy Be Used?

The gold standard for examining the posterior or peripheral retina is contact lens slit-lamp biomicroscopic ophthalmoscopy. Because a contact lens is used, topical anesthesia and a contact lens coupling gel or fluid are required. The coupling gel is typically a clear, viscous liquid, such as methylcellulose (Goniosol), or a less viscous solution, such as Celluvisc. Saline may be used and is advisable if high-quality fundus photography or angiography is subsequently planned. The lenses are applied to an anesthetized eye by having the patient first look up with placement of the contact lens and coupling agent on the surface of the eye centered on the inferior limbus. The patient then directs his or her gaze toward the examiner to center the lens on the cornea, thus providing a view of the posterior structures of the eye centered on the posterior pole.

Several different types of contact lenses are suitable for viewing the retina. The Goldmann three-mirror lens comprises a central viewing area for the posterior retina surrounded by three mirrors of different sizes and angle orientation to view specific parts of the eye. The smallest thumbnail-shaped mirror allows visualization of the anterior chamber structures as well as the far retinal periphery. Because this is a mirror, the location of the area that is examined is 180 degrees opposite from the position of the mirror. The middle-sized mirror has a different angle of orientation and allows visualization of the retina anterior to the equator. The larger mirror is used to study the retina between the equator and the macula. A Goldmann lens can be rotated 360 degrees so that all areas of the retina and the anterior chamber can be observed. It is helpful to understand that if the patient looks toward a mirror, the observer will see a more posterior region of the retina. A high-quality, magnified view of the peripheral retina can be obtained by using the Goldmann three-mirror lens combined with scleral depression. The technique is challenging, and many retina specialists prefer depression of peripheral lesions with indirect ophthalmoscopy.

Specific macular lenses also have been designed that feature flanges on the ocular contact surface that are compressed against the globe by the patient's eyelids. This type of design makes it harder for the patient to dislodge a contact lens. These specialized macular lenses are placed on the eye in a fashion similar to that used with the Goldmann lens and also provide a high-quality, magnified stereoscopic macular view but do not allow the clinician to observe peripheral retina.

Another useful contact lens for fundus biomicroscopy is the panfunduscopic or Rodenstock lens. This lens comprises a meniscus lens and a spherical lens. The image produced is real, inverted, and minified. This lens is especially useful for obtaining a wide-angle view of the retina, particularly in eyes with poor pupillary dilation. The disadvantage of this lens is the small image size and lower resolution views of the retinal periphery. It is, however, very useful for peripheral or panretinal laser photocoagulation. There

are other panfunduscopic lenses available, such as the Mainster lens, which produces less magnification than the panfunduscopic lens with only a slight reduced field of view. More peripheral areas of the retina can be viewed with the panfunduscopic lens by tilting the lens slightly and having the patient direct his gaze slightly away from the area of interest.

Summary

Clinical examination of the posterior structures of the eye requires specialized equipment, a facility with this equipment, and active observational processes. Direct ophthalmoscopy permits a limited field of view but is generally the most easily mastered method of examination. Indirect ophthalmoscopy is more challenging but affords the most efficient views of the peripheral retina. Slit-lamp contact or noncontact lens ophthalmoscopy provides the highest resolution of the posterior structures of the eye.

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4

Clinical Examination of the Ocular Fundus

RICHARD F. SPAIDE AND SILVANA NEGRAO

Many kinds of diseases can affect the posterior segment of the eyes. To make a correct diagnosis and establish an adequate treatment, one must combine a proper history of the patient's symptoms with a detailed ocular examination. Determination of the nature and duration of the visual symptoms, including past ocular and systemic history, should be the first step toward the correct diagnosis. Ophthalmic examination in children, in particular, requires a special combination of patience and energy because of the limited communication and cooperation possible with this group of patients.

Following the history, we proceed with measurement of the visual acuity, slit-lamp biomicroscopic examination, and the ophthalmoscopy, which always should be done with the patient's pupils dilated to allow a wider view of the periphery of the ocular fundus. Numerous ophthalmoscopically visible features of the vitreous, for example, are anomalies attributable either to structural changes, such as the floaters of syneresis and the ringlike form associated with posterior vitreous detachment, or to invasive elements, such as blood, white blood cell masses, or fibrovascular tissues. The retina is also normally transparent, allowing the choroid and retinal pigment epithelium (RPE) to be visible. With injury, the retina may become opaque, obscuring the retinal vessels and underlying details. There are also complementary imaging diagnostic procedures, such as fluorescein (FA) and indocyanine green (ICG) angiography, ultrasonography, optical coherence tomography (OCT), and electrophysiologic testing, that can be used as adjunct methods of examining the posterior fundus and retinal function.

Slit-Lamp Biomicroscopy of the Ocular Fundus

This technique uses an essential instrument for fundus examination, particularly when a high degree of magnification is desired. It is used in conjunction with a handheld lens or a diagnostic contact lens and provides a high-quality magnified stereoscopic image of the fundus. It is also useful in determining whether the location of a lesion is *preretinal* (neovascularization, vitreous hemorrhage), *intraretinal* (cotton-wool exudative spots, flame-shaped hemorrhages), or *subretinal* (choroidal neovascularization, drusen); in detecting cystoid macular edema; and in diagnosing clinically significant macular thickening.

This technique provides optical sections of the vitreous body. If an elevation or depression of a chorioretinal lesion is present, the slit beam on the retina will appear curved rather than straight. In some cases, when there is very little subretinal fluid, illumination of the retinal vessels with the slit beam produces shadows of the vessels at the level of the RPE, indicating the presence of retinal elevation. If a slit beam of the biomicroscope is placed across an elevated retinal lesion, the behavior of the scattered light also provides important diagnostic clues. Often the borders of a small serous detachment or RPE detachment can be made to glow by positioning the slit beam across the elevation, making the lesion easier to demarcate. This technique is useful in evaluating the posterior pole for the presence of a macular hole or for detecting cystic spaces within the retina.

Noncontact lens slit-lamp biomicroscopy more often is performed with aspheric 60-, 78-, or 90-diopter lenses. They all produce a real, inverted image for the examiner. The lens is held in front of the patient's eye, and the slit lamp is used to produce a vertical beam to illuminate the retina. The higher the power of the lens, the less the magnification. This technique is good for the study of the vitreous, retina posterior to the equator, and optic nerve. It has the advantage of not disturbing the cornea, and so it can be used before an angiogram is performed. The difficulty

with this method is that the examiner does not have control over the movement of the patient's eye; and, as with other forms of indirect ophthalmoscopy, the image is inverted.[1]

Contact lens slit-lamp biomicroscopy should be performed with the patient under topical anesthesia and a coupling gel, which usually is methylcellulose. To place the lens, the patient should look up while the examiner puts the lens in the inferior limbus. Then the patient directs his or her gaze toward the examiner to center the lens on the cornea, thus providing a view of the posterior pole. The Goldmann three-mirror lens is the most common contact lens. Its three mirrors are of different size and angle orientation. The smaller the mirror, the more peripheral image it produces. During the examination, the lens can be rotated 360 degrees so that all areas of the retina and anterior chamber can be evaluated.[2]

Contact lens biomicroscopy is needed to differentiate a macular cyst from a macular hole. The "slit-beam sign" described by Watzke-Allen[3] and later modified by Margherio and colleagues[4] is a reliable test. Using a contact lens, a slit-beam light slightly narrower than the lesion is focused on the retina, and the patient is asked to describe what he or she sees. If a complete interruption or an interruption greater than one half the width of the slit is seen, the patient is considered to have a full-thickness hole. No interruption or distortion in the slit correlates best with a pseudohole, or lamellar hole. Panfunduscopic lenses, such as the Rodenstock lens, Volk Quadraspheric, and Mainster lens, are very useful for examination, panretinal photocoagulation, and angiography.

Ophthalmoscopy

Helmholtz introduced the direct ophthalmoscope in 1850, although prior descriptions of primitive tools existed before then; since that time, light sources have evolved from candle to electric light.[5] The direct ophthalmoscope is the simplest and most common way to examine the fundus, and it is widely used by medical students and nonophthalmologists.

The basic principle of this method consists of illuminating the patient's fundus and looking at the patient's retina. The difficulty of this method is to align optically both axes of illumination and observation. Some other disadvantages of this method include the position of the ophthalmoscope close to the patient's eye, the small field of view, restricted visualization of the periphery, significant media opacities that greater limit the resolution of the images, and finally the monocular image produced. On the other hand, it is a relatively inexpensive and portable device that can be used without pupillary dilation. Magnification of the patient's fundus can be calculated by considering the dioptric power of the eye, which is about 60 diopters, acting as a magnifier for the retina. This magnifier will be in focus when held one sixtieth of a meter from the retina. By convention, the usual viewing distance is considered to be one fourth of a meter. The ratio of these two fractions expresses the magnification offered by the direct ophthalmoscope: 15 times.

Schepens first introduced the binocular indirect ophthalmoscope in 1947, and since that time, it has been the standard ophthalmic instrument for examining the posterior structures of the eye, supplanting the limitations of the direct ophthalmoscope.[5] It consists of an illuminating headpiece with modified oculars and an energy source. It is used with a condensing lens, and the field of view (usually 45 degrees) depends on the pupillary dilation and dioptric power of the viewing lens. This method permits stereopsis, examination of the entire retinal periphery (with scleral depression in some cases), and examination through media opacities usually not seen with direct ophthalmoscopy. The principal disadvantage of this method is the learning process necessary to understand the real inverted image produced by this method of examination.

To obtain good images, we must adjust the headpiece and eyepieces first. To align each ocular, one must close one eye at a time, followed by setting the illumination in a way that the light fills the superior part of the field of view, thereby avoiding the glare produced by the returning light from the ocular fundus. The patient's pupils should be dilated, and the condensing lens should be held 2 to 3 inches from the patient's eye, with its most convex side facing the examiner between the thumb and the first finger. The right hand is free to hold the patient's eyelids and complete the retinal drawings. The examiner moves the lens slightly toward or away from the eye until the image of the fundus completely fills the lens. The magnification obtained with indirect ophthalmoscopy can be calculated by dividing the dioptric power of the eye by the dioptric power of the viewing lens. For a typical eye and a 20-diopter lens, the magnification is $60/20$ or -3 times. The negative sign implies that the image is inverted.

The examiner should have a systematic routine to cover all quadrants of the fundus, beginning with the periphery and ending with the posterior pole. Because of Bell's phenomenon, the patient initially will look up when first confronted with a bright light; so the examiner should start looking at the superior quadrants first, followed by a clockwise examination of the periphery, and ending with examination of the macula. The patient should keep both eyes opened during the examination. If the patient does not re-

spond to verbal direction, the examiner should ask the patient to look at the examiner's thumb with the fellow eye while being examined.

Additional information can be obtained by determining how light diffuses through objects in the fundus using various ophthalmoscopic techniques. This is especially true for fluid-filled structures, such as pigment epithelial detachments. It is also possible to use retroillumination, particularly when using slit-lamp biomicroscopy, to view certain structures in the vitreous. This is an important way to look for inflammatory cells in the posterior vitreous. The plane of focus is shifted a few millimeters or so in front of the retina. Using light reflected from the retina to retroilluminate the vitreous, inflammatory cells are seen as small, dark dots. These same dots are light tan when viewed directly. When using retroillumination, it is easier to find and see a greater number of cells than with direct illumination.

In diabetic patients, sometimes microaneurysms are difficult to differentiate ophthalmoscopically from dot hemorrhages. The first are seen as tiny, well-defined lesions, whereas the dot hemorrhages have fuzzier borders and are deeper in the retina. FA may help by showing microaneurysms as hyperfluorescent dots; hemorrhages, on the other hand, are hypofluorescent lesions.

It is more difficult to distinguish neovascularization from an intraretinal microvascular abnormality (IRMA). This is particularly true if an IRMA is extensive and neovascularization has not yet developed wheel-like networks or other typical characteristics. IRMAs are shunt vessels between an artery and a vein within the retina, whereas neovascularization forms tufts of vessels, usually from veins, with a tendency to grow in an anteroposterior direction using the vitreous as a scaffold. In these cases, biomicroscopy with a contact lens provides the best way to recognize these features.

TABLE 4–1. Fundus Color Code

Color	*Fundus Characteristic*
Red	Attached retina, retinal arterioles, choroidal vessels, intraretinal hemorrhages, inner portion of retinal breaks (holes or tears). The center of the macula.
Blue	Detached retina, retinal veins, outlines of retinal breaks.
Green	Vitreous opacities, vitreous hemorrhages, preretinal hemorrhages, intraocular foreign bodies, vitreous membranes.
Brown	Uveal tissue, melanomas, border of ora serrata
Black	Pigment clumping in or under the retina, demarcation lines, pigmented scars, lattice degeneration.

Scleral depression can be used to bring the peripheral retina into view in cases where the ophthalmoscopy alone is insufficient or to study the vitreous traction at the vitreous base. It can be done with a metal depressor or with a cotton-tipped applicator. To move the depression circumferentially, the depressor is moved in the opposite direction of the image on the lens because the image is inverted.

The retinal map is the summary of the retinal examination, and the location and different kinds of lesions are standardized by colors (Table 4–1). To draw the lesions, some examiners place the retinal drawing paper on the supine patient's chest, with the 12 o'clock position toward the feet of the patient. In that way, the drawing represents what is visualized in the condensing lens; at the end, all that must be done is to turn the paper upside down to have the actual drawing. The second outer line on the paper represents the ora serrata, and the equator corresponds to the next innermost ring. The posterior pole is the area defined by an imaginary circle, formed by the radial clock hour marks, and the optic disc is the small circle offset from the center.

Visual Function Diagnostic Tests

The nature of the visual dysfunction may be specific or unique in some inherited dystrophies. Therefore, judicious use of visual function tests might determine both the nature and the site of visual dysfunction and confirm or rule out a diagnosis. These tests measure the visual process at different levels and, combined, offer a noninvasive anatomic dissection of retinal function and dysfunction.

These tests can be divided into two groups: psychophysical tests and electrophysiologic tests. *Psychophysical tests* are subjective requiring the participation and cooperation of the patient. They include visual acuity, contrast sensitivity, color vision, visual field, dark adaptation, and retinal sensitivity profiles. The first three tests measure central function exclusively, whereas the last three measure central and peripheral function.

The *electrophysiologic tests* are objective and do not require active participation of the patient. Two electrophysiologic tests, which measure general retinal function, are the electroretinogram (ERG) and electrooculogram (EOG). Two other objective tests that measure central function are the focal ERG, an exclusive test of outer retina, and the visually evoked cortical potential response (VER), a measure of central vision from the receptor back through the optic nerve to the visual cortex. VER can be done in infants as young as 6 months of age.[6] Amblyopia or damage in the visual pathways can be determined by comparing the responses from each eye.

The characteristics of an ERG that identify its relative normality are its waveform and its amplitude. Focal abnormalities of the retina reduce the amplitude of the ERG but have little effect on its waveform if the involved area is electrically silent, as in retinal detachment. Diseases that involve the inner retina, such as diabetic retinopathy, result in a loss of oscillatory potentials and the B-wave with relative preservation of the A-wave. Diseases involving receptors usually are associated with a reduction of ERG, and variability in ERG amplitude has been associated with refractive error,[7] age,[8] sex,[8] and pigmentation.[9]

The EOG is an adjunct to ERG. It is generally abnormal when the ERG is abnormal, but the reverse is not true. An abnormal EOG, for example, with a normal ERG, is the hallmark for Best disease.

The VER represents the responses of the brain to a sudden stimulus. The temporal half of the retina causes a response in the cortex of the same side, the nasal in the contralateral cortex. These responses are summed in the recording, and VER abnormalities can result from abnormalities from the retina, optic tracts, optic radiations, or visual cortex. In persons with advanced retinal disease, such as retinitis pigmentosa, where the ERG may not be recordable, the flash VER may be a useful test for the evaluation of the visual function. In addition, its bright stimulus can be used to advantage in the presence of opaque media, such as vitreous hemorrhage, when it is impractical to perform a standard flash VER or ERG.[10]

Fluorescein Angiography

Fundus angiography is done with two different dyes, one principally for retinal angiography (i.e., sodium fluorescein) and one for choroidal angiography (i.e., ICG). FA was developed first, and more is known about the correlation between histopathology and angiographic findings with fluorescein than for indocyanine green. Therefore, FA serves as the prototype for learning fundus angiography. ICG angiography has become practical more recently with the development of digital imaging systems, but the significance of many of the indocyanine green angiographic findings is not known with certainty; however, ICG angiography has offered new insights into the pathophysiology of several disease states.

Analysis of the movement of the dye reveals information about blood flow dynamics and in the process also shows the anatomy of the retinal vessels. Certain diseases cause a breakdown in the blood ocular barrier, which results in the presence of fluorescein in areas or structures that ordinarily do not contain fluorescein. These areas then are more fluorescent than they otherwise should be and are called *hyperfluorescent* (Table 4–2). By convention, leakage of fluorescein into a space results in pooling of the fluorescein, whereas leakage into a tissue causes staining. Hyperfluorescence can also be the result of fluorescein in vascular structures being more easily visible (Fig. 4–1).

TABLE 4–2. Hyperfluorescence

Transmitted fluorescence	Geographic atrophy, Bull's-eye maculopathy, macular hole, atrophic scars.
Leakage	
Abnormal vessels	Angiomas, hemangiomas, vascular tumors
Choroid	Melanoma, CNV, hemangioma
Optic nerve	Peripapillary vascular loops
Retina	Occlusive diseases, neovascularization
Pooling	Neurosensory detachment, RPE detachment
Staining	Scleral, interstitial tissue

CNV, choroidal neovascularization; RPE, retinal pigment epithelium.

To interpret a fluorescein angiogram properly, it is necessary first to have a good mental picture of how a normal fundus should look. The fluorescein angiogram in question is compared with the mental picture of the normal angiogram. How the two differ offers clues to the pathophysiology involved. The fluorescein angiogram is examined for the principal location of the abnormality, which helps to limit the number of possibilities. Next the pattern of fluorescence is evaluated. Is the principal change hyperfluorescence (Table 4–2) or hypofluorescence (Table 4–3)? Integration of anatomic location and pattern of fluorescence further limit the possibilities. If the angiogram shows hyperfluorescence that seems to be predominantly in the vitreous, for example, the number of possibilities is limited to diseases like proliferative diabetic retinopathy, proliferative sickle cell retinopathy, and other retinovascular diseases.

Fluorescein angiography is used in diabetic retinopathy to evaluate macular edema, capillary nonperfusion, and retinal neovascularization. Although the diagnosis of these entities usually is made by careful ophthalmoscopy, angiography helps to quantify and document the degree of pathology present. This documentation also extends to measuring the response to treatment.

Diabetic patients (Fig. 4–2 and Chapter 12's Fig. 12–5) often have a breakdown in the competency of the blood ocular barrier. This is manifested by dye leakage from the retinal capillaries. This leakage occurs in two main forms: The first is leakage from small aneurysmal dilations called, appropriately enough, *microaneurysms*. Leakage from microaneurysms is seen as focal areas of hyperfluorescence, increasing during the angiographic study, centered on the microaneurysms. Some capillaries leak diffusely throughout their entire length. Patients with diffuse leakage often

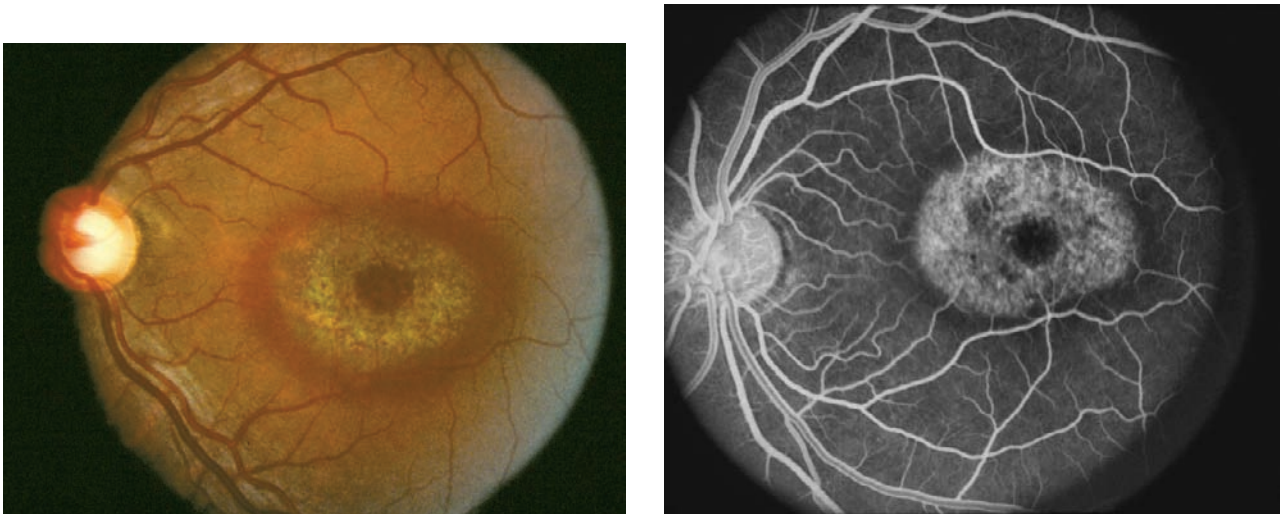


FIGURE 4–1. Chloroquine retinopathy. (A). This patient developed atrophy of the retinal pigment epithelium (RPE) in the macula surrounding the fovea. (B). During fluorescein angiography, the lack of pigment at the level of the RPE allows more excitation light to enter the choroid and more of the fluorescence from the choroid to travel back to the camera. Therefore, the affected area is much brighter. This lack of pigment creates a transmission defect.

have boggy maculae with widespread edema. The second form of leakage is from larger areas of capillary nonperfusion found in later stages of diabetic retinopathy. The leakage may come from either the arteries or the veins and is commonly ascribed to consequences of ischemia, even though the arterioles presumably contain oxygenated blood.

Other retinal vascular changes best seen in the early phases of the angiogram are venous beading, retinal neovascularization, and tractional detachment of the retina and retinal vessels. Venous beading is seen as abrupt alterations in the diameter of the larger veins. When found in a diabetic patient with no neovascularization, they are predictive of the eventual development of neovascularization; however, many patients with venous beading already have neovascularization present. These findings are described in greater detail in the chapter devoted to diabetic retinopathy.

Retinal neovascularization is seen as lacy loops of vessels arching away from a larger retinal vessel, most commonly a retinal vein. These newly growing vessels are not competent and freely leak dye. This dye leakage is seen as hyperfluorescent clouds surrounding the new vessels. With time, the dye concentration within the retinal vessels decreases and the hyperfluorescent clouds become larger because of diffusion of the dye into the overlying vitreous. By examining the early phases of the angiogram, we learn about the anatomy of the vessels. By looking at the changes over time, we can learn about the physiology of the vessels, particularly the competence of the blood ocular barrier. The neovascularization grows along the posterior vitreous face, and therefore the neovascularization is often elevated from the surface of the retina. On occasion, traction by the vitreous on the fibrovascular proliferation can cause an elevation of the retina, producing a tractional retinal detachment. Both retinal neovascularization and tractional elevation of the retina can be seen best by looking at stereoscopic angiographic pairs. Many patients with neovascularization also have bleeding into the vitreous cavity, seen as larger areas of hypofluorescence from blocking the underlying fluorescence.

Arterial occlusion results in delayed or absent perfusion of the involved segment (Fig. 4–3). In patients with venous occlusion, the initial filling of the veins during the fluorescein angiogram is slower than normal and the arterial–venous time is prolonged (Fig. 4–4A,B and Chapter 12's Figs. 12–7 and 12–8). Multiple retinal hemorrhages are seen as dark splinters against the backdrop of the capillary flush of the retina and choroid (Fig. 4–4C). Later in the study, fluorescein leaks from the retinal capillaries and there is a diffuse hyperfluorescence in the fundus, which causes

TABLE 4–3. Hypofluorescence

Blocked retinal fluorescence
Vitreous or retinal hemorrhage
Blocked choroidal fluorescence
Outer retinal, subretinal, sub-RPE and choroidal pathology (hemorrhage, lipid, pigment)
Vascular filling defects
Retinal, choroidal, or optic nerve occlusive diseases
Atrophy

RPE, retinal pigment epithelium.

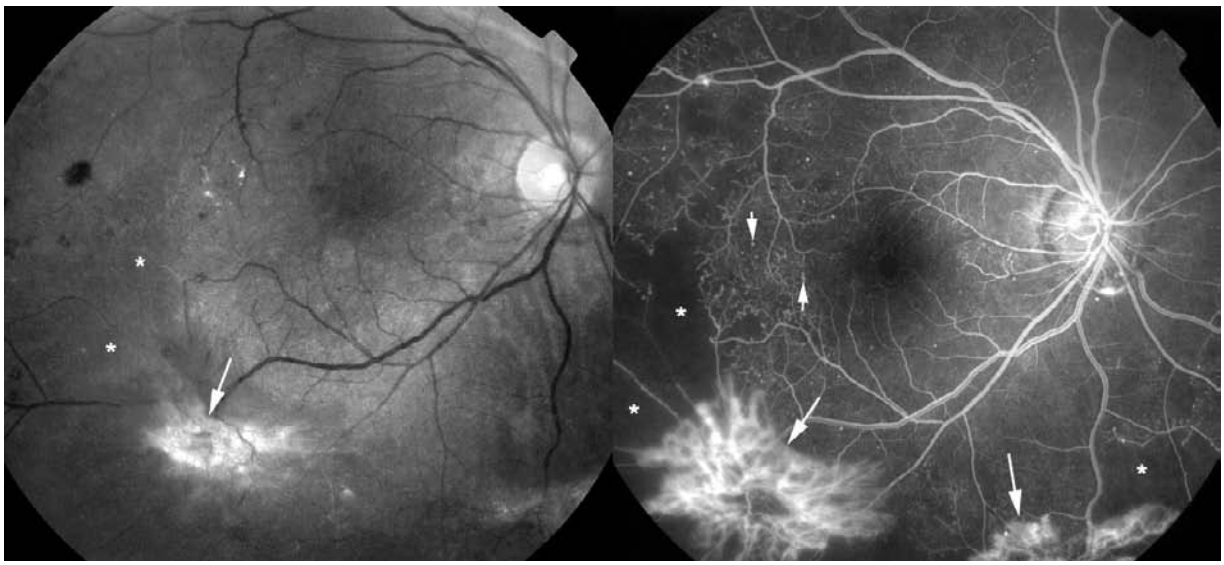


FIGURE 4–2. Diabetic retinopathy. (A). The patient has an area of preretinal neovascularization with admixed fibrosis (arrow). Distal to this area are featureless areas of retina consistent with capillary nonperfusion (asterixes). The macular region demonstrates microaneurysms and flecks of intraretinal lipid. (B). After injection of the fluorescein, the abnormalities of the retinal vessels and the neovascularization are much easier to appreciate. Note the prominent neovascularization (arrows) and the areas of nonperfusion (asterixes). The microvascular disease in the fovea is evidenced by the capillary telangiectasis and microaneurysms (small arrows).

staining of the nerve. In some cases of vein occlusion, there may be areas of capillary nonperfusion and associated retinal capillary telangiectasis. Additional cases are illustrated in the chapter devoted to retinal vascular disease.

In cases of choroidal neovascularization, the vessels may extend into or above the level of the RPE (Fig. 4–5). Exudative detachments of the retina and RPE are commonly seen. They eventually develop hemorrhage and scarring in the macula. Visual loss is related to the combined effects of the leakage, hemorrhage, and scarring.

During FA, some cases of choroidal neovascularization show a lacy wheel of vessels that leak through the course of the angiogram. In other patients, the actual vessels are not seen, but they develop an area of hyperfluorescence that has borders that are clearly demarcated; these cases are said to be well defined. In most patients, varying amounts of blood, exudation, scarring, and pigmentary changes overlie and obscure visualization of the new vessels. Complete visualization of the vessels and their resultant hyperfluorescence may not be possible in these patients, and these cases are said to be ill defined or occult choroidal

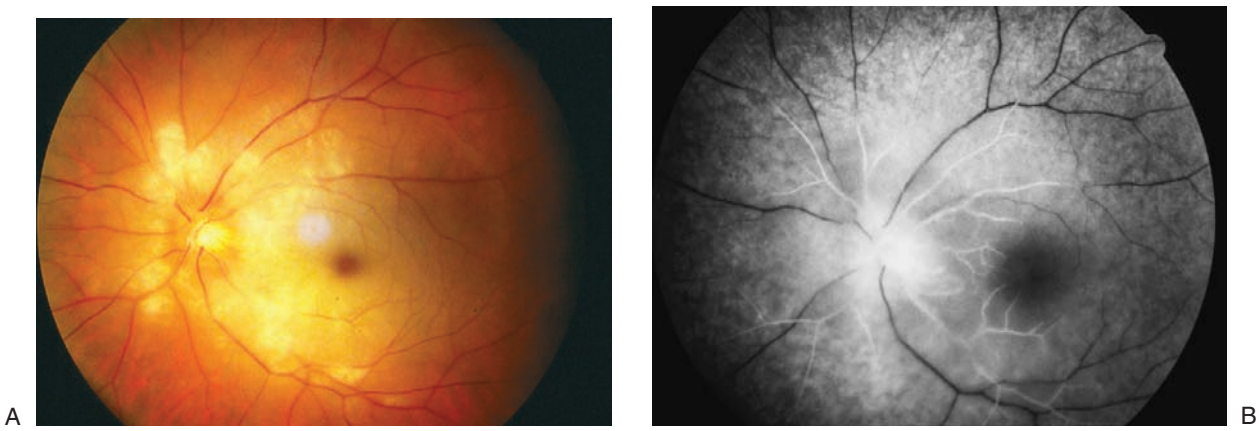
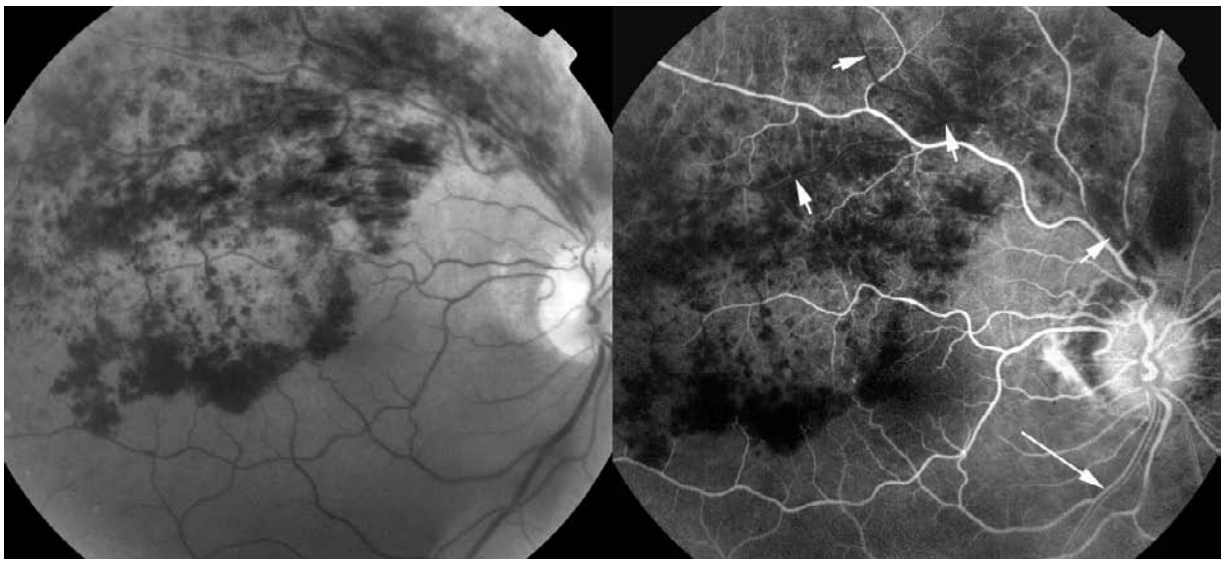


FIGURE 4–3. (A). The patient had multiple cotton-wool spots and ischemic inner retinal whitening. Note the cherry red spot. (B). Two minutes after fluorescein injection in the arm, the retinal vessels show a dye front.



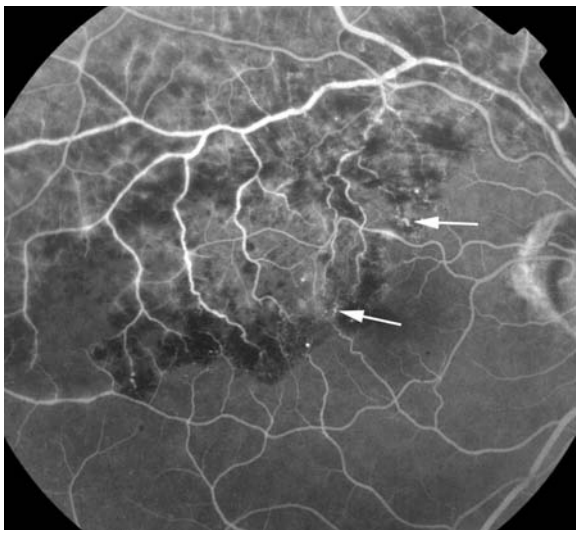


FIGURE 4–4. Branch retinal vein occlusion. (A). There is a triangular-shaped area of intraretinal hemorrhage and edema extending along the superotemporal arcade. (B). There is a delay in the filling of the superotemporal branch retinal vein (small arrows) as compared to the inferior branch (large arrow). (C). Blocking of the underlying choroidal fluorescence by the hemorrhages is evident. Microaneurysms are evident (arrows) and are commonly seen at the juncture of the abnormally perfused section of the retina and the normally perfused portion.

neovascularization (CNV). Occult CNV includes two fluorescent patterns. First, fibrovascular pigment epithelium detachment (PED) consists of irregular elevation of the RPE with stippled hyperfluorescence that is not so bright or discrete as classic CNV within 1 to 2 minutes after fluorescein injection, with persistence of staining or leakage of fluorescein dye within 10 minutes after injection. Second, late leakage of undetermined source consists of areas of leakage at the level of the RPE in the late phase of the angiogram not corresponding to an area of classic CNV or fibrovascular PED discernible in the early or middle phase of the angiogram to account for the leakage.[11]

When should a fluorescein angiogram be obtained for a patient? The principal reasons to perform FA are to help establish the diagnosis, to document the patient's fundus condition before the start of treatment, and to quantify disease severity and the response to treatment. Unfortunately, FA is used on occasion as a defensive test to document the state of the fundus before treatment. For example, FA often is obtained for a patient with proliferative diabetic retinopathy, even though careful ophthalmoscopy supplemented with stereophotography of the fundus is an excellent method of diagnosing proliferative diabetic retinopathy.

Indocyanine Green Video Angiography

Since its introduction in the 1960s, intravenous FA has played a crucial role in the diagnosis and treatment of various retinal diseases. As ICG absorbs and fluoresces in the near infrared spectrum, there is an enhancement of visualization through the RPE, serosanguinous fluid, shallow hemorrhages, and lipid exudate that block emitting light in FA. Although the fluorescence efficiency of ICG is much lower than that

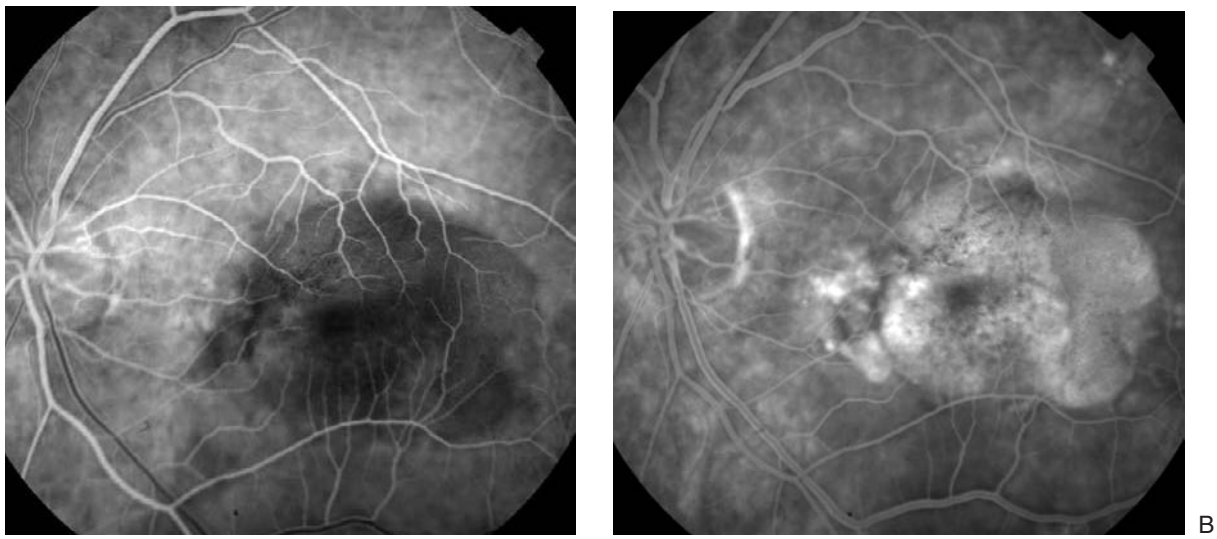


FIGURE 4–5. Occult choroidal neovascularization. (A). The patient has a large neurosensory detachment involving the macula, and after injection of fluorescein there is a large area of hypofluorescence. (B). Later in the angiographic evaluation there is hyperfluorescence in the macular region, but the hyperfluorescence is not homogeneous. The elevation of the retinal pigment epithelium shows irregular notching at its outer border. This pattern of occult choroidal neovascularization has been termed *vascularized retinal pigment epithelial detachment*.

of sodium fluorescein, the higher transmittance of light above 800 nm and the strong intravascular retention of the ICG dye allow better visualization of the choroidal vascular architecture than in FA. In 1989, Scheider and Schroedel[12] reported on the use of the scanning laser ophthalmoscope for ICG video angiography. This technique involves the use of real-time imaging with scanning laser technology, with the images stored on videotape and digital transferring to a computer by frame grabbing. Newer scanning laser ophthalmoscopes use digital technology to record and store ICG images.

Yannuzzi and associates demonstrated that ICG video angiography is useful in identifying well-demarcated areas of neovascularization in what had been classified by standard FA as occult CNV[13] (Fig. 4–6). They also pointed out that ICG angiography offers a potential advantage of identifying recurrent CNV following prior laser treatment. Occult CNV was classified as "hot spots," which were defined as an area of occult CNV that is both well delineated and no more than one disc diameter in size on ICG angiography. On the other hand, a larger area of CNV measuring more than one disc diameter was considered a *plaque*.[14] Pilot studies were carried out to determine the practicality of utilizing ICG angiographic guidance for treatment of occult CNV. Slakter and associates performed ICG-guided laser treatment in 79 eyes with occult CNV; 57% of these patients had stabilization of visual acuity at 1 year.[15]

Indocyanine green binds to protein and possibly to certain types of cells in a manner different from fluorescein, which makes images of inflammatory chorioretinopathies differ in several ways from FA, and may offer insights into the pathophysiology of these disorders. In birdshot chorioretinopathy, for example, the typical clinical appearance of ovoid, cream-colored lesions deep to the retina is easily recognizable on examination. With ICG angiography, the lesion appears as ovoid, well-demarcated areas of hypofluorescence, which seem to lie deep to the layer of the choriocapillaris. They have "vasotropic orientation" following along the distribution of the larger choroidal vessels.[16,17] Patients with multiple evanescent white-dot syndrome have transiently decreased visual acuity associated with white dots. With ICG angiography, a circular pattern of hypofluorescent spots is noted that is similar to that seen in the FA study.[18] In later phases of the ICG study, however, more widely distributed areas of hypofluorescent spots extend into the far periphery.

Central serous chorioretinopathy (CSC) is a condition that causes idiopathic serous detachments of the retina, usually affecting the macula. In the midphases of the ICG angiographic study, patients with CSC reveal a widespread choroidal vascular hyperpermeability.[19,20] With ICG angiography, numerous small serous RPE detachments can be seen; these detachments are hyperfluorescent in the early phases as a result of transmission of the hyperpermeable choroidal

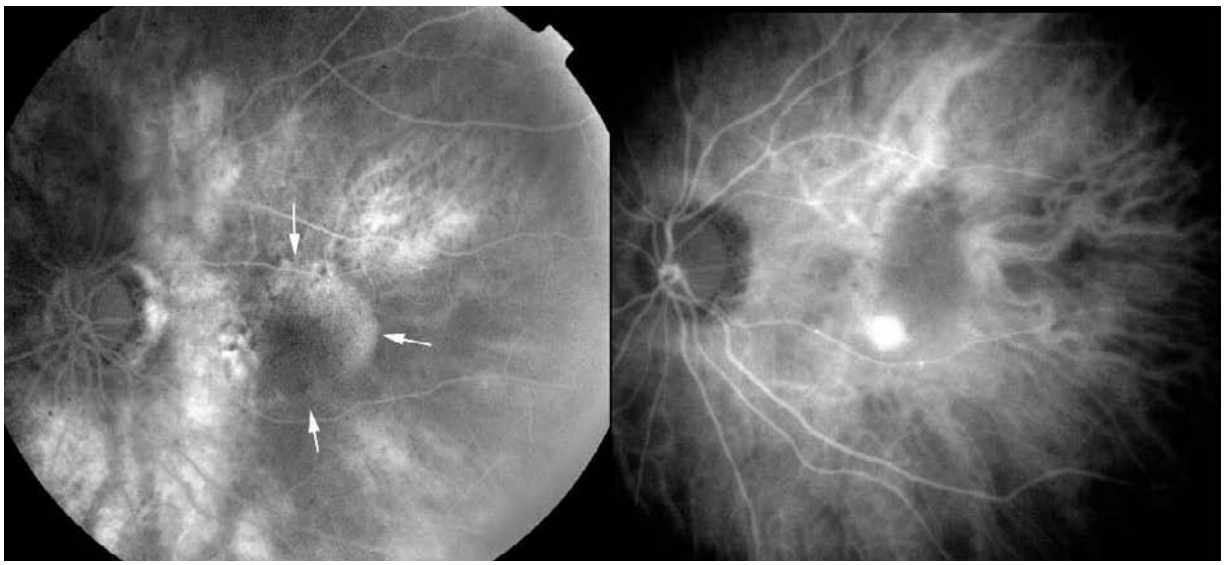


FIGURE 4–6. (A). A notched, shallow, retinal pigment epithelial detachment is evident during fluorescein angiography (arrows). (B). During indocyanine green angiography, an underlying intensely fluorescent area of choroidal neovascularization is evident.

vessels. In later stages, the PEDs become hypofluorescent centrally, with a ring of hyperfluorescence at their margin. ICG angiography is also useful in evaluating older patients with CSC when the diagnosis of occult neovascularization is in question.[21]

Idiopathic polypoidal choroidal neovascularization was first described in older black women who exhibited acute exudative changes in the posterior pole, including subretinal hemorrhage and lipid in association with unusual choroidal vascular changes.[22–24] ICG images of this lesion revealed a network of vessels terminating in polypoidal or aneurysmal excrescences at the level of the choroid.[25] These characteristic vascular changes appear to account for the secondary exudative and hemorrhagic detachments of the RPE and neurosensory retina. Furthermore, ICG angiography is able to differentiate between the aneurysm-like and secondary choroidal neovascularization, a known complication of this chronic disease.

Angioid streaks are a dehiscence of Bruch membrane with consecutive degenerative changes in the RPE and choriocapillaris.[26] This clinical entity can be associated with systemic conditions such as pseudoxanthoma elasticum (PXE) or Paget disease.[27,28] In ICG angiography, angioid streaks appear hyperfluorescent in early frames and do not stain in late phases unless a fair amount of fibrotic material, or even neovascular tissue, is involved. Although FA is typical in these cases, ICG angiography can add more information about the extent of peau d'orange mottling or reticular pigmentary dystrophy, which are RPE changes associated with angioid streaks.[29]

In cases of choroidal hemangioma, there is marked progressive hyperfluorescence, particularly in the early and middle phases of the angiographic series. A speckled pattern within the lesion with stellate borders has been noted in some patients.[30,31] Better visualization can be achieved because of improved imaging through the serosanguinous retinal elevations typical for hemangiomas. A pattern of small vessels during the early ICG angiogram is characteristic of choroidal osteomas.[30,31] ICG shows late hyperfluorescence noted diffusely, with the areas containing bony involvement exhibiting variable blockage throughout the study. These studies do not, however, add much new information to that obtained by slit-lamp indirect ophthalmoscopy and ultrasonography in establishing the diagnosis.

In summary, ICG angiography has provided new and interesting insight about a number of choroidal anomalies. So far, the impact on choroidal tumors and on ischemic and idiopathic diseases of the choroid has been limited. With inflammatory diseases, additional information obtained by ICG angiography may offer new insights into the pathogenesis of these disorders. Most important, some patients with occult choroidal neovascularization secondary to age-related macular degeneration may be imaged better under the addition of ICG angiography. Controlled trials will provide us with more definite information about the diagnosis and treatment of patients with occult CNV. Advancement of angiographic techniques, such as wide-field angiography, which provides a field of view of up to 160 degrees, or digital subtraction ICG

angiography, which allows visualization of the filling of separate elements in the vascular circuit, may increase our ability to diagnose and treat retinal and choroidal abnormalities.[32]

Ultrasonography

Contact B-scan ultrasound is a safe, noninvasive, dynamic tool for providing images of the intraocular contents, particularly in cases with media opacification. Other important indications include evaluation of intraocular tumors, determination of the configuration and extent of retinal detachments, evaluation of choroidal detachments, evaluation of eyes after trauma, and endophthalmitis. It is also commonly used for measurement of axial lengths for intraocular lens calculation.

In quantitative echography, the same information on reflectivity, internal structure, and sound attenuation of a lesion can be obtained using the A-scan trace on the bottom of the screen. Ultrasound allows a reliable evaluation of the vitreoretinal interface, and it is one of the best methods to assess the presence of a posterior vitreous detachment (PVD). When the posterior vitreous face detaches from the optic nerve, it may pull some epipapillary glial tissue from the nerve. This is seen as a ring of tissue, called a *Weiss ring*, on the posterior vitreous face. In some patients, the posterior vitreous face is poorly reflective and is seen as a linear train of dots. When the patient moves his or her eye, the train of dots will move together, which helps the examiner appreciate their mutual connection. It is often easier to see the PVD by ultrasonography than by ophthalmic examination because the ultrasonographic confirmation of the PVD is not obstructed by the lens or pupil limitations.

B-scan ultrasonography is an integral tool in planning vitreoretinal surgery. It is important for the vitreoretinal surgeon to know the location of the posterior vitreous face preoperatively. In some conditions, traction by the vitreous on the retina produces pathologic effects with loss of vision. Vitreomacular traction syndrome is a condition in which the vitreous partially detaches but retains a persistent attachment with traction to the macula. Patients with epimacular membranes have a PVD in front of the macula, and this finding helps to differentiate epimacular membranes from vitreoretinal traction syndrome, where the posterior hyaloid is still attached to the macula.

Rhegmatogenous retinal detachments appear on B-scan ultrasonography as a bullous, mobile, membrane attached anteriorly to the ora serrata and posteriorly to the optic nerve head (Fig. 4–7). In the presence of a giant retinal tear, it is possible to observe both the free edge of the detached retina and the anterior flap. The mobility of a retinal detachment depends on the duration of the detachment. Recent bullous detachments may be highly mobile, whereas chronic detachments with proliferative vitreoretinopathy appear stiff and do not demonstrate much after-movement during dynamic ultrasound examination. With contracture of the proliferating membranes, the retina shortens and may stretch across the chord diameter the eye. Chronic retinal detachments may develop intraretinal cysts, which have the ultrasonic appearance of sonolucent, round to oval lesions in the thickness of a retinal detachment.

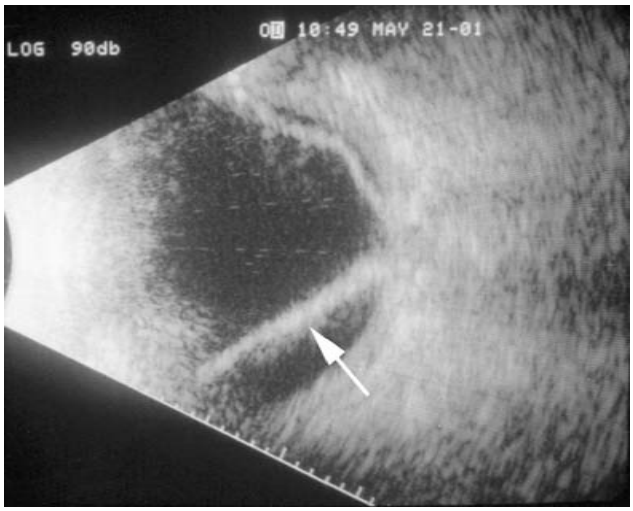


FIGURE 4–7. B-scan ultrasonography of a retinal detachment. This patient had a funnel detachment secondary to proliferative vitreoretinopathy. The shortened inferior retina (arrow) subtends the chord diameter between the optic nerve and the ora.

Contact B-scan is important in the management and diagnosis of choroidal detachment. In massive choroidal detachment, choroid from opposite fundus areas may touch in the middle of the vitreous cavity (kissing choroidals). A choroidal detachment is usually thicker and more reflective than a retinal detachment and usually extends anteriorly to involve the ciliary body. Retinal detachments stop at the ora serrata. With ocular movement, choroidal detachments are not particularly mobile and do not show after-movements, which are typical of a rhegmatogenous retinal detachment. B-scan ultrasound can differentiate between an exudative choroidal detachment, which appears sonolucent, and a hemorrhagic choroidal detachment, which presents multiple mobile echoes in the suprachoroidal space. B-scan evaluation can help to locate preoperatively the preferred sites for drainage.

B-scan ultrasonography is used for topographic localization, size measurement, shape evaluation, and

tissue characterization of tumors. Tumor height can be measured both in A-scan and in B-scan mode. While measuring the size of the tumefaction, it is important to evaluate the shape. Melanomas begin as a dome-shaped, solid thickening of the choroid protruding into the vitreous cavity. If the Bruch membrane ruptures, the mass expands freely toward the vitreous cavity, pushing the retina and RPE in front of it. The lesion then assumes a collar-button or mushroom configuration, which is pathognomonic of malignant melanoma.

In general, melanomas are fairly homogeneous tissues that have little internal reflection. Hemangiomas have a "spongy" character composed of stroma, blood vessels, and blood, and consequently they have a highly echogenic interior. Metastatic lesions usually have a moderate to high internal reflectivity. This differentiation based on ultrasonography is not absolute. Differences in acoustic impedance and architectural pattern of tissues can vary widely, and it is best to combine the ultrasonic findings with all the available clinical information to make a diagnosis.

Ultrasound is an accurate means of evaluating eyes after blunt and penetrating ocular trauma. It is possible to reliably detect retinal detachment, the condition of the lens, retinal dialysis, intraocular foreign body (IOFB), vitreous and choroidal hemorrhage, and posterior scleral wounds in the presence of media opacity.[33,34] It must be remembered, however, that ultrasound is a complement to other diagnostic modalities. It does not exclude the use of conventional ophthalmic equipment, such as radiographic examination, computed tomographic scan, and metal detector.

Typically, an IOFB causes high absorption of sound waves so that an area of shadowing appears posterior to the IOFB. Precise assessment of size is not possible, although some estimation can be made. A number of structures in the eye can mimic an IOFB. Optic-nerve head drusen and choroidal calcification may produce a strong reflection. Small bubbles of air that enter the globe at the time of the injury may simulate a foreign body.

In children, contact B-scan ultrasonography is used to evaluate cases of leukocoria, a finding suggestive of retinoblastoma. Although ophthalmoscopic examination is the best means of diagnosing retinoblastoma, B-scan ultrasonography offers important adjunctive information. Retinoblastoma is seen as a dense tumefaction arising from the ocular wall and commonly has associated calcification, which appears as punctate hyperechogenic spots within the tumor. Evidence of more than one intraocular lesion and vitreous seeding are also signs suggestive of retinoblastoma.

Ultrasound is particularly useful in evaluating the shape of the globe. Staphylomas are clearly visible as localized or diffuse elongation of the eye. In phthisis bulbi, the hypotonic globe is smaller and has a squarer appearance because of distortion exerted by the extraocular muscles. Diffuse calcification of the choroid, including intraocular bone formation, is often present.

Ultrasound evaluation of postvitrectomy eyes often is complicated by the presence of intraocular tamponades, such as silicon oil and long-acting gasses. The posterior profile of a gas bubble produces a membranous highly reflecting echo that can easily be confused as a recurrent retinal detachment.

Optical Coherence Tomography

High-resolution cross-sectional imaging of the retina may be useful in identifying, monitoring, and quantitatively assessing macular diseases. The OCT scanner, has a superluminescent diode light that operates at 830 nm, coupled to a fiber-optic delivery system, providing the necessary illumination on the retina. The location of the OCT probe beam on the fundus may be established by slit-lamp observation of an infrared light source placed coincident with the probe beam and retina with an infrared-sensitive video camera.[35]

A false-color tomogram of optical reflectivity is produced to enhance the differentiation of retinal layers. Bright colors, like red and white, represent highly reflective areas, whereas dark colors, such as blue and black, represent regions with low reflectivity. OCT provides a noninvasive, cross-sectional, structural analysis of the retina with resolution in the 10- to 20-μ range and therefore allows high resolution of the retinal anatomy.[36–38]

Because OCT is a noninvasive method that uses infrared illumination of the fundus, this technique seems to be comfortable and well tolerated by patients. Cross-sectional imaging of the fovea is potentially useful in diagnosing and monitoring progression of a macular hole. In patients with full-thickness macular holes, histologic features can be observed, including a sharply defined, full-thickness excavation of the retina, a marginal halo of retinal detachment, and the presence of small, nonreflective cysts in the outer plexiform and inner nuclear layers.[39] It also can be useful in monitoring risks for the fellow eye. Differential diagnosis between a full-thickness macular hole and a lamellar hole is also possible by using this method.[40,41] It may assess the vitreoretinal interface with higher resolution than kinetic ultrasound, which can detect a minimum separation of only 500 μ[41] (see Chapter 14's Fig. 14–5). Distinction between epiretinal membrane and retinal tissue, both displaying high reflectance, from the posterior hyaloid, which is minimally reflective, is also possible with this method. It measures the retinal thickness that accompanies many retinal dis-

eases and diseases of the optic nerve. Fluid accumulation, such as in macular edema, can be localized and quantified. Detachments of the neurosensory retina and RPE detachments also can be studied.[42]

Quantitation of the thickness of the nerve-fiber layer in the peripapillary region is directly relevant for the early diagnosis and monitoring of glaucoma, where intraocular pressure often does not reliably affect disease progression,[43] ophthalmoscopy and stereo fundus photography are subjective,[44] and visual-field defects occur only after irreversible damage to the nerve-fiber layer already has taken place.[45] OCT can identify other retinal and choroidal pathologies, including choroidal nevi, hemorrhagic exudate, tumors, and other inflammatory diseases.

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5

Expanding on the Primary Complaint to Get to the Diagnosis

TRAVIS MEREDITH

Symptoms

Almost every patient evaluation begins with a chief complaint or the patient's statement of the predominant symptom. In some cases, a single symptom will be almost pathognomonic of a particular entity. More often, the complaint will be associated with other symptoms, and the pattern will be useful in constructing a differential diagnosis.

In a large number of retinal diseases, the symptom complex and a complete ocular examination will be enough to establish the diagnosis. For the retina patient, the complete examination includes distance and near vision, refraction, external examination, pupil examination, confrontation visual fields, slit-lamp examination, intraocular pressure, biomicroscopic study of the vitreous and retina, and indirect ophthalmoscopy, usually with scleral depression. Amsler grid is often useful in localizing disease to the macula. Fluorescein angiography is commonly used to document the degree of disease, to elucidate a diagnosis, and to guide therapy. The study of the posterior segment by ultrasonography is helpful when the media are obscured either by anterior segment disease or vitreous hemorrhage or when a mass is identified in the fundus. Visual fields, color vision testing, optical coherence tomography, and the retina thickness analyzer all have their place in studying more complex problems.

Why Obtain an Ophthalmic History?

The vast majority of retinal diagnoses can be established from examination alone. Nevertheless, taking a history is important for a number of reasons. First, it helps to establish a differential diagnosis and therefore focus the examination to distinguish between entities. Second, it is important to understand the patient's concerns. From the history, the physician should not only elucidate details of the symptomatology but should listen sympathetically so that he or she understands the fears and anxieties caused by the symptoms. The patient will have certain expectations of the encounter with the physician that also can be extracted from the conversation. The choice of terms in explaining the disease can give the physician clues about the patient's level of knowledge and sophistication regarding ocular problems. The interchange between the physician and patient also may be valuable to understanding what coping mechanisms the patient may be using to deal with these new complaints. Finally, a careful history will allow the physician to predict accurately the examination findings in many cases.

What General Questions Should Be Asked about Symptoms?

One of the most important questions to ask about a symptom is the relative intensity. Is the scotoma complete or only relative? Is the visual loss mild or severe? If pain is involved, for example, is it slightly annoying or is it disabling? Current Medicare guidelines mandate that pain be considered one of the key pieces of information elicited in every examination.

The next pertinent question is, How long has the symptom been present? For visual symptoms, the answer to this question is often vague. When there is a definite onset to the symptom ("I was sitting at the table, and I began to notice floaters"), it is helpful in pinpointing the duration of the problem. In other cases, the symptom may seem acute to the patient, but the disease process may be well established. A classic example of this phenomenon is the patient who wakes up to look at the clock and notes that because one eye is occluded by the pillow, he or she cannot see the clock with the other eye. In this situation, the visual

loss may have been present for a long time before its discovery.

An additional important question is, Is the symptom stable or becoming worse? Some disorders, such as macular pucker, have an acute onset and often remain stable. Others, however, are slowly progressive over months to years. In trying to establish duration, it may be helpful to ask the patient if he or she can recall whether the symptom was present at some specific time, such as a past holiday, or if the symptom might have been present 1 year or 2 years or 5 years previously. Vitreous floaters from a posterior vitreous detachment follow another pattern; they appear suddenly and fade over time.

Further, the following question is also important: Is the symptom intermittent or constant? Intermittent symptoms may suggest vascular phenomena, acute variations in intraocular pressure, or symptoms associated with increased intracranial pressure. Often, however, intermittent symptoms may be attributed to changes in ambient lighting or to difficulties with specific visual tasks.

Symptom Complexes

A patient may present with a single symptom, but more often there are multiple interrelated symptoms. Table 5–1 lists some common retinal diagnoses with their usual associated symptoms.

Which Visual Symptoms Suggest Anterior Segment Disease?

Blurred vision may be a symptom of anterior or posterior segment disease. Symptoms of itching (allergy), exudate, dry eyes, tearing, and foreign-body sensation most often point toward external ocular disease. Many patients describe these along with complaints more suggestive of retinal disease. Once the posterior diagnosis is established, the patient should be reassured that the anterior symptoms do not relate to the posterior problem. Monocular diplopia and triplopia most often are encountered with a particular set of glasses or problems with the crystalline lens, such as juvenile nuclear sclerosis.

Which Symptoms Suggest Vitreous Disease?

Floaters are the hallmark of disease in the vitreous. Floaters are usually caused by small bits of collagen in the vitreous cavity, by inflammatory cells in the vitreous, or by vitreous hemorrhage (Table 5–2).

TABLE 5–2. Some Causes of Vitreous Hemorrhage

Retinal breaks
Subretinal hemorrhage
Trauma
Neovascularization
Diabetic retinopathy
Occlusive diseases
Branch retinal vein occlusion (BRVO)
Central retinal vein occlusion (CRVO)
Sickle cell retinopathy
Inflammatory diseases
Sarcoidosis
Peripheral vasculitis
Blood dyscrasias
Abnormalities in clotting cascade (e.g., von Willebrand disease)
Leukemia

TABLE 5–1. Usual Symptom Complexes for Common Posterior Disorders

	Blurred vision	*Central scotoma*	*Metamorphopsia*	*Image size change*	*Color vision change*	*Floaters*	*Photopsia*	*Visual field loss*
Vitreous detachment	X					X	X	
Vitreous hemorrhage	X					X		
Retinal detachment	X					X	X	X
Vitreitis	X					X		
Retinitis	X					X		X
Tumor	X						X	X
CSR	X	X		X	X			
Epiretinal membrane	X		X	X				
SRNVM	X	X	X		X			
Macular hole	X	X						
CME	X		X					
BRVO	X		X					X
CRVO	X		X				X	
Cone dystrophy	X				X			

X, indicates possible symptoms associated with diagnosis; CSR, central serous retinopathy; SRNVM, subretinal neovascular membrane; CME, cystoid macula edema; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion.

Which Symptoms Suggest Macular Disease?

Central scotoma (either relative or absolute), metamorphopsia, changes in image size, and acquired color vision change all suggest the possibility of macular disorders.

Which Symptoms Suggest Peripheral Retinal Disease?

Peripheral retinal disease is suggested by loss of visual field, flashes, and nyctalopia (decreased vision at night).

Which Diagnoses Are Suggested by Halos around Lights?

It is classically taught that corneal edema caused by sudden increased intraocular pressure causes halos around lights. Lenticular opacity and debris in the vitreous also may cause similar symptoms. Most patients note these halos or sunbursts around oncoming car lights when driving at night.

What Questions Should Be Asked of a Patient Who Complains of Blurred Vision?

Almost all patients consulting a retinal specialist complain of blurred vision, but it is the least specific symptom. The patient may complain, "I can't see good," "I can't see the television," or "My eye goes all dark-like." They may be much more specific, for example, stating, "I have a dark spot in the middle." Numerous questions must be asked to characterize the loss and to define a symptom complex.

The first task is to discern whether the concern is bilateral or unilateral. Unilateral visual loss may be asymptomatic to the patient for a long time and may be discovered incidentally when the eye is blocked. Other patients will not notice that their vision is decreased until they try to accomplish a monocular task, such as sighting a rifle.

Of particular importance is whether the symptoms are constant or intermittent. The patient who notes a graying-out of the vision in one eye leads the examiner to consider amaurosis fugax, pressure on the optic nerve, or increased intracranial pressure. Some patients describe an intermittent blur of vision that is likened to a lace curtain or gauze that floats in front of their vision; this symptom suggests vitreous opacities, particularly if the haze is mobile and floats back and forth at a different rate than eye movement.

It is particularly important to focus on whether the visual loss is considered to be diffuse, central, or peripheral. Central visual loss strongly points to macular disease, whereas peripheral loss suggests vascular disease, peripheral retinal disease (degeneration, infection, retinal detachment), optic nerve disease including glaucoma, or neurologic changes.

Specific conditions under which the visual loss is noted are of essential importance. Greater loss of clarity at near than distance is most commonly found in presbyopia, but in the patient with possible retinal disease, this phenomenon suggests a macular origin of the problem. Diabetic maculopathy classically creates greater degrees of near visual disturbance than distance vision change.

When visual loss is bilateral, it may be important to assess it with the patient's systemic condition. Relatively acute bilateral vision changes can occur in diabetic patients whose blood sugar rises out of control. Changes in the hydration of the lens because of the difference between the intralenticular and extralenticular concentration of sugars is thought to account for much of this blurring. A drop of one or two lines of vision in each eye of patients with rapid decompensation of glucose control sometimes is noted even in pseudophakic patients. In the patient with the crystalline lens intact, spontaneous recovery may take as long as 6 weeks after the blood sugar is stabilized. Sudden bilateral vision loss, such as in homonymous hemianopia, may suggest neurologic disease. Episodic bilateral visual loss may occur in patients whose hypertensive medications have been changed and who develop temporary postural hypotension when they stand up.

The patient may notice other problems associated with unilateral visual loss that are mentioned only when specific questions are asked. For example, loss of stereopsis may lead the patient to miss the glass when attempting to pour water or to experience difficulty parking the car accurately.

Difficulty reading is a common complaint of patients with blurred vision. Whereas some patients are completely unaware of visual loss in one eye, loss of several lines of vision for others may lead to fairly significant difficulties. Patients may note a sense of confusion when trying to read and may block off the affected eye even when the vision is as good as 20/40. This sense of confusion may be more likely to occur if the dominant eye is affected by the disease process.

If visual loss is transient, several nonretinal diseases are suggested. In a young person with visual loss of approximately 20 minute duration, migraine is the likely diagnosis, whereas the older patient probably suffers from amaurosis fugax, suggesting ipsilateral carotid disease. A patient who has bilateral fleeting visual loss, particularly when engaging in activities that cause a Valsalva maneuver, will often be found to have bilateral disc edema. A unilateral presentation of

the same symptoms may be found in the patient with a congenital disc anomaly.

How Is the Patient with Symptoms of a Central Scotoma Evaluated?

The presence of a central scotoma indicates macular or optic nerve disease. Historically, if the patient is young, the differential diagnosis would include optic neuritis, central serous chorioretinopathy, subretinal hemorrhage, and inflammatory conditions of the macula or nerve, such as toxoplasmosis, histoplasmosis, and papillophlebitis. In older patients, optic nerve disease is a lesser possibility, and subretinal hemorrhage and macular hole assume greater importance in the differential diagnosis.

In the younger patient, associated symptoms such as pain on extraocular movement and neurologic symptoms tend to indicate optic neuritis. A pupillary examination is most helpful to establish the optic nerve as the site of abnormality. If subretinal neovascularization is suspected, ocular histoplasmosis and angioid streaks lead the list of possible diagnoses. Questions should include whether the patient has been under any undue stress (often thought to be associated with central serous chorioretinopathy) and whether the patient has spent time in the histoplasmosis geographic belt as a younger person.

The quality of the description of the abnormality gives some clue to the diagnosis. Patients with central serous retinopathy often notice a round area of defect in the vision, which they describe as being gray. Patients with a macular hole describe a smaller scotoma and may notice a loss of individual letters or words while reading. The scotoma tends to be denser in these cases. In patients with subretinal hemorrhage, the scotoma is more likely to be of irregular shape and more absolute or darker.

From a practical diagnostic viewpoint, the presence of an afferent defect is an important dividing line in pursuing the diagnosis (Fig. 5–1). In the patient with a significant afferent pupillary defect, optic neuritis should be considered; after the appropriate full ocular examination, color vision testing, and visual fields, a cranial magnetic resonance imaging (MRI) should be considered. In the patient without an afferent defect or a minimal afferent defect, the diagnosis will tend to subdivide on the basis of age.

In the younger patient, examination of the nerve for an optic pit is important if there is subretinal fluid. The most important test in the patient with subretinal fluid or suspected subretinal neovascularization in either age group is the fluorescein angiogram. Macular holes may be somewhat difficult to diagnose. The Watzke–Allen test is important in differentiating and can be performed easily. A narrow slip beam is shined on the macular hole; with a full-thickness hole, the patient may perceive a break in the line. Ocular coherence tomography and fluorescein angiography may be useful tests in establishing the correct diagnosis.

How Is the Patient with Metamorphopsia Evaluated?

When the patient complains of distorted vision, the examiner must be sure that there is actually metamorphopsia. Some patients use the word *distortion* to indicate general blurring. In ophthalmologic terms, metamorphopsia usually indicates that straight lines are bent or distorted. The Amsler grid may be used to demonstrate what the examiner means by *metamorphopsia* and to confirm its presence. This symptom points to a macular cause and most often indicates subretinal fluid or blood, epiretinal membrane, or venous occlusive disease producing cystoid macular edema. In determining whether the patient has true metamorphopsia, questions about the appearance of straight lines and the usual visual environment are sometimes helpful. Many patients will note that there is actually a distortion on a line of print so that one set of letters moves upward. Others notice a small scotoma or complain that the words tend to "jump around." Many patients notice that straight lines, such as door frames, telephone poles, or telephone lines, are "bent." Many patients already have been given an Amsler grid and will consult the physician because of changes on the Amsler grid itself.

Once the patient's pupils are dilated, a thorough biomicroscopic examination of the macula is indicated. Fluorescein angiography is often useful to search for the cause of the distortion of the macula, which is almost invariably found as the cause of the distortion of vision.

How Is the Patient with the Change in Image Size Evaluated?

Patients often notice a difference in image size if a refractive error produces greater than a 2.5-diopter difference between the two eyes. More often, the alteration in image size is acquired and is accompanied by other symptoms, usually blurring of vision. The first question to ask is whether the altered image is larger or smaller. In general, patients are able to make this distinction and are able to tell which eye is involved. A larger image is almost pathognomonic of epiretinal membrane with macular distortion (Fig. 5–2). A smaller image is highly suggestive of a neurosensory detachment of the macular retina.

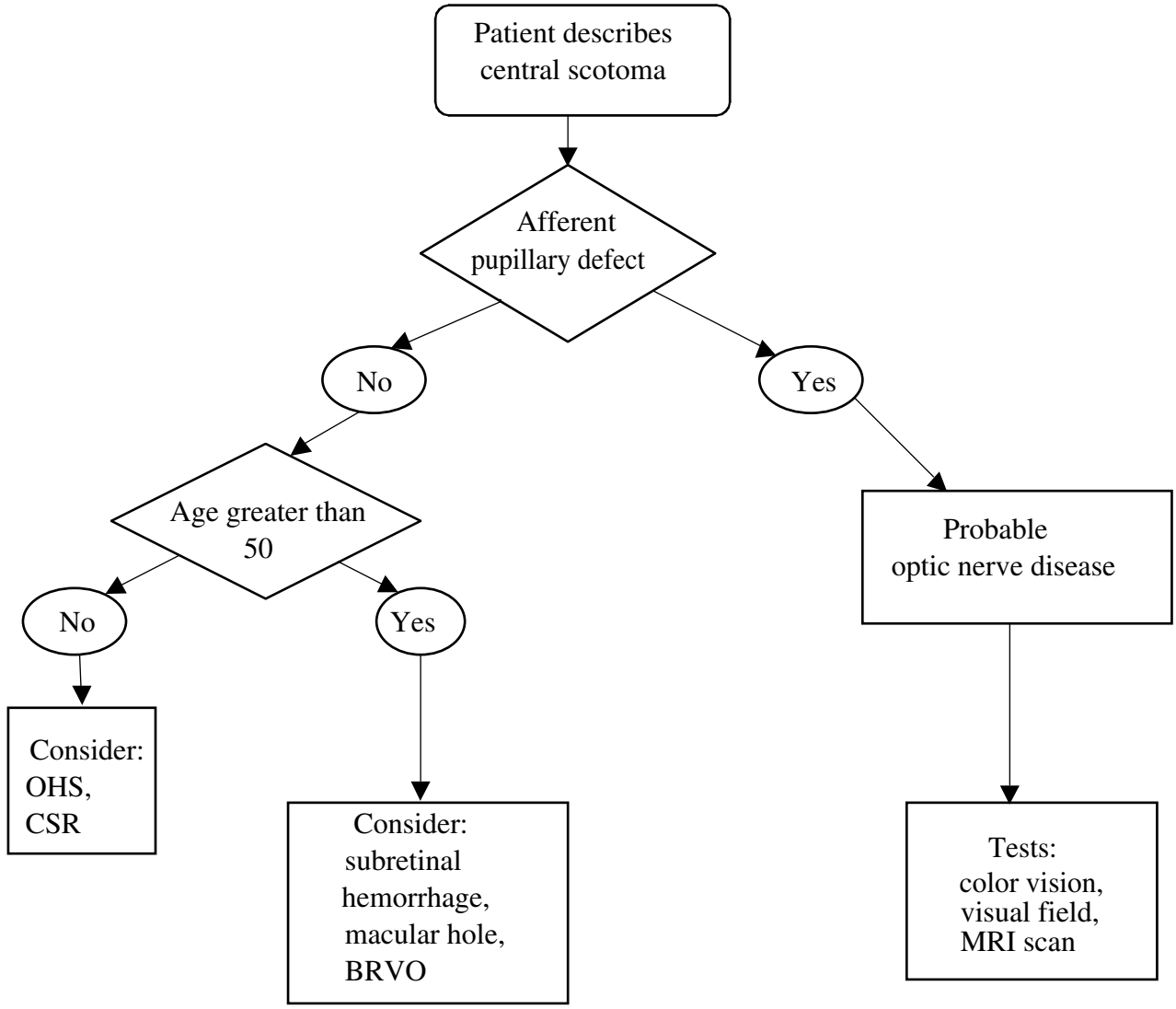


FIGURE 5–1. Clinical pathway: Central Scotoma. OHS, ocular histoplasmosis; CSR, central serous retinopathy; BRVO, branch retinal vein occlusion; MRI, magnetic resonance imaging.

With subretinal fluid beneath the macula, there is induced hyperopia, and visual clarity may be improved with a slight hyperopic correction in the range of +0.5 to +0.75. The fundus should be carefully examined for the source of the fluid. In the younger patient, central serous retinopathy is the leading cause. Micropsia may be a complaint when subretinal fluid is caused by neovascularization (as with ocular histoplasmosis) or by an adjacent tumor or suspicious nevus. In the older patient, micropsia may occur as the earliest onset of subretinal fluid associated with either age-related macular degeneration or tumor.

The initial examination should be done to confirm the presence of subretinal fluid and to look carefully for signs of subretinal neovascularization, including subretinal blood, subretinal lipid, or the presence of a gray-green membrane. The nerve should be examined carefully for the presence of an optic pit, the macula and near periphery for a choroidal mass. Fluorescein angiography is typically definitive in arriving at the diagnosis.

How Is the Patient Who Complains of a Change in Color Vision Evaluated?

Color vision changes have a different significance in younger than older patients. Older patients may complain of a desaturation or a loss of color as lenticular opacity develops. They may not notice this change until the lens is removed in one eye, allowing appreciation of the difference between the two eyes. Patients may also notice color vision changes with loss of dis-

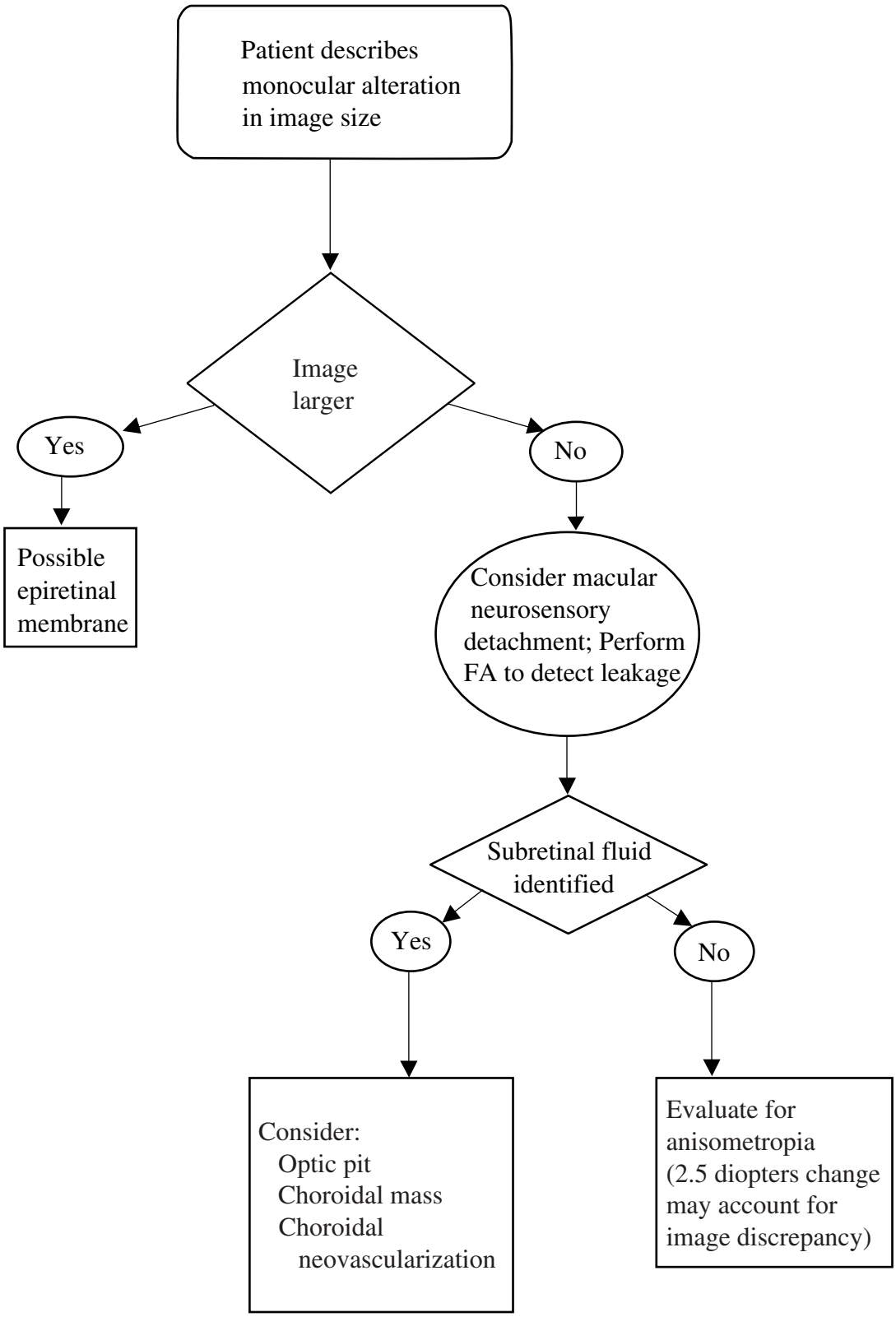


FIGURE 5–2. Clinical pathway: Monocular alteration in image size. FA, fluorescein angiogram.

crimination as they develop macular degenerative changes. Therefore, in both these situations, loss of color vision usually is accompanied by some loss of clarity at the same time.

Bilateral color vision decline may herald the onset of acquired cone or cone-rod degeneration, especially in younger patients. These symptoms usually develop slowly and subtly over many years. For example, patients who present with cone disease in their late twenties or early thirties may have failed the color vision test that is given when trying to enlist in the Armed Services. Other patients may have been unsuccessful at color-specific tasks, such as working with color-coded electrical wiring. In other instances, a homemaker may have tried to match colors in decorating the house and found that while working alone she produced an unsatisfactory result and had to have the decorating redone. Parents may have noted a "jiggling eye" that the patient later learns to suppress with age. Usually, these color complaints are accompanied by mild to moderate loss of visual clarity.

Other concurrent symptoms may suggest hereditary degeneration. Many patients have photophobia or photoaversion disproportionate to the apparent degree of visual abnormality, and this may be the presenting complaint rather than the color vision change. They may sometimes be helped by miotics. Patients with cone degeneration may note better vision in the twilight of dim illumination (hemeralopia) but often need to be asked specific questions to elicit this symptom.

As many as 8% of male patients in this country have congenital mild color vision deficits and function well without any complaints because they have never been aware of not having these color abilities. In acquired progressive disease, however, a careful family history is frequently helpful. On the other hand, sudden changes in color vision in one eye only should suggest optic neuritis.

The Ishihara color plates or the Farnsworth–Munsell testing are useful screening devices, and the Nagel anomaloscope can help to quantify color abnormalities. The United States Navy gives the only specific test that relates to actual job performance by testing whether recruits can differentiate between the red and green lanterns used onboard ships. The electroretinogram also may be helpful, and perimetry is important in diagnosing and following cone or rod dystrophies or achromatopsias.

How Is the Patient with Flashes Evaluated?

Flashes are a nonspecific symptom that suggest either retinal abnormalities or neurologic disorders. Patients may describe "flashers." Typical retinally induced flashes are experienced in the temporal periphery. Retinal flashes are much more common in the dark or in dim illumination. Whereas most authorities believe these represent vitreous traction, some believe that they are actually a result of the vitreous bumping into the retina and causing mechanical stimulation. Patients also sometimes notice flashes in other fields with exudative retinal detachment. An occasional pseudophakic patient describes flashes in daylight resulting from the intraocular lens.

Photopsias or light sensations are distinct from flashes. Photopsias may be more centrally located and may go through an alternating pattern. Photopsias are found in retinal diseases such as acute zonal outer occult retinitis or cancer-associated retinopathy, or they may even be part of a migraine pattern. Patients who have had laser photocoagulation often note that postoperatively they have small twinkling lights in their vision.

Patients who present with flashes have various differential diagnoses, depending on age. Younger patients are more likely to have flashing lights as part of a migraine pattern (Fig. 5–3). These patients will not have floaters. They should be questioned about the pattern of their flashes. Their light symptoms sometimes are described as being like looking at the filament in an incandescent bulb or like a pattern of irregular but continuous flashing. In a classic migraine, these flashes may be preceded by an aura, will last for about 20 minutes, and are followed by a headache. Family history, history of motion sickness, and discussion of emotional or environmental triggers for these symptoms help to assure the physician that migraine is the proper diagnosis.

The most important differentiating feature is whether or not there has been an acute onset of floaters following or accompanying the onset of the flashes. In most cases, this combination of symptoms will indicate the presence of a posterior vitreous detachment (PVD), but about 6% of posterior vitreous detachments present with flashes alone.

In the absence of a retinal break in a PVD and any of these signs, subretinal fluid may be the cause of the patient's symptoms. Exudative detachments may be found in several entities but are seen most commonly accompanying a tumor. In these cases, patients may be aware of both photopsias and field loss. In some cases, the fluid is predominantly in the macula and may produce micropsia and decreased vision as well.

How Is the Patient with Floaters Evaluated?

The most important feature to learn about the patient's floaters is whether they are chronic and intermittent or whether they are of recent acute onset.

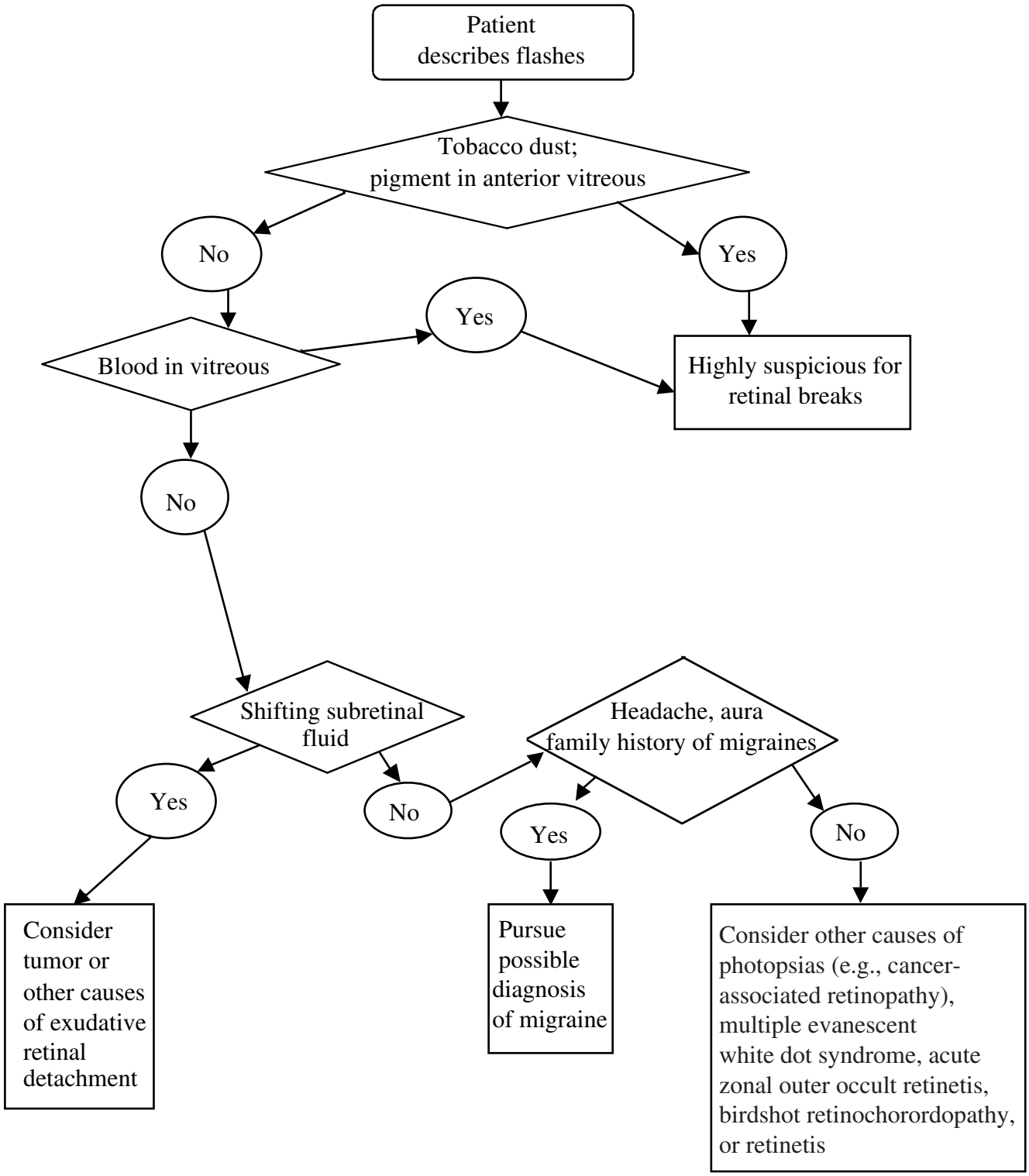


FIGURE 5–3. Clinical pathway: Patient describes flashes.

Many myopic patients in particular notice chronic floaters that are not disturbing to them and usually are not symptomatic of disease.

The acute onset of floaters may suggest a PVD, a vitreous hemorrhage, vitreitis, or retinitis. A clinical setting helps to arrange the differential diagnosis in the proper order.

In the patient with myopia or previous lens surgery or the patient with a history of contralateral retinal detachment, the most likely diagnosis with flashes and floaters is PVD. Patients with vitreous floaters often describe a sudden shower of many spots in their vision. These have been called *muscae volitantes* (little flies) in older European literature. Even one floater of acute onset may indicate a vitreous detachment. In some cases, the patients may actually see the C-shaped or O-shaped floater indicating the Weiss ring.

Floaters of this type are quite disturbing to patients, who may perceive them as something in the field of vision and frequently have the sense that they should be able to brush them away with their hand. As they describe the symptom, they often make a waving motion with their hands. Even in patients with normal vision, floaters can provide a significant distraction, particularly early after the acute onset. Some patients describe the floaters as being like smoke flowing in front of the eye. Others note a general moving, indistinct, or poorly defined obscuration of vision, like a lace curtain in front of their vision. While explaining these symptoms, the physician must realize that although he or she is concerned that they indicate a retinal tear, the patient is actually more concerned with the symptoms themselves.

In diabetic patients, floaters often are described as strings or globs when vitreous hemorrhage is the culprit. The patient will often describe the hemorrhage as "spreading out" in their vision and becoming more diffuse, sometimes causing a marked, dramatic drop in visual acuity. Vitreous hemorrhage usually is experienced as black, although the occasional patient experiences a red haze, almost always indicating blood. Often, if the hemorrhage occurs during the daytime, the patient can pinpoint the area from which it arises, which helps the surgeon know the area of the fundus to examine for the source. Most vitreous hemorrhages from diabetes, however, occur at night. If the patient is young and has sickle cell disease, the presentation of the floaters is more often in the peripheral field and alerts the physician of the probability of peripheral neovascularization.

In young patients with a chronic slow onset of floaters associated with pain, photophobia, or redness, the cause of floaters is most likely to be vitritis or intermediate uveitis. In acquired immune deficiency syndrome (AIDS), patients with cytomegalovirus (CMV) retinitis may describe floaters as being fairly static in the area in which they arise and say that they do not float back and forth like those of the patient with a posterior vitreous detachment. In the AIDS patient, there is often field loss as well, indicating retinitis as the culprit.

The first clues to the cause of floaters come from the slit-lamp examination of the vitreous (Fig. 5–4). If there is blood in the vitreous, there is a high likelihood of a retinal break in the patient with a posterior vitreous detachment. In the diabetic patient, particularly one with known vascular disease, it is highly suspicious, however, for neovascularization. In older patients, subretinal hemorrhage (often from subretinal neovascularization) can break through into the vitreous cavity, causing floaters; severe central vision loss usually occurs simultaneously. In the sickle cell patient, the likelihood of peripheral neovascularization is high.

If the anterior vitreous contains inflammatory cells, then vitreitis or retinitis is the most likely cause. Tobacco-dust pigment in the anterior vitreous, however, strongly indicates the likelihood of a retinal tear or retinal detachment. Fundus biomicroscopy with a 60- or 90-diopter lens will disclose a Weiss ring in most cases of PVD. If there are floaters, then fundus biomicroscopy or slit-lamp examination of the anterior vitreous is important. The presence of tobacco-dust pigment indicates the likelihood of a retinal tear; hemorrhage in the vitreous suggests that a retinal tear or other source of hemorrhage must be sought.

A thorough fundus examination is in order. If PVD is found, particularly if there is tobacco-dust pigment or vitreous hemorrhage, then a retinal break must be sought. About 15% of all symptomatic PVDs result in a retinal break. If vitreous hemorrhage accompanies the posterior detachment, the likelihood of a retinal break rises to almost 50%, whereas the presence of tobacco-dust pigment is an almost pathognomic sign of a retinal break.

How Is the Patient with Visual Field Loss Evaluated?

Symptomatic loss of visual field usually represents peripheral retinal disease or neurologic disease. Loss of visual field in glaucoma disease patients typically occurs over longer periods and usually is not noted acutely.

Acute or semiacute bilateral visual field loss is most often from neurologic disease. The pattern of field loss helps to pinpoint the location of the problem within the visual system. Bilateral field loss, however, also may be seen with an acute bilateral infectious process such as CMV retinitis in AIDS. In rare instances, a

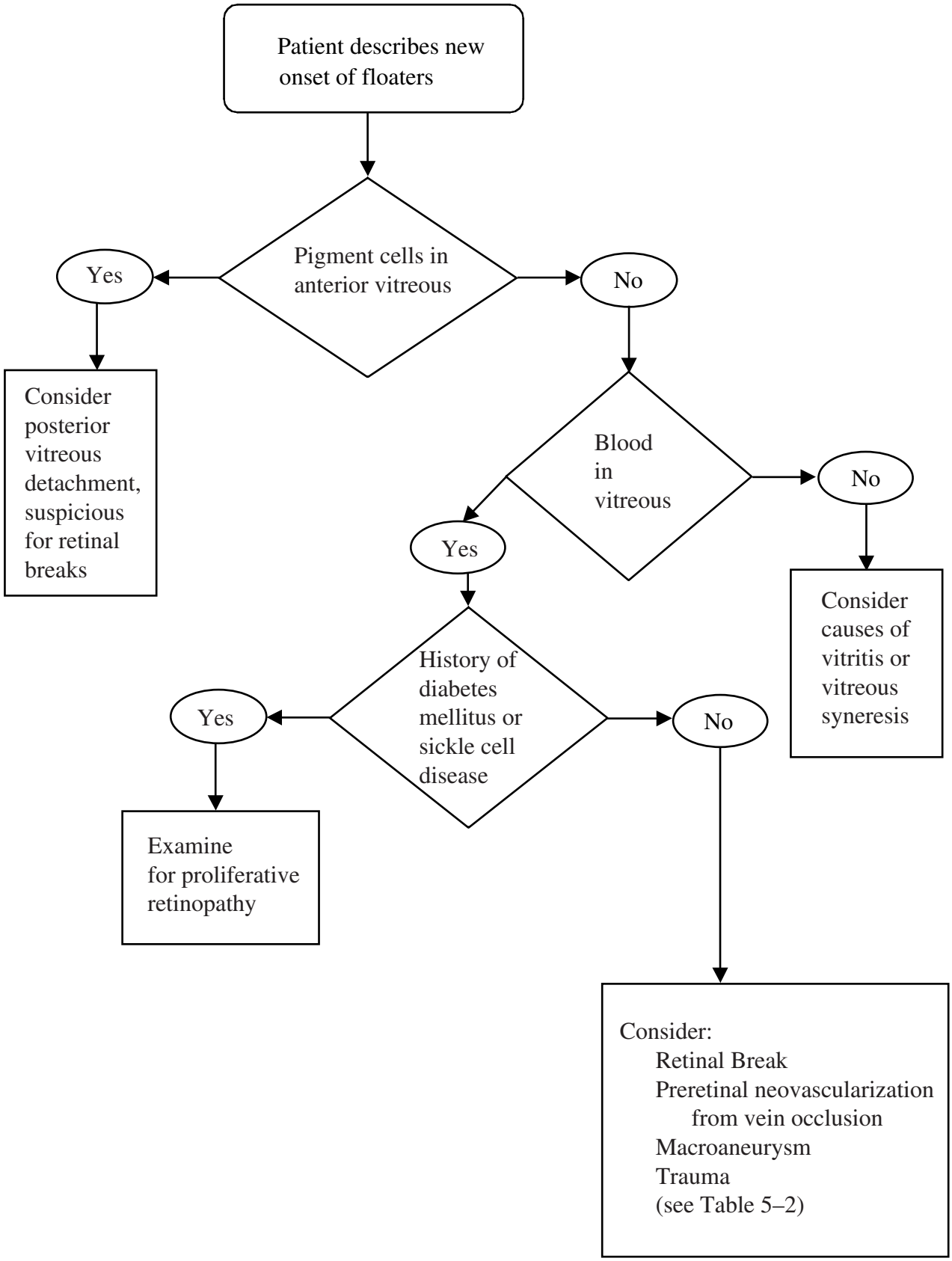


FIGURE 5–4. Clinical pathway: New onset of floaters.

patient may develop field loss from retinal detachment and realize that he or she also has field loss of the other eye from a chronic subacute detachment.

Most acute visual field loss presents as a monocular phenomenon. Retinal detachment, infectious retinitis, and vascular events are the usual culprits, although acquired optic nerve disease, such as optic neuritis and ischemic optic neuropathy, also should be considered. Retinal detachment is most often preceded by flashes and floaters and is progressive over hours to days. The direction from which the field loss progresses often gives the physician a clue as to the location of the break that initiated the retinal detachment, keeping in mind that the detaching retina produces symptoms in the exact opposite field. Thus, an inferior nasal field defect indicates a developing detachment in the superotemporal quadrant.

Vascular field loss usually respects the horizontal meridian and occurs acutely without progression. Arterial occlusions have a slightly greater tendency to cause symptomatic field loss than do venous occlusions because of the density of the scotoma they produce.

Retinitis produces field loss usually associated with some floaters. The field loss may be in any quadrant or in multiple quadrants and is not bound by the horizontal raphe.

In the clinical setting, the field loss is usually confirmed by confrontation testing before the pupils are dilated. For the most accurate mapping of the field loss, a Goldmann visual field should be performed before pupillary dilation. A full fundus examination, indirect ophthalmoscopy, and fundus slit-lamp biomicroscopy usually will indicate the cause of the field loss.

How Is the Patient with Nyctalopia Evaluated?

Nyctalopia is technically defined as night blindness associated with hereditary retinal dystrophies. Many older patients complain of difficulties with night vision, and some particularly begin to fear driving because they do not see as well. This night vision loss is most often due to lenticular opacity; macular degenerative changes with overall decrease in acuity and contrast sensitivity may reduce night function. Myopes also have more difficulty with vision at night.

If true nyctalopia is suspected, the physician often will need to probe for symptoms. Particularly in younger patients, nyctalopia usually indicates the slow onset of rod photoreceptor disease. In very young children, parents may notice the child's inability to function at night. This may be noted for the first time when the family goes into an environment where there is none of the usual lighting available at home. Patients may first notice difficulties on a camping trip, when they are unable to see when they move away from the circle of the campfire. In other cases, the patient may not be able to find his or her way in a darkened movie theater or may not be able to go to the bathroom at night without a nightlight.

Some patients lose the ability to see stars at night, and this symptom often is revealed only through specific questioning. A useful question is to ask patients to compare their visual abilities in darkened environments with those of a family member, provided the family member does not also suffer from a hereditary rod degeneration. Careful questioning may reveal that the patient has given up driving, even though he or she is young, for fear of not seeing well in poorly lighted environments. Often in true nyctalopia, the onset is so gradual that patients may deny symptoms even when questioned carefully.

Careful examination of the fundus is necessary to evaluate nyctalopia when a retinal degeneration is suspected. Early in the course of retinal degeneration, only mild pigmentary changes may be seen in the peripheral fundus; these often are accompanied by mild vitreous cell and very subtle retinal arteriole attenuation. It is only in later stages that there is the typical intraretinal pigment migration described as bone spiculation.

Optic atrophy is a common finding. If a peripheral degeneration is suspected, a visual field is a good initial test. Perimetry is also useful in monitoring the progress of disease and for establishing whether affected patients meet state requirements to maintain a driver's license. If suspicion is high, electrophysiologic testing is added to the evaluation.

Electrophysiologic patterns are helpful both for diagnosis and, to a lesser degree, for tracking the progress of disease. In the younger patient, the electronegative waveform of electroretinogram (ERG) distinguishes congenital stationary night blindness from retinitis pigmentosa. Rod photoreceptor degenerations show progressive loss of the total electrical response attained on ERG testing. As the name suggests, congenital stationary night-blindness patients demonstrate a stable ERG.

How Is the Patient with Ocular Pain Evaluated?

Often pain is not a feature of a retinal diagnosis. Some specific types of pain, however, do orient the physician toward a specific differential diagnosis. Photophobia with mild inflammatory changes of the conjunctiva often suggests iritis as a component of the diagnosis. Anterior chamber reaction or vitreous cell confirm some form of uveitis as the proper diagnosis.

Intense aching pain is found in several clinical settings in association with retinal disease. Severe in-

flammatory disease can produce such symptoms on rare occasions. The sudden onset of suprachoroidal hemorrhage after either an anterior segment procedure or a retinal detachment procedure may produce a sudden onset of deep-aching ocular or periocular pain. Some patients with acute scleritis develop an exquisitely aching painful eye that is remarkably responsive to systemic steroid therapy.

Postoperative pain also can have an aching quality. Interestingly, postoperative pain after retinal procedures or ocular trauma may often be referred to the ipsilateral temple and experienced as a unilateral headache. The sudden onset of severe pain that presents in the temple in the older patient without known eye disease should be suspected to be temporal arteritis. The classic symptom triad for temporal arteritis is unilateral temporal pain, a jaw claudication, and unilateral scalp tenderness. Patients usually have a palpable tender area on the scalp so severe that they cannot lay that side of the head on a pillow, or they may have noticed pain when brushing their hair. Sometimes jaw claudication is thought to be dentally related and will cause a few patients actually to change their eating habits, in some instances even leading to weight loss, because they cannot finish eating their meals. Constitutional symptoms of malaise and fatigue further suggest temporal arteritis. The erythrocyte sedimentation rate and a temporal artery biopsy are the main tests to be considered in establishing this diagnosis. A combination of these symptoms with ischemic optic neuropathy or central retinal artery occlusion is strongly suggestive of temporal arteritis.

SECTION II

Lesions Associated with a Flat or Minimally Elevated Retinal Surface

6

Areas of Fundus Whitening: White or Yellow Spots

AMY S. NOFFKE AND LEE M. JAMPOL

Acute Posterior Multifocal Placoid Pigment Epitheliopathy

Who Is Affected?

The typical patient is a healthy young adult in the second or third decade of life. Men and women are affected equally.[1–5]

What Symptoms Are Typical?

The patient develops rapid, painless loss of vision in one or, more commonly, both eyes.[1–5]

What Are Possible Associated Systemic Features?

Many patients report an antecedent viral illness.[2,4,6] Symptoms of meningismus, headaches, and transient hearing loss may develop.[7,8] Cerebral vasculitis, rarely fatal, with spinal fluid pleocytosis and elevated protein can occur.[9–13] Acute nephritis with hematuria has been reported.[14,15]

What Are the Characteristic Ocular Manifestations?

Multiple flat, creamy white, placoid lesions are seen at the level of the retinal pigment epithelium (RPE) and outer retina (Fig. 6–1). They are typically bilateral and found in the postequatorial retina.[1–5] Inflammatory cells may be seen in the vitreous or anterior chamber. Associated episcleritis,[16] disc edema,[16] and perivenous exudation[1] have been reported. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) should be distinguished from other conditions presenting with geographic or placoid lesions (Fig. 6–2).

What Does Angiography Show?

Early hypofluorescence with late staining of the lesions is seen on fluorescein angiography.[1] Hypofluorescence of lesions is also seen on indocyanine green (ICG) angiography.[17]

What Is the Course of the Disease?

Within 1 to 2 weeks following onset of symptoms, the lesions begin to fade and evolve into areas of RPE atrophy and clumping. The visual prognosis is excellent: Most patients recover 20/30 or better vision. The vision typically improves rapidly within the first 2 to 3 weeks, although in a few patients visual recovery may take up to 6 months. Recurrences, although rare, do occur,[4,18,19] and choroidal neovascularization has been reported.[20] Residual paracentral scotomata may persist in some patients.

Is There Any Treatment?

The natural history of the disease is favorable without treatment. There is no evidence that corticosteroids speed visual recovery or improve visual outcome, although a short course may be justified in cases where the fovea is involved and visual acuity is poor.

Multiple Evanescent White-Dot Syndrome

Who Is Affected?

Multiple evanescent white-dot syndrome (MEWDS) typically affects young, healthy women.[21–23]

What Symptoms Are Typical?

Patients frequently present with blurred vision, shimmering photopsias (especially in the temporal field), and paracentral scotomata.[21–23]

What Are Possible Associated Systemic Features?

Patients frequently report a flulike illness prior to the onset of visual symptoms.[21] Elevated serum immuno-

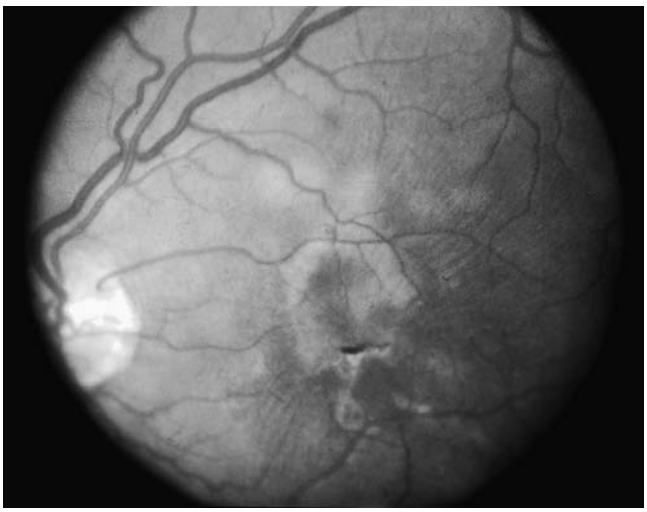


FIGURE 6–1. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE). Creamy white placoid lesions at the level of the RPE are seen in differing stages of evolution. Pigment clumping is associated with the older, central lesion, whereas newer, smaller lesions are seen at its periphery.

globulin M (IgM) and immunoglobulin G (IgG) values have been detected in a patient with MEWDS.[24] Cases of MEWDS following varicella infection[25] and after hepatitis B vaccination[26] have been reported.

What Are the Characteristic Ocular Manifestations?

Typically, MEWDS is unilateral, although bilateral MEWDS, which may be either simultaneous or sequential, has been reported.[22,27–29] This disorder is characterized by multiple small, gray-white spots found in the perimacular area at the level of the RPE and outer retina (Fig. 6–3) and may be associated with vitreous cells. A granular foveal appearance can help to distinguish MEWDS from other retinal "white-dot" disorders (Fig. 6–4). Optic disc edema and retinal vascular sheathing may also be present.

What Does Angiography Show?

Early hyperfluorescence with late staining of the lesions, often in a wreath-shaped pattern, is seen on fluorescein angiography.[21,23] Leakage from disc capillaries also may be seen. ICG angiography reveals multiple hypofluorescent lesions, some corresponding to the white dots.[30]

Are Other Tests Helpful?

An enlarged blind spot may be seen on visual field testing.[31,32] Electroretinography may demonstrate profoundly decreased a-wave and b-wave amplitudes acutely, with normalization of the electroretinogram (ERG) during the recovery phase.[33]

What Is the Course of the Disease?

Visual acuity returns to baseline, the white dots fade, and disc edema resolves over the course of several weeks. It may take months before photopsias and scotomata fully resolve. A chronic form of bilateral MEWDS with multiple recurrences has been reported.[27]

Is There Any Treatment?

Usually, MEWDS is a self-limited disease with an excellent visual prognosis, and no treatment is indicated.

Birdshot Retinochoroidopathy

Who Is Affected?

Women are affected more commonly than men (60% versus 40%), typically in the fifth and sixth decades of life.[34,35] The age at presentation is older than that of other "white-dot" disorders, such as multifocal choroiditis (Fig. 6–4).

What Symptoms Are Typical?

Patients note floaters, blurred vision, and photopsias initially, with nyctalopia and color vision deficits later in the course of the disease.[34,35]

What Are the Characteristic Ocular Manifestations?

Multiple ill-defined, yellowish, deep retinal or choroidal lesions posterior to the equator are associated with vitreous inflammation, optic disc edema, and cystoid macular edema[34–36] (Fig. 6–5).

What Does Angiography Show?

Many of the lesions show no change in background choroidal fluorescence, although some demonstrate early hypofluorescence with late hyperfluorescence. Perivascular leakage, optic disc staining, and cystoid macular edema are seen.[34–36] ICG angiography may reveal hypofluorescent spots.

Are Other Tests Helpful?

The association of birdshot with human leukocyte antigen (HLA)-A29 (90%) is the strongest of all HLA-associated diseases.[37,38] Electroretinography is typically abnormal.[36,39] Electrooculography may be either normal or subnormal.[35,39]

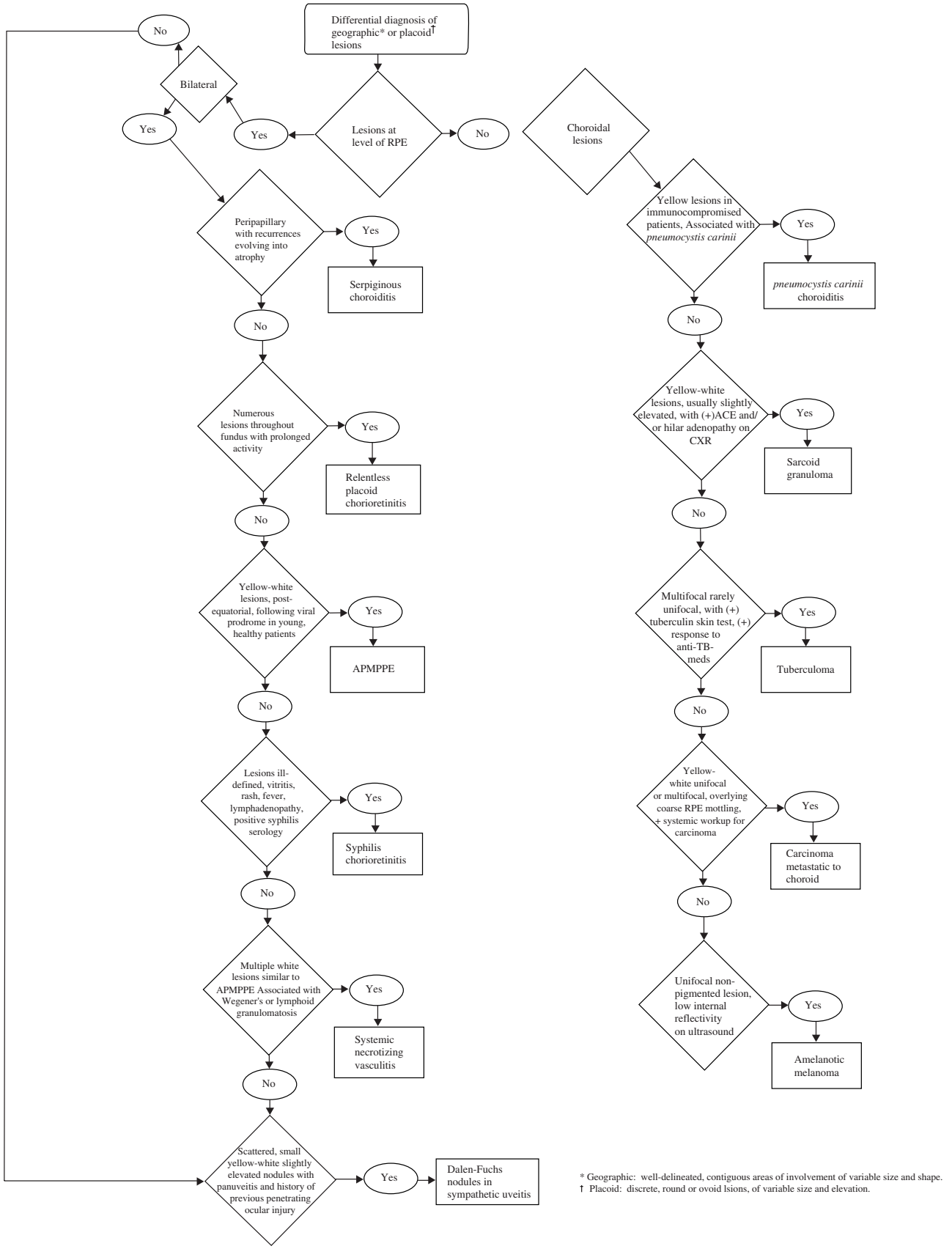


FIGURE 6–2. Differential diagnosis of geographic or placoid lesions. RPE, retinal pigment epithelium; APMPPE, acute posterior multifocal placoid pigment epitheliopathy; CXR, chest x-ray; ACE, angiotensin convecting enzyme.

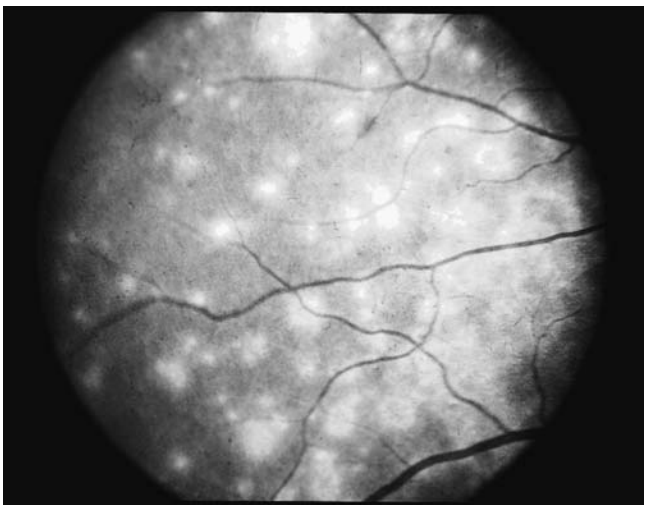


FIGURE 6–3. Multiple evanescent white-dot syndrome (MEWDS). Multiple gray-white spots at the level of the retinal pigment epithelium and outer retina are seen just nasal to the optic nerve. This is a particularly severe case of MEWDS; in other patients the lesions may be fewer and more subtle.

What Is the Course of the Disease?

Birdshot retinochoroidopathy is a chronic disease characterized by remissions and exacerbations. Half of affected eyes can be expected to retain a visual acuity of 20/60 or better.[36] Chronic cystoid macular edema is the most common cause of visual acuity loss. Choroidal neovascularization, macular epiretinal membrane formation, macular hole, macular scar, and cataract also may be responsible for reduced visual acuity.

Is There Any Treatment?

Initial treatment consists of systemic or periocular corticosteroids. The use of cyclosporine, cyclophosphamide, azathioprine, or methotrexate may be indicated for patients with systemic or ocular steroid intolerance or for those with progressive visual loss despite steroid therapy.[40] Low doses of systemic corticosteroids or immunosuppressive agents may be required for sustained suppression of intraocular inflammation.

Stargardt Disease (Fundus Flavimaculatus)

Who Is Affected?

Patients typically present with symptoms in the first two decades of life. Patients affected with classic Stargardt disease demonstrate an autosomal-recessive mode of inheritance, although a few pedigrees with a condition resembling Stargardt disease have been reported to exhibit an autosomal-dominant inheritance pattern.[41,42] Autosomal-recessive Stargardt disease has been mapped to the *ABCR* gene,[43] an adenosine triphosphate (ATP)-binding transporter gene located on the short arm of chromosome 1.[44] Autosomal-dominant Stargardt disease has been mapped to the short arm of chromosome 6[41] and the long arm of chromosome 13.[42]

What Symptoms Are Typical?

Patients with Stargardt disease usually present with gradual bilateral visual loss during childhood or early adulthood. Patients without macular changes or with late macular involvement may not experience symptoms until midlife. Symptoms of cone dysfunction may accompany loss of central vision.[45,46]

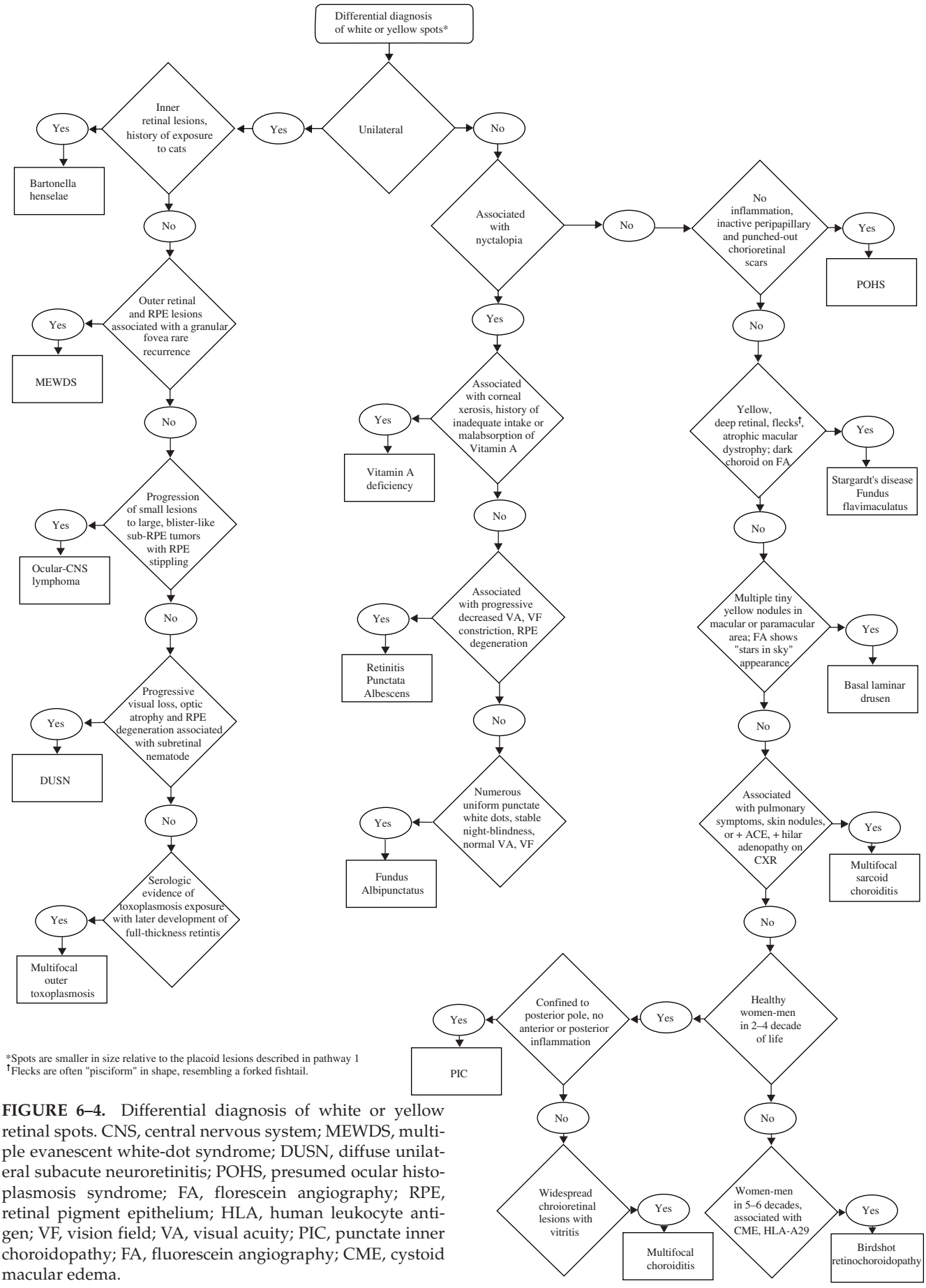
What Are the Characteristic Ocular Manifestations?

Historically, the term *fundus flavimaculatus* has been used to describe cases of yellowish deep retinal flecks either confined to the posterior pole or extending to the midperipheral fundus, and the term *Stargardt disease* has referred to an atrophic macular dystrophy associated with similar flecks. Both conditions have been mapped to the *ABCR* gene on the short arm of chromosome 1.[44] These terms are now frequently used interchangeably in the literature and are considered to represent different expressions of Stargardt disease.[45,46] The appearance may correlate with the specific mutation in the *ABCR* gene, but intrafamilial variable expression suggests modifying factors.

Initially, the fundus may appear relatively normal, or it may exhibit a vermillion color because of lipofuscin storage in the RPE that blocks choroidal detail. Loss of the foveolar reflex may be the first ophthalmoscopic sign. An oval or bull's-eye area of atrophic macular change described as "beaten bronze" commonly develops. Flecks may not be present early in life and then may be observed on subsequent follow-up examinations.[45,47,48] The flecks commonly surround the area of macular atrophy and may extend into the midperiphery (Fig. 6–6). Some patients develop diffuse atrophy of the RPE and narrowing of the retinal vessels in addition to the changes already noted.[45]

What Does Angiography Show?

Choroidal fluorescence is often obscured on fluorescein angiography by diffuse lipofuscin storage in the RPE, resulting in a "dark" or "silent" choroid that allows retinal capillaries to be more clearly visible. The presence of a dark choroid is found in most patients and may be helpful in distinguishing Stargardt disease from other disorders (Fig. 6–4). A dark choroid is



*Spots are smaller in size relative to the placoid lesions described in pathway 1
†Flecks are often "pisciform" in shape, resembling a forked fishtail.

FIGURE 6–4. Differential diagnosis of white or yellow retinal spots. CNS, central nervous system; MEWDS, multiple evanescent white-dot syndrome; DUSN, diffuse unilateral subacute neuroretinitis; POHS, presumed ocular histoplasmosis syndrome; FA, florescein angiography; RPE, retinal pigment epithelium; HLA, human leukocyte antigen; VF, vision field; VA, visual acuity; PIC, punctate inner choroidopathy; FA, fluorescein angiography; CME, cystoid macular edema.

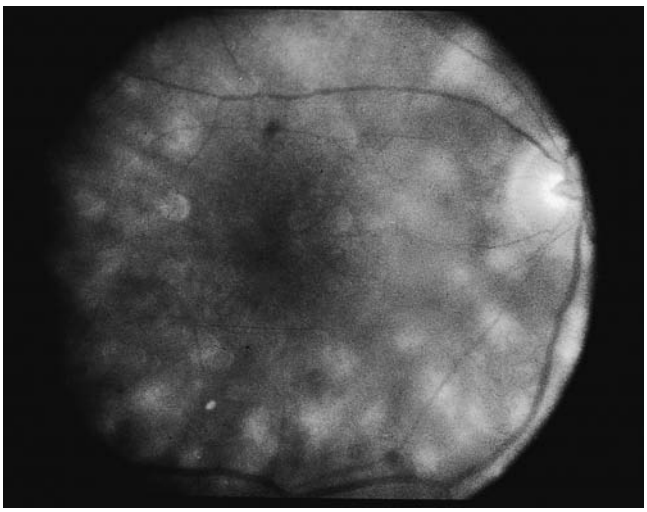


FIGURE 6–5. Birdshot retinochoroidopathy. Multiple ill-defined deep retinal or choroidal lesions are found in the macula and the post-equatorial retina. The macular details are hazy because of vitreous inflammation. Cystoid macular edema is present.

not absolutely necessary for the diagnosis of Stargardt disease[49] and in early life may not be present, subsequently developing along with other manifestations of the disorder.[50] Hyperfluorescent window defects are seen in areas of macular atrophy. Flecks may show an irregular pattern of hyperfluorescence or may appear nonfluorescent.

Are Other Tests Helpful?

Electroretinography is usually normal, although the amplitudes may be moderately decreased in long-standing cases.[45,46,50] The electrooculogram (EOG) also may be subnormal.[45,46,50] Color vision testing can show a mild red–green dyschromatopsia.[45,46,50] Some patients exhibit a prolongation in dark adaptation.[45]

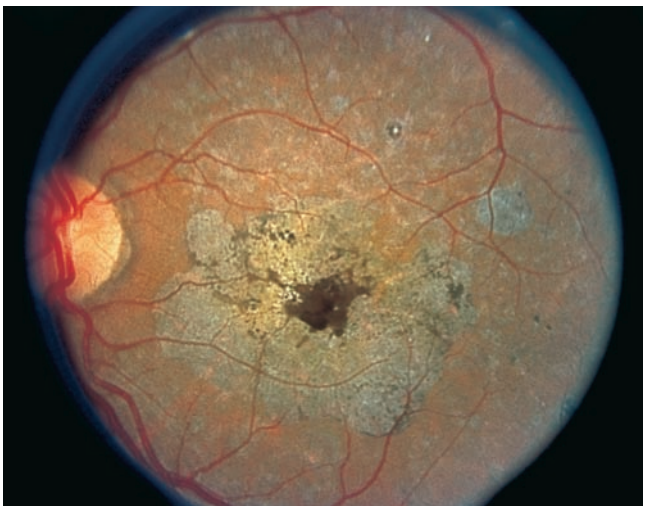


FIGURE 6–6. Stargardt disease. A central area of "beaten-bronze" macular atrophy with pigment clumping is present, surrounded by numerous deep retinal flecks.

What Is the Course of the Disease?

Once visual acuity decreases to a level of 20/40, many patients exhibit a rather rapid deterioration of vision to 20/200.[49] Vision tends to stabilize at 20/200, although it may fall to finger counting in longstanding cases. Although visual loss is usually symmetric, asymmetry may exist between the two eyes. The clinical course may be influenced by the specific mutations present and perhaps by other modifying genes or environmental factors.

Is There Any Treatment?

Whereas no treatment exists for Stargardt disease at present, the avoidance of light exposure (i.e., wearing sunglasses) may be beneficial.

Age-Related Maculopathy

Who Is Affected?

The International Epidemiological Age-Related Maculopathy Study Group has defined age-related maculopathy (ARM), also called age-related macular degeneration, as a degenerative disorder of persons aged 50 years or older. It is characterized by the presence of soft drusen at least 63 μ in the greatest linear dimension, and areas of hyperpigmentation or hypopigmentation associated with drusen.[51] The incidence and prevalence of ARM increase with advancing age. Ethnicity appears to be an important determinant of ARM. Early ARM is observed more frequently among white than among black and Hispanic persons,[52–54], and the rate of visual loss from choroidal neovascularization is much greater in white populations. Certain families have been reported to manifest a predilection for the development of ARM.[55–57] The respective roles of genetics or of shared environmental factors in these familial cases have yet to be elucidated.

What Symptoms Are Typical?

Many patients with early ARM are asymptomatic, and the diagnosis is made on routine ophthalmic examination. Patients with centrally located drusen may present with blurred vision or metamorphopsia. Difficulty with reading, especially in dim light, and decreased dark adaptation are common symptoms. Contrast sensitivity is frequently diminished, at times to a greater extent than Snellen acuity. An acute drop in vi-

sual acuity or the abrupt onset of metamorphopsia is suggestive of neovascular ARM.

What Are the Characteristic Ocular Manifestations?

Nonneovascular ARM is characterized by drusen, geographic atrophy, and focal hypopigmentation or hyperpigmentation of the RPE. Drusen are focal, whitish yellow sub-RPE nodules that vary widely in size and morphology. They may be categorized as hard (small, round, and discrete) or as soft (larger and poorly defined), or calcific. Drusen typically are clustered in the macula, but they may be found anywhere in the fundus. Whereas the number and size of drusen tend to increase with time, in some cases they disappear, occasionally leaving areas of geographic atrophy in their wake.

In neovascular ARM, new blood vessels grow from the choriocapillaris through damaged Bruch membrane into the sub-RPE or subretinal space. Clinical manifestations may include intraretinal, subretinal, or sub-RPE blood; fluid beneath the RPE or retina; cystoid macular edema; intraretinal or subretinal hard exudates; subretinal gray or pigmented membranes; or subretinal fibrous tissue.

Well-defined, blister-like retinal pigment epithelial detachments (PEDs) are seen in ARM and may result from blood (hemorrhagic PED), fluid (serous PED), or choroidal neovascularization (fibrovascular PED) beneath the RPE, or from coalescent drusen (drusenoid PED).

What Does Angiography Show?

The appearance of drusen on fluorescein angiography is variable. Hard drusen more frequently hyperfluoresce early and fade with the background choroidal fluorescence, whereas larger, soft drusen typically do not fluoresce until the later phases of the angiogram.

The cause of retinal PEDs may be elucidated by fluorescein angiography. Hemorrhagic PEDs show blocked fluorescence; serous PEDs exhibit early, well-delineated, uniform hyperfluorescence that persists into the late phase of the angiogram; fibrovascular PEDs present with stippled hyperfluorescence, which leaks in the late phase; drusenoid PEDs hyperfluoresce early or late and variably stain in the late phase of angiography.

Choroidal neovascularization (CNV) is classified as either classic or occult. Classic CNV can be identified by its early, well-delineated hyperfluorescence that leaks into the later phases of the angiogram.[58] Discrete vessels may be identified in the early phases. Occult CNV is characterized by two types of patterns on fluorescein angiography: (1) a fibrovascular pigment epithelial detachment, an irregular elevation of the RPE with ill-defined, stippled hyperfluorescence in the midphase of the angiogram and late leakage; or (2) late-phase leakage of an undetermined source.[58]

Often ICG angiography is of benefit in determining the presence of CNV or in better localizing CNV in the presence of hemorrhage or with serous PEDs, where the bright early hyperfluorescence on fluorescein angiography may obscure the CNV. Choroidal neovascularization may appear as a "hot spot," a small, discrete area of hyperfluorescence one disc area or smaller in size; as a plaque, an area of hyperfluorescence greater than one disc area in size that may be well or poorly defined; or as a combination of the two.[59]

What Is the Course of the Disease?

Patients with drusen and RPE mottling frequently exhibit only mild to moderate visual loss. Those who develop advanced geographic atrophy of the central macula or neovascular ARM are likely to become legally blind in that eye. Patients over the age of 65 with bilateral drusen have a 24% chance over 3 years of developing a new atrophic or neovascular lesion that results in visual loss.[60] Multiple large drusen and focal RPE hyperpigmentation are high-risk features for subsequent choroidal neovascularization.[61] Patients with CNV in one eye have a reported risk of 7 to 10% per year of developing CNV in the fellow eye;[62,63] this risk increases to 60% over 5 years if both large drusen and RPE hyperpigmentation are present.[63]

Is There Any Treatment?

There is currently no proven treatment for nonneovascular ARM. Dietary intake of green, leafy vegetables containing the carotenoids lutein and zeaxanthin was found to be associated with a decreased risk of severe ARM.[64] The Age-related Eye Disease Study (AREDS) (see Chapter 21) demonstrated the efficacy or evaluated the side effects of micronutrient supplementation. A strong positive association between smoking and both wet and dry ARM has been demonstrated in large, prospective studies,[65,66] and smoking cessation should be strongly encouraged.

Neovascular ARM with extrafoveal or juxtafoveal CNV should be treated according to the Macular Photocoagulation Study (MPS) guidelines.[67,68] For subfoveal CNV that is predominantly classic, photodynamic therapy (PDT) with verteporfin has been shown to reduce the risk of visual loss.[69] Verteporfin therapy also has been demonstrated to reduce the risk of moderate and severe vision loss significantly in subfoveal CNV that is occult with no classic component.[70]

Basal Laminar (Cuticular) Drusen

Who Is Affected by Basal Laminar Drusen?

Patients of all racial backgrounds may be affected by basal laminar drusen, which present in early adulthood to middle age.[71,72] No pattern of heredity has been established.

What Symptoms Are Typical?

Patients are characteristically asymptomatic unless a vitelliform serous exudative detachment develops; this is when patients typically present with metamorphopsia and a moderate degree of visual loss.[71,73]

What Are Associated Systemic Features?

The vast majority of patients with this condition have no associated systemic condition; however, basal laminar drusen have been reported to occur in patients with type II membranoproliferative glomerulonephritis.[74,75] These patients may develop choroidal neovascularization at an early age.[76]

What Are the Characteristic Ocular Manifestations?

A myriad of tiny, discrete, round, yellow nodules that may be scattered randomly or grouped in clusters in the macular or paramacular area are seen on fundus examination. These drusen are more apparent angiographically than clinically.[71,72]

Some patients, usually middle-aged or older, may develop yellow serous exudative detachments of the macula in one or both eyes.[71–73] These detachments may resemble the vitelliform lesions seen in Best disease or with pattern dystrophy (Fig. 6–7). The subretinal fluid typically resolves spontaneously over the course of several months. Although some patients regain excellent visual acuity, in others geographic atrophy and poor visual acuity result following resolution of the fluid.[72]

What Does Angiography Show?

Hundreds of drusen fluoresce brightly in the early phases of the fluorescein angiogram, creating a "stars in the sky" appearance.[71,72] In serous detachments, the yellow subretinal fluid typically blocks fluorescence early in the course of the angiogram, with late fluorescein filling of the detachment.[71–73]

Are Other Tests Helpful?

Both ERG and EOG are normal in patients with basal laminar drusen.[72]

What Is the Course of the Disease?

Many patients retain excellent visual acuity. Those patients who develop geographic atrophy following resolution of serous detachments may have significant loss of vision. Choroidal neovascularization may develop, although probably less frequently than in those patients with ARM.[71]

Is There Any Treatment for Basal Laminar Drusen?

There is no known treatment for basal laminar drusen or for the vitelliform serous detachments that may occur. In the event that choroidal neovascularization develops, the treatments for CNV apply.

Best Disease (Vitelliform Dystrophy)

Who Is Affected?

Best's disease is inherited in an autosomal-dominant fashion with variable penetrance and expressivity. Some persons who carry the defective gene have a normal fundus and visual acuity, although their EOGs exhibit the same decrement as affected patients.[77] Men and women are equally affected. The gene for Best disease has been mapped to chromosome 11q13.[78]

What Symptoms Are Typical?

Visual acuity is initially normal, and the early lesions may be found on routine ophthalmoscopy. Decreased visual acuity is the main symptom and most frequently presents in later childhood or young adulthood.

What Are the Characteristic Ocular Manifestations?

Best's disease evolves through a series of stages.[79,80] In the *previtelliform stage*, the fundus appears normal or may exhibit a small yellow dot centrally. In most cases, the typical vitelliform lesion appears in the first few years of life, although in some patients the fundus and visual acuity remain normal. In some patients, multiple vitelliform lesions may be observed in the posterior pole, a variant described as multifocal Best disease[81] (Fig. 6–8).

In the *vitelliform stage*, a large yellow, yolk-like lesion appears in the macula at the level of the RPE. These lesions, which appear in infancy or early childhood, are typically bilateral and symmetrical. Visual acuity is usually normal at this stage.

In the *scrambled-egg stage*, there is disintegration of the vitelliform material with irregular subretinal deposits. Visual acuity may be reduced to the 20/30 to 20/40 level.

The *pseudohypopyon stage* occurs when the yellow material gravitates inferiorly in the subretinal space. Areas of RPE atrophy and pigment clumping may be

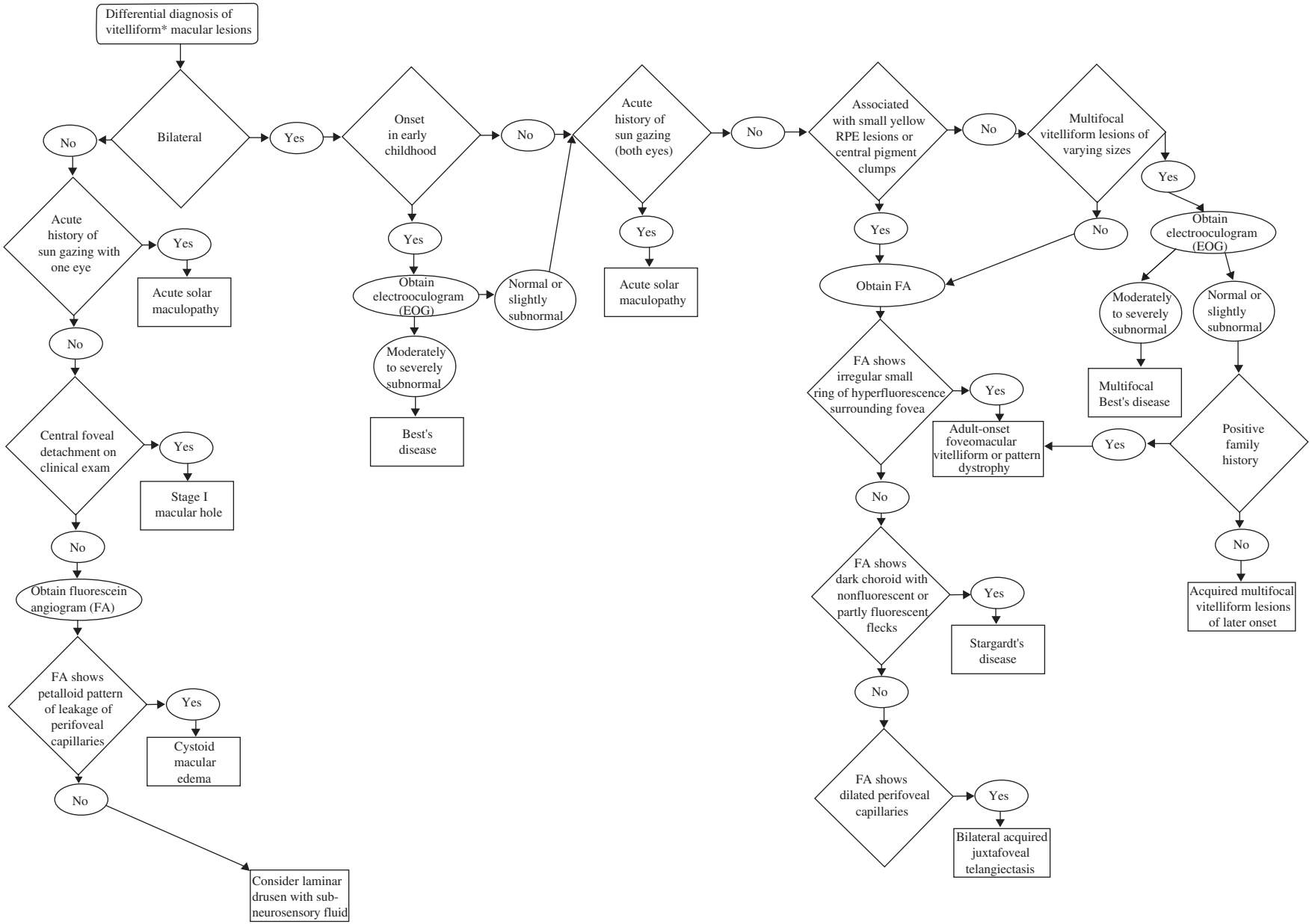


FIGURE 6–7. Differential diagnosis of vitelliform macular lesions. RPE, retinal pigment epithelium.

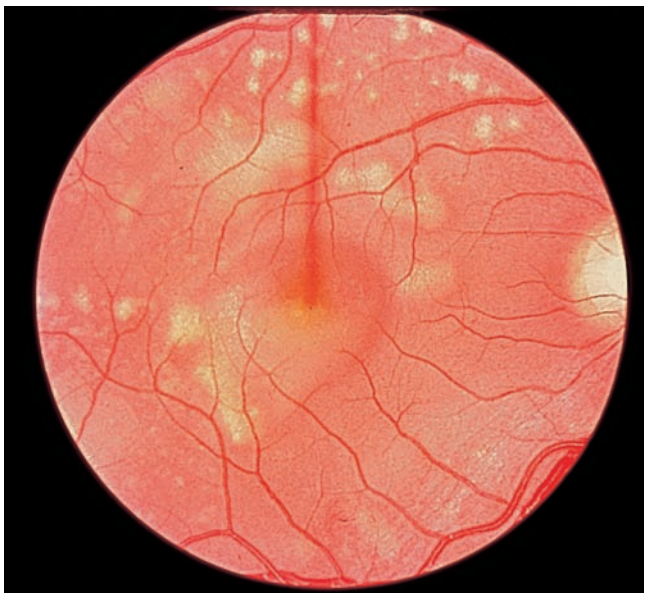


FIGURE 6–8. Multifocal Best disease. The central vitelliform lesion is in the "pseudohypopyon" stage, with layering of the yellow material inferiorly. Multiple smaller vitelliform lesions are present in the posterior pole.

observed. This stage is frequently reached in the teen years.

Ultimately, the vitelliform lesion disappears completely, leaving a round area of geographic atrophy, referred to as the *atrophic stage*. White fibrous scar tissue without choroidal neovascularization can develop in the macula, but CNV may also occur adjacent to chorioretinal scars.[82]

What Does Angiography Show?

There is blockage of fluorescence by the vitelliform material in the *egg-yolk stage*. With disruption of the vitelliform lesion, hyperfluorescent window defects from atrophic RPE changes become apparent. Fluorescein and ICG angiography are useful in detecting CNV.

Are Other Tests Helpful?

A definitive diagnosis of Best's disease can be made with EOG.[83] An Arden (light-to-dark) ratio of less than 1.5 is characteristic, allowing differentiation of Best disease from other conditions with vitelliform macular lesions (Fig. 6–7).

What Is the Course of the Disease?

Typically, a gradual decrease in vision over a period of years is the norm, although vision loss may be sudden with CNV. Visual loss is frequently asymmetric despite similar fundus findings.[84] Eyes with an atrophic macula or a fibrous macular scar have worse visual acuity than eyes with other stages of the disease.[81] Of patients aged 40 years and younger, 76% were found to have 20/40 or better visual acuity in their better eye, although only 20% of patients older than 40 years retained this level of visual acuity.[84]

Is There Any Treatment for Best Disease?

There is no known treatment for vitelliform dystrophy, although secondary CNV may at times be treatable. Genetic counseling is important because persons with the defective gene have a 50% chance of passing it to each biological child.

Fundus Albipunctatus

Who Is Affected?

Fundus albipunctatus demonstrates an autosomal-recessive inheritance pattern. Mutations in the *RDH5* gene located on chromosome 12q13-q14 have been identified in patients with the disorder.[85,86]

What Symptoms Are Typical?

Patients present with night blindness in childhood. The disorder is congenital and nonprogressive.[87] Visual acuity, color vision, and visual fields are normal.[87–89]

What Are the Characteristic Ocular Manifestations?

There is a distinctive fundus picture of a multitude of small, regularly spaced, discrete white spots at the level of the RPE (Fig. 6–9). The lesions are most dense posteriorly, spare the central macula, and extend to the midperiphery. The number of spots may increase over time.[87]

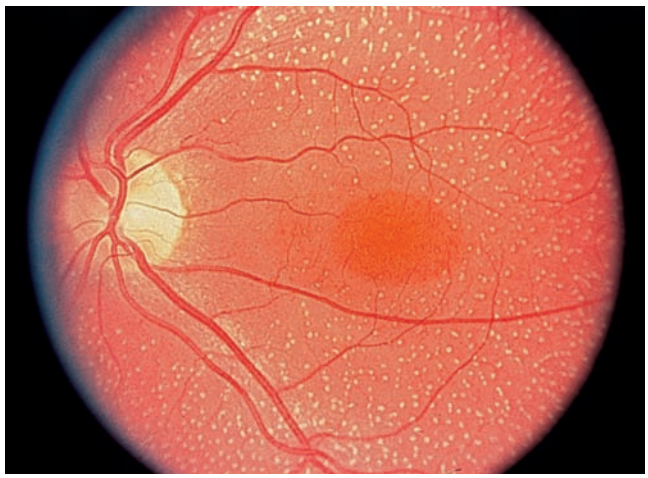


FIGURE 6–9. Fundus albipunctatus. A distinctive pattern of uniformly spaced, discrete white spots which spare the macula is characteristic of this disorder.

What Does Angiography Show?

On fluorescein angiography, there is a mottled pattern of hyperfluorescence throughout the midperiphery of the fundus that spares the macula. These focal window defects do not appear to correlate with the white spots.[88,89]

Are Other Tests Helpful?

A markedly delayed regeneration of both rod and cone visual pigments results in the prolongation of dark adaptation of both rod and cone segments.[90] ERG and EOG results may be subnormal, but normalize following dark adaptation.[88–90]

What Is the Course of the Disease?

Fundus albipunctatus is a congenital, nonprogressive condition,[87] which helps to distinguish it from retinitis punctata albescens (Fig. 6–4), a disorder with a similar appearance in childhood that exhibits progressive degenerative retinal changes both clinically and electrophysiologically.

Is There Any Treatment?

There is currently no treatment for this disorder.

Tamoxifen Retinopathy

Who Is Affected by Tamoxifen Toxicity?

Tamoxifen citrate is a nonsteroidal antiestrogen used in the treatment of patients with breast cancer. Patients receiving high doses of tamoxifen may develop a crystalline retinopathy with macular edema and retinal pigment epitheliopathy. Early reports of this condition were in women who had received doses of greater than 180 mg per day for greater than 1 year.[91] Currently, the drug is used at much lower doses. Cases of retinopathy occurring with long-term, low-dosage tamoxifen have also been reported[92–94] but are rare and do not affect vision significantly in most patients.

What Symptoms Are Typical of Tamoxifen Retinopathy?

Patients usually present with decreased vision, although crystalline retinopathy has been reported in asymptomatic patients.[95]

What Are the Characteristic Ocular Manifestations?

Small white refractile deposits in the inner retinal layers are most concentrated in the paramacular area (Fig. 6–10). Punctate gray lesions at the level of the RPE, cystoid macular edema, and corneal opacities may occur in conjunction with the crystalline retinopathy. Optic disc edema and retinal hemorrhages have been reported to develop shortly after the onset of low-dose tamoxifen therapy,[96] but it is unknown if these changes are truly related to the tamoxifen.

What Does Angiography Show?

On fluorescein angiography, the white macular crystals are nonfluorescent, the gray pigmentary lesions may block fluorescence, and late frames may demonstrate cystoid macular edema.

Are Other Tests Helpful?

Although it is not essential in making the diagnosis, ERG testing reveals decreased photopic and scotopic a- and b-wave amplitudes.[97]

What Is the Course of the Disease?

Macular edema resolves and visual function improves following cessation of tamoxifen therapy, but the crystalline deposits remain unchanged.[94,96]

Is There Any Role for Routine Screening of Patients Receiving Low-Dose Tamoxifen?

At current low dosage regimens of 10 to 20 mg per day, retinopathy is unusual, and routine screening of asymptomatic patients is not indicated.[95] Tamoxifen should be discontinued in symptomatic patients with clinical evidence of toxicity.

Canthaxanthine Retinopathy

Who Is Affected?

Canthaxanthine is a naturally occurring carotenoid dye that has been used in food coloring, in the treatment of a variety of dermatologic disorders, and in high doses as an oral tanning agent. The incidence of retinopathy correlates with the total dose of canthaxanthine ingested.[98] Persons with preexisting retinal disease and those using beta carotene are predisposed to developing retinopathy at a lower drug dose.[99,100]

What Symptoms Are Typical?

Patients are usually asymptomatic.

What Are the Characteristic Ocular Manifestations?

Golden crystalline particles found in the inner retina are distributed in a ring-shaped pattern around the fovea (Fig. 6–11). This distinctive funduscopic appearance in the setting of canthaxanthine ingestion is diagnostic (Fig. 6–10).

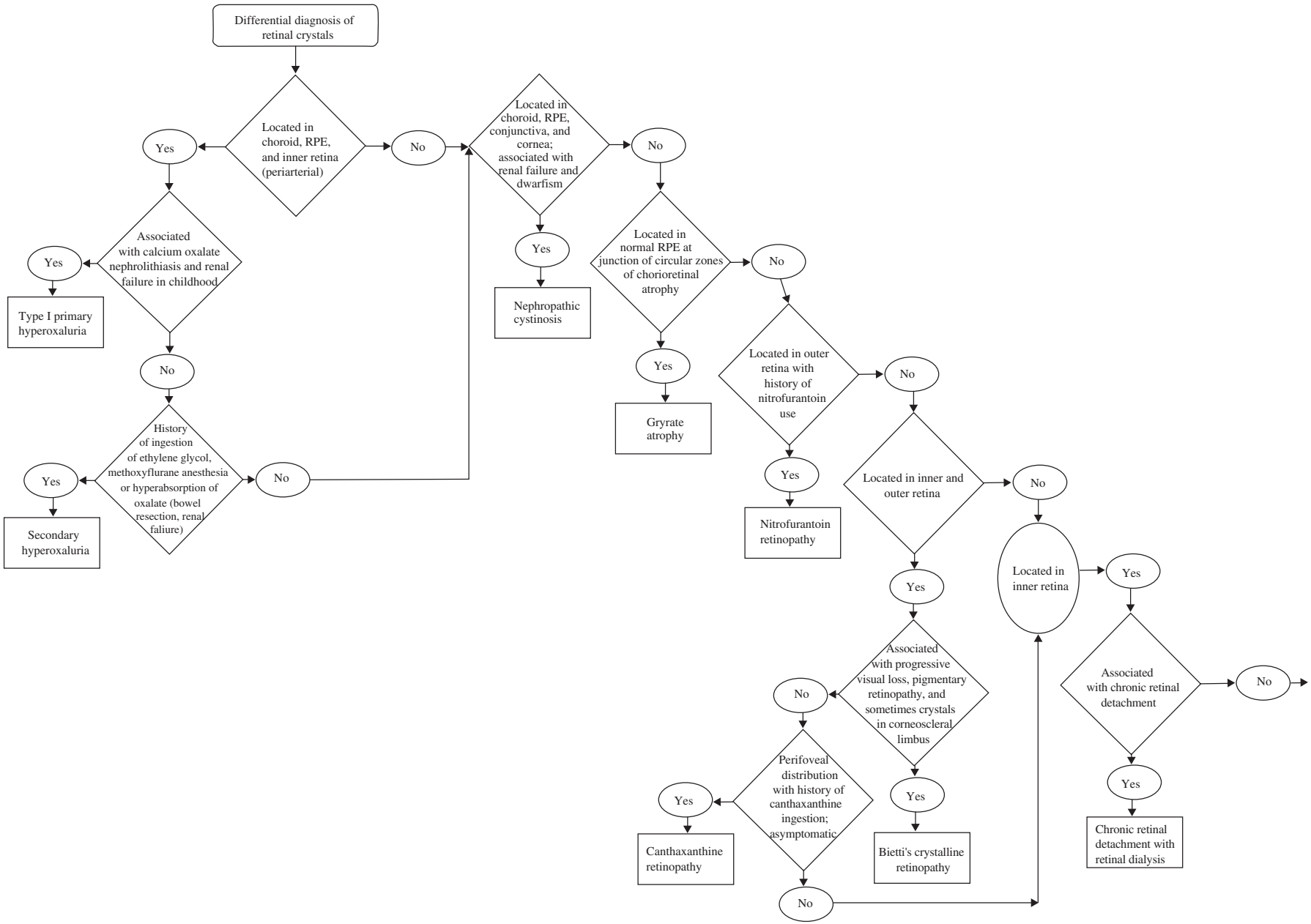


FIGURE 6–10. Differential diagnosis of retinal crystals. RPE, retinal pigment epithelium; CME, cystoid macular edema.

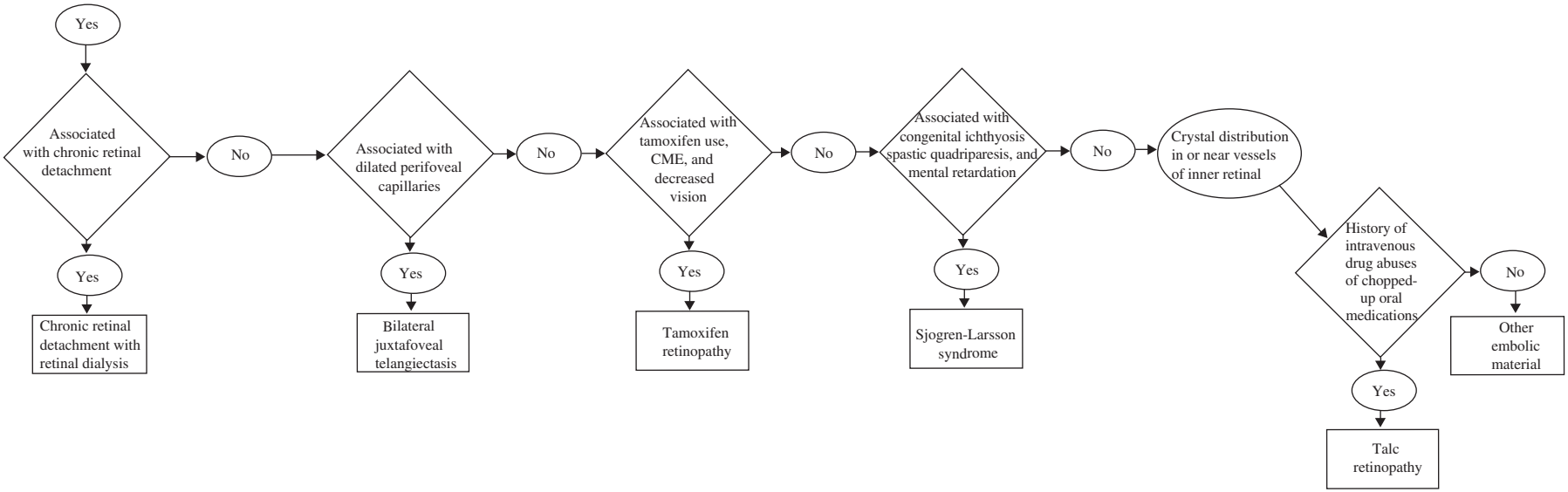


FIGURE 6–10. *Continued*

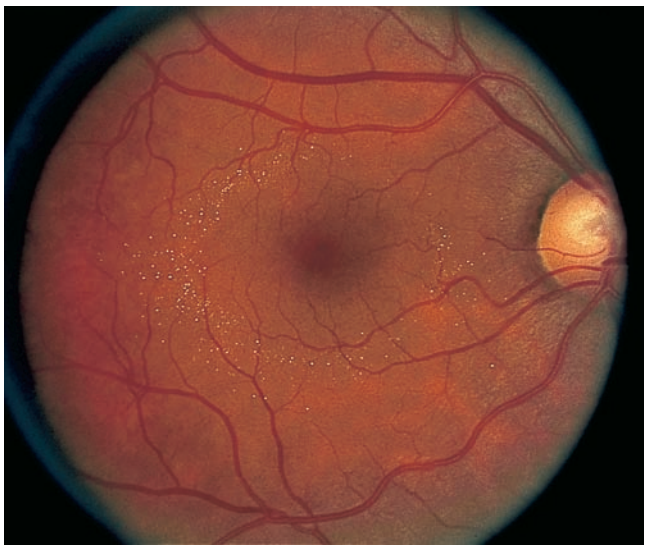


FIGURE 6–11. Canthaxanthine retinopathy. Highly refractile golden crystals surround the fovea in a ring-shaped pattern.

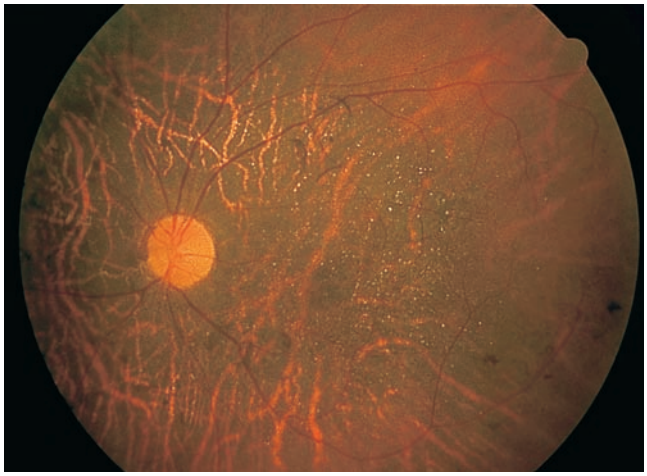


FIGURE 6–12. Bietti dystrophy. Crystals are seen most prominently in the temporal macula. Note the widespread area of atrophic retinal pigment epithelium and choriocapillaris with pigment clumping.

What Does Angiography Show?

Fluorescein angiography is usually normal, although a faint bull's-eye pattern of hyperfluorescence occasionally may be seen.

Are Other Tests Helpful?

Reduced retinal sensitivity using static threshold perimetry has been shown in patients with canthaxanthine retinopathy.[101] Electroretinography may be abnormal in some patients but may normalize following discontinuation of the drug.[102]

What Is the Course of the Disease?

The crystals disappear slowly, over a period of years, after canthaxanthine ingestion has stopped.[103]

Bietti Dystrophy

Who Is Affected?

Most patients become symptomatic between ages 20 and 40. Families with both autosomal-recessive and autosomal-dominant modes of inheritance have been studied, although most cases are sporadic. A gene for Bietti has been mapped to chromosome 4q.[104] One of the authors (L.M.J.) described a patient with Bietti crystalline dystrophy who had a mutation in the x-linked retinoschisis gene. The disease phenotype probably results from several distinct genetic mutations.

What Symptoms Are Typical?

Patients typically present with a slowly progressive decline in visual acuity.

What Are Possible Associated Systemic Features?

Analysis of peripheral blood lymphocytes and skin fibroblasts of affected patients has revealed cholesterol and complex lipid inclusions, suggesting that this condition may be a systemic disorder of lipid metabolism.[105]

What Are the Characteristic Ocular Manifestations?

Crystals are scattered throughout the posterior fundus in all layers of the retina (Fig. 6–10). Multiple areas of geographic atrophy of the RPE and choriocapillaris are seen in the posterior fundus, with crystals less apparent in these areas.[107,108] (Fig. 6–12) Crystals may be seen in the anterior stroma of the peripheral cornea.[106,107] The optic disc and vessels are normal in the early stages of the disease. With time there is progressive RPE atrophy and a decrease in the number of crystals.[107,109] Attenuation of retinal vessels and optic nerve pallor may also become apparent.[109]

What Does Angiography Show?

Hyperfluorescence secondary to window defects from RPE atrophy or blockage of fluorescence from pigment clumping may be seen. With progressive atrophy of the RPE and choriocapillaris, areas of hypofluorescence with prominent large choroidal vessels are present.

Are Other Tests Helpful?

Visual-field testing may reveal defects corresponding to areas of RPE atrophy. ERG and EOG testing have

been reported to be both normal and subnormal.[107,110,111]

What Is the Course of the Disease?

The disease tends to be slowly progressive. Areas of RPE and choriocapillaris atrophy become confluent and extend into the peripheral fundus. A progressive decline in ERG amplitude is noted, and symptoms of nyctalopia may become apparent.[109]

Is There Any Treatment?

There is no known treatment for Bietti dystrophy.

Cystinosis

Who Is Affected?

Cystinosis is an autosomal-recessive condition in which cystine accumulates within lysosomes because of a defect in its transport across the lysosomal membrane. Three distinct forms of cystinosis exist, in descending order of severity: infantile, juvenile, and adult. Infantile cystinosis has been mapped to chromosome 17p13.[112,113] The juvenile and adult forms of cystinosis are possibly allelic with the infantile form.[113]

What Symptoms Are Typical?

Photophobia and painful corneal erosions may occur as a result of superficial corneal crystals.

What Are the Associated Systemic Features?

The infantile form is associated with dwarfism and renal failure by the first decade. In juvenile cystinosis, renal dysfunction begins in adolescence. These patients have no associated growth abnormalities. Patients with adult cystinosis have normal renal function.

What Are the Characteristic Ocular Manifestations?

Patients with the infantile form of cystinosis may develop patchy mottling of the RPE, more marked in the periphery than in the macula, in early childhood.[114,115] Fine crystals within the choroid and RPE may be visible in some patients with the infantile form of the disease (Fig. 6–10).[116–119] Crystals of the cornea and conjunctiva are seen in all three forms of cystinosis. Crystals within the sclera, uvea, and extraocular muscles have been documented in the infantile and juvenile forms of the disease.

Are Other Tests Helpful?

Reduced rod and cone amplitudes on ERG and elevated dark-adaptation thresholds may be seen.[118]

What Is the Course of the Disease?

Renal transplantation is usually required by age 10 years in infantile cystinosis. There is continued accumulation of crystals in ocular tissues following transplantation, which may be accompanied by progressive photophobia, blepharospasm, and impairment of visual function.[118]

Is There Any Treatment for Cystinosis?

Topical cysteamine drops have been useful in decreasing corneal crystal deposition and in controlling symptoms of photophobia and surface irritation.[120]

Pneumocystis carinii (P. carinii) *Choroiditis*

Who Is Affected?

Pneumocystis carinii choroiditis is found in patients who are immunosuppressed. Patients with AIDS who contract this disease usually have a CD4 count below 200.[121]

What Symptoms Are Typical?

Patients may have visual symptoms if the foveal area is involved, but they may also be asymptomatic.[122]

What Are Possible Associated Systemic Features?

Choroiditis may be associated with *P. carinii* pneumonia (PCP). *P. carinii* choroiditis was more common when nonsystemically absorbed aerosolized pentamidine was used for prophylaxis of PCP[122,123] but is rarely seen now with systemic PCP prophylaxis.

What Are the Characteristic Ocular Manifestations?

Multiple yellow, round lesions with irregular borders are seen most frequently in the posterior pole or midperiphery (Fig. 6–13). These thickened, plaque-like choroidal lesions contain *Pneumocystis* organisms.[124,125] Lesions are bilateral in 75% of cases.[122] There is no associated vitreal or anterior segment inflammation.

What Does Angiography Show?

There is initial hypofluorescence with late staining of the lesions on fluorescein angiography.[122]

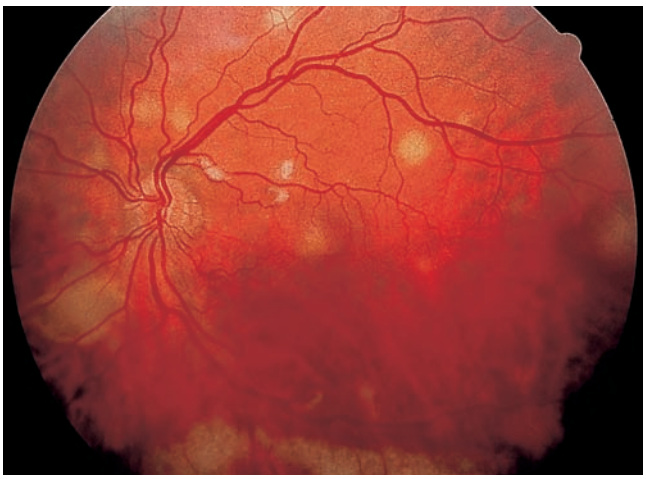


FIGURE 6–13. *Pneumocystis carinii* choroiditis. Multiple round, yellow choroidal lesions are found in the posterior pole of a patient with acquired immunodeficiency syndrome, or AIDS. The cotton-wool spots and intraretinal hemorrhage seen just temporal to the optic nerve are characteristic of human immunodeficiency (HIV) retinopathy.

Are Other Tests Helpful?

Biopsy and histopathologic examination of the choroidal infiltrates definitively establish the diagnosis.[126] A presumptive diagnosis may be made with a characteristic fundus appearance in the setting of PCP or disseminated pneumocystosis (Fig. 6–2). If the lesions fail to respond to treatment, the possibility of a coexisting infection of the choroid with organisms such as *Cryptococcus neoformans* or *Mycobacterium avium-intracellulare* should be considered.[127,128]

What Is the Treatment?

Intravenous or oral pentamidine, dapsone, or trimethoprim–sulfamethoxazole may be effective in the treatment of *P. carinii* choroiditis.[122,123,129]

What Is the Course of the Disease?

The lesions enlarge slowly before initiation of systemic anti-*Pneumocystis* therapy and then may take weeks to months to resolve.[122]

Hard Exudates

What Are Hard Exudates?

Hard exudates are small, discrete yellow deposits found most commonly in the posterior pole. They are formed when lipid residues precipitate in the inner and outer plexiform layers of the retina following resorption of serous fluid.

In Which Conditions May Hard Exudates Be Seen?

Hard exudates may be seen in diabetic retinopathy, hypertensive retinopathy, retinal venous occlusions, choroidal neovascular membranes, parafoveal telangiectasis, arterial macroaneurysm, retinal capillary hemangioma, Coats disease, radiation retinopathy, and Leber stellate neuroretinitis.

Are Patients with Hard Exudates Symptomatic?

Hard exudates themselves may result in loss of vision if located in the fovea, although the conditions with which they are associated may cause loss of vision unassociated with the hard exudates.

What Does Angiography Show?

There is no blockage or uptake of fluorescein by hard exudates.

With What May Hard Exudates Be Confused?

Drusen, crystals, or talc emboli at times may be confused with hard exudates. Drusen are located deeper, at the level of the RPE and Bruch membrane, than are intraretinal hard exudates. Crystals have a more refractile appearance and typically a more regular, distinctive distribution than do hard exudates. Talc emboli have a more glistening appearance than do hard exudates and are seen within the retinal vasculature.

Photocoagulation Burns

How Do Photocoagulation Burns Appear on Fundus Examination?

The burns are seen as gray to white circular spots at the level of the RPE and outer retina immediately after treatment. They fade initially, with subsequent well-demarcated gray or yellow atrophic spots with variable degrees of pigmentation.

In What Conditions Is Laser Photocoagulation Used?

In ischemic retinopathies with neovascularization of the retina or iris, laser photocoagulation is used to reduce selectively the amount of ischemic retina and decrease the release of angiogenic factors with resultant regression of neovascularization. Macular focal or scatter laser is used in diabetic retinopathy or in branch retinal vein occlusions to treat macular edema. Focal thermal laser also may be used to ablate choroidal neovascular membranes in ARM or in other conditions.

Are Patients with Photocoagulation Burns Symptomatic?

Decreased central visual acuity may occur with laser burns to the center of the macula. Patients may note paracentral scotomas with laser burns to the juxtafoveal or perifoveal area, particularly with the heavy focal laser used to treat CNV membranes. Over time, macular laser scars may enlarge and coalesce, possibly resulting in decreased visual acuity. Rupture of Bruch membrane with subsequent development of choroidal neovascularization can occur. Patients who have received extensive panretinal photocoagulation may note constriction of the visual field or decreased amplitude of accommodation.

What Does Angiography Show?

Window defects with RPE atrophy, blockage of fluorescence from pigment clumping, and hypofluorescence secondary to atrophy of the choriocapillaris may be seen on fluorescein angiography. Staining of the edges of the scars is seen in late frames.

With What May Photocoagulation Burns Be Confused?

The punched-out scars of multifocal choroiditis or the ocular histoplasmosis syndrome may at times resemble laser scars, although typically they are fewer and of a more random distribution.

Cotton-Wool Spots

What Are Cotton-Wool Spots?

Cotton-wool spots are nerve-fiber layer infarcts that appear as areas of superficial retinal whitening, typically less than one-fourth disc area in size, and may be found singly or in multiples. Typically, they are located in the distribution of the radial peripapillary capillaries or along the retinal vascular arcades.

In Which Conditions Are Cotton-Wool Spots Seen?

Cotton-wool spots may occur in diabetic retinopathy, hypertensive retinopathy, collagen vascular diseases, AIDS, cardiac valvular diseases with emboli, retinal vein occlusions, retinal artery occlusions, ocular ischemic syndrome, radiation retinopathy, anemia, leukemia, papilledema, and many other conditions.

Are Patients with Cotton-Wool Spots Symptomatic?

Cotton-wool spots usually do not cause visual symptoms.

What Does Angiography Show?

Hypofluorescence with focal areas of retinal capillary nonperfusion corresponding to the areas of cotton-wool spots may be seen on fluorescein angiography.

With What May Cotton-Wool Spots Be Confused?

In AIDS patients, an early patch of CMV retinitis may be confused with a cotton-wool spot. A cotton-wool spot has feathery borders, whereas CMV retinitis has a more granular appearance and may be associated with mild anterior chamber or vitreous inflammation.

Dalen–Fuchs Nodules

What Are Dalen–Fuchs Nodules?

Small, discrete, yellow, elevated infiltrates are commonly seen in the midperipheral fundus of patients with sympathetic uveitis. They consist of lymphocytes and epithelioid cell collections between Bruch membrane and the RPE.[130] Similar changes may be seen with Harada disease.

In Which Patients Are Dalen–Fuchs Nodules Seen?

Dalen–Fuchs nodules are seen in patients with sympathetic ophthalmia, a bilateral, granulomatous panuveitis that follows penetrating ocular injury, intraocular surgery, or laser cyclocoagulation (Fig. 6–2).[131–134]

What Symptoms Are Typical of Sympathetic Ophthalmia?

Patients present with decreased visual acuity, photophobia, conjunctival injection, and decreased amplitude of accommodation.

What Are the Characteristic Ocular Manifestations?

A granulomatous panuveitis, generalized retinal edema, perivasculitis, papillitis, choroiditis, choroidal granulomas, and neurosensory retinal detachments may be present.[135]

What Does Angiography Show?

Multiple pinpoint areas of hyperfluorescence are seen at the level of the RPE, and these areas may enlarge during the course of angiography. Less frequently, hypofluorescent areas corresponding to gray choroidal granulomas are seen. They may appear similar to the angiographic findings of APMPPE, although the lesions of sympathetic ophthalmia stain less well in the late phase of angiography than do those in APMPPE.[135–138]

Are Other Tests Helpful?

Sympathetic ophthalmia is a clinical diagnosis. No serologic or immunologic tests are helpful in establishing the diagnosis. Ultrasonography demonstrates choroidal thickening.

What Is the Treatment for Sympathetic Ophthalmia?

Large doses of oral steroids typically are required to suppress inflammation initially.[135] After the inflammation has been controlled, the steroids should be tapered and the patients continued on a maintenance dose for several months to prevent recurrence of the inflammation. In some cases, other immunosuppressive agents may be required in addition to steroids to suppress severe inflammation or in place of steroids in patients who are unable to tolerate steroid therapy.[139–141]

What Is the Course of the Disease?

With early aggressive treatment, many eyes retain useful vision. Relapses following treatment are common, in some cases with long intervals between episodes of inflammation.[142,143] Long-term complications of recurrent inflammation include cataract, glaucoma, band keratopathy, proliferation of subretinal fibrous tissue, exudative and rhegmatogenous retinal detachments, hypotony, and phthisis bulbi.[144]

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7

Areas of Fundus Whitening: Geographic Whitening

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What Is Fundus Whitening, and Why Does It Exist?

Caucasians often have orange–yellow fundi, whereas persons with darker skin frequently have reddish brown fundi. The funduscopic color is a result of the pigment distribution in choroidal melanocytes and the retinal pigment epithelium (RPE). In addition to proper pigment distribution, a fundus of normal color also implies that the three main components of the fundus, the neurosensory retina, RPE, and choroid, are intact and functioning properly. Disruptions in pigmentary or structural components of the fundus may lead to color changes, including retinal whitening. Fundus whitening is often abnormal and may indicate the presence of ischemia, deposition of toxic or metabolic compounds (in the RPE or choroid), infection, or degeneration.

The macula contains xanthophyll (yellow) pigment. The foveal avascular zone (FAZ), a small, slightly concave area devoid of retinal capillaries and occupied by cones, is in the center of the macula. The anatomic fovea and foveola are contained within the center of the FAZ. The central retinal artery, derived from the ophthalmic artery, and its branches are located in the inner retina and supply circulation to all of the inner retinal layers, extending as posteriorly as the inner portion of the inner nuclear layer. The outer retina, from the outer portion of the inner nuclear layer to the RPE, is supported by the choriocapillaris. In some eyes, a cilioretinal artery, which branches from the ciliary circulation, supplies circulation to a portion of the inner retina between the optic nerve and center of the macula.[1]

The RPE is a single layer of cuboidal cells derived from neuroectoderm. The RPE extends from the margin of the optic disc to the ora serrata and is continuous with the pigment epithelium of the ciliary body. It is phagocytic and continually ingests membranes and disks shed by the outer segments of the photoreceptor cells. This process of shedding, phagocytosis, and photoreceptor renewal follows a daily rhythm. Some pathologic changes occur when the process of phagocytosis and renewal is impaired or affected by genetic defects, senescence, drugs, or dietary insufficiency[1] and may be affected by changes in color.

Other pathologies may occur when the RPE is affected or stimulated, leading at times to RPE, hyperplasia, migration, atrophy, and metaplasia. These changes may account for hyperpigmentation or geographic whitening.[1]

The choroid, a densely pigmented and richly vascularized layer, encases and nourishes the outer retina and RPE. The choroidal circulation is separate from the retinal circulation and is supplied by the short and long posterior ciliary arteries and anterior ciliary arteries. Choroidal arteries branch and decrease in diameter to form a monolayer of capillaries, the choriocapillaris. The four vortex veins located in the midperiphery drain blood from the choroid and anterior uvea. The stroma of the choroid has collagenous and elastic tissue with a variable number of melanocytes. The pigment in these melanocytes and in the RPE contributes to the orange color of the posterior segment. Thus, when there are disturbances in the choroid, such as in types of hereditary choroidal diseases or inflammatory conditions, the fundus changes its normal color and frequently appears to whiten.[1]

This chapter considers some of the conditions that may present as geographic fundus whitening. In cases of geographic fundus whitening, a thorough medical and ocular history of the patient is important to discern the class of disease: vascular diseases, choroidal dystrophies and degenerations, retinal dystrophies and degenerations, bull's-eye maculopathy; tumors, infections, uveitis, or idiopathic entities. Once the

class of disease is identified, a differential diagnosis associated with that category can be made.

It may be challenging to determine the correct diagnosis for geographic fundus whitening, but the process is facilitated by a carefully inquisitive and systematic approach.

What Are the Major Types of Fundus Whitening?

There are two major types of fundus whitening: (1) white or yellow spots and (2) geographic areas. The differential diagnosis for white or yellow spots is extensive and includes immunologic, infectious, and toxic causes and is addressed in Chapter 6.

What Can Cause Geographic Fundus Whitening?

Idiopathic, vascular, hereditary, toxic, metabolic, immunologic, and degenerative causes can present clinically as geographic fundus whitening. Careful recognition and identification of the disease location, extensive review of the patient's history and clinical course, and the proper use of diagnostic tools are necessary for proper diagnosis and management.

The appearance of the whitening is helpful in the differential diagnosis. Myelinated nerve fibers, for example, will block the underlying retinal vessels and atrophy, permitting visibility of the choroid, such as choroideremia, gyrate atrophy, and central areolar choroidal dystrophy will permit visibility of the overlying retinal vasculature. Associated signs such as vitreous cells may lead the clinician to the diagnosis of an infectious or inflammatory condition such as acute retinal necrosis (ARN).

Idiopathic Retinal Phenomena That Can Present as Geographic Whitening

Some funduscopic findings are "whitish" in appearance but are not linked to specific causes. Frequent observations include peripheral cobblestone degeneration, nonspecific chorioretinal atrophy, history of previous cryotherapy, and white with and without pressure. Among these, white with and without pressure are the most common incidental findings (Table 7–1).

White With Pressure, White Without Pressure

What Are These Changes?

These terms describe geographic areas of whitening in the midperipheral, equatorial, and peripheral retina. During indirect ophthalmoscopy without scleral depression, these areas are described as *white without pressure*. When a white reflex is detected with scleral depression, it is termed *white with pressure*.

What Is the Significance of These Observations?

The phenomena were described by Schepens in 1952 and initially were considered to predispose to retinal tears.[2] Freeman noted an increased risk for giant retinal tears in fellow eyes with white without pressure at the vitreous base.[3] Since then, no prognostic or diagnostic significance has been assigned to these reflexes.[4] White, with and without pressure, can be

TABLE 7–1. Differential Diagnoses of Incidental Findings of Geographic Fundus Whitening

Differential Diagnoses	*Decreased Vision*	*Vitreous Inflammation*	*Occasional Retinal Hemorrhages*	*History of Ocular Trauma*	*Presentation*		*Risk of Retinal Detachments, Tears*	*Asymptomatic*	*History of retinal detachments, Tears*
					Systemic Disease	*Visual Complaints*			
Acute retinal necrosis	X	X	X			X	X		
Progressive outer retinal necrosis	X	X	X		X	X			
Berlin edema (commotio retinae)				X		X			
Purtscher retinopathy				X	X	X			
Cobblestone degeneration								X	
History of previous cryotherapy									X

detected with coincidental posterior vitreous detachment, thought to represent an equatorial area where the vitreous remains attached to the retina.[5] It may also be present in eyes without apparent vitreous detachment. The nature and significance of these phenomena remain controversial.

What May Be the Pathophysiologic Mechanism of These Findings?

A light reflex results when the incident light is tangential to more dense bundles of vitreous collagen; this can lead to the appearance of white both with and without pressure.[6] Reflection of light from the collagen bundles can cause a white reflex or no reflex, depending on the orientation of the fiber bundles. Therefore, during examination with scleral depression, white or no white may be visible, depending on how scleral indentation distorts the globe and affects the reflex from the collagen fibers.[6]

How Are These Findings Treated?

Meticulous examination of the retina with scleral depression is indicated. In addition, careful documentation of such findings should be made in the medical records for future reference. Patients should have follow-up examinations every 6 to 12 months or sooner, if new symptoms of vitreous traction are experienced.

Retinal Vascular Diseases That Can Present as Geographic Whitening

Retinal tissues whiten when there is a lack of blood supply associated with arteriolar occlusion or ischemia. If the retina is damaged and opacified, the white color may persist even after perfusion is reestablished. Over time, the whitening fades as the inner retinal layers atrophy and become thinner. The three most common vascular diseases that lead to retinal whitening are ocular ischemic syndrome and central and branch retinal artery occlusion (Fig. 7–1).

Ocular Ischemic Syndrome

What Is Ocular Ischemic Syndrome?

Ocular ischemic syndrome (OIS), described by Kearns and Hollenhorst,[7] most often results from severe carotid artery obstructive disease or thrombosis. It has also been called *ischemic ocular inflammation*[8] and *ischemic coagulopathy*.[9,10]

Who Is at Risk for Ocular Ischemic Syndrome?

There is no racial predilection associated with OIS, but men are affected more frequently than women. OIS often affects older persons; patients usually are diagnosed in the fifth to the eighth decade of life.[11] Either eye can be affected; bilateral ocular involvement occurs in 20% of patients.[11] Generally, 90% or greater stenosis of the ipsilateral carotid arterial system is present in eyes with OIS.[10] Often, a 90% carotid stenosis is required to reduce the perfusion pressure of the ipsilateral central retinal artery perfusion pressure by about 50%.[12,13]

What Are the Ocular Manifestations of Ocular Ischemic Syndrome?

Both the anterior and posterior segment are involved in OIS. Anterior segment manifestations include rubeosis iridis, neovascular glaucoma, and uveitis (cells and flare). Rubeosis iridis occurs in up to 67% of eyes with OIS at the time of presentation and often is accompanied by flare.[10] Only 20% of eyes experience actual anterior chamber cellular inflammatory response, however.[10] Only 50% of eyes with OIS and rubeosis iridis have or develop elevated intraocular pressure, even if the anterior chamber angle is closed by fibrovascular tissue.[10] Neovascular glaucoma is seen in 35% of eyes with OIS.[10]

Posterior segment manifestations of OIS can include narrowed retinal arteries (in greater than 90%), dilated retinal veins (in greater than 90%), retinal hemorrhages (80%), neovascularization of optic disc (35%) and retina (8%), cherry-red spot (12%), cotton-wool spots (6%), spontaneous retinal arterial pulsations (4%), vitreous hemorrhages (4%), cholesterol emboli (2%), and ischemic optic neuropathy (2%).[10]

Most patients (more than 90%) with OIS have a history of visual loss in the affected eye(s). In two thirds of cases, the visual loss is gradual, whereas in 12% of patients, the visual loss is sudden. In cases of abrupt visual loss, a cherry-red lesion is often detected on funduscopic examination.[10,11]

In as many as 40% of cases, pain in the affected eye or orbital region is present. The pain, termed *ocular angina*, often is described as a dull ache.[10] The visual acuity of OIS patients varies tremendously at presentation, from as good as 20/20 to finger counting or worse.

What Causes the Cherry-Red Spot in Ocular Ischemic Syndrome?

Retinal whitening occurs secondary to ischemia, usually caused when the intraocular pressure exceeds the perfusion pressure within the central retinal artery, especially in eyes with neovascular glaucoma,[10] or less frequently from embolic obstruction in the central retinal artery. The fovea with residual perfusion from

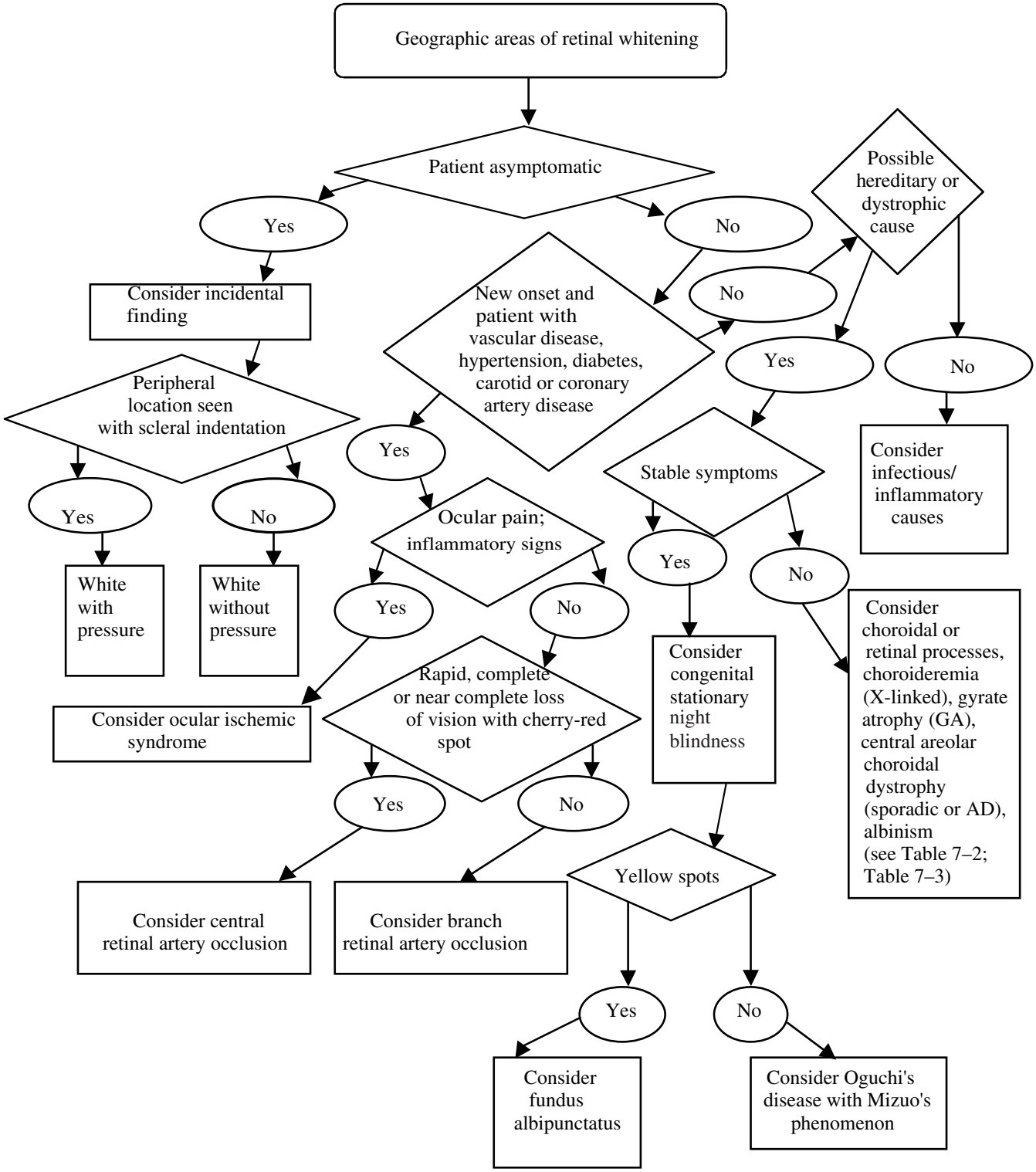

FIGURE 7–1. Clinical pathway: Geographic areas of retinal whitening. AD, autosomal dominant.

the underlying choroid can remain red and appears as a "cherry-red spot" in comparison with the surrounding white retina.

How Is Ocular Ischemic Syndrome Treated?

The diagnosis of OIS should be established and confirmed with ancillary studies such as fluorescein angiography, which can show a well-demarcated, leading edge of fluorescein dye within a retinal artery,[11] or electroretinography (ERG), which may reveal a diminution or absence of the amplitude of the A- and B-waves.[10] Carotid artery imaging is a required study. Duplex ultrasonography has less potential for serious complications and thus is preferred over carotid angiography.[14] In addition, ophthalmologists should correspond with primary care providers to arrange systemic evaluations for peripheral vascular diseases, cardiovascular diseases, hypertension, and diabetes.

Carotid endarterectomy is recommended and indicated when there is significant carotid disease. When there is 100% carotid artery obstruction, extracranial to intracranial bypass surgery, usually from the superficial temporal artery to the middle cerebral artery, may yield some benefits.[11] Medical therapy should be used to lower the intraocular pressure. After ipsilateral carotid endarterectomy, ocular hypertension can occur, which may require, in addition to medical therapy, ciliary body destructive procedures or glaucoma filtering surgery to control. In ocular ischemic eyes with rubeosis iridis and posterior segment neovascularization, panretinal laser photocoagulation may be required.[15]

Central Retinal Artery Occlusion

Who Is at Risk for Central Retinal Artery Occlusion?

Both men and women suffer from central retinal artery occlusion (CRAO); however, men are affected more frequently. The incidence of CRAO is estimated to be 1 per 10,000 outpatient visits.[16,17] The mean age at the time of presentation is in the sixth decade. Bilateral involvement occurs in 1 to 2% of cases.[18]

What Are the Ocular Manifestations?

Most patients with acute CRAO have a history of abrupt, painless visual loss. Unlike in OIS, the anterior segment is usually normal. If rubeosis iridis is detected at the time the obstruction occurs, the presence of concomitant carotid artery occlusion and a diagnosis of OIS should be considered.[17]

In acute CRAO, whitening occurs as a result of ischemic necrosis in the affected inner half of the retina.[17] The superficial retina becomes opacified and white-yellow, except in the foveolar region, where a cherry-red spot is present (Fig. 7–2). As in OIS, the cherry-red spot can vary in size, depending on the width of the foveola.

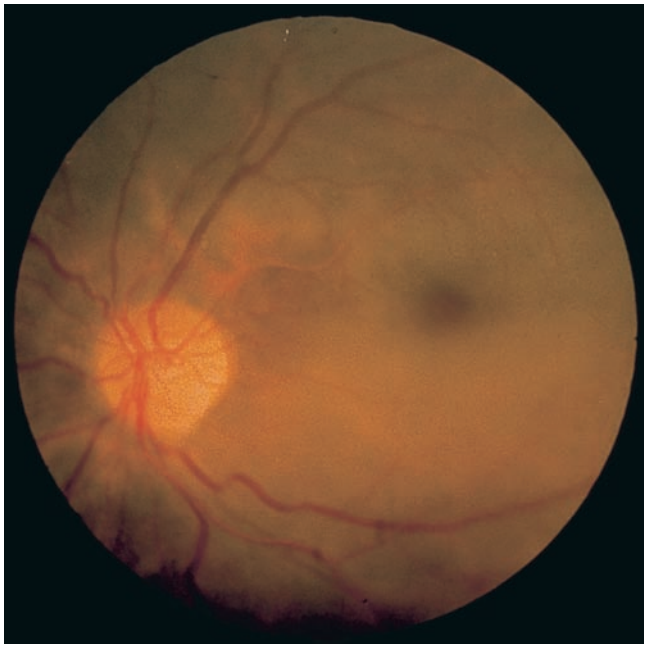

FIGURE 7–2. Central retinal artery occlusion (CRAO) in a 68-year-old woman with coronary artery disease and hypercholesterolemia. The retina has become opacified and has taken a white-yellow appearance, except in the foveolar region, where a cherry-red spot is present.

What Causes the Cherry-Red Spot?

In CRAO, most of the retina outside of the macula whitens secondary to ischemia; however, circulation to the foveolar region is partially supplied by the underlying choroid, thereby preventing complete ischemia when the central retinal artery is occluded. The foveolar region retains its reddish hue within the surrounding whitened retina, producing the cherry-red spot.[17] Retinal pigmentary changes may be seen if the choroidal circulation is involved. Segmentation of the blood column, or "boxcarring," may occur in arteries and veins when there is severe obstruction.[17]

What Is the Visual Prognosis?

Often, CRAO has severe visual morbidity. More than 90% of eyes with CRAO have visual acuity ranging between finger counting to light perception on initial presentation.[18] The presence of an embolus in the fundus usually is associated with poor vision. In about

25% of eyes with acute CRAO, there is a patent cilioretinal artery that supplies part or all of the papillomacular bundle.[19] If only part of the papillomacular bundle is spared, the visual acuity remains poor and is often no better than 20/100. If the patent cilioretinal artery spares the foveolar region, which occurs in approximately 10% of eyes, visual acuity can be maintained at 20/50 or better.[17,19] Initially, patients retain little central vision; however, a large degree of peripheral field often returns.[17]

How Is Central Retinal Artery Occlusion Treated?

There is no proven treatment for CRAO. The inner retina is highly sensitive due to loss of perfusion; thus, intervention usually is not attempted in any patient with an obstruction more than 72 hours old.

When a patient with acute CRAO is seen within 24 hours after the onset of visual loss, ocular massage can be attempted digitally with a Goldmann contact lens.[20] Administration of carbogen, (a mixture of 95% oxygen and 5% carbon dioxide) and anterior chamber paracentesis yield moderate success in some cases.[21] Some studies suggest that a high concentration of oxygen, such as with a hyperbaric oxygen chamber, may improve visual function.[22] Antifibrinolytic agents have been used,[23] although systemic complications, such as cerebrovascular accidents, can occur with this treatment. Systemic anticoagulants are not usually used.[24]

Branch Retinal Artery Occlusion

What Are the Characteristics of Branch Retinal Artery Occlusion?

Branch retinal artery occlusion (BRAO) occurs in 38% of acute retinal artery occlusion cases,[25] compared with CRAO (57%) and cilioretinal artery obstruction (5%). Based on clinical observations, the temporal retinal vessels are often involved in BRAO (in more than 90% of cases).[25] Nasal branch retinal arterial obstructions also commonly occur, but they often go unnoticed because they are asymptomatic.[17]

What Are the Ocular Manifestations?

Branch retinal artery occlusion appears as a localized region of superficial retinal whitening, most prominent in the posterior pole, along the distribution of the obstructed or occluded vessel.[17] Axoplasmic flow in the nerve-fiber layer is blocked as it reaches the hypoxic retina; this blockage leads to further whitening at the borders of ischemic areas.[17]

What Is the Visual Prognosis?

The visual prognosis in eyes with BRAO is much better than that of CRAO if the central foveola is not involved and not surrounded by retinal whitening. About 80% have a visual acuity of 20/40 or better, although residual field defects may remain.[16] There is no treatment for BRAO.

Hereditary Choroidal Diseases That Can Present as Geographic Whitening

Hereditary choroidal dystrophies can present with focal or generalized regions of choroidal whitening secondary to a degenerative process. Often, the initial diagnosis is made by physical examination; patients may have decreased central vision and a visual field defect. Ophthalmoscopy and fluorescein angiography usually demonstrate bilateral fundus abnormalities. Electroretinogram (ERG) and electrooculogram (EOG) may not be affected until the latter stages of the diseases. Hereditary choroidal dystrophies can be categorized into localized dystrophies (central areolar choroidal dystrophy, Sorsby fundus dystrophy, peripapillary choroidal dystrophy, progressive bifocal chorioretinal atrophy, and Bietti crystalline retinopathy) and generalized choroidal dystrophies (choroideremia and gyrate atrophy) (Table 7–2).[26]

Gyrate Atrophy

Gyrate atrophy is a type of progressive disorder associated with chorioretinal degeneration and autosomal recessive inheritance. It was first described as an atypical form of retinitis pigmentosa.[26] Gyrate atrophy is rare, reported to have an incidence of only one case per 50,000 individuals in Finland.[27]

TABLE 7–2. Differential Diagnoses of Geographic Fundus Whitening in Patients with Hereditary Choroidal Dystrophies

History of previous cryotherapy
Bietti crystalline retinopathy
Sorsby fundus dystrophy
Progressive bifocal chorioretinal atrophy
Peripapillary choroidal dystrophy
Kearns-Sayre syndrome
Age-related macular degeneration
Stargardt disease
Best disease
Pattern dystrophies
North Carolina dystrophy

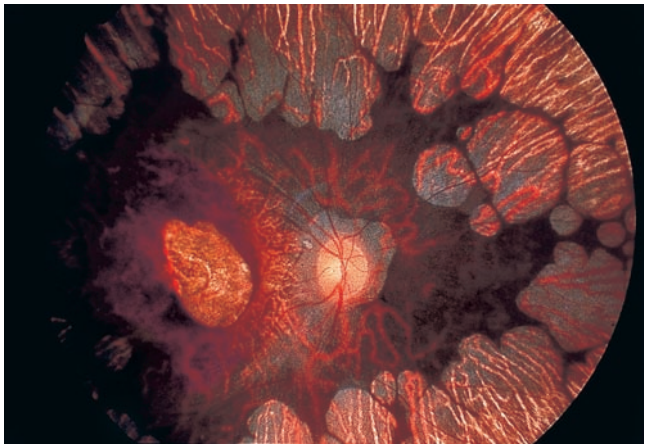

FIGURE 7–3. Gyrate atrophy. Areas of circular, well-circumscribed regions of chorioretinal atrophy, which have coalesced in a whitish, "scalloped" pattern. (Courtesy of Dr. Yozo Miyake and Dr. Koji Nishiguchi, Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan)

What Are the Clinical Manifestations of Gyrate Atrophy?

Nyctalopia, high myopia, and astigmatism are most often detected during the first decade. Posterior subcapsular cataracts usually develop by the second decade.[27,28] The disease continues to progress into the fourth and fifth decades with increasingly constricted visual fields and subsequent loss of central visual acuity.[27,28]

Circular, well-circumscribed areas of chorioretinal atrophy in the midperipheral retina are the hallmarks of gyrate atrophy. These areas enlarge and coalesce in a whitish, scalloped pattern (Fig. 7–3) spreading anteriorly and posteriorly. As the disease progresses to the macula, central vision is threatened.[26] Although gyrate atrophy is in the differential diagnosis of retinal whitening, its unique pattern of lesions is distinctive; thus, gyrate atrophy often is diagnosed clinically.

What Is the Genetic Defect in Gyrate Atrophy?

Patients with gyrate atrophy have been found to have plasma ornithine levels 10 to 20 times higher than those of controls, secondary to a deficiency in ornithine aminotransferase (OAT),[29] with two thirds of patients having no detectable OAT activity.[26,30] Other biochemical abnormalities include hyperornithinemia and reductions in plasma lysine, creatine, glutamine, and glutamate.[26,30]

The gene for OAT has been linked to chromosome 10q26 and has been cloned.[31] There have been more than 60 distinct mutations described in gyrate atrophy.[26,32]

How Is Gyrate Atrophy Treated?

Therapy has been geared to reducing plasma ornithine levels. In a small number of patients with the pyridoxine-responsive form of gyrate atrophy, supplemental pyridoxine reduces ornithine levels, although the effects on visual prognosis are not known.[33] In some patients, diets low in arginine, the precursor of ornithine, have been shown to delay the progression of visual deterioration.[34]

Choroideremia

Choroideremia[26] is an X-linked recessive disorder characterized by the progressive degeneration of the RPE, retina, and choroid.[35] In the first and second decades of life, patients present with problems with dark adaptation. By the sixth or seventh decade of life, patients may have varying degrees of central visual acuity loss and severe constriction of visual fields.[26]

What Is the Genetic Defect in Choroideremia?

The gene for choroideremia has been linked to chromosome Xq13-q22 and cloned.[36] The protein product of this gene in humans has been found to be identical to rat Rab escort protein (*REP1*), which is required for the function of Rab geranylgeranyl transferase in intracellular vesicular transport.[37] Although multiple mutations have been discovered in this gene, including deletions and translocations, they all result in protein truncation.[38]

What Are the Clinical Manifestations of Choroideremia?

Areas of pigment stippling and whitish focal atrophy of the RPE are initial fundus abnormalities, seen as early as the first decade in affected males and asymptomatic female carriers. The early features are similar to those seen in retinitis pigmentosa. With disease progression, choroidal atrophy increases, causing areas of whitening from greater visibility of the sclera. There is also photoreceptor and RPE loss, exposure of the choroidal vessels, and sparing of small areas of choroid in the macula and periphery[26] (Fig. 7–4). Visual function is severely impaired. There is no treatment to prevent or reverse choroideremia at present.

Central Areolar Choroidal Dystrophy

Central areolar choroidal dystrophy is a slowly progressive bilateral disease beginning in the second to fourth decade of life.[39] Most cases are sporadic, but some have autosomal-dominant inheritance. One gene has been localized to chromosome 17p25.[40]

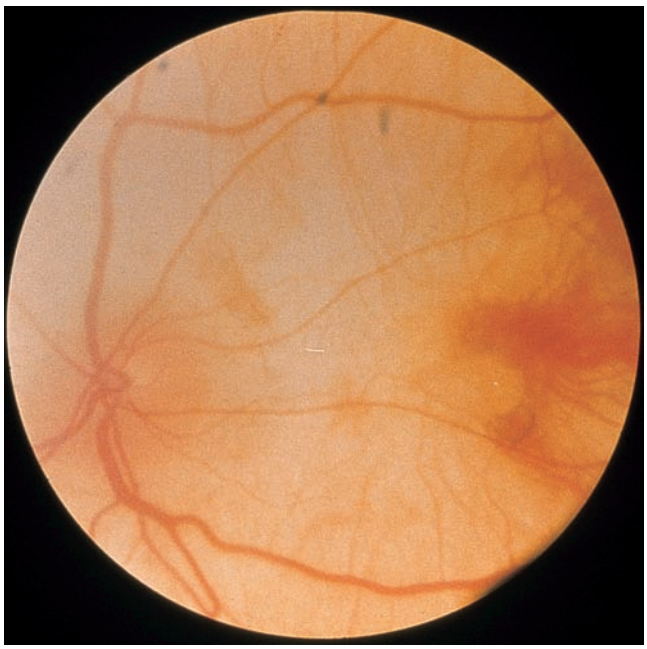

FIGURE 7–4. Choroideremia. The choroidal whitish atrophy has extended throughout the posterior pole with subsequent exposure of choroidal vessels.

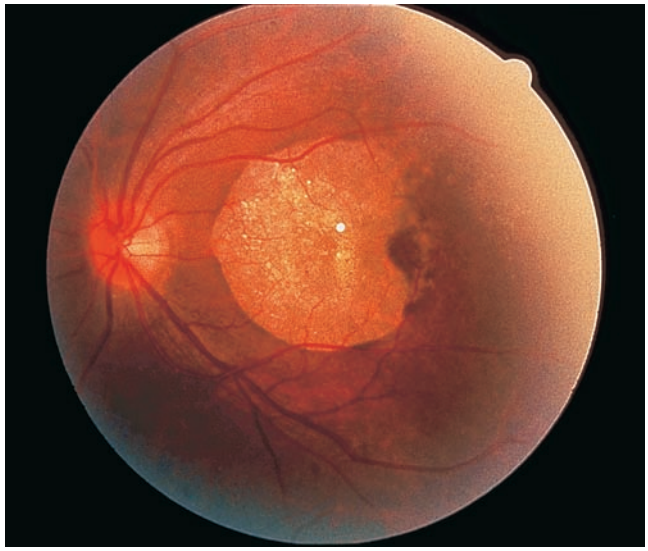

FIGURE 7–5. Central areolar choroidal dystrophy. A well-demarcated, circumscribed area of whitish atrophy of the photoreceptors, retinal pigment epithelium, and choriocapillaris has developed in the macula. (Courtesy of Dr. Yozo Miyake and Dr. Koji Nishiguchi, Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan)

WHAT ARE THE CLINICAL MANIFESTATIONS OF CENTRAL AREOLAR CHOROIDAL DYSTROPHY?

Initially, patients with central areolar choroidal dystrophy have normal visual acuity, but vision deteriorates by the fourth and fifth decades of life; at this stage, vision rarely becomes worse than 20/100. Visual acuity may fall to 20/200 by the seventh and eighth decades.[41]

In the early stages, there is nonspecific granular hyperpigmentation of the fovea.[42] Fluorescein angiography reveals window defects, indicating areas of RPE loss.[26] Later, a well-demarcated, circumscribed area of atrophy, representing loss of photoreceptors, RPE, and choriocapillaris,[43,44] develops in the macula (Fig. 7–5), permitting visibility of the underlying choroidal vessels.[43] Fluorescein angiography reveals early filling of the large choroidal vessels without a choriocapillaris flush and without physiologic blocking by RPE melanin of underlying fluorescence, indicating that the RPE and choriocapillaris are both severely affected.[26]

The diagnosis may be difficult to establish because other degenerations may present with a central area of RPE atrophy and choriocapillaris loss. Some conditions include geographic atrophy in age-related macular degeneration, late stages of Stargardt macular dystrophy, butterfly-shaped pattern dystrophy, and cone dystrophy.[26]

Retinal Degenerations and Dystrophies That Can Present as Geographic Whitening

Retinal degenerations and dystrophies can present with geographic fundus whitening. Age-related macular degeneration can be associated with geographic atrophy, fibrovascular scars, or confluent drusen leading to patches of whitening. Oculocutaneous albinism can be associated with conditions caused by a metabolic abnormality (e.g., tyrosinase deficiency). Cone dystrophy and some forms of congenital stationary night blindness, such as fundus albipunctatus and Oguchi disease (Fig. 7–6), are associated with areas of retinal whitening. Retinal degeneration associated with systemic conditions is seen as Kearns-Sayer and Bassen-Kornsweig syndrome.

Oguchi Disease

WHAT ARE THE CLINICAL MANIFESTATIONS OF OGUCHI DISEASE?

Oguchi disease is an autosomal-recessive form of congenital stationary night blindness. The disease is characterized by a gray–white discoloration of the retina with a metallic sheen in the posterior pole[45] (Fig. 7–6) that disappears after prolonged dark adaptation (Mitsuo phenomenon). On repeated exposure to light, however, the retina slowly reverts to its original metallic color.[46,47]

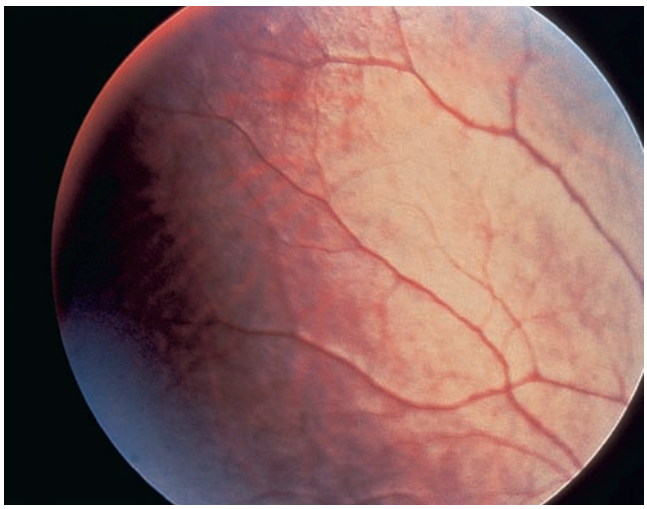

FIGURE 7–6. Oguchi disease. This form of congenital stationary night blindness is characterized by a gray-white discoloration of the retina that gives a metallic sheen to the funduscopic appearance. (Courtesy of Dr. Yozo Miyake and Dr. Koji Nishiguchi, Department of Ophthalmology, Nagoya University School of Medicine, Nagoya, Japan)

What Are Electroretinographic and Histopathologic Findings in Oguchi Disease?

The first ERG abnormality described was absence of the B-wave.[48] Later studies by Nagata found some evidence of scotopic function.[49] Studies by Carr and Gouras[50] found a normal scotopic response to the initial stimulus, with loss of this response after subsequent stimuli.[51]

An abnormal layer between the outer segments of the photoreceptors and the RPE was characterized by histopathologic and electron microscopic analysis and found to be abnormal cytoplasmic structures of the photoreceptor cell bodies (rods and cones).[52,53]

Recently, the unusual tapetal reflex and reversion to normal coloration following dark adaptation has also been described in cone dystrophy,[54] Stargardt disease,[55] and X-linked retinoschisis.[56]

Albinism

Albinism is associated with an inborn error of amino acid metabolism affecting the production of melanin. There are two common forms: oculocutaneous albinism and ocular albinism.

What Is Oculocutaneous Albinism?

Oculocutaneous albinism can be inherited as an autosomal-recessive or -dominant trait.[57] Most patients with ocular symptoms have the recessive form of the disease.[58] Patients without tyrosinase in their hair bulbs have whitish-blond hair, pale skin, severe photoaversion, nystagmus, macular dysplasia, subnormal visual acuity, light-colored irides with diffuse transillumination, and lack of pigmentation in the fundi.[58] Patients with tyrosinase in the hair bulbs usually have more ocular pigmentation and have fewer visual symptoms.[58]

There are three subtypes of tyrosinase-negative and eight subtypes of tyrosinase-positive oculocutaneous albinism. Chediak–Higashi and Hermansky–Pudlak syndromes, tyrosinase-positive types, have systemic associations. Patients with Chediak–Higashi syndrome have reticuloendothelial incompetence, which makes them susceptible to infection and lymphomatous disease, lymphadenopathy, hepatosplenomegaly, mental retardation, cytoplasmic inclusions in leukocytes, and death in childhood.[59] Patients with Hermansky–Pudlak syndrome often have a blood clotting abnormality (caused by defective glutathione peroxidase activity) and Cross syndrome (microphthalmos, opacified and vascularized corneas, skeletal anomalies, athetosis, and mental retardation).[60]

What Is Ocular Albinism?

Ocular albinism occurs in patients with a defect in melanogenesis confined to ophthalmic manifestations. The three major forms of ocular albinism are Nettleship–Falls X-linked type (the most common type of the three categories),[61,62] Forsius–Eriksson X-linked type (Aland Island disease),[63] and the autosomal-recessive type. The three types present with impaired visual acuity, translucent irides, photoaversion, hypopigmentation of the fundi, and macular dysplasia.[58] Some female carriers of the Nettleship–Falls type may demonstrate patchy areas of iris transillumination and a coarsely mottled or irregular change in the peripheral RPE.[58]

There is no known therapy for oculocutaneous albinism or ocular albinism.

Bull's-Eye Maculopathy That Can Present as Geographic Whitening

Bull's-eye maculopathy describes a number of conditions that cause RPE and, later, choriocapillaris and degeneration.

The toxic insults to the retina and RPE, such as from hydroxychloroquine, chloroquine, thioridazine, Thorazine, and deferoxamine; age-related macular degeneration; and a vast number of heredodystrophic diseases, including Stargardt disease and cone dystrophy, cause a bull's-eye appearance (Table 7–3 and Fig. 7–7).

TABLE 7–3. Differential Diagnoses of Geographic Fundus Whitening in Patients with Bull's-Eye Maculopathy

Age-related macular degeneration
Stargardt disease
Best disease
Pattern dystrophies
North Carolina dystrophy
Medication toxicity: hydroxychloroquine, chloroquine
Cone dystrophy
Batten disease
Fenestrated sheen macular dystrophy
Central areolar choroidal dystrophy
Metabolic dystrophies
Olivopontocerebellar atrophy

Toxic Diseases That Can Affect the Pigment Epithelium and Retina

Chloroquine and Hydroxychloroquine Retinopathy

Chloroquine and hydroxychloroquine are used to manage amebiasis, rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus. Prolonged use of chloroquine or hydroxychloroquine can lead to degeneration of the RPE and neurosensory retina.[64–67] Most patients who develop retinopathy have received daily doses of chloroquine greater than 250 mg or hydroxychloroquine more than 750 mg for at least a total dose of between 100 and 300 g.[68] The incidence of retinotoxic effects is lower following hydroxychloroquine therapy (see Chapter 21).[68–70]

What Are the Clinical Manifestations of Hydroxychloroquine/Chloroquine Maculopathy?

Paracentral visual field loss is an early sign of toxicity and may occur before the development of ophthalmic or electrophysiologic abnormalities.[67] The Amsler grid can be helpful in detecting early field defects.[71–74] Small paracentral scotomata to red light can be detected early in chloroquine toxicity.[74] The earliest ophthalmoscopic and angiographic changes in the RPE also occur in the parafoveal area,[67] with paracentral scotomata or minimal to no loss of visual acuity. Fluorescein angiography may demonstrate the faint bull's-eye pattern of hyperfluorescence preceding its biomicroscopic detection, particularly in patients with blond fundi.[67] In patients with darkly pigmented fundi, funduscopic evidence of RPE changes may precede angiographic changes.[67,73] An enlarging ring of RPE atrophy surrounding the fovea leads to a bull's-eye-like lesion that may be indistinguishable from other causes of bull's-eye maculopathy.[67] In later stages, the RPE degeneration extends into the foveolar area, causing central vision loss. Other disturbances caused by chloroquine include whitening of the lashes, a whorl-like pattern of subepithelial corneal deposits, decreased corneal sensitivity, and extraocular muscle palsies.[72]

How Is Hydroxychloroquine/Chloroquine Maculopathy Managed?

Any patient who requires more than 200 mg of chloroquine or who takes hydroxychloroquine daily should have periodic eye examinations; for example, every 6 months, including visual acuity and visual fields. Fundus photography is also useful for longitudinal follow-up. If there is biomicroscopic evidence of an RPE abnormality, sign of retinal degeneration, or family history of retinal degeneration, fluorescein angiography, perimetry, and other testing should be considered.[67] When chloroquine or hydroxychloroquine maculopathy is diagnosed, the medications should be altered or discontinued promptly.

Heredodystrophic Disorders That Affect the Pigment Epithelium and Retina

Cone Dystrophy

What Is Cone Dystrophy?

Cone dystrophy is a heritable dystrophy, often sporadic, but sometimes autosomal dominant or X-linked, that affects mainly the cone system. Late rod deficiency may develop in cases of cone-rod dystrophy.[75] The rate of progression and severity varies. The age of onset ranges from childhood to adulthood.[58]

What Are the Clinical Manifestations of Cone Dystrophy?

According to Gass,[58] the clinical features include (1) progressive visual loss, (2) disturbance of color vision even with minimal acuity loss, and (3) impaired vision in bright illumination and improvement in twilight or dim illumination and day blindness (hemeralopia). Signs include (1) normal or near-normal fundi in the early stages and later RPE atrophy in the macula, often progressing to a bull's-eye pattern; (2) temporal pallor of the optic disc; (3) evidence of depigmentation of the RPE in the macula, often preceding visible alterations in the fundi, on fluorescein angiography; (4) central scotoma with normal peripheral fields; and (5) abnormal photopic and flicker ERG responses.[58]

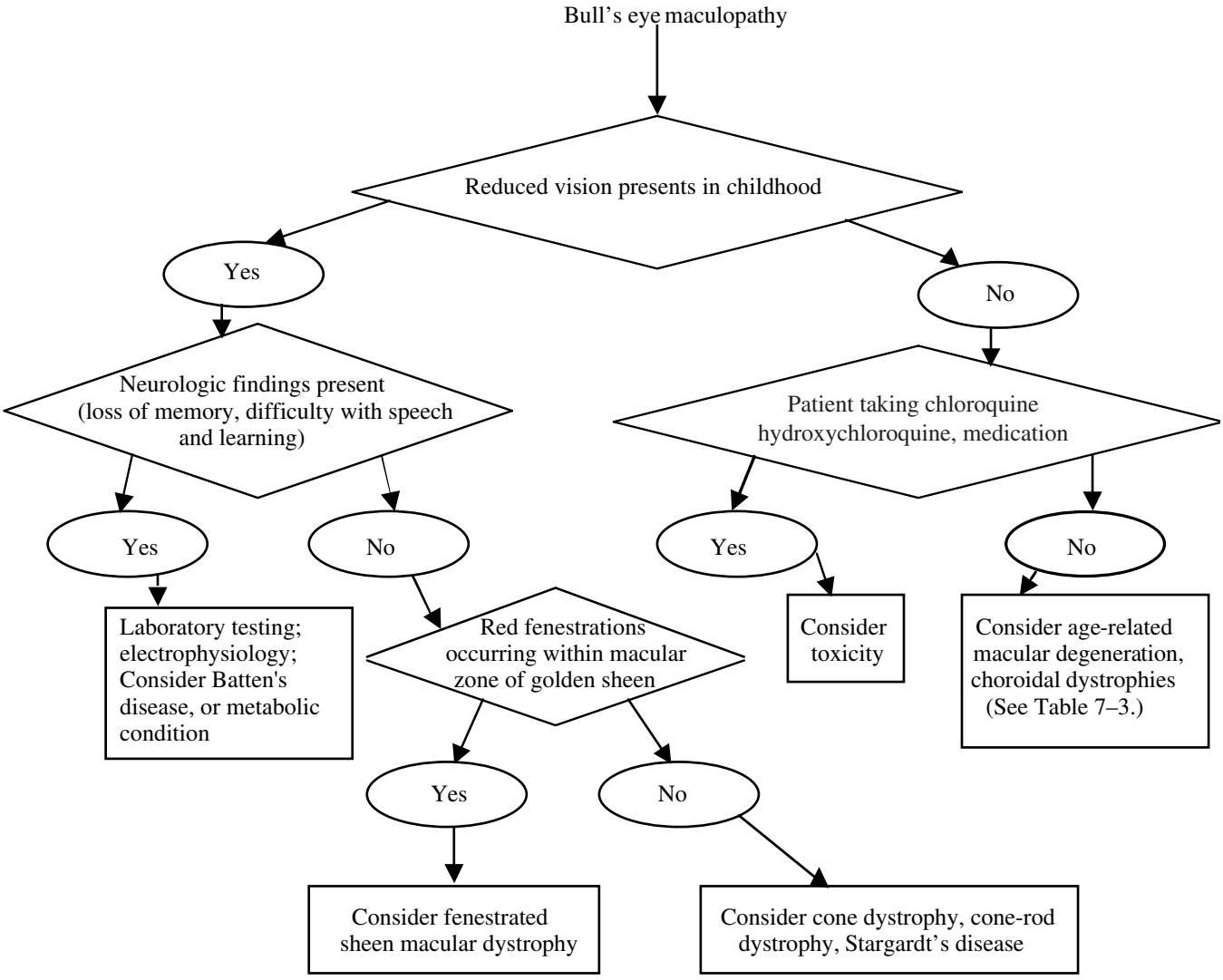

FIGURE 7–7. Clinical pathway: Geographic fundus whitening in patients with bull's-eye maculopathy.

The macula can be normal or demonstrate mottling and clumping of the pigment, a bull's-eye pattern of depigmentation, and focal chorioretinal atrophy.[76] The most common biomicroscopic and angiographic changes are the bull's-eye pattern of RPE atrophy and a corresponding zone of hyperfluorescence surrounding a central nonfluorescent spot.[58]

Patients with cone dystrophy and early onset of visual symptoms have a more aggressive form of the disease. Visual loss is usually, but not always, symmetric. Visual acuity varies from 20/20 in early stages to 20/200 or less in the later stages.[58]

Batten Disease

What Is Batten Disease?

Patients with Batten disease have a lysosomal storage abnormality that involves the accumulation of insoluble fluorescent lipoproteins, ceroid, and lipofuscin, pigments normally associated with aging[77–81] within multiple cell types, including neurons, smooth-muscle cells, glandular cells, Schwann cells, and vascular endothelium.[79–81] Patients with Batten disease can be divided into four groups on the basis of age of onset and the location of autofluorescent pigment deposition:[58] (1) infantile group (Haltia–Santavuori type); (2) late infantile group (Jansky–Bielchowsky type); (3) juvenile group (Spielmeyer type); and (4) adult form (Kuf disease).

What Are the Clinical Manifestations of Spielmeyer Disease, the Most Common Subgroup of Batten Disease?

The juvenile group (Spielmeyer type) constitutes the major subgroup of Batten disease. The disease is often

detected in childhood, with a peak age of 6 to 7 years, because of early advanced visual symptoms.[58,79] Neurologic disturbances such as loss of recent memory, speech difficulties, and learning disabilities often accompany the visual difficulty.[58,79]

Funduscopic examination initially may show mild RPE abnormalities. Later, the macula develops bull's-eye atrophy, followed by progressive changes in the RPE throughout the fundus. Narrowing of the retinal vessels and optic atrophy occur.[58] Fluorescein angiography can detect the early signs of the disease. Before onset of definite neurologic diseases, electroencephalography and ERG, often flat within the first decade, may be helpful to confirm the correct diagnosis.[58] Diagnostic findings in the juvenile type may include peripheral blood evaluation, which demonstrates vacuolated lymphocytes.[58,79–81] The patients suffer progressive neurologic symptoms, including seizures, often 1 to 2 years after the onset of symptoms, tremors, ataxia, dementia, and paralysis. Death usually occurs by age 20 years.[58]

Fenestrated Sheen Macular Dystrophy

Fenestrated sheen macular dystrophy is a rare autosomal-dominant macular disorder that usually is detected in young patients. Tiny red fenestrations occur in a central macular zone that has a golden sheen.[82] Multifocal areas of RPE hypopigmentation in the paracentral region develop in young adulthood and progress to a circular zone of depigmentation by the fourth or fifth decade of life.[82]

Visual acuity can be mildly affected in late adulthood. Disturbances in ERG, EOG, and color vision may develop.[58] There is a persistent sheen reflex that appears between the RPE and retinal vessels, but the central fenestration disappears as more changes in the RPE occur.[58]

Tumors of the Choroid That Can Present as Geographic Whitening

Distinguishing between choroidal malignancies, such as melanomas, and benign processes, such as choroidal nevi, is challenging and critical; erroneous diagnoses can lead to mortality. When the nevus and melanoma are amelanotic, distinction is further complicated because each may present as geographic chorioretinal whitening.

Choroidal Osteoma

Choroidal osteoma is an osseous tumor of the choroid.[83] The tumor is characterized as amelanotic, flat, and often located in the peripapillary region. Choroidal osteoma occurs most frequently in white women,[84] but it also has been diagnosed in men and in Asians and African Americans.[85,86] The tumor is typically seen in young adults, but it also occurs in children.[85] Bilateral choroidal osteoma occurs in 20 to 25% of cases.[87,88] The cause of choroidal osteoma is unknown, although it has been associated with recurrent choroiditis, optic nerve edema,[89] and orbital inflammatory pseudotumor.[90]

What Is the Visual Prognosis?

Most patients with choroidal osteoma maintain good vision, with 80% having vision of 20/30 or better.[91] Patients may be asymptomatic or may have metamorphopsia or central visual reduction.[85,92] About 10% of patients develop vision of 20/200 or worse.[91] The most common cause of acute visual loss is secondary to choroidal neovascularization (CNV), occurring in about one third of cases.[87,92–95] Gradual visual loss occurs from degeneration of the overlying RPE and neurosensory retina.[94]

What Are the Clinical Manifestations?

A choroidal osteoma is typically elongated and has scalloped edges. It can range from a few millimeters to greater than 20 mm in basal dimension, is less than 2.5 mm in height, and has irregular elevations and depressions within the tumor.[95] It can exist as a solitary macular lesion, but more commonly it has a juxtapapillary location.[86,95] Choroidal osteoma is yellow–white to orange–red.[94] The variation in thinning, depigmentation, and hyperplasia of the overlying RPE leads to the color variation of the tumor.[94] There are osteoblastic and osteoclastic components inside the osteoma; thus, it may progress gradually or regress spontaneously.[94,96]

Vascular tufts, or spiders, may be present in areas of depigmented RPE associated with choroidal osteoma.[95] The vascular tufts are channels inside of bone that link the larger choroidal vessels to the choriocapillaris; they are uncommon, but when present they are pathognomonic.[95, 97]

What Is the Differential Diagnosis?

Other yellow–white lesions in the juxtapapillary or macular area include amelanotic choroidal melanoma, amelanotic choroidal nevus, metastatic carcinoma of the choroid, circumscribed choroidal hemangioma, organized submacular hemorrhage, previous cryotherapy, various uveitic entities (e.g., serpiginous chorioretinitis), and fibrovascular scarring in age-related or other macular degenerations.[94]

How Is Choroidal Osteoma Diagnosed?

Ultrasonography is useful in differentiating choroidal osteoma from other lesions. The A-scan shows a highly reflective spike from the surface of the bony, calcific tumor that remains prominent at reduced gain.[94] The B-scan demonstrates a highly reflective, slightly elevated choroidal lesion.

Fluorescein angiography reveals early patchy hyperfluorescence with diffuse late leakage. Choroidal neovascularization manifests as a lacy hyperfluorescent area that demonstrates increasing leakage throughout the study.[94]

The magnetic resonance imaging (MRI) features a bright, hyperintense signal on T1-weighted images and a relatively low intensity on T2-weighted images.[98] The computed tomography (CT) scan reveals a radiopaque lesion, similar to the density of bone, at the level of the choroid.[94]

How Is Choroidal Osteoma Managed?

A choroidal osteoma often has a benign clinical course and requires no treatment.[94] No therapeutic intervention is known to alter its growth.[94] CNV, if present, can be treated with argon or krypton laser therapy for lesions located outside the fovea.[87,93] Photodynamic therapy (PDT) may be considered for subfoveal lesions.

Infectious Retinitis That Can Present as Geographic Whitening

Retinal and choroidal infections will lead to areas of retinal whitening, sometimes with associated retinal hemorrhages. Examples include acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), cytomegalovirus (CMV) retinitis, toxoplasmosis chorioretinitis, and candidal retinitis, among others.

Acute Retinal Necrosis Syndrome

What Are the Ophthalmic Manifestations?

Acute retinal necrosis is characterized by vitreitis, acute necrotizing retinitis, retinal arteritis, choroiditis, and late-onset rhegmatogenous retinal detachment.[99] It occurs bilaterally in 36% of cases. Bilateral involvement has been reported as soon as 6 weeks to more than 34 years after the initial event,[100–102] and can occur even after treatment with acyclovir is started. [103]

Initial manifestations ARN may include episcleritis, scleritis, periorbital pain, and anterior uveitis. Subsequently, extensive vitreous reaction causing media opacification, necrotizing scleritis, and optic neuritis or neuropathy may occur, causing a significant decrease in vision.[104–106]

The retinitis is characterized by deep, multifocal, yellow–white patches, often starting in the peripheral fundus and circumscribing and spreading toward the posterior pole (Fig. 7–8); often the macula is spared initially. There may be perivascular hemorrhages, sheathing, terminal obliteration of arterioles by thrombi, and exudative retinal detachment.[100,105,107–109]

As the syndrome improves, pigmentary changes are detected in the peripheral lesions, beginning in the posterior margins. Retinal tears may develop at the junction of normal and necrotic retina.[105] Rhegmatogenous retinal detachment occurs in 75% of eyes, generally within 1 to 2 months after the onset of the disease.[105] Proliferative vitreoretinopathy, resulting from severe vitreous inflammation, can contribute a traction component to the retinal detachment.[105] In the fellow eye, the risk of retinal detachment may be lower.[110]

What Is the Differential Diagnosis?

The diagnosis, according to the criteria set forth by the American Uveitis Society in 1994,[109] depends solely on the observed clinical findings and their progression and not on the patient's immune status. The differential diagnosis of ARN includes infections such as PORN (Fig. 7–9), CMV retinitis (Fig. 7–10), syphilitic retinitis, toxoplasmosis, toxocariasis, fungal or bacterial retinitis, as well as other causes of retinal whitening, such as large cell lymphoma; Behçet disease, lupus retinopathy, or choroidopathy and other collagen-vascular diseases; sarcoidosis; traumatic causes

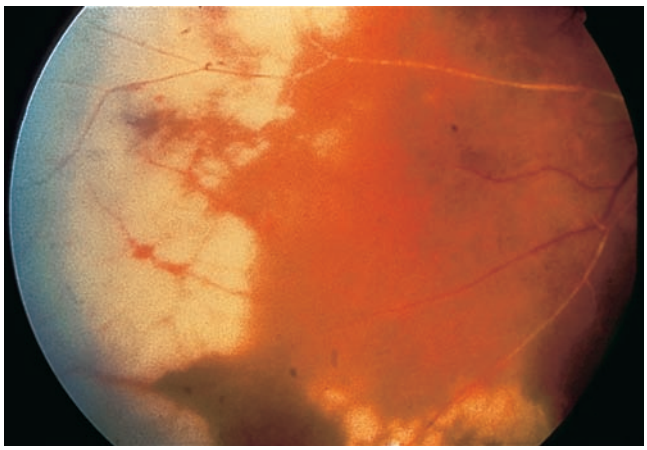

FIGURE 7–8. Acute retinal necrosis syndrome (ARN). The retinitis appears as deep, multifocal, yellow–white patches, beginning in the peripheral fundus and then becoming concentrically confluent and spreading toward the posterior pole. The macula is spared in this 67-year-old man with a history of dermal zoster.

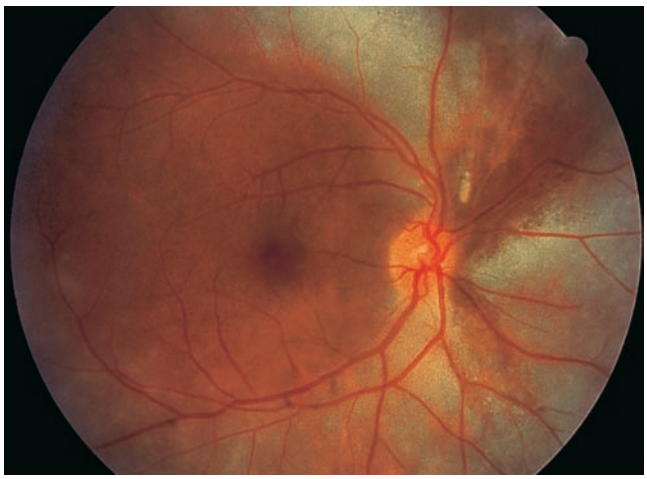

FIGURE 7–9. Progressive outer retinal necrosis syndrome (PORN). The patient is a 35-year-old homosexual man with acquired immunodeficiency syndrome (AIDS) and CD4+ cell count of 35. Extensive retinitis extends throughout the posterior pole. There are no vitreous cells.

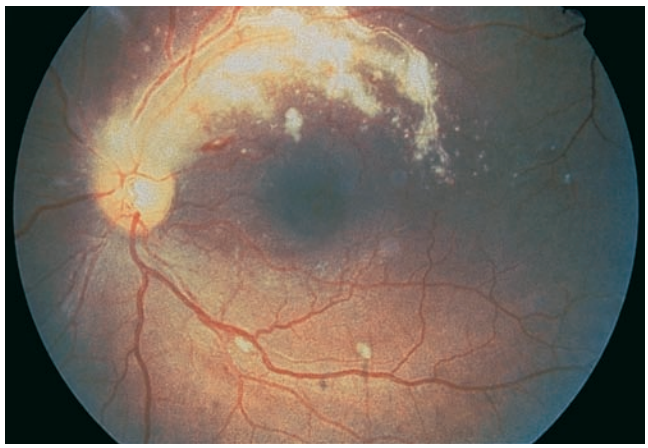

FIGURE 7–10. Cytomegalovirus (CMV) optic neuritis and retinitis in a 25-year-old man with acquired immunodeficiency syndrome (AIDS) and CD4+ cell count of 10. Fluffy white retinitis, accompanied by hemorrhages, extends from the optic disc along the superior arcades.

such as commotio retinae, Purtscher retinopathy; central retinal artery or ophthalmic artery occlusion; and retinoblastoma.[105]

WHO IS AT RISK?

Acute retinal necrosis may occur in healthy or sick patients of either sex and of any age. Patients do not have to be immunocompromised or systemically ill.[105] Progressive outer retinal necrosis, described in immunocompromised patients, shares many features with ARN, but generally follows a fulminant course[111] and often requires two-drug therapy (e.g., ganciclovir and acyclovir).

WHAT CAUSES ACUTE RETINAL NECROSIS?

Varicella zoster has been most commonly implicated in ARN, having been found in retinal tissue of infected eyes.[112,113] CMV[114] and herpes simplex virus[115–117] also have been implicated. Cerebrospinal fluid of patients with ARN syndrome often reveals pleocytosis,[118] and intrathecal production of antibodies against herpes viruses has been demonstrated in selected cases.[119]

HOW IS IT TREATED?

The natural history of ARN syndrome is poor,[100] with 28% of affected eyes achieving a final visual acuity better than 20/200. Rhegmatogenous retinal detachment occurs frequently (in 75% of affected eyes). Vision is poor secondary to optic neuropathy or macular involvement.[105] Treatment with antiviral therapy, prophylactic laser photocoagulation, and vitrectomy for retinal detachment has reduced vision loss to less than one third of cases.[120,121]

Acyclovir reduces the direct cytotoxic effect of virus on retinal tissues. It is given intravenously (13 mg/kg every 8 hours) and yields an intravitreal acyclovir level greater than three times the median effective dose (ED50; the dose required for a 50% reduction of virus plaque in tissue culture) for ARN.[113] Intravenous therapy usually is maintained for 7 to 10 days and is followed by oral acyclovir at the varicella zoster dosage (800 mg orally five times daily if patients have normal renal function) for up to 6 weeks after the onset of infection and longer in immunocompromised patients.[101] Long-term antiviral prophylaxis may be beneficial in preventing bilateral disease.[108] The recently developed prodrugs of acyclovir, such as valacyclovir and other new antiviral agents including famciclovir, have better systemic absorption than acyclovir and may be useful for prophylaxis against involvement of the fellow eye.[122,123]

Complicated combined traction-rhegmatogenous retinal detachment often results from retinal breaks at the junction of normal and necrotic retina.[101] The benefit of prophylactic laser photocoagulation posterior to areas of active retinitis has been demonstrated in some studies.[124,125] Although laser therapy cannot halt progression of the viral retinitis, the overall incidence of retinal detachment appears less in treated eyes. It is often difficult to treat infected eyes, however, because of hazy media from vitreous cells.

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8

Pigmented Lesions of the Fundus: Discrete Small to Medium Size

CAROLINE R. BAUMAL AND BRAD J. BAKER

What Is "Normal" Fundus Pigmentation?

The natural pigmentation of the fundus is provided by the retinal pigment epithelium (RPE), which is located between the retinal photoreceptors and the Bruch membrane. The RPE is a monolayer of hexagonal pigmented cells with the apical portion enveloping the photoreceptors and the basal aspect forming the innermost portion of the Bruch membrane. These cells contain melanosomes of neuroectodermal origin that develop during the second trimester. The RPE cells are most dense in the posterior pole, where they assume a low cuboidal configuration. The functions of the RPE layer include phagocytosis of the outer segments of the rods and cones, formation of the outer blood-ocular barrier, vitamin A metabolism, and absorption of radiant energy that is subsequently dispersed via the choriocapillaris.

Changes in the RPE can be caused by a variety of mechanisms, including trauma, inflammation, retinal detachment, or congenital alterations. Hypertrophy shows an increase in the size of the RPE cells with large spherical melanin granules. This change may be congenital or acquired through aging or trauma. Hyperplasia of the RPE also displays an element of hypertrophy, but there is migration of the RPE cells and pigment into the neurosensory retina, which can give the appearance of fine bone spicules, often in a perivascular distribution. Atrophy of the RPE is the result of loss of pigmentation within these cells, which can result in a complete loss of RPE and degeneration of the overlying photoreceptors.

Many of the pigmentary changes are congenital in nature. Lightly pigmented persons may exhibit a "blonde"-appearing fundus where visualization of the underlying choroidal circulation through lightly pigmented RPE is possible. A blonde fundus may also occur with autosomal-recessive oculocutaneous albinism, where there is a reduction in the amount of primary melanin deposited in each melanosome of the RPE cells. A similar fundus appearance may be observed with ocular albinism, where there is a reduction in the number of melanosomes. Ocular albinism is inherited as an X-linked disease.

How Are Fundus Pigmentary Changes Evaluated?

Evaluation of the patient should begin with a careful history for related family conditions or prior ocular trauma. Consideration should be given to whether the pigmentary changes are congenital or acquired. Fundus changes may be similar throughout generations in inherited disorders, and identification of these patterns may prompt medical attention. A complete medical history may reveal a systemic disorder associated with the observed fundus pigmentation, such as that seen with Gardner syndrome or with metastatic lesions to the choroid. Previous surgical intervention may alter the fundus appearance and produce diagnostic confusion without knowledge of the ocular history.

Slit-lamp evaluation of the anterior segment, followed by dilated fundus examination with biomicroscopy or with a contact lens, can demonstrate changes in pigmentation with a stereoscopic advantage. Adjustment of the illumination beam may allow localization of the pigmentation within the layers of the posterior pole and show the extent of elevation. Indirect ophthalmoscopy with scleral depression can demonstrate the extent of fundus pigmentation and

reveal any additional pathology. External transillumination can demonstrate the margins and the anterior extent of a pigmented lesion.

What Role Does Ancillary Testing Have in Identifying Small to Medium Discrete Lesions of the Fundus?

Fluorescein angiography is useful in delineating the retinal circulation and demonstrating variations in the retinal pigmentation. Generally, areas of increased pigmentation are hypofluorescent throughout the phases of the angiogram. This hypofluorescence is due to static blockage of the underlying choroidal flush by the pigmentation, which may be helpful in differentiating vascular or inflammatory lesions from strictly pigmented areas.

Indocyanine green (ICG) angiography is useful to demonstrate the choroidal circulation and to identify choroidal pathology. Areas of increased fundus pigmentation are typically hypofluorescent in the early phase ICG angiogram. ICG angiography is most useful for differentiating choroidal hemangioma from other choroidal lesions. The choroidal hemangioma shows hyperfluorescence during the venous phase with late hypofluorescence (*washout phenomenon*). Demonstration of choroidal melanoma may show an abnormal choroidal circulation and marginal late dye leakage.[1] Subretinal neovascularization may also be demonstrated with ICG as a hyperfluorescent hot spot or a larger plaque.

Ultrasonography is an extremely useful ancillary tool to evaluate pigmented lesions. A B-scan ultrasound can identify elevated pigmented lesions and quantitatively measure their height and basal dimensions. It can also identify subretinal fluid associated with elevated pigmented areas. Ultrasound technology, A-scan, is able to measure the axial length of an eye and further support, for example, the diagnosis of pigmentation associated with axial myopia. Internal reflectivity of an elevated pigmented lesion is discerned with the A-scan, and this may aid in distinguishing a malignant from a benign lesion. Ultrasound biomicroscopy (UBM) is a high-resolution measure of the anterior segment anatomy that uses high frequencies in the 40 to 100 Mhz range to produce images to a depth of approximately 2 to 6 mm in the anterior chamber. This tool is useful in demonstrating pathology of the trabecular meshwork and angle, ciliary body, iris, and other anterior segment structures.

Another test that may be helpful in diagnosing ocular disease associated with abnormal fundus pigmentation is the electroretinogram (ERG). This test measures the electrical activity and interaction of the photoreceptors with other retinal components. It is a reflection of all rods or cones of the fundus in response to a brief flash of light. Rod and cone responses may be isolated through various testing techniques and dark or light adaptation. The ERG may be reduced or extinguished in forms of retinitis pigmentosa, and it plays a critical role in the diagnosis of this disorder. The electrooculogram (EOG) is a test to measure the electrical potential generated by the RPE cells. It is most specific for involvement of the RPE when other studies show the retina to be normal. It is most useful to confirm the diagnosis of autosomal dominant vitelliform dystrophy (Best disease).

Optical coherence tomography (OCT) is an imaging technique that is analogous to ultrasound B-scan, except optical rather than acoustic reflectivity is measured. A cross-sectional image of the retina with high resolution up to 10 μ in the Z-axis is obtained with OCT. OCT is useful to assess retinal pathology such as macular thickening and to evaluate the clinical course and response to therapy.

How Are Dark Brown or Black Pigmented Lesions of the Fundus Categorized?

Fundus pigmentation can present in a number of forms, thus offering diagnostic challenges to the ophthalmologist. These areas can be classified by whether they are congenital or acquired, whether the vision is normal or reduced, and by the location and characteristics of the lesion. A systematic approach based on clinical observation and the use of ancillary testing can lead to the proper diagnosis and direct treatment (Table 8–1).

Congenital lesions are generally stable and do not cause progressive visual loss. Pigmented lesions from birth are derived from neural crest cells and represent abnormal RPE location or aggregation. Congenital lesions may cause visual disturbances if the optic nerve or macula is involved. In rare cases, the visual loss may be due to vascular compromise or accumulation of subretinal fluid.

What Is the Differential Diagnosis of Optic Nerve or Peripapillary Pigmented Lesions?

Lesions located on the optic nerve head should be examined for distinguishing characteristics such as color, border, elevation, and appearance on ancillary testing (Fig. 8–1). A melanocytoma is often a jet-black accumulation of pigment covering or adjacent to the optic nerve head (Fig. 8–2). This is a congenital lesion with fibrillated edges, and it may be slightly elevated. The feathery edges may be due to interspersion of pigmented cells in the nerve fiber layer. It comprises

TABLE 8–1. Evaluation of Patients with Small to Medium Pigmented Fundus Lesions

Topics or Elements to Include	*Reason*
In the patient history:	
Family history	Inherited forms of RP and Gardner Syndrome
Prior eye trauma or surgery	Hyperplasia of retinal pigment epithelium, laser, or cryotherapy scars
Myopia	Lacquer cracks, Fuchs spot, lattice degeneration
In the examination:	
Slit-lamp biomicroscopy	Level of pigmentation can guide diagnosis, determine extent of elevation of lesion
Indirect ophthalmoscopy	Identification of peripheral lesions and evaluation for retinal breaks
Ancillary testing	
Fluorescein angiography	Double circulation in choroidal melanoma Early hyperfluorescence in choroidal hemangioma
Indocyanine green angiography	Demonstrates subretinal neovascularization Hyperfluorescence during the venous phase with late hypofluorescence in choroidal hemangioma
B-scan ultrasonography	Defines lesion elevation and internal reflectivity Long axial length associated with pigmentary changes in myopia
Electroretinogram	Reduced or extinguished in retinitis pigmentosa Variable in pattern dystrophies

magnocellular nevus cells that are darkly pigmented and differ from the slender melanosomes found in other pigmented lesions. Angiographically, the area is hypofluorescent in the early phases. Elevation noted by slit-lamp biomicroscopy can be confirmed by B-scan ultrasonography. The clinical characteristics can be found in Table 8–2. Other lesions include combined hamartoma of the retina and RPE, nevi, congenital hypertrophy of the RPE (CHRPE), and acquired hyperplasia of the RPE.

Does a Melanocytoma Cause Visual Symptoms?

An enlarged blind spot, often asymptomatic, may be noted on visual field testing. Infrequently, blurring of vision may occur if there is associated subretinal fluid extending to the macula. Vascular occlusions with resultant visual loss have been reported as a result of the constrictive nature of enlarging melanocytomas.[2,3] No treatment is recommended unless there is growth documented by serial examinations and photographs. Although an optic nerve melanocytoma is usually benign, enlargement on occasion may signal malignant transformation. This finding has been rarely reported in the literature.[4,5]

How Do Combined Hamartoma of the Retina and Retinal Pigment Epithelium Present?

A similar lesion located on the optic nerve head or the peripapillary area is a combined hamartoma of the retina and RPE; Table 8–3 lists the clinical characteristics. Presenting symptoms may be strabismus, leukocoria, or a painless decrease in vision; most lesions are discovered during childhood. The pigmentation is deep gray to black and may have associated preretinal gliosis. This discrete small to medium-sized pigmented area also has adjacent vascular tortuosity and superficial telangiectatic vessels. Subretinal fluid accumulation and retinal striae may cause moderate to severe visual loss if the optic nerve or macula is involved. Generally, these lesions are minimally elevated. Fluorescein angiography demonstrates early hypofluorescence resulting from the pigmentation. Late hyperfluorescence and leakage from the abnormal vessels are observed and are characteristic of the combined hamartoma of the retina and RPE.[6–8] There may be areas of retinal capillary nonperfusion peripheral to the lesion.

Are There Any Systemic Disorders Associated with Combined Hamartoma of the Retina and Retinal Pigment Epithelium?

An association has been described between persons with neurofibromatosis type II (NF2) and this ocular lesion.[9,10] A less common association has been reported with NF1. When there is not an established diagnosis of NF2 and a combined hamartoma of the retina and RPE is found, imaging studies may display bilateral acoustic neuromas. There is no local potential for this lesion to undergo malignant transformation. This lesion often is noted in the posterior pole, but peripheral retinal involvement is also possible. Visual symptoms are more common when the location is peripapillary. Treatment usually consists of observation, although pars plana vitrectomy and epiretinal

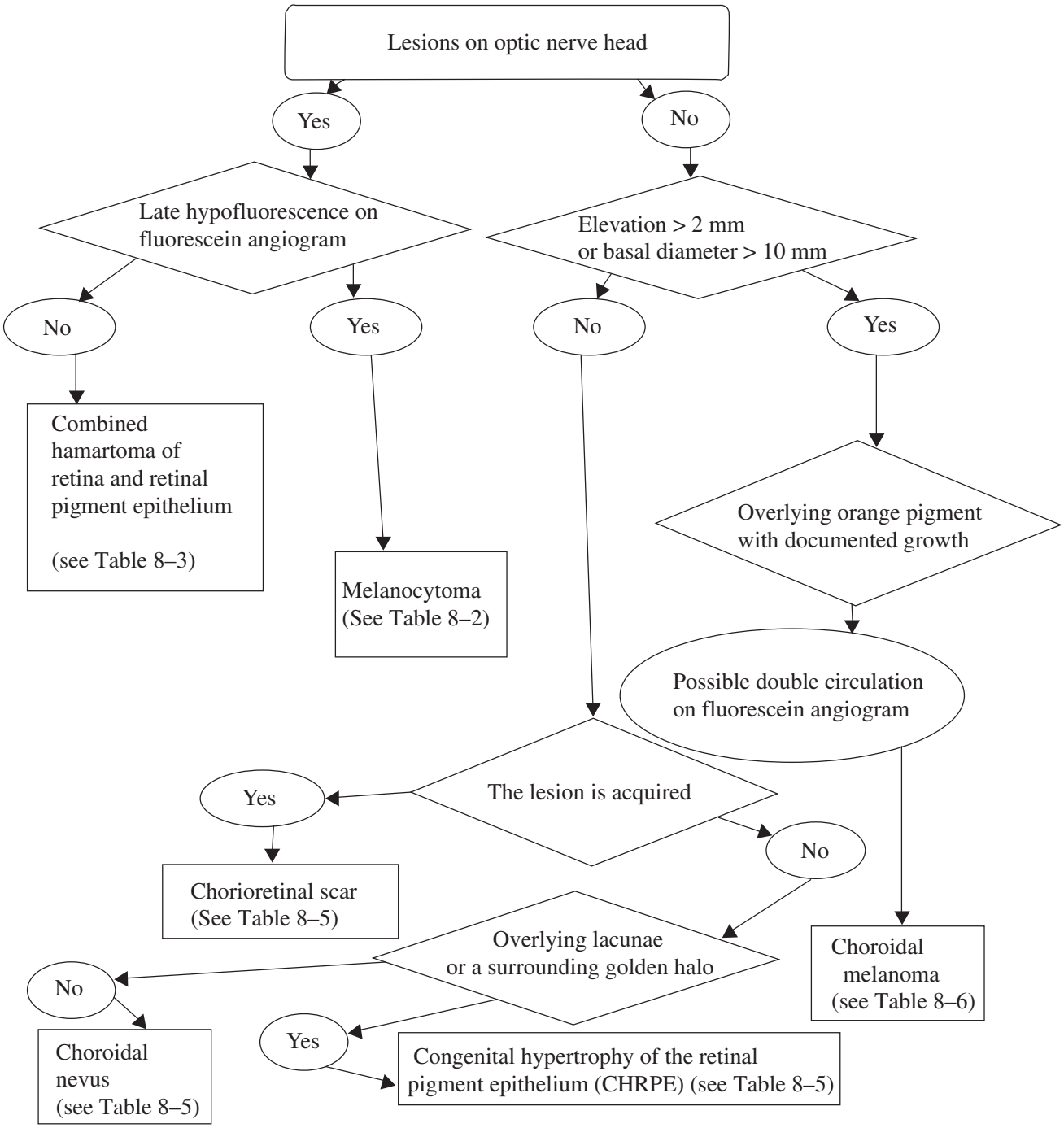

FIGURE 8–1. Clinical pathway: Small to medium-sized pigmented lesions on the optic nerve or peripapillary area. CHRPE, congenital hypertrophy of the retinal pigment epithelium.

membrane removal have been attempted with overall poor visual recovery.

Is There an Acquired Pigmented Lesion of the Peripapillary Area?

Peripapillary acquired pigmented lesions that are well circumscribed are also encountered, and the clinical characteristics can aid in the diagnosis. Chorioretinal scars in the posterior pole may appear as distinct areas of pigmentation. This acquired hyperplasia of the RPE is a reaction to trauma or disruption of the underlying Bruch membrane. Trauma, inflammation, or neovascularization may cause the chorioretinal scars. The lesions may expand but usually do not cause visual symptoms unless the macula is involved

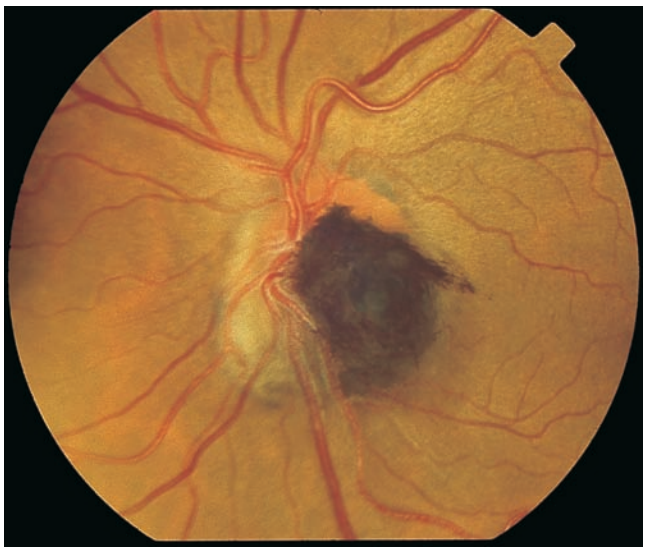

FIGURE 8–2. Jet-black pigmentation with feathered edges overlying the optic nerve characteristic of a melanocytoma.

or recurrent subretinal neovascularization occurs. Fluorescein angiography demonstrates early hypofluorescence in the areas of pigmentation without late leakage. There is no treatment for areas of pigmentation that represent a stable scarring process.

Are There Other Peripapillary Pigmented Lesions That Are Relatively Flat?

Areas of pigmentation found on or adjacent to the optic nerve may represent a unique type of CHRPE (Table 8–4). Although more commonly found in the retinal periphery, this accumulation of pigmented cells may be found at the optic nerve head. The clinical appearance is usually that of a dark-brown to black area, frequently with overlying lacunae. CHRPE may extend slightly over the optic nerve, but it does not appear centered over the papilla. A surrounding golden halo may be present. Histopathologically, the pigment granules within the hypertrophied RPE cells are of normal size and do not demonstrate mitoses. The choriocapillaris and choroid are normal. The surrounding halo represents RPE cell depigmentation or dropout.

TABLE 8–2. Clinical Features of Melanocytoma (Magnocellular Nevus)

Jet black to brown pigmentation
Flat to mildly elevated
Fibrillated edges
Minimal visual symptoms, possible enlarged blind spot
Hypofluorescent on fluorescein angiography
Stable to minimal growth over time

TABLE 8–3. Clinical Features of Combined Hamartoma of the Retina and Retinal Pigment Epithelium

Deep gray to black pigmentation
Associated preretinal gliosis
Adjacent vascular tortuosity and telangiectatic vessels
Retinal striae
Early hypofluorescence due to pigment followed by late hyperfluorescence
Possible adjacent retinal vascular nonperfusion
Some cases associated with neurofibromatosis type II

A choroidal nevus is the most common intraocular tumor observed on dilated fundus examination, and the location may be found on or adjacent to the optic nerve head (Table 8–5). A choroidal nevus is flat to minimally elevated and usually displays distinct borders (Fig. 8–3). Retinal vessels overlying the nevus may demonstrate a variable appearance from normal to sclerotic attenuation. The basal diameter is usually less than 10 mm, and there may be drusen overlying the brown to black pigmentation. Hypofluorescence in the early phase of the fluorescein angiogram is common because of the choroidal pigmentation and the lack of internal vessels. Binocular examination for elevation is key for distinguishing a potential progressive malignant process from a stable benign lesion. Documentation of a lack of growth, clinically and photographically, is also important in establishing the proper diagnosis.

Do Peripapillary Choroidal Nevi Cause Visual Symptoms?

Choroidal nevi can cause visual symptoms if there is associated subretinal fluid.[11] The fluid extending to the macula may cause metamorphopsia and generalized visual loss. Laser demarcation along the posterior edge of the nevus, with careful attention to the optic nerve head and the macula, may be successful in walling the fluid. Laser delivered at low power to create light treatment to the nevus also may be helpful in resorption of the subretinal fluid over time. Choroidal neovascular membranes (CNV) also may arise from a choroidal nevus and produce visual symptoms.[12]

TABLE 8–4. Clinical Features of Congenital Hypertrophy of the Retinal Pigment Epithelium

Elevation less than 2 mm
Brown to jet-black appearance
Usually less than 10 mm basal diameter
Hypofluorescence on fluorescein angiography due to pigment
Overlying lacunae and surrounding halo
Generally well-defined borders

TABLE 8–5. Clinical Features of Choroidal Nevus

Brown to black pigmentation
Possible overlying drusen or orange hue
Elevation less than 2 mm and basal diameter usually less than 5 mm
Generally normal overlying vessels
Hypofluorescence on fluorescein angiography and indocyanine green angiography
Possible associated subretinal fluid with decreased vision

TABLE 8–6. Factors Associated with Pigmented Lesions Suspicious for Choroidal Melanoma

Basal diameter greater than 10 mm
Thickness greater than 2 mm
Geographic orange pigment overlying lesion
Bullous subretinal fluid or associated exudative retinal detachment
Visual symptoms
Documented growth
Ciliary body involvement

These CNV can be treated with laser photocoagulation. Photodynamic therapy may be considered for subfoveal CNV. Although subretinal fluid or CNV associated with choroidal nevi is uncommon, the treatment for these may pose a challenge. Choroidal nevi associated with foveal RPE derangement also cause visual symptoms. Generally, observation and monitoring of asymptomatic choroidal nevi are recommended, with use of photographs to evaluate for growth of suspicious lesions.

What Clinical Features Increase Suspicion That a Pigmented Choroidal Lesion Is a Choroidal Melanoma?

Growth is one of the factors triggering suspicion for the development of choroidal melanoma from a preexisting choroidal nevus. Most choroidal melanomas arise *de novo*, with only an estimated one in 5000 originating from a choroidal nevus.[13] Tables 8–6 and 8–7 review the features of lesions suspicious for choroidal melanoma and features predictive of growth.[14] The lesion is suspicious when it exceeds 2 mm in height or 10 mm in basal diameter. Penetration through the Bruch membrane may allow for a "mushroom" or "collar-button" pattern of growth with dispersion of pigmented cells into the vitreous. Pigmentation may be similar to the choroidal nevus, but overlying orange pigmentation is more commonly seen in choroidal melanomas than nevi. Subretinal fluid may accumulate in association with a choroidal melanoma, producing visual loss. Overlying retinal vessels also may have a variable appearance. There is no pathognomonic pattern on fluorescein angiography for a choroidal melanoma, and the appearance depends on the amount of pigmentation, the size, and the associated subretinal fluid; however, the angiogram may help to exclude other simulating disorders. Large choroidal melanomas may display a "double circulation" pattern, with simultaneous fluorescence of the retinal and choroidal vessels in the early venous phase. Fundus photography to document the appearance of the lesion along with B-scan ultrasonography to define the dimensions should be performed. The A-scan ultrasound will demonstrate low to medium internal reflectivity in a choroidal melanoma.

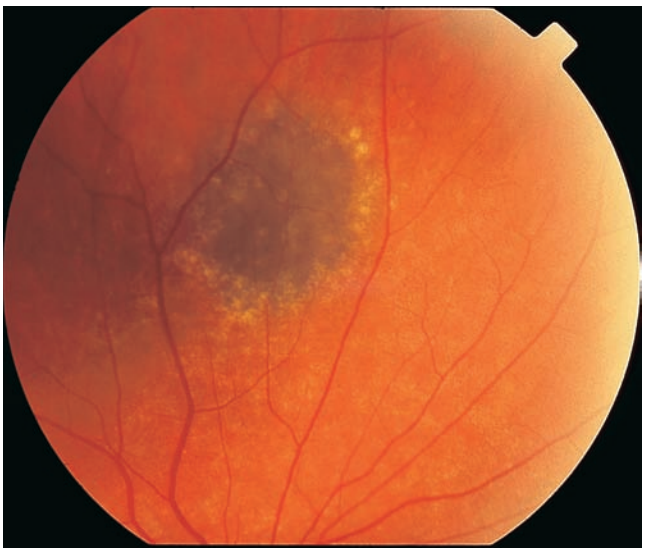

FIGURE 8–3. Flat choroidal nevus with brown pigmentation and overlying drusen.

What Are the Treatment Options for Choroidal Melanoma?

The treatment options for choroidal melanoma may include enucleation, radiotherapy (plaque or proton beam), transpupillary thermotherapy, observation, and rarely scleral wall dissection. The clinical characteristics of the choroidal melanoma, the visual potential of the eye, and the factors of the patient will dictate which modality is used

Surgical intervention plays a role in the management of choroidal melanoma. Enucleation is fre-

TABLE 8–7. Factors Associated with Growth of Small Choroidal Melanocytic Tumors

Thickness greater than 2.0 mm
Subretinal fluid
Visual symptoms
Orange pigmentation
Location adjacent to the optic nerve head

quently performed when the choroidal melanoma is too large to be treated with other means, such as radiotherapy, or when there is limited visual potential. It is also used in eyes with severe secondary glaucoma, chronic retinal detachment, or optic nerve invasion by direct extension. In 1978, Zimmerman and associates hypothesized that primary enucleation for choroidal melanoma may be a cause for distant metastasis.[15] This hypothesis was investigated indirectly by the Collaborative Ocular Melanoma Study (COMS), which evaluated survival in patients treated with enucleation versus radiotherapy followed by enucleation for large choroidal melanoma. The results were published in 1998 and showed that there was no difference in survival for patients treated with preenucleation radiotherapy followed by enucleation compared with enucleation alone.[16] Another surgical choice is scleral wall dissection with tumor resection. This is an option for small, peripherally located melanomas or ciliary body involvement. Scleral wall dissection is technically challenging and infrequently performed. Observation and periodic examination of small melanomas also may be an option. This may be considered in patients with very poor health or concurrent terminal conditions, in patients with melanoma that appears dormant, or in monocular patients with rare slow growth of a small melanoma.

Plaque radiotherapy often is used in small melanomas and in larger lesions where there is remaining vision. It is used most frequently when the melanoma is peripheral and well defined and when visual acuity outcomes depend on numerous factors.[17] Visual acuity is preserved best in eyes with small tumors outside a radius of 5 mm from the optic disc and foveola.[18] Specially designed notched plaques can be used to treat a choroidal melanoma located at the optic nerve head or in the peripapillary area. External proton-beam radiation may treat well-defined melanomas in the posterior pole or the optic nerve head region or when large amounts of subretinal fluid accompanying the lesion. Delayed-onset radiation retinopathy or papillopathy or both can complicate either type of treatment.

Transpupillary thermotherapy (TTT) is another treatment option that has been effective for small to medium-sized lesions located in the peripapillary region or the posterior pole.[19,20] This is most successfully performed when the thickness is less than 4 mm to allow adequate penetration of the laser. The mechanism of this local treatment is controlled heating of the tumor to induce cellular disruption and tumor necrosis. Local complications include retinal vascular obstruction, retinal traction, retinal neovascularization, and retinal holes with detachment.[21,22] Scotomas are present in the areas of treatment. This technique may be used in conjunction with plaque radiotherapy for maximal effectiveness.

The benefits of intervention versus the morbidity of treatment must be weighed in these patients. In all cases of choroidal melanoma, consultation and treatment in conjunction with an internist or oncologist are recommended to evaluate for systemic involvement (see also Chapter 15).

Is There a Survival Difference between Primary Enucleation and Iodine-125 (^{125}I) Brachytherapy for Choroidal Melanoma?

A comparison between survival rates for primary enucleation versus ^{125}I brachytherapy for medium-sized choroidal melanoma was undertaken by COMS.[23] Medium-sized lesions were defined as having an apical height from 2.5 to 10 mm and a basal diameter of no more than 16 mm. The inclusion criterion was originally 3.1- to 8.0-mm thickness, but this range was modified in 1990. Tumors within 2.0 mm of the optic nerve were eligible only when the tumor was contained within a 90-degree angle with the apex at the center of the optic disc and when there was confidence that plaque would cover the tumor with a 2-mm margin apart from that bordering the optic disc. The inclusion criteria were strict and included the absence of other carcinomas or other coexisting disease that threatened survival for 5 years. The survival rates at 5 years were 81% for the enucleation group and 82% for the ^{125}I brachytherapy patients. Based on these results, there appeared to be no difference in mortality outcomes for this selected group of patients with medium-sized choroidal melanoma enrolled in the COMS at 5 years. Care must be taken in extrapolating these results for melanomas that differ from the characteristics outlined in the study.

What Are the Most Common Sites for Systemic Metastases from Choroidal Melanoma?

Metastatic uveal melanoma is hematogenously spread from the primary intraocular source to distant sites throughout the body. Local treatments of the primary tumor show an effective 5-year survival in most cases, but in a proportion of these patients, metastatic disease will arise.[24] Ciliary body involvement increases the risk of future metastasis.[25] The COMS examined autopsy results for patients with large choroidal melanomas,[26] defined as greater than 10 mm in apical height or at least 16 mm in diameter or 8 to 10 mm in apical height but too close to the optic nerve for effective radiation treatment without irreversible damage. The patients were treated by either enucleation preceded by external-beam radiotherapy or enucleation only. At 5 years, the survival rates were 62% for pretreatment with external-beam radiotherapy and 57% with enucleation alone. No statistically significant

difference between the two groups was found.[16] Biopsy-proven metastatic melanoma was found in 62% of these deaths. The results showed the liver as the leading site for metastasis. Other common metastatic sites include the lung, bone, skin or subcutaneous tissue, and lymph nodes. Multiple metastatic sites were identified in 87% of the autopsies. Death generally occurred within 6 months of the discovery of metastasis.

Does Choroidal Melanoma of the Periphery Differ from Lesions Found Elsewhere?

Choroidal melanoma in the periphery displays the same characteristics as in other sites. Choroidal melanoma in the retinal periphery may arise *de novo* or from a preexisting choroidal nevus. Ancillary testing and photography should be performed for any lesion suspicious for choroidal melanoma. Basal diameters greater than 10 mm, an axial height greater than 2 mm, double circulation on fluorescein angiography, orange pigment on the tumor, and associated subretinal fluid are factors that heighten suspicion. In the periphery, the option of treatment with plaque radiotherapy is available.[16] The radioactive isotope is fixed to a leaded or gold alloy plaque and sutured to the sclera overlying the entire extent of the melanoma with a 2- to 3-mm margin. The plaque is left in place until the proper calculated dose is delivered and then is surgically removed. External-beam radiation is also an option for some melanomas. Transpupillary thermotherapy may be an option if the entire lesion is accessible to the laser spot. Enucleation is also an option for treatment when the lesion is very large or there is intractable glaucoma.

How Does the Pigmentation of Melanoma Change after Treatment?

Treatment with radioactive plaque, external-beam radiation, and transpupillary thermotherapy will result in atrophic changes overlying the treated area. Patchy pigmentation replaces the preoperative appearance and vascular components. Generally, a sharply demarcated area is around the area of treatment. With successful treatment, the lesions often decrease in size with resolution of subretinal fluid.

What Does Pigmentation of the Posterior Pole and Macula Represent?

Many lesions of the optic nerve head and peripapillary region also are found on funduscopic examination in the posterior pole and macular region. Melanocytoma, CHRPE, combined hamartoma of the retina and RPE, chorioretinal scars, choroidal nevus, and choroidal melanoma, as well as pattern dystrophies, all may be found in this region. Extension of the primary source of pigmentation and possible subretinal fluid can cause visual compromise when the macula is involved. Figure 8–4 outlines the various pigmented lesions found in the macular area.

Pigmentary changes of the posterior pole and macula are frequently associated with myopia. Intermediate myopia may have spherical equivalents between −5.00 and −8.00 diopters and axial lengths between 25.5 and 32.5 mm. *Pathologic myopia* is defined as changes in the retina associated with the abnormal elongation of the globe (Fig. 8–5). Refractive errors are usually greater than −8.00 diopters, or the axial length is longer than 32.5 mm. Fuchs spots are small to medium-sized flat, pigmented spots that represent prior areas of regressed subretinal neovascularization. The break in the Bruch membrane involutes and leaves a focus of proliferating RPE cells. Recurrent subretinal neovascularization may originate at Fuchs spots. Lacquer cracks are also a manifestation of pathologic myopia, representing breaks in the Bruch membrane caused by thinning secondary to the increased axial length. These linear areas of hypopigmentation often are surrounded by mottled pigmentation and may be adjacent to a Fuchs spot. Additional manifestations of irregular pigmentation found in the posterior pole in pathologic myopia include exposure of bare sclera in the form of peripapillary atrophy or a posterior staphyloma. This presents as a partial or complete area of depigmentation surrounding the optic nerve. Table 8–8 presents a summary of clinical characteristics associated with pathologic myopia.

How Are the Pigmentary Changes of Pathologic Myopia Treated?

Pigmentary changes in the posterior pole and macula caused by pathologic myopia are generally observed. Choroidal neovascularization poses a challenge because of the thinning of the Bruch membrane and the high incidence of recurrence and extension of scars following laser treatment. Photodynamic therapy (PDT) may provide a treatment option when vision is threatened by subretinal neovascularization because of pathologic myopia. Preliminary results have shown a greater chance of stabilizing or improving vision after PDT in patients with subfoveal CNV due to myopia compared with placebo.[27]

Are There Inherited Forms of Pigmentation in the Macula?

An inherited form of flat, pigmented lesions that affect the macula and posterior pole are pattern dystrophies. Although they have distinct funduscopic appearances, the term *pattern dystrophies* is an inclusive

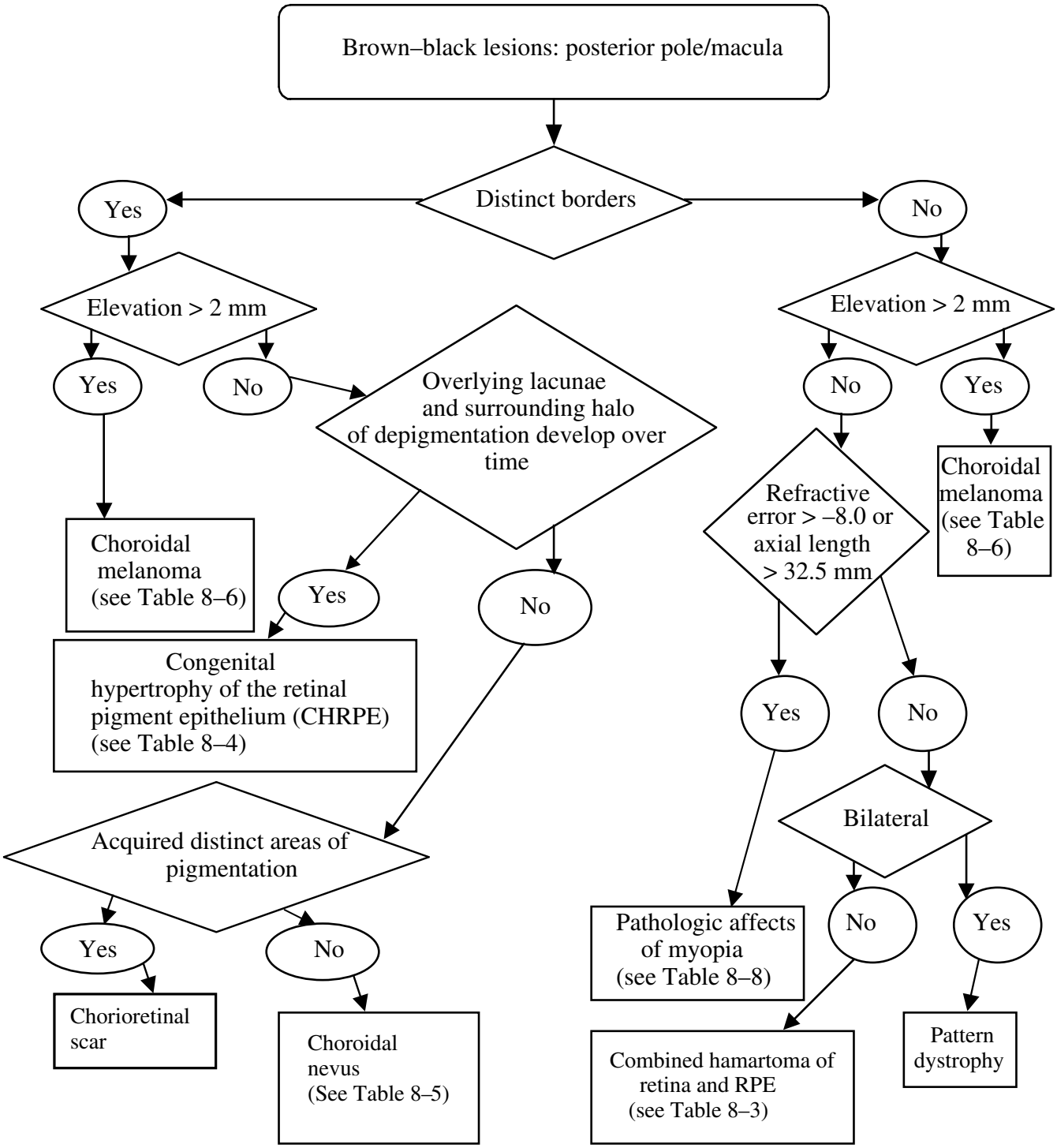

FIGURE 8–4. Clinical pathway: Brown–black lesions of the posterior pole. RPE, retinal pigment epithelium.

term to distinguish these maculopathies from Stargardt disease and familial drusen. These rare dystrophies may be seen at any age, but the pigmentation eventually may fade and be replaced by atrophy. The pigmentation of pattern dystrophies is at the level of the RPE and emanates from the macula without drusen.[28]

Butterfly dystrophy displays a gray to yellow pigmentation that radiates from the macula in a well-defined pattern. The descriptive name originates from

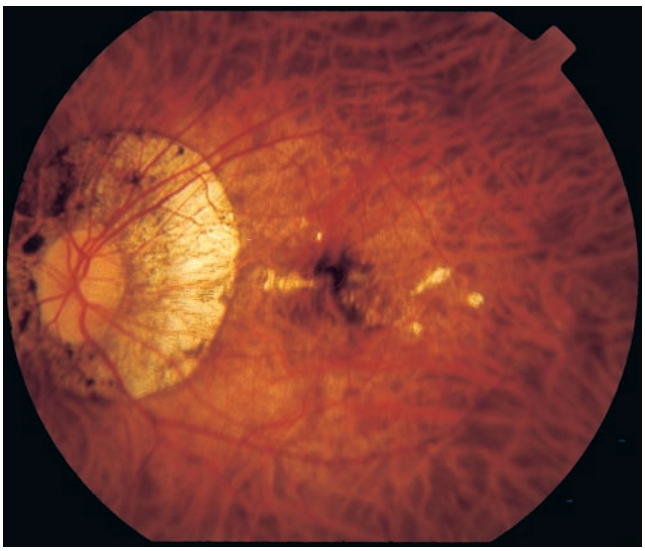

FIGURE 8–5. Posterior staphyloma and pigmented Fuchs spots and lacquer cracks in the macular are found in pathologic myopia.

the similarity to the wings of a butterfly. The optic nerve and retinal vessels are normal in this autosomal-dominant condition. Reticular dystrophy is autosomal recessively inherited with mottled pigmentation radiating outward from the macula. The pigmentary pattern, which has been compared with knotted fishnet, usually does not advance past the posterior pole. The areas of pigmentation are well visualized on red-free photographs and demonstrate hypofluorescence on fluorescein angiography. There is frequently a rim of hyperfluorescence surrounding the pigmentation. Adult-onset foveomacular vitelliform dystrophy is considered by some investigators to be included in the pattern dystrophies. It is characterized by bilateral yellow subfoveal lesions with a central pigmented core. These lesions appear in the fourth to sixth decade of life and are smaller than the vitelliform lesions of Best disease. The dystrophy is also distinguished from Best disease by not being dominantly inherited and by usually having a normal EOG.

TABLE 8–8. Possible Fundus Findings in Myopia

Tilted optic nerve head
Peripapillary atrophy
Fuchs spot-pigmented area following involution of a choroidal neovascular membrane
Lacquer crack
Lattice degeneration
Choroidal neovascularization
Posterior staphyloma
Posterior vitreous detachment
Retinal break

Are There Visual Symptoms Associated with Pattern Dystrophies?

Visual acuity is relatively preserved in the early stages. The most common presenting symptom is a mildly diminished visual acuity or slight metamorphopsia. On many occasions, the lesions are originally discovered on routine ophthalmologic examination. Gradual decline in vision may occur after the fifth decade of life as a result of atrophic changes. Choroidal neovascular membranes also may develop and most commonly are seen in butterfly dystrophy. Electrophysiologic testing with ERG is normal, but the EOG is variably affected. Genetic testing may reveal mutations in the peripherin/*RDS* gene found in multiple generations accompanying the fundus appearance. There is no treatment available, and observation and examination of family members are recommended.

What Pigmentary Lesions Are Found in the Periphery of the Fundus?

Small- to medium-pigmented lesions often are found in the peripheral retina and can represent a number of conditions that potentially affect the visual acuity. Some of the pigmentary changes are nonprogressive and will not cause visual symptoms. Others may signify systemic involvement or an inherited pattern. Recognition of the clinical characteristics can aid in the proper diagnosis and guide treatment if necessary. Figure 8–6 outlines the diagnostic characteristics of peripheral small- to medium-pigmented lesions.

Many of the pigmented lesions found at the optic nerve head and in the macular region may also be observed in the periphery. Benign lesions such as CHRPE are characterized by flat, well-circumscribed areas of dark-brown to black pigmentation usually ranging from 1 to 6 mm in diameter (Table 8–4). There may be overlying lacunae of depigmentation and a surrounding hypopigmented halo. They are usually unilateral solitary areas with normal overlying retinal vessels and the overlying vitreous is generally clear. Observation of these lesions may reveal subtle enlargement over a period of many years.[29] CHRPE tends to be larger when occurring in the peripheral fundus than when occurring in the peripapillary region. CHRPE in the periphery will end abruptly at the ora serrata and does extend into the ciliary pigment epithelium. Choroidal nevi also are found in the periphery with a similar appearance to those found elsewhere. Although typically benign, the nevus found here may have malignant potential and should be fol-

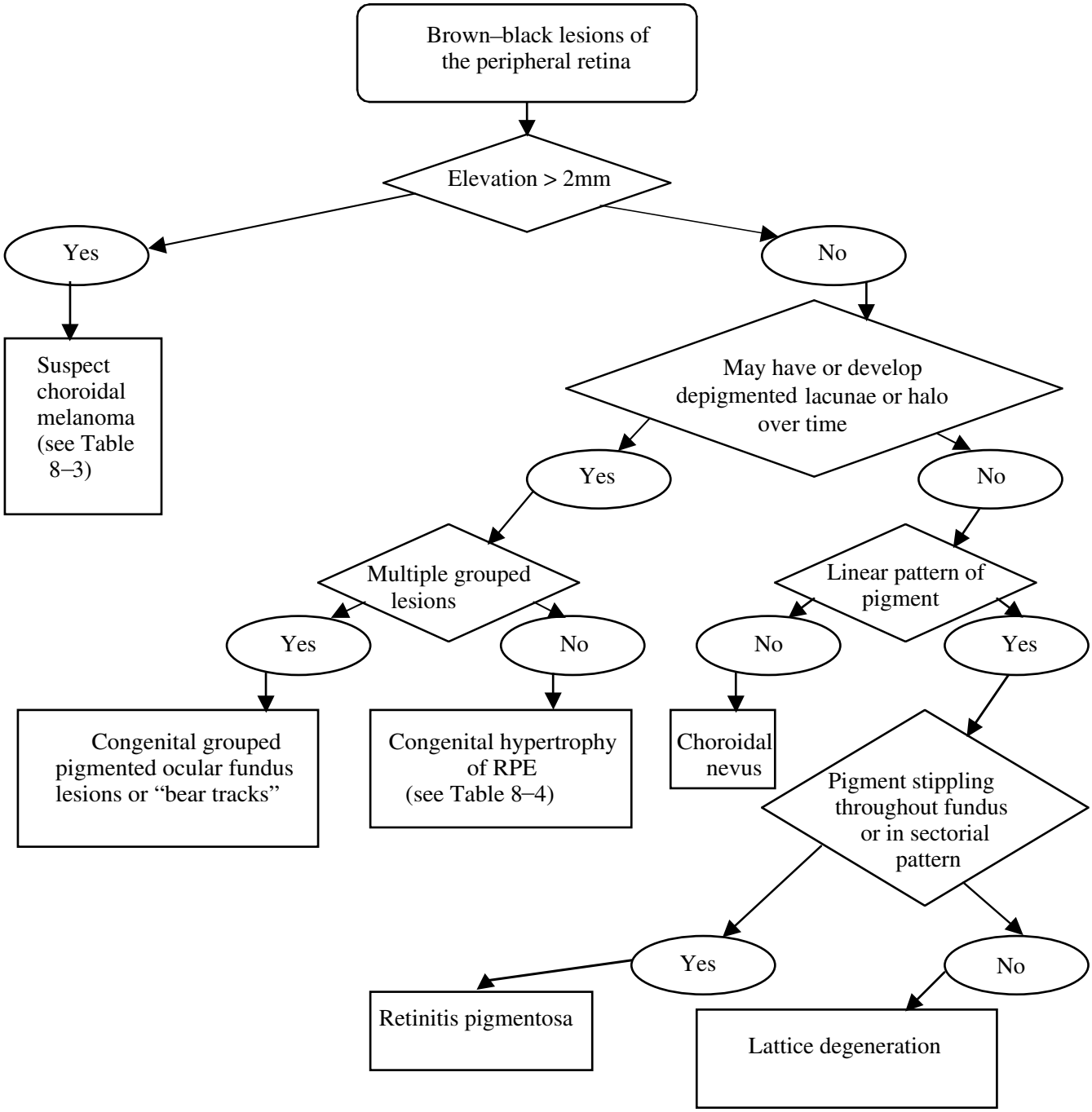

FIGURE 8–6. Clinical pathway: Brown–black lesions of the peripheral retina. RPE, retinal pigment epithelium.

lowed up both clinically and photographically on a regular basis.

Are There Pigmented Peripheral Lesions That Predispose to Retinal Detachment?

Pathologic myopia has pigmentary changes in the periphery that may be found with changes in the posterior pole and peripapillary areas (see previous section). One of the peripheral pigmented lesions is lattice degeneration, characterized by arcuate or linear pigmentation anterior to the equator. Multiple areas of lattice degeneration are frequently present, and they may be bilateral. Histologic examination reveals localized retinal thinning, vitreous condensation with vitreoretinal attachments at the borders, and an overlying pocket where the vitreous is absent. A fine wicker pattern with sclerotic vessels may overlay the

area. Pigmented atrophic retinal holes may be best identified with scleral depression. Horseshoe tears can develop at the edge of lattice degeneration because of vitreous traction, increasing the possibility of retinal detachment. Lattice degeneration is estimated to be the underlying cause in 20 to 30% of rhegmatogenous retinal detachments.

Should Lattice Degeneration Be Treated?

Observation is usually the treatment of choice for asymptomatic lattice degeneration without retinal breaks. Laser photocoagulation may be performed when there is an associated horseshoe tear or when the patient is acutely symptomatic and there is evidence of an adjacent retinal hole or subretinal fluid. The fellow eye may also dictate treatment. If there has been a retinal detachment associated with lattice degeneration in one eye and there are suspicious areas of lattice degeneration with retinal breaks in the contralateral eye, some ophthalmologists advocate prophylactic laser treatment. Laser spots are placed surrounding the pigmented area in confluent rows, especially along the posterior border. The signs and symptoms of retinal detachment should be reviewed with the patient.

Are There Inherited Forms of Pigmented Lesions in the Periphery?

Another form of peripheral pigmentation is associated with retinitis pigmentosa (RP). There are autosomal-dominant, autosomal-recessive, and X-linked forms of RP. This condition does not involve an inflammatory condition as the name implies but instead involves an apoptosis of the rod photoreceptors.[30,31] The presentation is highly variable, ranging from sectorial involvement to diffuse pigment found in the entire periphery. Onset in infancy or childhood with a diffuse loss of rod sensitivity, absent-rod ERG, and night blindness represents a severe form of RP. In contrast, RP patients may have regional loss of rod and cone function and adult-onset nyctalopia and maintain a recordable ERG into adulthood. The typical fundus appearance of RP is a lacy brown to black pigment in the periphery with fine stippling along its borders (Fig. 8–7). The pigmentation often is located in the perivascular region and has been described as *bone spicules*. The pigmentary changes of retinitis pigmentosa are considered a reactionary process to photoreceptor degeneration, not a contributing factor to disease progression.

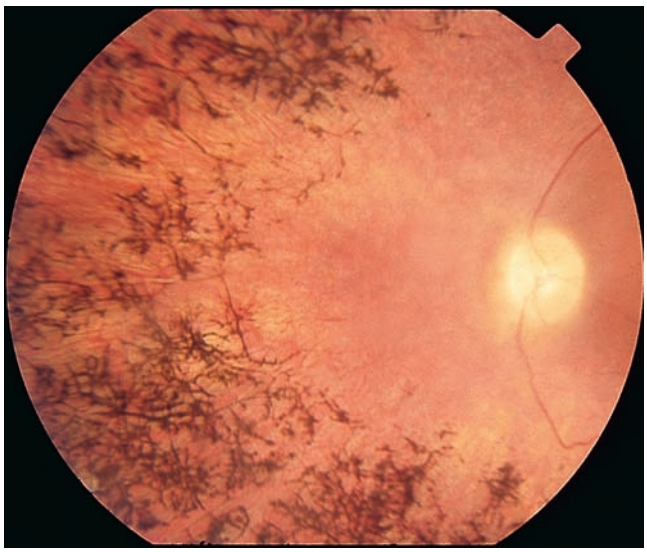

FIGURE 8–7. Lacy black peripheral pigmentation in retinitis pigmentosa. Note attenuated vessels and waxy pallor of the optic disc.

What Visual Symptoms Occur with Typical Retinitis Pigmentosa?

The age of onset of visual symptoms is variable. Nyctalopia is usually the earliest symptom found in patients with RP. Afflicted children often have difficulty ambulating in poorly lit rooms or become disoriented at night. Often, children are referred for nonspecific decreased vision or pigmentary changes found on routine ophthalmoscopy. Visual compromise is also due to a typical progressive constriction of the visual field that may begin as a midperipheral scotoma and later coalesce into a complete ring scotoma. This leads to legal blindness in many patients with RP when there is less than 20 degrees of central visual field. Clinical examination may show bone-spicule pigment changes, posterior subcapsular cataract, attenuated retinal vessels, vitreous cells, and waxy pallor to the optic nerve head.

What Role Does Ancillary Testing Have in Retinitis Pigmentosa?

Retinitis pigmentosa does not always present in a typical fashion, and ancillary testing may be helpful in determining the diagnosis early in the disease. The ERG provides the most useful information in both the early and advanced stages. The ERG typically shows a loss or marked reduction of both rod and cone signals, although the effect on the rod response is more pronounced. Implicit times of the B-wave are generally prolonged and reduced in amplitude. Full-field ERG measurements may display an extinguished pattern in advanced cases of RP. Multifocal ERG has the advantage of localizing the areas of photoreceptor degeneration and displaying progression over time. Visual fields are also of value in assessing the visual impairment from RP and evaluating for progression.

Ring scotomas and generalized constriction are patterns observed in the typical form of RP. Fluorescein angiography in the early stages of RP can demonstrate a normal choroidal flush and variable mottling due to the overlying RPE changes. Cystoid macular edema may be present. Later in the course, there may be choroidal hypofluorescence in areas of RPE atrophy, but this is not a universal finding.

Which Genes Have Been Implicated in Retinitis Pigmentosa?

Multiple genetic subtypes of RP have been identified through the use of DNA linkage studies.[32] Mutations in the rhodopsin (3q21-q24) and peripherin/*RDS* (6p22.1-cen) genes are associated with the dominant phenotype. Recessive phenotypes have been linked to the rhodopsin and rod cyclic guanosine monophosphate (cGMP) phosphodiesterase and channel protein genes. There are also X-linked forms of RP with separate gene involvement. The field of molecular genetics continues in efforts to identify mutations that would reveal distinct functional mechanisms of RP.

What Are the Systemic Disorders Associated with Retinitis Pigmentosa?

Usher syndrome is the most common syndrome associated with RP. It is associated with congenital deafness and has an incidence of about 1.8 to 4.4 cases per 100,000.[33] Four subtypes have been identified. Type I Usher syndrome presents profound deafness, vestibular symptoms, and childhood-onset RP. Type II is characterized by partial deafness and a milder form of RP. Type III, or Hallgren syndrome, is associated with psychosis. Type IV is characterized by mental retardation, deafness, and RP.

Numerous other systemic disorders are associated with RP. Some researchers consider these to be "pseudo-retinitis pigmentosa" because of associated metabolic disturbances. These include Bassen–Kornzweig syndrome, Refsum disease, Laurence–Moon syndrome, Bardet–Biedl syndrome, neuronal ceroid lipofuscinosis, and Kearns–Sayre syndrome. Each disorder shares the common visual decline associated with RP. Bassen–Kornzweig syndrome is due to an inability to synthesize apolipoprotein B, with a decrease in fat-soluble vitamins (A and E). Children with the syndrome also display acanthocytosis, ataxia, fat intolerance, and RP. Supplementation with vitamin A in sufficient amounts may lead to a reversal of previously reduced dark adaptation and ERG. Refsum disease is caused by phytanic acid accumulation in swollen RPE cells causing sensory retinal deterioration. Systemic findings include ataxia, peripheral neuropathy, deafness, anosmia, and increased cerebrospinal fluid (CSF) protein without pleocytosis. Laurence–Moon and Bardet–Biedl syndromes share common features of mental retardation, hypogenitalism, short stature, and pigmentary retinopathy. Laurence–Moon demonstrates spastic paraplegia, whereas Bardet–Biedl displays polydactyly and obesity. Neuronal ceroid lipofuscinosis is characterized by an accumulation of autofluorescent lipopigments in neurons and nonneuronal tissues. The disease ranges from the infantile, late-infantile, and juvenile forms in which there are mental and motor abnormalities associated with retinal degeneration to the relatively benign adult onset form. Kearns–Sayre syndrome is a mitochondrial myopathy that often presents as progressive external ophthalmoplegia. There may also be small stature, dysphasia, facial weakness, and cardiac conduction defects, including complete heart block.

Is There Any Treatment for Retinitis Pigmentosa?

No effective treatment has been established to reverse visual loss associated with RP.[34] Clinical trials in transplantation of RPE or neuroretinal cells may reveal promise in the future. Genetic counseling and examination of family members may be helpful in identifying carrier states and offering visual aids to improve visual capabilities. Low-vision consultation also may increase the visual capabilities of those affected by this progressive disorder.

Are There Other Pigmented Lesions in the Periphery Associated with Systemic Disease?

Multiple discrete areas of pigmentation may represent the inherited condition associated with Gardner syndrome.[35,36] Congenital grouped pigmented ocular fundus lesions, or "bear tracks," may have a number of configurations, but collections of four or more are highly suggestive of familial adenomatous polyposis (FAP).[37] The pigmented lesions found in the periphery may be ovoid, teardrop, or spear shaped, or they may be small, round areas (Fig. 8–8). Generally, the pigmented ocular fundus lesions are found at birth and have a stable appearance. Histopathologically, the lesions are large, spherical melanin pigment granules found within the RPE cells.[38] These granules differ from the normal slender melanin granules. The lesions range from a single layer of hypertrophied RPE cells to a layer spanning the full thickness of the retina. There is no reported malignant transformation.

What Is the Inheritance of Gardner Syndrome, and What Treatment Is Necessary?

Treatment of the patient with congenital grouped pigmented ocular fundus lesions is based on identifying any systemic involvement. Gardner syndrome is an

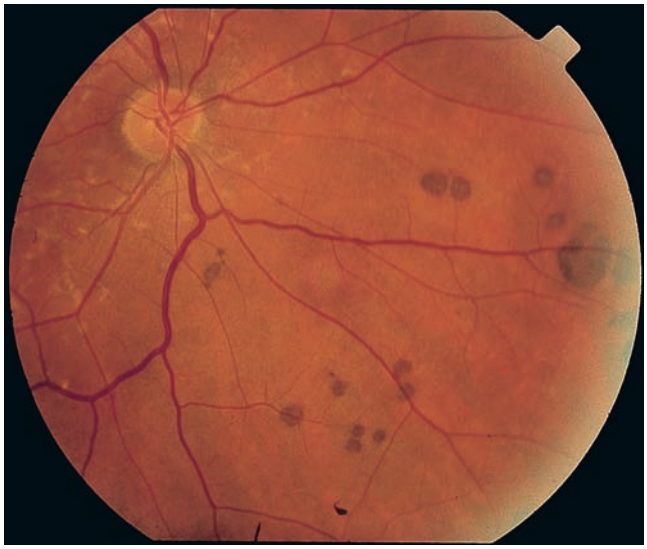

FIGURE 8–8. Small, discrete brown-pigmented ocular fundus "bear tracks" in a patient with Gardner syndrome. Incidentally, the patient has findings of fundus flavimaculatus.

autosomal-dominant condition in which multiple colonic polyps develop as a precursor to adenocarcinoma of the colon. All patients with Gardner syndrome will develop colon cancer if not treated with prophylactic colectomy. Turcot syndrome is associated with FAP in which brain tumors develop.[39] Genetic discoveries of a deletion involving the long arm of chromosome 5, later mapped to chromosome 5q21-q22, have been implicated in FAP.[40] Coordination of treatment with an internist for colonoscopy and arrangement for systemic treatment are indicated. Examination of family members often reveals a similar appearance and grouping. No treatment other than observation is necessary for the ocular pigmentary findings.

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9

Brown–Black Lesions: Fine Hyperpigmented Spots

MARCIA D. CARNEY

Hyperpigmented Spots

What are some of the disease associations with hyperpigmented lesions of the fundus?

Fine, hyperpigmented lesions of the fundus may be associated with infectious and inflammatory retinal diseases, or they may exist with dystrophic and degenerative diseases of the retina. Common causes of these hyperpigmented lesions of the fundus include hyperplasia of the retinal pigment epithelium (RPE) in response to infections or inflammatory diseases (uveitis), hereditary or congenital disorders of the retina, such as rod-cone (retinitis pigmentosa), or cone–rod dystrophies (Fig. 9–1). Degenerative diseases of the retina and RPE include central or peripheral retinal degeneration and associated choroidal disease or neovascularization (CNV), which may present with fine, hyperpigmented lesions. In diseases such as age-related macular degeneration, fine, hyperpigmented lesions may be seen as a part of the disease involving the RPE-Bruch membrane complex. Peripheral retinal degenerative diseases, such as peripheral cystoid degeneration may present with areas of pigment epithelial atrophy and hypertrophy, possibly presenting as fine hyperpigmented lesions.

What Are Symptoms of Fine, Hyperpigmented Spots?

Symptoms associated with hyperpigmented spots may include floaters if an underlying infectious or inflammatory (uveitis entities) disease of the retina and choroid is present. If these fine, brown–black spots are located centrally, that is, within the macular area, they might be associated with the complaint of a central scotoma.

Disease entities such as syphilis may be associated with retinitis or vitreitis, and the patient may present with floaters or reduced vision. Any of the causes of uveitis, such as sarcoidosis or Vogt–Koyanagi–Harada, may present with floaters. The floaters associated with sarcoidosis, for example, often are associated with retinitis or an inflammatory cellular response in the vitreous. Postinflammatory changes such as fine hyperpigmented spots may be seen with many of the infections or inflammatory diseases of the retina.

Floaters are less likely to be seen with hereditary, congenital dystrophic diseases or degenerative diseases of the retina. Fine, hyperpigmented spots. If these spots are located within the macular area, and associated with diseases like cone-rod dystrophy or age-related macular degeneration, can be associated with reduced color vision, reduced contrast sensitivity, scotoma, or metamorphosia.

Rubella

Congenital and Acquired Rubella

Rubella, caused by an RNA virus of the togavirus group, can be associated with congenital and acquired postnatal infections.

What Is Congenital Rubella?

The association between congenital rubella and infection of mothers in the first trimester of pregnancy was recognized as early as 1941.[1] The virus was isolated in 1962, and a vaccine was developed in 1969; subsequently, occurrence of the virus decreased.[2] Infections during the first trimester of pregnancy may result in spontaneous abortion or stillbirth. Children who acquire the virus in utero may present postnatally with a spectrum of findings known as the congenital rubella syndrome. This maternal rubella syndrome is characterized by mental retardation, congenital heart

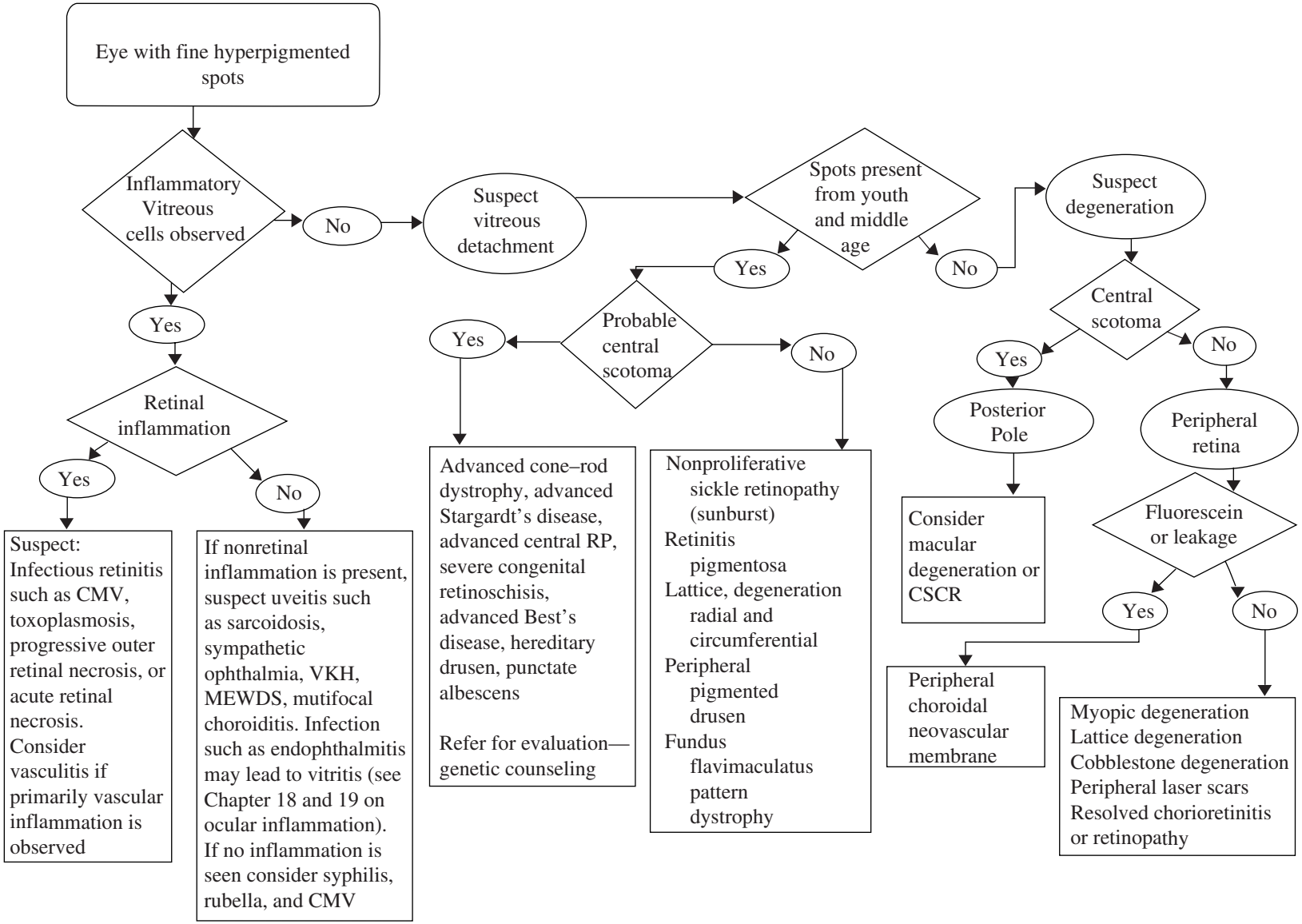

FIGURE 9–1. Clinical pathway for the diagnosis and management of patients presenting with brown-black lesions: Fine hyperpigmented spots. VKH, Vogt-Koyanagi-Harada syndrome; MEWDS, multiple evanescent white-dot syndrome; CMV, cytomegalovirus retinitis; CSCR, central serous chorioretinopathy; RP, retinitis pigmentosa.

disease, and deafness and has associated ophthalmic findings that include cataracts and anterior and posterior segment inflammation.

What Is Acquired Rubella?

When the infections occur postnatally or are acquired, there is a mild, self-limited illness with associated fever, adenopathy, and skin rash.

What Are the Characteristics of Rubella Retinopathy?

The pigmented changes that occur with rubella retinitis can be fine and dust-like in character, or there may be large, discrete areas of hyperpigmentation. The pathognomonic retinal appearance and the fine, powdery granular appearance usually suggest the diagnosis of rubella retinitis. Rubella retinitis is seen in 25% or more of infants with the syndrome. Anterior-segment inflammation and vitreous inflammation can be present. Along with the granular hyperpigmented and hypopigmented changes, optic disc pallor may be present. The course of the retinitis is most often benign. Histopathologic changes can include necrosis of the iris pigment epithelium, chronic granulomatous inflammatory changes of the iris, and alternating areas of RPE hyperplasia and atrophy.

Maternal immunization provides a protective effect against fetal acquired viral diseases. With maternal immunization, immunoglobulin G (IgG) antibodies are produced, cross the placenta, and provide immunization for the mother and the fetus. Immunization of pregnant women with viral vaccines for poliovirus, influenza viruses, and rubella are safe for both the mother and the fetus.[3]

Carrier States Associated with Fine, Hyperpigmented Spots

What Are the Symptoms and Signs of the Carrier States in Choroideremia and X-linked Retinitis Pigmentosa?

X-LINKED RETINITIS PIGMENTOSA

Retinal degenerations and dystrophies such as retinitis pigmentosa are characterized by progressive loss of vision (with the time course often dependent on the genetic heterogeneity), particularly night vision. These retinal degenerations are characterized by the loss of photoreceptors or photoreceptor outer segments, particularly rod photoreceptors in the earlier course of the disease. The genetic heterogeneity of the degeneration often expresses the degree of severity of vision loss. With the prevalence of 1 in 4000 worldwide, Bundey and Crews projected the genetic incidences to be 19% autosomal dominant, 19% autosomal recessive, 8% X-linked, 8% undetermined, and 46% simplex or sporadic.[4] Often retinitis pigmentosa and allied diseases have characteristic retinal, electrophysiologic, and psychophysiologic changes. The retinal examination may include vascular attenuation, intraretinal bony spicule pigmentation, and areas of RPE depigmentation throughout the midperiphery. The optic discs appear pale, macular edema may be present, and vitreous syneresis or opacities may be present. Characteristic electrophysiologic changes include subnormal to abnormal B-wave and A-wave amplitudes and prolonged B-wave implicit times, particularly in dark-adapted patients tested with blue light. The 30-Hz flicker electroretinogram (ERG), which evaluates cone system responses, is delayed in the early stages of retinitis pigmentosa.

The inheritance of an X-linked trait depends on the segregation of maternal X-chromosomes. X-linked recessive inheritance is typified by the expression of traits in males; females are carriers of the X-linked traits. These disorders are expressed by all males inheriting the mutant gene but are seen only in females homozygous for the recessive allele. For some diseases such as X-linked retinitis pigmentosa, choroideremia, ocular albinism, and the mucopolysaccharidoses, the carrier state may be detected in females. One of the two X-chromosomes in each of a female's cells is randomly inactivated by a process referred to as lyonization. If a disproportionate number of normal X-chromosomes are inactivated, mild manifestations of the disorders may occur. Carriers of these X-linked forms of disease may show a spectrum of disease dependent on the extent of inactivation of the normal X-chromosome and may show slowly progressive retinal degeneration.[5] Female carriers of X-linked retinitis pigmentosa may show a patch of bony spicule pigment or may have an abnormal macular tapetal reflex. Electrophysiologic testing may be helpful in detecting female carriers of X-linked retinitis pigmentosa.[5,7] This can be detected by ophthalmoscopy or full-field ERG testing or both. These females have a 50% chance of having an affected male carrier and a 50% chance of having a carrier daughter.[6]

Choroideremia

X-linked inherited choroideremia presents in young men with often normal vision, increased dark-adaptation thresholds, and full visual fields to large test objects, even at the time when granularity and depigmentation of the RPE can be seen around the retinal periphery. Presenting in the first or second decade of

life, these patients progressively develop problems with dark adaptation progressing to night blindness and constriction of visual field. Central vision is severely impaired by the fifth decade of life. This condition is characterized by a progressive degeneration of the RPE, retina, and choroid. Electrophysiologic responses may be affected within the first decade, and the ERG responses may be extinguished as the disease progresses. Fundus abnormalities with patchy depigmentation and stippling of the RPE may occur in affected individuals as early as the first decade of life and also can be seen in asymptomatic female carriers of choroideremia. As the disease progresses with RPE and choroidal atrophy, only small scalloped areas of intact choroid in the macula and periphery may remain. In carriers, histologic studies reveal scattered areas of reduced photoreceptors, RPE atrophy, pigment clumping, and associated areas of choriocapillaris loss.[8] Choroideremia is related to a gene isolated by linkage analysis to Xq13-q22, whose protein product, Rab escort protein (REP-1), is noted to be absent in peripheral lymphocytes. The absence of REP-1 results in protein truncation either by deletions, translocations, or mutations. MacDonald developed a simple immunoblot assay using anti-REP-1 antibodies to diagnose patients with choroideremia.[9]

Ocular Albinism

In ocular albinism, characterized by subnormal to abnormal vision and pendular nystagmus, patients may present with symptoms of photoaversion, clinical evidence of iris transillumination defects, and a hypopigmented fundus. The fovea is hypoplastic, with no foveal reflex or yellow macular pigmentation and an absence of the foveal pit on histology. True ocular albinism is divided into ocular and oculocutaneous albinism. In oculocutaneous albinism, the skin and eye may be affected; in ocular albinism, the eyes are clinically affected with some degree of cutaneous pigmentary change. Oculocutaneous albinism is inherited as an autosomal-recessive trait. Ocular albinism is transmitted as an X-linked disease and results from a reduction in the number of melanosomes. Female carriers of ocular albinism may have iris transillumination defects, macular pigment epithelial mottling, and irregular areas of patchy hypopigmentation in the midperiphery of the fundus. Female carriers of Nettleship-Falls ocular albinism (X-linked) can be identified by skin biopsy showing macromelanosomes or giant pigment granules in the RPE, the ciliary epithelium, and the keratinocytes and melanocytes of the skin. Macromelanosomes are lacking in the Forsius-Erickson type of X-linked ocular albinism.[10] Genetic analysis of the ocular albinism 1 gene demonstrated seven presumed pathogenic mutations in nine families examined with X-linked ocular albinism, with five single nucleotide substitutions predicting a change in the conserved amino acids. The mutations present predict crucial changes in the protein structure that is involved. Clinical examination failed to identify any phenotype–genotype pattern.[11]

Mucopolysaccharidoses

These cellular lysosomal storage diseases result from deficiencies of specific lysosomal exoenzymes involved in the degradation of dermatan, heparan, or keratan sulfate, inborn errors of lysosomal glycosaminoglycan metabolism. Mucopolysaccharides (MPSs) that have been incompletely degraded accumulate in organs and connective tissues and are excreted in the urine. The syndromes are varied but may produce skeletal deformities, coarse facies, visceromegaly, cardiac disease, deafness, mental retardation, and ocular involvement. Subclassification of the syndromes may occur on clinical grounds alone. The MPSs usually are transmitted as autosomal-recessive traits, except type II (Hunter), which is X-linked recessive. The MPS syndromes, particularly the autosomal-recessive syndromes associated with storage of heparan sulfate, such as MPS Hurler and MPS Scheie syndromes, may have an associated retinal dystrophy. MPS II, or Hunter syndrome, with X-linked inheritance, may demonstrate a pigmentary retinopathy. The patients may also have corneal clouding, coarse facies, dwarfism, and mental retardation. The enzymatic defect is a deficiency in iduronate sulfatase, an enzyme needed in the sequential degradation of heparan sulfate and dermatan sulfate. The Hunter syndrome is further divided into type A and type B. Type A Hunter syndrome includes patients with symptoms by age 1, who die early. MPS II-B begins at about age 4 years. These patients have less severe symptoms, and may live into their sixties. Ophthalmic manifestations of MPS II include progressive retinal dystrophy and papilledema. The ERG may be reduced or extinguished. Night blindness and continued deterioration of vision may be common. Bony spicule pigmentation and pigment epithelial atrophy may be noted in the midperipheral fundus. Not all patients show elevated glycosaminoglycan levels in the urine, and enzyme assays with evaluation of the electrophoretic patterns of the affected glycosaminoglycans (GAGs) become necessary. Carriers can be identified by the quantitation of fructose-1 phospate in fibroblast cultures, determination of iduronate sulfatase activity in hair roots, and enzymatic assays of GAGs.[12]

Syphilis

What Are the Signs and Symptoms of Syphilis?

Since the discovery of penicillin in 1943,[13] the incidence in syphilis has decreased, particularly in the 1970s, with this specific therapy; however, there has been a resurgence in incidence since the 1990s along with the increased incidence of human immunodeficiency virus (HIV). Following the initial infection, there is a humoral and cellular response. Clinical manifestations include primary, secondary, latent, tertiary syphilis, cardiovascular syphilis, and neurosyphilis in acquired disease. Congenital syphilis results from transplacental transmission of primary or secondary syphilis.

Ocular manifestations of secondary and tertiary syphilis include the following anterior segment changes: conjunctivitis, keratitis, iris nodules, iridocyclitis, episcleritis, and scleritis. Posterior segment changes include retinitis, choroiditis, vasculitis, disc edema, vasculitis, neuroretinitis, choroiditis, choroidal effusion, optic neuritis, and exudative retinal detachments. Choroidal neovascular membranes have been reported. Healed areas of neuroretinitis, particularly in the peripapillary region, may result in a pigmentary retinopathy similar in appearance to retinitis pigmentosa.[14,15]

Secondary syphilis, occurring 6 weeks to 6 months after primary infection, may be associated with a granulomatous or nongranulomatous anterior uveitis and vascularized iris papules. Following the posterior segment uveal involvement, the patient may have extensive gliosis and atrophy of the RPE in the posterior pole.

Can Syphilis Occur Concurrently with Other Infections?

With the increase in HIV during the early to mid-1990s, there have been reports of syphilis occurring concurrently in HIV-positive patients. These patients may present with uncharacteristic clinical manifestations of syphilis. In addition, acute retinal necrosis and acute retinitis have been associated with syphilis in patients coinfected with HIV.[16] Regression of these areas of retinitis may lead to small, hyperpigmented spots in the retina.

What Are the Characteristics of Congenital Syphilis?

Congenital syphilis is characterized by keratouveitis from acute interstitial keratitis occurring in patients aged between 5 and 25 years and later will result in interstitial keratitis. Congenital syphilis may also result in a bilateral salt-and-pepper fundus that may occur throughout the fundus. There is no progression of the retinopathy and little effect on the visual acuity.

What Are the Characteristics of Acquired Syphilis?

Ocular syphilis is often referred to as the "great masquerader." Its presentation with anterior and posterior granulomatous or nongranulomatous uveitis or diffuse inflammation of the anterior segment, posterior segment, and optic nerve often allows the presentation to include the differential diagnosis of sarcoidosis, sympathetic ophthalmia, Vogt–Koyanagi–Harada syndrome, Behçet syndrome, acute retinal necrosis syndrome associated with herpes family viruses, toxoplasmosis, and other causes of acute anterior and posterior uveitis.

What Are the Serologic Tests for Syphilis?

Serologic screening tests include the rapid plasma reagent (RPR) or the Venereal Disease Research Laboratory (VDRL) test. Infection with *Treponema pallidum* stimulates antibodies against cardiolipin. The VDRL test may become negative, but it is usually positive in patients with primary and secondary syphilis. The VDRL test may become negative later in the disease, particularly tertiary disease, and becomes negative after treatment. More specific tests to confirm infection include the fluorescein treponema antibody absorption (FTA-ABS) test, which is more sensitive than the VDRL test at all stages of the syphilitic infection.

What Is the Treatment of Syphilis?

Primary and early secondary syphilis is treated with 2.4 million units intramuscularly; daily for 10 days. Most authorities believe that tertiary and ocular syphilis and neurosyphilis should be treated with 2–4 million units of intravenous penicillin every 4 hours for 10 days to 2 weeks. Patients allergic to penicillin are treated with doxycycline or erythromycin.

Age-Related Macular Degeneration (Age-Related Maculopathy)

What Is the Background and Epidemiology of Age-Related Macular Degeneration?

As the population over the age of 60 years continues to increase, age-related macular degeneration (AMD, ARMD, or ARM) will continue to be the leading cause of irreversible blindness in developed countries.[17] AMD is classified as the exudative type associated with choroidal neovascular membranes, occurring in 10 to 15% of cases, and the nonexudative, or dry type, occurring in 85 to 90% of cases and characterized by abnormalities of the RPE with atrophy or hyperplasia

and drusen. Changes in macular pigmentation can be found in both forms of AMD. To standardize communications about AMD, an international classification and grading system has been suggested. Early age-related maculopathy (ARM) in this classification is characterized by the presence of drusen and RPE abnormalities. Drusen, subretinal, yellow deposits, may vary in size. Hard drusen are <63 μm and soft drusen are 125 μm. Large drusen may become confluent and coalesce into drusenoid RPE detachments. These areas may progress to areas of geographic atrophy or exudative disease. Late ARM is characterized by geographic atrophy of the RPE and neovascular disease. Late AMD is the most likely to be associated with severe visual loss.[18]

Age-related macular degeneration is the leading cause of severe central visual acuity loss in people over 65 years of age in the United States and in other white populations. Persons over the age of 75 have a 30% chance of manifesting some of the early forms of AMD with drusen and RPE abnormalities. Of those remaining, 23% will have evidence of AMD over the subsequent 5-year period.[19,20] In a population of 3583 adults, Klein and colleagues studied the incidence and progression of retinal drusen and retinal pigmentary abnormalities and the signs of late AMD. Persons over the age of 75 years, compared with those between 43 and 54 years of age, had a higher 5-year incidence of the following: (1) larger drusen (125 to 249 μ) in 17.6% versus 2.1%; (2) soft drusen in 16.3% versus 1.8%; and (3) RPE abnormalities in 12.9% versus 0.9%, exudative macular degeneration in 1.8% versus 0.07%, and geographic atrophy in 1.7% versus 0%. Late AMD was more likely to develop in eyes with soft, indistinct drusen (6.5% versus 0.1%) or RPE abnormalities (7.1% versus 0.1%).[19] A meta-analysis of the Beaver Dam Eye Study, the Rotterdam Study, and the Blue Mountain Eye Study (14,752 participants with gradable photos) indicates that there is 0.2% prevalence of AMD in patients between ages 55 to 64 years; this prevalence increases to 13% in the population over the age of 85 years.[21]

What Is the Current Thought on the Use of Micronutrients in the Treatment of Nonneovascular Age-Related Macular Degeneration?

Micronutrients such as zinc, vitamin C and E, and beta-carotene have been proposed to reduce vision loss from AMD because of their antioxidant potential. These antioxidants were suggested based on the theory that oxygen free radicals liberated by light exposure might cause damage to the pigment epithelium and outer retina.[22] Micronutrients such as zinc and selenium, cofactors that facilitate antioxidant enzymes, have also been considered as micronutrient supplements. Until recently, studies had failed to give convincing evidence that dietary modification or micronutrient supplementation would alter the course of nonneovascular AMD.[23] In groups who are at risk for developing early (ages 40 to 59 years) or late (ages 60 to 79 years) ARM, higher levels of lutein and zeaxanthin in the diet were related to lower odds for pigmentary abnormalities, one sign of early AMD and late AMD, after adjustment for age, gender, alcohol use, hypertension, smoking, and body mass index.[24] Results from the Age-Related Eye Disease Study (AREDS) support micronutrients to reduce progression of disease and vision loss in AMD.

Does Exposure to Sunlight Cause Macular Degeneration?

Although there is an association between ultraviolet light exposure and development of cataracts,[25] clinical studies, such as the Beaver Dam Eye Study[26] and the Chesapeake Bay Waterman Study,[27] to date have not supported the association between light exposure and the risk of developing AMD. Reevaluation of the Beaver Dam Eye Study, a longitudinal, population-based study, found that leisure time spent outdoors increased the risk of early ARM. Participants with red or blond hair were slightly more likely to develop early ARM than were people with dark hair. Exposure to sunlight may be associated with the development of early ARM.[28]

What Are the Risk Factors for Age-Related Macular Degeneration?

Epidemiologic studies have identified increasing age, not gender, as a risk factor for AMD.[19,20] Some epidemiologic studies have implicated smoking, hypertension, and other cardiovascular risk factors in the occurrence of AMD.[29–31] The age-related macular degeneration risk factors study, a case-control study for risk factors of neovascular and non-neovascular macular degeneration evaluated 1222 patient sets of available photographs, and concluded that neovascular AMD was associated with moderate to severe hypertension, and particularly among patients receiving antihypertensive treatment. The group promoted the hypotheses that neovascular and nonneovascular AMD may have a different pathogenesis and that neovascular AMD and hypertensive disease may have a similar underlying cause and effect.[32]

Drusen and RPE changes are also risk factors for further development of AMD[19–21] (Fig. 9–2). Sunlight or ultraviolet light may be a risk factor, particularly in patients with red or blond hair.[28] Frank and colleagues, in reexamining the relationships between race, iris color, and AMD in a series of 306 sequential patients 60 years of age or older, confirmed the previ-

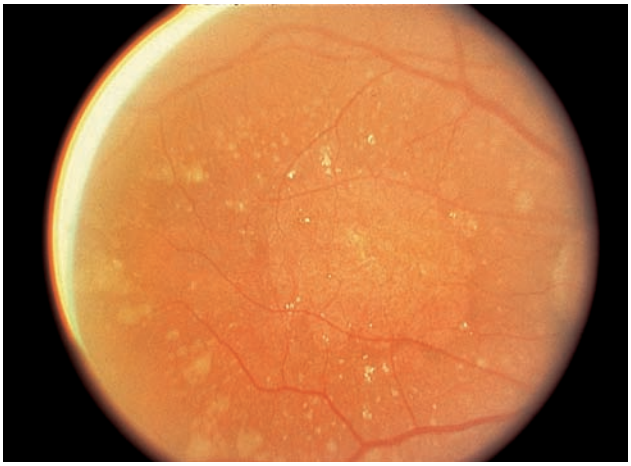

FIGURE 9–2. Color photograph of retinal pigment epithelium atrophy and soft drusen, risk factors for age-related macular degeneration.

ous findings of a higher prevalence of AMD in white persons than in black persons. White subjects with light-colored irides have a higher prevalence of AMD than do those with dark-colored irides.[33] The prevalence of the exudative type of AMD is higher among first-degree relatives with exudative disease. Other possible risk factors may include genetic heritage. More studies are needed to study the genetic susceptibility of AMD.[34] Except for the association of beer drinking with retinal drusen in men, consumption of alcoholic beverages is not likely to be an important risk factor for the incidence of AMD.[35]

What Are the Types of AMD?

Age-related macular degeneration is classified a nonneovascular (or dry macular degeneration) (Fig. 9–3A) and exudative-neovascular degeneration (also called the wet form of macular degeneration) (Fig. 9–3B). Each form has its own hallmark characteristics. Loss of the RPE, choriocapillaris, and choroidal atrophy, are associated with loss of photoreceptors. Nonneovascular AMD is characterized by RPE changes, drusen, and in the late stages visual loss. Neovascular AMD may have all the characteristics of dry AMD; however, its hallmark characteristic is CNV.

In 1995, the International Age-Related Maculopathy Study Group outlined a classification and grading system of clinical features of AMD, which allows more meaningful comparison of other AMD studies.[18] Nonneovascular AMD is diagnosed when patients present with areas of change within the RPE or with evidence of drusen.

What Are Drusen and Their Characteristics?

Drusen are deposits beneath the RPE that are characteristic of but not uniquely associated with AMD. AMD is associated with two types of drusen, with different appearances and likely different prognoses. Hard drusen, less than 63 μ in diameter, have distinct borders. They appear as yellow, small nodules beneath the RPE and can precede the development of atrophic AMD. Soft drusen appear large (usually larger than 125 μm in diameter) and pale yellow or grayish white. They may be dome-shaped elevations that may resemble localized serous RPE detachments. As drusen disappear, areolar atrophy may be seen. Spontaneous drusen regression probably involves RPE atrophy.[36]

Clinicopathologically drusen appear to be either focal lipoidal degeneration of RPE cells or localized accumulation of hyaline material in the inner and

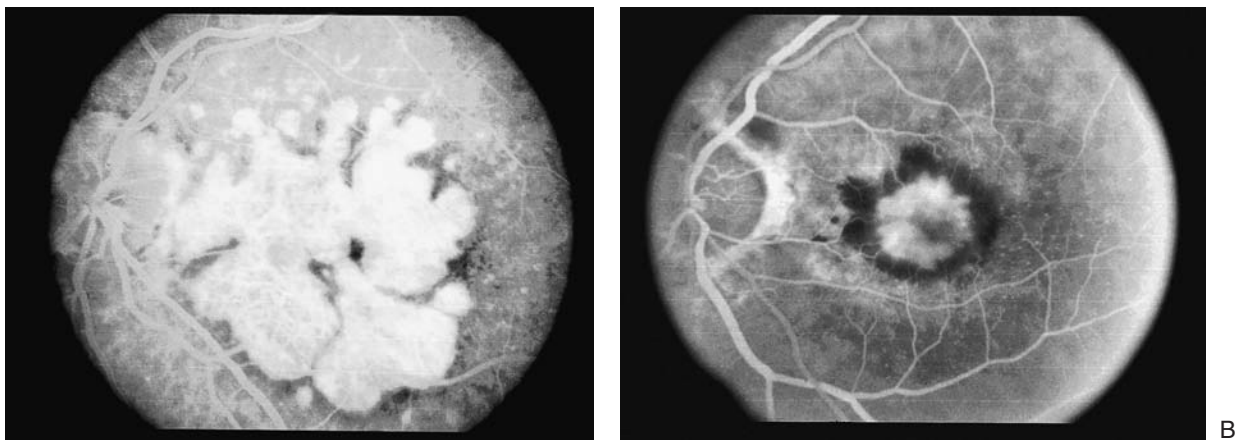

FIGURE 9–3. (A). A fluorescein angiogram showing hyperfluorescence in an area of retinal pigment epithelium atrophy, a "window defect." (Reproduced with permission of Novartis Ophthalmics, Inc.) (B). A fluorescein angiogram of a patient with hyperfluorescence and leakage associated with a choroidal neovascular membrane. (From Ophthalmologica. 2001;215:247–253, reproduced by permission from S. Karger AG).

outer collagenous zones of a normal Bruch's membrane.[37] In this study, Green and Enger observed few RPE degenerative changes with hard drusen. During fluorescein angiography (FA), hard drusen hyperfluoresce. Histopathologically, soft drusen represent localized detachments of the RPE. Drusen may be associated with basal linear or basal laminar deposits. Basal linear deposits refer to material located external to the RPE basement membrane, lying within the inner collagenous zone of the Bruch's membrane. These deposits consist of granular and vesicular lipid-rich material with wide-spaced collagen. Basal linear deposits are commonly seen histologically in eyes with vision loss and are associated with geographic atrophy or subretinal neovascular membranes. In contrast, basal laminar deposits are found between the plasma membrane and the basement membrane of the RPE. On electron microscopy, these lesions consist mainly of wide-spaced collagen and electron-dense bodies. Soft drusen are small pigment epithelial detachments which can appear hypofluorescent or hyperfluorescent on FA. Soft drusen are believed to be a hallmark of AMD, associated with abnormalities of the RPE–Bruch's membrane complex. The development of CNV and geographic atrophy of the RPE appears to be associated more frequently with soft drusen than with hard drusen.

Spraul and colleagues performed a histopathologic and morphometric study aimed to investigate the correlation among characteristics of choroidal vessels, the RPE, and Bruch's membrane and the types of AMD present. Characteristics of nonexudative and exudative macular degeneration were evaluated. The nonneovascular components that were evaluated in both the macular and the extramacular regions included the degree of calcification of the Bruch's membrane, fragmentation of the Bruch's membrane, the number and types of drusen, basal laminar deposit, and seven morphometric variables of the choroid. Surgically excised subfoveal membranes also were processed. The observations included no statistically significant differences between eyes with neovascular and nonneovascular AMD. The single most important difference between eyes was the amount of basal laminar deposit. Eyes with AMD had significantly more basal laminar deposit in the macular area than controls as well as soft, diffuse, and large drusen. Eyes with AMD displayed fewer large choroidal vessels in the submacular choroid than did eyes without AMD. The submacular choriocapillaris density was higher in eyes with AMD. The peripheral choriocapillaris displayed the same pattern as the macular choriocapillaris. Compared with controls, a statistically significant difference was observed in the degree of calcification and fragmentation of Bruch's membrane in eyes with exudative AMD. These differences did not reach statistical significance in eyes with nonexudative AMD. This morphometric and histopathologic study concluded that AMD is a dynamic process with early proliferation and subsequent atrophy of capillaries of the choriocapillaris. Calcification and fragmentation of Bruch's membrane; soft, diffuse, and large drusen; and basal laminar deposit, but not hard drusen, strongly correlate with the histologic presence of AMD. The degree of calcification and fragmentation of Bruch's membrane was more prominent in exudative AMD. These investigators concluded that the formation of choroidal neovascular membranes represents a stereotypic, nonspecific wound repair response independent of the underlying disease.[38]

What Are the Abnormalities of the RPE in Nonneovascular Age-Related Macular Degeneration?

Abnormalities of the RPE represent another form of nonneovascular AMD, including atrophy or hyperpigmentation. These changes may present as fine, hyperpigmented lesions of the fundus. Geographic atrophy of the RPE may take the form of a perifoveal, reticulated, hyperpigmented, or hypopigmented appearance; these areas enlarge and coalesce slowly over time. Large, soft, confluent drusen can develop into geographic atrophy (GAP).[39] Clumps of pigmented cells at the level of the RPE may appear as focal areas of hyperpigmentation. These focal clumps of pigment may correlate with an increased risk of the development of a choroidal neovascular membrane or RPE atrophy.[40] Patients with GAP may witness a significant decline in vision over time. Areas of atrophy continue to enlarge, even when they are large at baseline. This combination of decreased vision and continued enlargement of the area of atrophy, occurring bilaterally in most patients, may lead to a significant loss of vision.

Geographic atrophy is the advanced form of atrophic AMD and is present in 3.5% of people aged 75 and older in the United States. Progression over time, even with sparing of the fovea until late in the course of the disease, is associated with a decrease in vision. Of eyes with geographic atrophy and good visual acuity at baseline, 40 to 50% lose three or more lines of acuity by 2 years, and 27% become worse than 20/200 by 4 years.[41] Patients with GAP may develop CNV. An eye with GAP whose fellow eye has CNV is at significant risk for the development of CNV in the GAP eye. A patient with bilateral GAP and no evidence of CNV is at relatively low risk for developing CNV.[42]

Loss of RPE in areas of areolar and geographic atrophy may have associated loss of photoreceptors. The remaining photoreceptors may be abnormal. The outer nuclear layer disappears so that the outer plexiform

layer is thinned and vacuolated with less effect on the inner nuclear layer. The cellular and molecular mechanisms underlying the death of photoreceptors and other retinal cells in AMD remain poorly understood.

When Should Patients with Nonneovascular AMD Be Watched Routinely for the Development of Neovascular Age-Related Macular Degeneration?

Patients with nonneovascular AMD presenting with drusen, particularly extensive small drusen (<63 microns), pigment abnormalities, intermediate size drusen (>63 microns), or large drusen (>125 microns), and geographic atrophy not involving the center of the macula, should be warned about the presence of macular degeneration and be advised of the need for continued monitoring with dilated examination and the use of the Amsler grid for daily monitoring. In patients with complaints of vision change, acute or chronic, fluorescein angiography is helpful in assessing changes in the pigment epithelium or evidence of CNV.

Are There Any Treatments, Experimental or Otherwise, That Are Currently Being Used for Nonneovascular Age-Related Macular Degeneration?

Antioxidant vitamins plus zinc are now being recommended for some patients with nonneovascular AMD. The Age-Related Eye Disease Study, in a randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss, has indicated that persons older than 55 years of age should have dilated eye exams to determine the risk of developing advanced AMD.

In this randomized, 11-center double-masked trial, 4757 participants were enrolled if they had extensive small drusen, intermediate or large drusen, noncentral geographic atrophy (GA), or pigment abnormalities in at least one eye, or advanced AMD, or vision loss due to AMD in 1 eye. In Category 1, defined as participants with few if any drusen, only 5 of these participants developed advanced AMD and the effects of antioxidant could not be assessed in this group. The report focused on 3640 participants. Of those enrolled, 1063 had extensive small drusen, pigment abnormalities, or at least 1 intermediate druse (Category 2); 1621 had extensive intermediate drusen, GA not involving the center of the macula, or at least 1 large druse (Category 3); and 956 had advanced AMD (GA involving the center of the macula, non-drusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the RPE, and/or subretinal fibrosis) or visual acuity less than 20/32 due to AMD in 1 eye (Category 4). Photographic assessment was used to evaluate the enrolled study participants, aged 55 to 80 years. The average follow-up was 6.3 years, with 2.4% lost to follow-up. Participants, with at least 1 eye with best-corrected vision of 20/32, were randomly assigned to receive daily oral doses containing one of the following: antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; antioxidants plus zinc; or placebo. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD and were excluded from the odds ratio determination for progression. The study demonstrated little or no benefit of the study formulations for persons in Categories 1 or 2. Although both zinc and antioxidants plus zinc significantly reduce the odds of developing advanced AMD (Categories 3 and 4), the only statistically significant reduction in rates of at least moderate visual acuity loss (approximately 25%) occurred in persons assigned to antioxidants plus zinc. This study has concluded that persons older than 55 years with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in at least one eye, or advanced AMD or vision loss due to AMD in one eye, and without contraindications, such as smoking, should consider taking a supplement of antioxidants plus zinc such as those outlined in the study.

Laser photocoagulation of drusen, to date used in nonneovascular AMD for the treatment of drusen, is one of the approaches being investigated for the management of drusen. Studies are being approached in the management of nonneovascular AMD to try to prevent the risk of visual loss and the development of CNV or pigment atrophy. Drusen may disappear from the RPE after focal laser to drusen; this disappearance may be related to the stimulation of macrophages.[45] Drusen also may disappear over time without treatment.[46] The Choroidal Neovascularization Prevention Trial (CNVPT), a recent randomized clinical, trial showed that light laser photocoagulation to fellow eyes of patients with CNV may increase the short-term incidence of CNV in the treated eye.[47] More long-term results, with the main outcome the measure of the change in visual acuity, indicate that laser-treated eyes with a reduction of 50% or more in drusen at 1 year had more one- and two-line increases in visual acuity and less loss of visual acuity compared with laser-treated eyes with less drusen reduction or with untreated (observed only) eyes. In this

study, laser-induced drusen reduction was associated with improved visual acuity and contrast sensitivity in eyes at 1 year. Long-term effects of laser-induced drusen reduction on visual function require additional observation. The overall potential value of laser treatment in eyes with high-risk drusen requires consideration of not only short-term effects on vision but also the effect of CNV and atrophy on vision and the usefulness of this procedure probably will be reassessed at a later date.[48]

Neovascular Age-Related Macular Degeneration

Whereas nonneovascular AMD is characterized by drusen, RPE, and changes in Bruch's membrane, the hallmark of exudative AMD (Fig. 9–3B) is CNV. This fibrovascular tissue, which originates from the choroidal circulation, is the leading cause of severe vision loss (SVL) in persons over the age of 65 years.[49] Although it accounts for only 8% of cases of AMD, this tissue is responsible for 85% of cases of SVL associated with AMD.[20] Exudative lesions may present as fine, hyperpigmented spots of the fundus if they are located in the subretinal space and associated with hemorrhage or retinal elevation.

Histopathologic studies suggest that diffuse thickening of the inner aspect of Bruch's membrane, clinically associated with large, soft drusen, predisposes Bruch's membrane to develop cracks through which ingrowth of fibrovascular tissue from the choriocapillaris can occur. These breaks, however, can be present in eyes not presenting with CNV.[50] Morphometric analysis of the choroid, Bruch's membrane, and the RPE in postmortem eyes with AMD indicates that the single most important difference between eyes with and without AMD is the amount of basal laminar deposit. A statistically significant difference has been observed in the degree of calcification and fragmentation of Bruch's membrane in eyes with exudative AMD compared with controls. The researchers concluded that AMD can be interpreted as a dynamic process with early proliferation and subsequent atrophy of capillaries of the choriocapillaris. Calcification and fragmentation of Bruch's membrane; soft, diffuse, and large drusen; and basal laminar deposit, but not hard drusen, strongly correlated with the histologic presence of AMD. Calcification and fragmentation of Bruch's membrane were prominent in eyes with exudative AMD. The formation of CNV membranes represents a stereotypic, nonspecific wound repair response independent of the underlying disease.[38] Some investigators believe that abnormalities of the extracellular matrix of RPE cells may promote a proangiogenic RPE phenotype that contributes to the development of CNV.[51] Accumulating evidence may suggest that endothelial growth factor (specifically vascular endothelial growth factor, or VEGF) may be implicated in chorioretinal angiogenesis. In studying the effect of VEGF on the experimental formation of CNV in rats, Honda and colleagues indicated that VEGF plays a crucial role in the formation of experimental subretinal neovascularization (SRN) and VEGF-soluble receptor gene transfection. Producing antibodies to VEGF inhibited the growth of CNV. Further studies in humans are projected, and future gene therapy for CNV in AMD is believed to be possible.[52]

In experimental laser-induced CNV, there is upregulation of VEGF expression, where it may be involved in promoting choroidal angiogenesis. In rats, macrophages may be a main source of VEGF in the early stage of the disease.[53] To study the potential angiogenic role of macrophages in the formation of choroidal neovascular membranes, Oh and colleagues investigated the distribution of inflammatory mediators such as interleukin (IL)-1-beta and tumor necrosis factor (TNF)-alpha and angiogenic cytokines such as VEGF to identify their cellular source in surgically excised choroidal neovascular membranes (CNVMs) of various origins. Eleven surgically excised CNVMs were studied using immunoperoxidase staining to identify cellular distribution and localization of cytokines. Cytokeratin-positive cells were detected in the RPE layer, in stromal cells, and around neovascular vessels. Macrophages had similar cytokeratin-positive cells. The neovascular vessels present were immunoreactive to IL-1-beta and TNF-alpha. It was believed that the IL-1-beta and TNF-alpha secreted by macrophages may promote angiogenesis in CNVMs by stimulating VEGF production in RPE cells.[54]

The development of CNV is likely multifactorial. This diffuse process involves the RPE, the photoreceptor cell layer, the choriocapillaris and can involve growth factors including vascular endothelial growth factor. The early morphologic change with the development of basal deposits is not visible ophthalmoscopically, but psychophysical testing may demonstrate reduced function. The secondary changes in the pigment epithelium, soft drusen, and CNV are visible. The CNV might represent reparative responses that result in disciform scars.[55] CNV may develop in eyes with GAP. An eye with GAP whose fellow eye has CNV is at significant risk for the development of CNV in the GAP eye. A patient with bilateral GAP and no evidence of CNV is at a relatively low risk for developing CNV.[56]

The morphologic features of angiogenesis reveal endothelial cell budding, pericyte enlargement, endothelial cell sprout formation, and development of intrachoroidal new vessels in preexisting choroidal capillaries. In one pathologic specimen, endothelial cell

sprout formation was seen continuous with an intrachoroidal vessel that penetrated Bruch's membrane. Examination of early sub-RPE new vessels show them to spread between the inner layers of Bruch's membrane within the space usually occupied by the basal linear deposit and drusen. This ultrastructural study described two phases of new vessel growth associated with the onset of CNV with AMD. The first phase, the intrachoroidal phase, appears to be a "low-turnover" form of neovascularization that may lead to new vessels penetrating Bruch's membrane. Extensive sub-RPE neovascularization, however, results from a "high-turnover" form of neovascularization characterized by extensive endothelial cell proliferation and migration, with each form characterized by the dynamics of angiogenesis.[57]

Multiple avenues are being investigated to inhibit CNV, including the use of oral protein kinase inhibitors,[58,59] corticosteroids,[60] and somatostatin analogs as possible effective therapies for CNV.[51]

What Are the Risk Factors for AMD?

The risk factors for exudative AMD and nonexudative AMD include the presence of focal hyperpigmentation and large drusen in the affected eye or fellow eye.

What Are the Symptoms of Exudative AMD or CNV?

Patients may complain of blurred or decreased vision and distortion or metamorphopsia. They may describe scotomas. Symptoms are often present when there is accumulated subretinal fluid or blood.

What Are Some of the Clinical Features of Exudative Age-Related Macular Degeneration or Choroidal Neovascularization?

Indirect ophthalmoscopy or biomicroscopy may reveal retinal elevation from subretinal blood or fluid or sub-RPE fluid, blood, or fibrovascular tissue, all of which may present as small, hyperpigmented, brown–black lesions of the posterior pole (Fig. 9–4). Slit-lamp biomicroscopy with a contact lens may reveal subtle subretinal fluid.

Symptomatic patients should undergo FA to detect CNV. Good stereoscopic early, middle, and late-phase angiographic frames help to determine the CNV membrane boundaries. Fluorescein angiograms being used for possible treatment of CNV should be no more than 96 hours old.

What Are the Types of Choroidal Neovascularization?

The Macular Photocoagulation Study[62–69, 70–82] helped to define the different types of CNVs by FA. The main types are classic CNVs and occult CNVs. The type of neovascularization portends prognosis and therapy recommendations.

Classic CNV is seen as a well-demarcated area of hyperfluorescence on the early transit phase of the angiogram (Fig. 9–5A). There is significant leakage apparent in the later-phase frames of the angiogram as

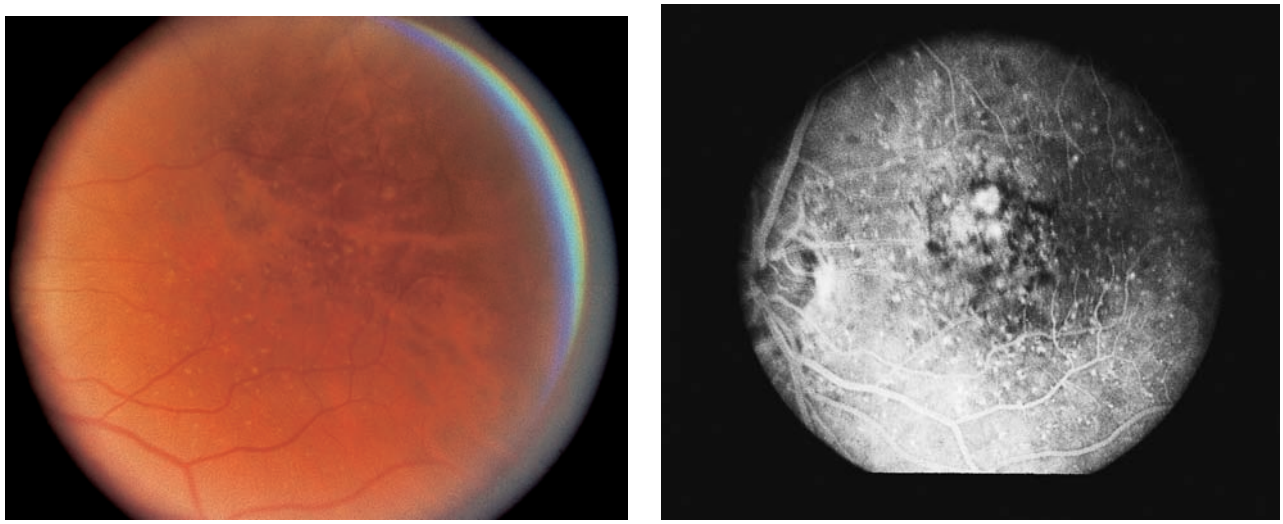

FIGURE 9–4. (A). A juxtafoveal choroidal neovascular membrane presenting as a small, brown–black, hyperpigmented lesion on color photography. (Courtesy of Dr. George Sanborn). (B). The fluorescein angiogram of the same patient shows an area of hyperfluorescence consistent with a choroidal neovascular membrane. (Courtesy of Dr. George Sanborn).

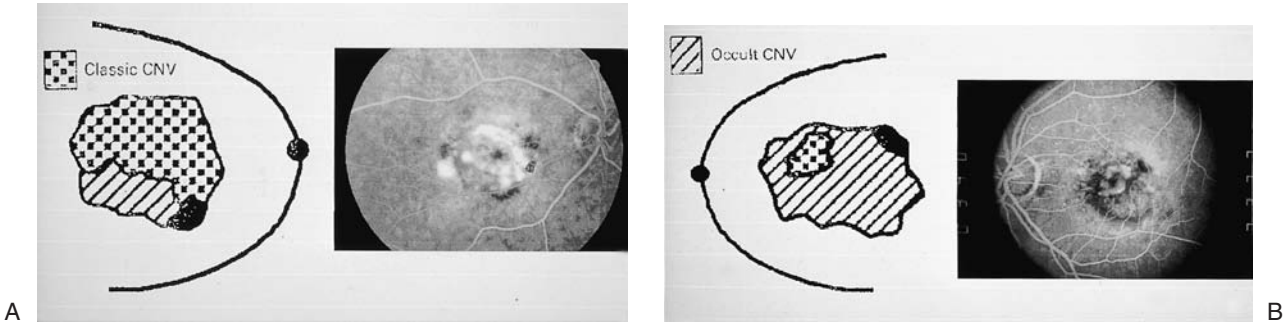

FIGURE 9–5. (A). Predominantly classic choroidal neovascularization (CNV) as defined by the Macular Photocoagulation Study Photodynamic Therapy Trials. (From Br J Ophthalmol. 2001;85:483–495, with permission from the BMJ Publishing Group.) (B). Predominantly occult CNV as defined in the Macular Photocoagulation Study Photodynamic Therapy Trials. (From Br J Ophthalmol. 2001;85:483–495, with permission from the BMJ Publishing Group.)

the dye pools in the subretinal space and obscures the boundary of the initially well-demarcated area of hyperfluorescence. A minority of these classic membranes may have a lacy appearance.

Occult CNV refers to two types of patterns of hyperfluorescence seen in eyes with AMD-related CNV (Fig. 9–5B). The first pattern, fibrovascular pigment epithelial detachment (PED), is best seen 1 to 2 minutes after fluorescein dye injection. There is an irregular elevation of the RPE stippled with hyperfluorescent dots. More diffuse leakage is present on the later frames of the angiogram. The second pattern of occult leakage is late leakage of an undetermined source. This refers to late choroidal-based leakage in which there is no clear identifiable classic CNV or FVPED. Initially, this pattern of occult CNV may appear as speckled hyperfluorescence with pooling of dye in the subretinal space in the later angiographic frames. Disciform scars are poorly demarcated early and late in the angiogram. Identification of the type of lesion becomes important when the type of treatment is outlined. The extent of treatment should include any other features that obscure the boundary of the CNV complex, such as blood or hypofluorescence or hyperplastic RPE. Elevated blocked fluorescence blocks the ability to outline well the CNV or determine whether it exists; if present, it is included in the membrane complex.[64,66,67]

Treatment of Exudative Macular Degeneration

The macular photocoagulation studies (MPS)[62–82] helped to define, via clinical trials, the thermal treatment of the different types of CNV, including subfoveal, extrafoveal, and juxtafoveal choroidal neovascular membranes. The MPS was designed to assess whether laser photocoagulation would prevent or delay SVL from CNV associated with AMD, the ocular histoplasmosis syndrome, and idiopathic CNV. The three major MPS studies were designed to assess the efficacy of laser treatment of extrafoveal, juxtafoveal, and subfoveal CNVs (Fig. 9–6).

How Did the Macular Photocoagulation Studies Define Extrafoveal Choroidal Neovascularization?

Extrafoveal CNV (Fig. 9–7) lesions have been described as well-defined lesions with a limited amount of blood in which the entire complex was located no less than 200 μ from the center of the foveal avascular zone in eyes with a visual acuity of at least 20/100 or better.

In the initial extrafoveal study (the argon study), patients were enrolled between 1979 and 1982. The MPS group reported in 1982 that argon blue–green laser photocoagulation treatment, applied with enough intensity to whiten the retina and cover the lesion, improved the visual prognosis of the treated eye compared with the natural course of extrafoveal CNV. At 18-month follow-up, argon laser photocoagulation reduced the risk of SVL from 69% in untreated eyes to 25% in treated eyes in AMD.[81,82] The treatment effect was greatest at 1 year; however, at 5-year follow-up, 64% of untreated eyes compared with 46% untreated eyes progressed to severe visual loss.[69] Recurrent neovascularization, either directly contiguous with the treatment scar or independent of the previous CNV, was common. At the 5-year follow-up, the recurrence rate of CNV was 54% in AMD. Of the patients with AMD who smoked more than 10 cigarettes per day, 85% suffered a recurrence compared with 51% of nonsmokers suffering a recurrence. At 3-year follow-up, patients with a recurrence had a visual acuity of 20/250; patients without a recurrence had an average visual acuity of 20/50.

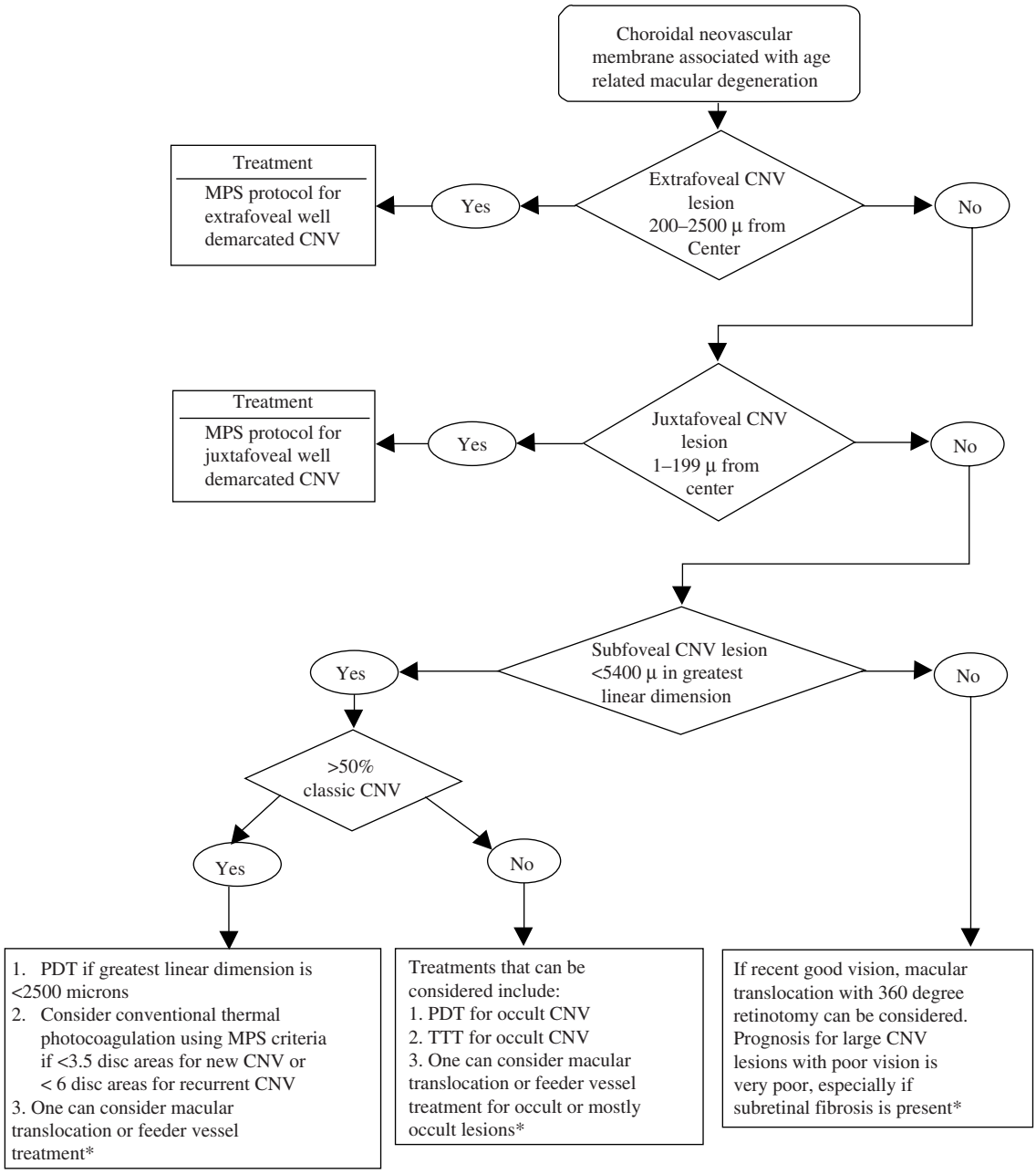

FIGURE 9–6. Diagnosis and treatment of exudative age-related macular degeneration. PDT, photodynamic therapy; CNV, choroidal neovascularization; TTT, transpupillary thermotherapy; MPS, macular photocoagulation studies.

After introduction of the thermal krypton laser in 1981, another trial (the Krypton Trial) was initiated to assess the efficacy of treatment of CNVs associated with AMD that were closer to the center of the fovea than 200 μ. This trial was also initiated to determine whether krypton laser photocoagulation would prevent severe visual loss in AMD. It was believed that, because krypton laser may spare the inner retina, treatment with krypton laser within 200 μ of the center of the foveal avascular zone (FAZ) would be efficacious.[83]

How Did the Macular Photocoagulation Study Define Juxtafoveal Lesions?

Juxtafoveal lesions (Fig. 9–7) were defined as lesions from 1 to 199 μ from the FAZ center, but not in the

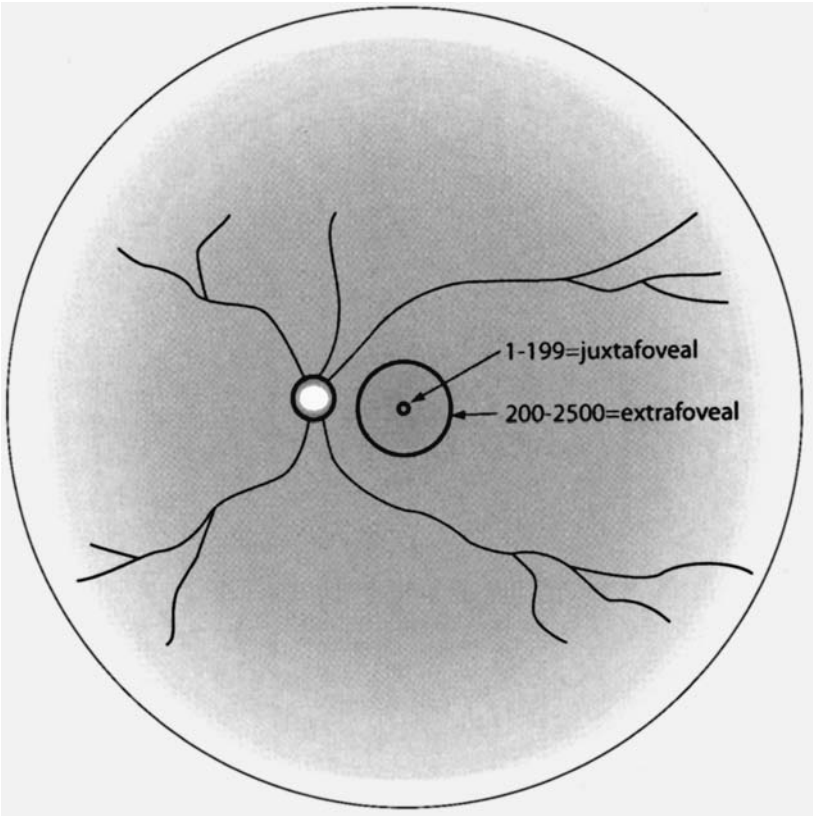

FIGURE 9–7. Depicted here is the location of the central macular region with a 199-μ radius, centered on the central fovea. The size is shown relative to the optic nerve. This region is used to define the location of extrafoveal and juxtafoveal choroidal neovascular membranes.

subfoveal region, or CNV 200 μ or farther from the FAZ center, with blood or blocked fluorescence extending 200 μ from the FAZ center. Minimal "thin" blood could extend through the FAZ, as long as the entire lesion could be defined on FA.[70]

The results of the juxtafoveal CNV trial indicated that 49% of treated eyes, compared with 58% of untreated eyes, had lost six or more lines of visual acuity, with average vision in the treated eye of 20/200 and in controls with 20/250, 3 years after randomization. Krypton laser reduced the risk of SVL by 10%. There was little or no treatment benefit in patients with hypertension. Persistence (defined as recurrence of the choroidal neovascularization within 6 months of treatment) was noted in 32% of eyes. Recurrence developed in 47% of patients over a 5-year period. Eyes without persistence or recurrence maintained a visual acuity of 20/80 to 20/100. Eyes with persistence or recurrence had visual acuity from the 20/200 to 20/250 range. Recurrence rates were more common in patients whose fellow eye had 20 or more drusen and nongeographic atrophy.

In 1991, the MPS group published revised criteria that better defined classic and occult CNV, permitting reevaluation of the results of the juxtafoveal AMD study and better-defined lesions for the subfoveal study.[67] Five years after randomization, persistence and recurrence rates were about 60 to 80% in eyes with classic, occult, or combined types of CNV. Treatment was most beneficial in classic-only lesions that were adequately treated (54% of treated compared with 72% of untreated lesions).

Thermal Treatment of Subfoveal Recurrent and New Subfoveal Choroidal Neovascularization

The high rate of recurrent CNV after photocoagulation for the juxtafoveal CNVs prompted establishment of the Subfoveal Recurrent CNV Study. The outcome measures for patients in this study were visual acuity, contrast sensitivity, and reading speed.[66] The average acuity at entry was 20/125 for patients randomized to either treatment or no treatment. The average acuity at 3 months and 24 months in treated eyes was 20/250. In untreated eyes, visual acuity at 3 months was 20/200; at 24 months, acuity dropped to 20/320. At 24 months, 9% of treated and 28% of untreated suffered severe visual loss. At 3 years, SVL was seen in 17% of treated and 39% of untreated eyes. Treated eyes maintained their initial contrast threshold for large letters; contrast threshold for untreated eyes worsened progressively. In the treatment group, average reading speed decreased by half, compared with two thirds in the untreated group at the 2-year follow-up.[66]

The Subfoveal New CNV Study[64] randomized eyes to thermal laser treatment with either argon-green or krypton-red and compared outcome data for treated and untreated eyes. At 3 months, 20% of treated eyes suffered SVL, compared with 11% of untreated eyes. At 24 months, however, 20% of treated versus 37% of untreated suffered SVL. Similar trends were noted at 4 years. Median contrast threshold and reading speed remained highest in treated patients at 24 months. Persistence or recurrence of CNV occurred in 51% of eyes but had no effect on vision loss compared with eyes without persistence or recurrence. Argon-green and krypton-red laser treatment were equally efficacious in the treatment of subfoveal CNV.[71] Four patterns of visual acuity and lesion size were outlined in this study to assess the effect of lesion size, visual acuity, and treatment. These groups were identified as A, B, C, and D. Treated groups in subgroup A lost less visual acuity than untreated eyes throughout follow-up. In subgroup B, treated eyes were worse at 3 and 6 months, but subsequently suffered less vision loss at 12 and 60 months. In subgroup C, the entry vision was already 20/200; only a small fraction of eyes lost an additional six lines of vision, but treated eyes lost slightly less vision. In subgroup D, including eyes with lesions larger than two MPS disc areas and vision 20/160 or better, the average vision was worse in treated eyes throughout the study.

Subgroup analysis in the Subfoveal New CNV Trial indicated that eyes with eligible lesions that were treated suffered less SVL than untreated eyes. Treatment benefit was apparent sooner for eyes with smaller lesions and worse initial visual acuity.[68]

Persistent CNV was present in 13% of eyes. Recurrent CNV developed in approximately 35% of eyes. Despite persistence or recurrence, there was little change in final visual acuities, which averaged 20/250, and 20/320 respectively. A guide to treatment of CNV based on lesion types is seen in Table 9–1.

How Are the Extrafoveal, Juxtafoveal, and Subfoveal Lesions Treated According to Macular Photocoagulation Study Criteria?

Treatment goals include photocoagulation of the entire lesion using the best laser wavelength (argon-green or krypton-red) that will allow adequate penetration of the ocular media. The MPS treatment protocol required that confluent laser of uniform intensity be applied to all components of the lesion complex, including classic and, if present, occult CNV as well as contiguous blocked fluorescence from hyperplastic or pigmented fibrous tissue, blood, or serous pigment epithelial detachment that may obscure areas of the CNV.[67] Greater than 50% of the lesion should be classic. Lesions that included more than 50% serous pigment epithelium detachment (PED) would not have met criteria for the MPS trials, and the treatment benefits may not apply. The fluorescein angiogram should not be more than 96 hours old. Retrobulbar anesthesia can be used when deemed necessary.

TABLE 9–1. Treatment of Choroidal Neovascularization in Age-Related Macular Degeneration

Type of CNV	*MPS-Thermal Laser*	*PDT*	*TTT*	*Feeder Vessel*	*Submacular Surgery*	*Macular Translocation*
A. Classification						
1. Classic	Yes	Yes (subfoveal only)	No	No	No	**Possible
2. Classic > occult	Yes (if well defined)	Yes (subfoveal only)	No	No	No	**Possible
3. Occult	No (for poorly defined lesions)	Yes (subfoveal only)	Possible** (subfoveal only)	Possible**	No	**Possible
4. Occult > classic	No (for poorly defined lesions)	Yes (subfoveal only)	Possible** (subfoveal only)	Possible**	No	**Possible
5. Pigment epithelial detachment	No	No	Unknown	Possible**	No	**Possible
B. Location						
1. Extrafoveal	Yes	No	No	No	No	**Possible
2. Juxtafoveal	Yes	No	No	No	No	**Possible
3. Subfoveal		Yes	**Possible		No	**Possible
a. New	Possible*			Possible**		**Possible
b. Recurrence	Possible*			Possible*		**Possible

MPS, macular photocoagulation studies; PDT, photodynamic therapy; TTT, thermal therapeutic therapy; *possible, with better treatments available; ** possible, needs further evaluation with clinical trials.

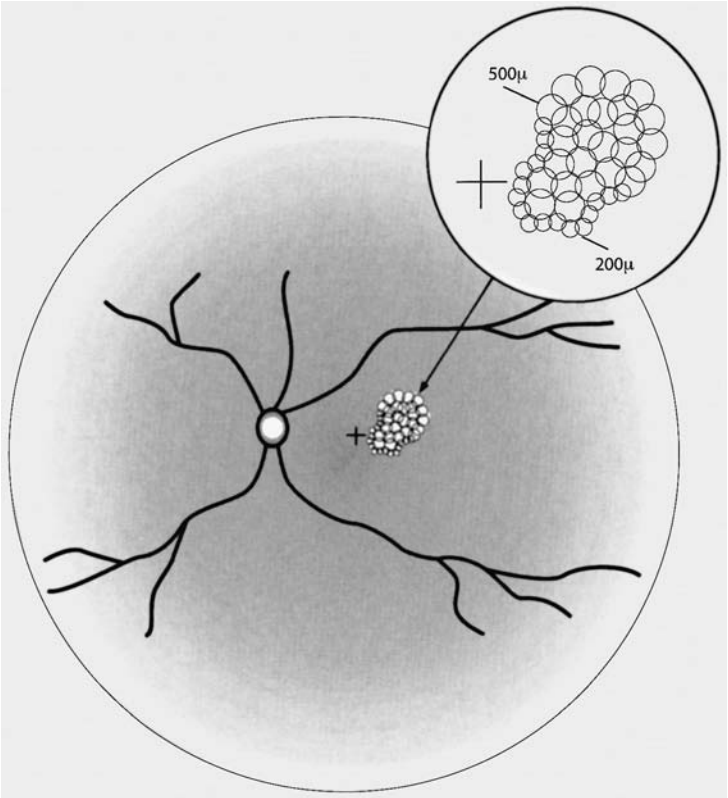

FIGURE 9–8. Classic juxtafoveal membrane requiring 2000-μ confluent spots on the foveal side and 200- to 500-μm spots over the surface of the lesion.

In the treatment of extrafoveal and juxtafoveal lesions, a 200-μ laser spot size of 0.2 to 0.5 seconds' duration is placed along the membrane perimeter, away from the foveal edge, to test power settings. The foveal edge of the CNV then is treated using 200-μ overlapping burns (Fig. 9–8). For extrafoveal lesions, treatment should extend 100 μ beyond all lesion components. For juxtafoveal lesions, treatment might be modified on the foveal side to cover only the lesion unless the CNV is greater than 100 μ from the FAZ center. When this occurs, treatment should extend 100 μ into any associated contiguous blood or lesion complex on the foveal side of the CNV. A 200-μ laser spot is used to demarcate the boundaries of the lesion, and 200- to 500-μ burns are used to fill in the center of the lesion. In the treatment of subfoveal lesions, the perimeter of the lesion is treated, first on the foveal side. After treating the foveal edge, the remainder of the membrane is outlined with laser burns, preferably treating the inferior edge first. If bleeding occurs, this area may be obscured. The treatment should extend 100 μ beyond all lesion components except areas of blocked fluorescence caused by blood. The treatment in this situation need not extend beyond the blood itself. In recurrent subfoveal lesions, treatment should extend 300 μ into the area of prior photocoagulation. If a feeder vessel is present in a recurrent lesion, treatment should be applied along the vessel overlapping the sides of the vessel by 100 μ and extending radially out from its base by 300 μ. The laser burns used should be of sufficient intensity to produce retinal whitening.

Posttreatment, a photograph of the fundus, using the same preoperative camera, should be taken and compared with the pretreatment angiogram to ensure complete coverage of the lesion. Patients with extrafoveal and juxtafoveal lesions should be followed up at 1 to 2 weeks after treatment with a postoperative angiogram to ensure lesion coverage. Patients with subfoveal lesions should be followed up at 6 weeks after treatment.

Patients with persistent or recurrent neovascularization should be reevaluated for retreatment, particularly when lesions recur outside of the FAZ. Treatment can be recommended in eyes with subfoveal recurrences that meet the criteria of the subfoveal recurrence trial.

Treatment complications are uncommon. Choroidal hemorrhages may be avoided by not using spot sizes smaller than 200 μ and by using long exposure times. Inadvertent treatment of the fovea may be avoided by meticulously identifying the FAZ before treatment. Delayed choroidal perfusion has been reported with the use of krypton-red laser. Usually, this has few permanent sequelae.[84] Retinal tears may occur in association with treatment of CNV[85] or may

occur in association with serous RPE detachments not undergoing treatment.[86]

ARE OTHER THERAPIES CURRENTLY AVAILABLE FOR THE TREATMENT OF CHOROIDAL NEOVASCULARIZATION, PARTICULARLY IN THE TREATMENT OF SUBFOVEAL LESIONS, WHERE THE VISUAL ACUITY, THOUGH MAINTAINED, WAS SO POOR?

Physicians must explain very carefully that in the treatment of subfoveal lesions, new or recurrent, according to the MPS protocol, the patient initially might experience vision loss. Alternative therapies are now available for the treatment of subfoveal lesions.

What Is Photodynamic Therapy?

Photodynamic therapy (PDT) involves the use of an intravenously injected photosensitizing dye combined with a low-intensity laser light that, when projected at the CNV, after injection of the photosensitizing agent, causes a photochemical reaction. It is believed that this reaction results in direct cellular injury to vascular endothelial cells and vessel thrombosis. This technique may more selectively destroy the CNV tissue. The function of surrounding retina, RPE, and choroid may be maintained.

Schmidt-Erfurth and colleagues demonstrated that the use of PDT with verteporfin could achieve temporary cessation of fluorescein leakage from CNVs. To evaluate the safety and short-term effect of PDT and verteporfin therapy on CNVs in AMD with fluorescein leakage, a randomized, multicenter, open-label phase 1 and 2 clinical trial was initiated using two different retreatment dosage regimens of verteporfin. The trial demonstrated that multiple applications of PDT with verteporfin achieved repetitive, short-term cessation of fluorescein leakage from CNV secondary to AMD. There was no associated loss of visual acuity. This strategy then was used in randomized clinical trials investigating the efficacy of verteporfin in PDT for recurrent fluorescein dye leakage from persistent or recurrent CNV following initial PDT treatment with verteporfin.[87]

The 1-year results of two randomized clinical trials using photodynamic therapy with verteporfin in the treatment of subfoveal CNV in AMD were reported in the treatment of AMD with PDT (TAP) study in October 1999. The clinical trials were designed to determine whether PDT could reduce the risk of vision loss in patients with CNV. Twenty-two ophthalmology practices in Europe and North America participated in these multicenter, double-masked, placebo-controlled, randomized clinical trials in which 609 patients were randomly assigned (2:1) either to verteporfin (6 mg per square meter of body surface area) or placebo. The protocol included the infusion of verteporfin (30 mL of Visudyne) over 10 minutes. Fifteen minutes after the beginning of the infusion, the patient underwent laser therapy (689-nm wavelength) delivered at 50 J per square centimeter at the intensity of 600 mW per square centimeter over 83 seconds using a spot size 1000 μ larger than the greatest linear dimension (GLD) of the CNV (Fig. 9–9). Follow-ups were performed every 3 months, and retreatments were performed if there was fluorescein leakage on the follow-up angiogram. Visual acuity loss was the primary outcome. Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were better in the PDT-treated eyes. In subgroup analyses, the visual acuity benefit (fewer than 15 letters lost) was demonstrated (67 versus 39%) when the CNV was predominantly classic or the classic component of the lesion occupied 50% or more of the area of the lesion. No treatment benefit was seen at 1 year with predominantly occult lesions. Few treatment side effects were reported, but the side effects included transient visual disturbances, injection-site adverse events, transient photosensitivity reactions, and infusion-related back pain. The 1-year results of the PDT clinical trials supported the use of verteporfin in the treatment of predominantly classic CNVs.[88]

The 2-year results of the TAP study supported the use of PDT for subfoveal CNVs in lesions with greater than 50% of the lesion classic or in predominantly

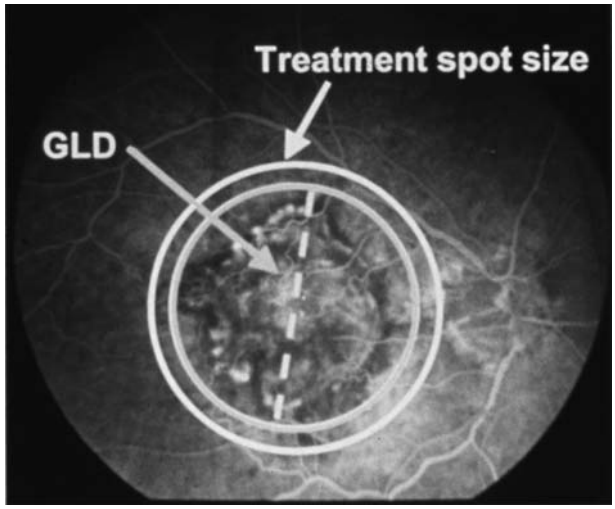

FIGURE 9–9. The greatest linear dimension (GLD) of subfoveal choroidal neovascularization plus 1000 μ, used as the treatment parameter for photodynamic therapy. (From Br J Ophthalmol. 2001;85:483–495, with permission from the BMJ Publishing Group.)

classic membranes.[89] The VIP trial also showed a benefit at 2 years in predominantly occult CNV.

What Are Other Forms of Treatment That Have Been Used in the Treatment of Subfoveal Choroidal Neovascularization?

Other forms of therapy that have been used in the treatment of subfoveal CNVs have included transpupillary thermotherapy and radiation. Transpupillary thermotherapy has been used in the thermal therapy of small choroidal melanomas, choroidal metastases, and choroidal vascular tumors.[90–92]

Transpupillary thermotherapy (TTT), with the use of the diode laser, has been used in the treatment of occult subfoveal CNV in patients with AMD. Reichel and colleagues presented information on a retrospective, noncomparative case series with 16 eyes of 15 consecutive patients presenting with occult subfoveal CNV. Pretreatment fluorescein angiograms were obtained on all patients, and patients were treated who were deemed untreatable by the MPS standard. TTT was delivered using a diode laser at 810 nm. A variable spot size of 1.2, 2.0, or 3.0 mm is used, depending on the size of the CNV. The diode laser was delivered through a contact lens; treatment was initiated in one spot for 60 seconds' duration at a power range between 360 and 1000 mW. The endpoint of treatment was an area of no visible color change to a light gray appearance. TTT acts in a subthreshold manner by elevating the choroidal temperature. Outcome measures included Snellen visual acuity and clinical examination. Preoperative and postoperative fluoresceins, optical coherence tomography (OCT), and examinations were available for 10 eyes. In six eyes, subretinal exudation was assessed by clinical examination alone. Fifteen eyes (or 94%) demonstrated decreased exudation on fluoresceins, OCT, or clinical examination. TTT showed no deleterious side effects in treating occult subfoveal CNV.[93] A recent pilot study demonstrated that 56% of treated eyes remained stable at 1 year, with only 25% losing two lines of visual acuity. Further study of the effectiveness of TTT will be assessed in the TTT4 CNV study.[94]

Radiation therapy has been used in the treatment of CNV, based on the theory that radiation may cause damage to rapidly proliferating tissue. There may be little efficacy of external-beam radiation for the treatment of subfoveal CNV. Char and colleagues, in a randomized, prospective trial of the treatment of subfoveal CNV, using single-fraction radiation (750 cGy) or observation, revealed no significant difference in fluorescein angiographic evidence of subretinal neovascular membranes in the treated, irradiated group compared with the control, untreated group.[95]

What Are Feeder Vessels, and What Is the Role of Feeder Vessel Treatment for Choroidal Neovascularization?

Feeder vessels are long, linear afferent vessels, averaging about 1 mm in length, that travel through the middle layers of the choroid for a distance of 1 mm or more before reaching to the choriocapillaris and potentially becoming a CNV. There is often only one feeder vessel per CNV lesion. These choroidal vessels are different from the penetrating vessels that originate in the choriocapillaris and travel to or through Bruch's membrane. These vessels may be parallel or perpendicular to the RPE. If these vessels supply a CNV, treatment of these vessels alone, without treatment of the entire CNV complex, may suffice in the treatment and decrease in size and leakage of the CNV supplied by the feeder vessel. The theory behind this technique of treatment has been around for many years and was suggested even in some of the earlier MPS studies.[66,67] Initially, the use of feeder vessel treatment was limited because these deep, choroidal vessels are difficult to visualize using FA alone.

What Technology, Other Than Fluorescein Angiography, Is Necessary for Feeder Vessel Treatment?

Feeder vessel treatment requires the use of indocyanine-green angiography, and the use of the confocal scanning laser ophthalmoscope or high-speed digital systems to identify choroidal vessels.

Indocyanine angiography uses a water-soluble dye with a molecular weight of 775 daltons and a peak absorption between 790 and 805 nm; the emission of the dye is at 835 nm. The dye is poorly seen in film-based angiography; however, improved image acquisition was obtained with infrared digital fundus video angiography, thus renewing interest in the use of the dye for identification of choroidal complexes. Higher-quality images are obtained using newer high-resolution (1024 lines) digital systems or scanning laser ophthalmoscope-based systems that have emerged more recently.[96–100] In the MPS trials, 85 to 95% of the CNV associated with AMD were not treatable, particularly when the borders of the lesions were not visible. In many cases, fluorescence of the CNV is blocked by hemorrhage. The wavelength of indocyanine green (ICG) allows for fluorescence that may penetrate blood better than sodium fluorescein. The ICG dye is about 98% protein bound and, as a large molecule, penetrates the fenestration of the choriocapillaris less rapidly than does fluorescein. With longer intravascular time, the ICG dye facilitates visualization of the choroidal vessels. The technique is similar to FA, with

a 2-mL, 25-mg bolus of dye injected into the antecubital vein. Digital photographs are taken rapidly for several seconds and then at 1-minute intervals for several minutes to cover complete filling of both the choroidal and retinal vessels. The near-infrared spectral properties of ICG allow greater penetration through RPE, macular xanthophyll, and blood. The properties of the dye make the angiographic examination of the choroid and choroidal abnormalities much easier. Middle-phase photographs are taken at 8 to 12 minutes and late-phase photos at 20 to 30 minutes. Often a remaining 1-mL bolus of dye is given just before the late-phase photos for better visualization of the choroidal and retinal vessels. Using ICG, some vessels that appear as occult CNV on FA may appear more well defined.[101,102]

The early phase of the ICG angiogram shows maximal fluorescence of both the retinal and choroidal vessels. As the study continues into the middle phase, the choridal fluorescence begins to fade after about 6 minutes; abnormalities begin to retain the dye and hyperfluorescence relative to the normal choroidal features. At 25 minutes (the late phase), the choriocapillaris is mildly fluorescent, the choroid; hypofluorescent retinal vessels or the optic nerve cannot be visualized.

High-speed (512 × 512 pixels) ICG angiography and high-speed FA, performed simultaneously, allowing for high-speed resolution, enhances the identification of afferent and efferent feeder vessels. The transit through the feeder vessels is rapid, with the feeder vessel visible for only one to several seconds during the high-speed ICG. Identification of the afferent and efferent feeder vessels is necessary to apply treatment to the afferent vessel if possible or the afferent and efferent vessels simultaneously.

The goal of feeder vessel treatment is to decrease the amount of fluorescein leakage and subretinal fluid, not to close the vessels completely. The classic component of lesions is the most difficult to treat. Multiple (two or three) treatment sessions may be necessary for feeder vessel treatment. If the vessels remain closed for 2 to 3 months, the recurrence rate may be 2 to 3%. The millipulse infrared laser or the microburst yellow laser is used for treatment. The millipulse infrared laser allows deep penetration and absorption of energy in the middle layers of the choroid, where the feeder vessels are located. The yellow laser light will be absorbed preferentially by the feeder vessel, resulting in occlusion of the vessel, with little or no damage to surrounding tissue. Careful mapping of the vessels and endpoint analysis is necessary. The thermal laser will use the RPE as a chromophore; the laser micropulses are placed beyond the level of the RPE (through the RPE) to avoid true burns at the level of the RPE. Once a thermal coagulation is formed at the level of the RPE, it is impossible to further penetrate into the choroid. The infrared micropulses allow penetration through the level of the RPE, using a 75- to 200-μ spot diameter; 200 to 250 mW of power are initially used, with an increase over 1.5 to 2.5 minutes until minimal blanching is obtained (endpoint) at the level of the RPE. Posttreatment studies may be performed to confirm the occlusion of the feeder vessel. If the afferent feeder vessel is not closed, additional lasers can be placed.[103,104] Studies now reveal different patterns of the CNV, such as classic or those associated with PEDs.[105,106] Treatment of these lesions with this technique may be expensive and may require some expertise in identifying and mapping the choroidal feeder vessels. A randomized controlled clinical trial may be necessary to investigate which treatment is better in the treatment of occult CNV, either PDT, TTT, or feeder-vessel treatment, particularly when associated with occult CNV. Feeder-vessel treatment, however, may be helpful in the treatment of PEDs where few treatment modalities have been helpful.

How Do You Manage Cases of Age-Related Macular Degeneration Associated with Large Submacular Hemorrhages, and How Do You Clear the Blood for Subsequent Fluorescein Angiography and Treatment?

Often, AMD is associated with large submacular hemorrhages that do not allow the visualization of perifoveal or subfoveal neovascularization. The management of submacular hemorrhage with intravitreal tissue plasminogen activator injection and pneumatic displacement, using expansile gas or air with prone positioning for 1 to 5 days, may prove very helpful in the displacement of large submacular hemorrhages. This facilitates visual improvement and may allow further identification of the types of CNV with angiography.[107]

Is Submacular Surgery More Effective than Laser in the Treatment of Choroidal Neovascularization in Age-Related Macular Degeneration, and What Did the Submacular Surgery Trial Demonstrate?

The Submacular Surgery Trial (SST) was designed to assess whether using laser to recurrent subfoveal CNV or surgery was more effective in the treatment of subfoveal CNV. In the study of 70 patients entered into a randomized, multicenter trial, patients treated with laser for subfoveal recurrent CNV (65%) and 50% who had undergone surgery had visual acuity that was two lines better or no more than one line worse than at the time of enrollment. There was no particular benefit for surgery treatment in these patients.[108]

What About the Status of Macular Translocation Surgery?

Several techniques have been described for macular translocation surgery. The literature to date contains several case series, with no control groups, wide ranges in follow-up, and variable visual outcomes. Complications may be frequent, and surgical morbidity appears to be an important factor. At present, it is difficult to assess the effectiveness of macular translocation surgery in treating visual loss from AMD.[109] A randomized, controlled clinical trial is needed to determine whether macular translocation is a safe and effective treatment for visual loss from AMD.

What Are the Other Forms of Choroidal Neovascularization Not Associated with Age-Related Macular Degeneration?

Choroidal neovascularization maybe associated with such clinical entities as pathologic or degenerative myopia in the presence of lacquer cracks or breaks in Bruch's membrane and angioid streaks, accompanied by alterations of the RPE. Angioid streaks may be associated with systemic diseases; establishing the associated diagnosis such as pseudoxanthoma elasticum (PXE), Paget's disease, or sickle cell disease, may be important. PXE may be associated with potentially serious gastrointestinal and cardiovascular complications (see Chapter 11).

The classic triad of ocular histoplasmosis includes peripapillary chorioretinal atrophy, punched-out chorioretinal scars, and exudative CNV. These patients present between ages 20 and 50 years and may have lived in the endemic Ohio–Mississippi River valley. Vision loss is associated with the CNV, which may require treatment.

Nonhereditary Peripheral Retinal Degenerations

What Nonhereditary Peripheral Retinal Degenerations Can Present with Fine, Hyperpigmented, Brown–Black Spots in the Fundus?

Peripheral hyperpigmented, fine lesions may be seen in association with dystrophic and degenerative retinal diseases. Many pigmented lesions, such as circumferential or radial lattice degeneration, and RPE "bony spicule" type changes may be noted in the periphery. Lesions such as lattice degeneration and vitreoretinal tufts may predispose to retinal detachment. Pigmented hyperplastic or atrophic lesions also may be associated with myopia (see Chapter 8).

Peripheral pigmented lesions not predisposing to retinal detachment include cobblestone or pavingstone degeneration. These lesions may be present in 22% of persons over 20 years of age. These peripheral brown–black spots are discrete areas of ischemic atrophy of the outer retina characterized by attenuation or absence of the choriocapillaris, loss of the RPE and outer retinal layers, with adhesions between the remaining inner layers and Bruch's membrane. These yellow lesions, surrounded by a rim of hypertrophic RPE, most frequently are located in the inferior quadrants and, with thinning of the RPE, may have large choroidal vessels visible.

Acquired RPE hypertrophy, a degenerative change seen with aging, is often seen in the periphery. The pigmentary changes, although associated with aging, are similar to the changes seen with congenital hypertrophy of the RPE. Fine, pigmented brown-black spots also may be seen in areas of previous trauma with RPE hyperplasia.

Summary

The location of the fine brown–black hyperpigmented spots in the posterior pole or in the periphery, in association with infections or inflammations or with vitreous cells or retinitis, may well help to define the entities associated with these small brown–black, hyperpigmented lesions (Fig. 9–1).

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10

Orange–Red and Gray Lesions in the Fundus

JONATHAN SHEINDLIN

What Are Gray or Orange Lesions in the Fundus?

Gray and orange–red lesions in the fundus represent localized or, at times, diffuse pathologic changes often originating from abnormalities in the vasculature of the retina, retinal pigment epithelium (RPE), or choroid. When these lesions are subretinal or located deep in the retina and associated with intraretinal fluid, the inherent transparency of the retina and view to the RPE and choroid are affected, making the diagnosis of these conditions challenging. Evaluation requires identification of the origin of the lesion, a thorough knowledge of the posterior segment anatomy, and an orderly approach to examination. A treatment strategy may be designed.

Why Do Fundus Lesions Have a Gray or Orange–Red Color?

The color of the lesion seen on fundus examination depends on the composition of the tissue and its location. Vascular lesions and blood are orange–red because of hemoglobin. Acute macular neuroretinopathy (AMN) and photic retinopathy may have a deep red appearance and the mechanism of the color change is not clearly understood. Depending on the location within the retinal layers or choroid, the lesions will have subtle differences in appearance. Vascular lesions appear red or orange–red when they are located within the neurosensory retina or subretinal space as a result of the transparent nature of the retina. When blood is present underneath the RPE, the melanin of the RPE blocks some of the red of hemoglobin, causing the lesion to appear darker or even gray. Often there may be support cells associated with the abnormal vasculature that influence the color. An example is a choroidal neovascular membrane (CNVM), in which fibroglial cells may mask the red of the vasculature.

The choroid is a large lobular vascular network that causes the fundus to appear orange–red. When there is an accumulation of fluid or blood underneath the RPE, the observer may see an orange–red nodular elevation. Examples of fluid beneath the RPE include central serous chorioretinopathy (CSCR) and posterior scleritis. Choroidal tumors, such as the nevus, melanoma, and osteoma, may appear orange–red at certain stages in their pathology.

Where Does the Examiner Begin When Evaluating Gray or Orange–Red Lesions?

Depending on the nature and location of the lesion, patients may present without complaints or have a variety of symptoms, including painful loss of vision. An orderly approach is thus needed to limit the differential diagnosis. A comprehensive examination with a review of the patient's medical, family, and social history is important. Additional history will identify patients at risk for signs of hypertension, neoplastic disease, and sickle cell retinopathy, for example.

At times, the medical history may not be available. A review of systems may be useful for discovering important systemic symptoms. Pointed questions may uncover symptoms of diabetes mellitus, medication use, or connective tissue disorders, for example. Because of the different presenting conditions, no guideline will always yield a diagnosis. The following is a general approach. The diagnosis may depend on the input of experienced subspecialists.

The examination begins with a methodical evaluation of the orbit and anterior segment structures, specifically looking for lid swelling, anterior chamber inflammation, iris nodules, or lens changes. Examination of the anterior and posterior vitreous for inflammatory cells, pigmented cells, or blood is performed.

It is important to determine the anatomic location of the fundus lesion. It is helpful to divide the anatomy into distinct areas, based on location near the vitreous or sclera. The retina includes the neurosensory retina and retinal vasculature. The subretinal space is a potential space between the retina and RPE, which may fill with serous fluid, blood, or fibrovascular tissue. The RPE–Bruch's membrane complex includes the RPE and Bruch's membrane. The choroid is a large vascular network beneath the RPE–Bruch membrane complex that provides circulation to the outer third of the retina.

It is useful to localize the lesion based on region: the peripapillary region, the posterior pole, and the periphery. The peripapillary area denotes the area adjacent to and including the optic nerve. The posterior pole includes the region within the vascular arcades. The periphery encompasses the region outside the vascular arcades to the ora serrata.

Why Is It Important to Determine the Anatomic Location of the Lesion?

The key to diagnosis within the posterior segment is determining the location of a lesion within or under the retina. Because a number of orange–red and gray lesions arise from vascular abnormalities, distinction between choroidal and retinal aberrations helps pinpoint the diagnosis. For example, choroidal neovascularization typically causes subretinal hemorrhage, whereas retinal vascular abnormalities are associated with intraretinal and preretinal bleeding.

Fundus abnormalities may derive from the choroidal or retinal vasculature. The two circulations are distinct. The retinal circulation supplies the inner two thirds of the retina, the choroidal circulation the outer third. Localization of a lesion and its depth within or below the retina can be facilitated by determining whether the lesion lies above or below the retinal vessels. Differentiating deep retinal, subretinal, and sub-RPE locations may be difficult, but signs such as blood, exudates, or fluid in the surrounding area can be helpful. Ophthalmoscopic examination techniques enable the examiner, through magnification and stereopsis, to localize the lesion. The use of imaging techniques, such as optical coherence tomography and scanning laser tomography, are also useful in determining the location with respect to the inner and outer retina and choroid.

Are Lesions Commonly Located in Only One Part of the Retina?

Depending on the size and nature of the lesion, more than one location may be involved. This refers not only to the location with respect to the retina and choroid but also to the topographic location of the lesion. For example, bleeding from macroaneurysms may occur at all layers in the posterior segment, including subretinal, intraretinal, and preretinal areas.[1–3] Macroaneurysms may be located anywhere there are retinal vessels. This includes the peripapillary area, posterior pole, and periphery.

Gray and orange–red lesions present in many ways. The diagnosis depends on recognizing patterns of signs and using them based on the history and symptoms of an individual patient. Although certain lesions classically occur in a particular location, an early stage of the pathology may present differently. Some lesions grow, whereas others remain dormant. A classic example is the differentiation between a choroidal nevus and a choroidal melanoma. A choroidal melanoma may reach a very large size if it is discovered late in its course. Choroidal nevi rarely demonstrate growth or malignant transformation.[4] An early choroidal melanoma may appear to be a nevus; distinguishing between these two is critical. Follow-up examinations are important in making this distinction.

What Is the Significance of Associated Hemorrhage or Exudates?

Orange–red and gray lesions, often vascular, can be associated with hemorrhage or exudates. These signs represent a breakdown in the blood–retina and blood–RPE barrier. To establish the localization of the lesion, it is helpful to localize the associated leakage. Vascular abnormalities derived from the choroid tend to be associated with fluid, blood, or exudates in the sub-RPE or subretinal space. Retinal vascular abnormalities present with blood, fluid, or exudates within the retina. There are, however, exceptions to this. Macroaneurysms can bleed into the subretinal space, and some cases of choroidal neovascularization may bleed into the retina or vitreous, obscuring the subretinal pathology.

In What Cases Is Fluorescein Angiography Helpful?

Fluorescein angiography (FA) can help to determine the vascular properties of a lesion, such as the double circulation in choroidal melanoma, or the extent of the CNVM.[28] We have learned from submacular surgery, however, that the neovascular membrane tends to be larger than seen on FA.[8]

FA is helpful to determine nonperfused retinal areas such as in Coats disease and sickle cell retinopathy. Angiographic features of RPE detachments aid in identifying patients with CSCR, large drusen, CNVM, and posterior scleritis. FA of the optic nerve may demonstrate disc leakage in Vogt– Koyanagi–Harada (VKH) syndrome, metastatic choroidal tumors, and

posterior scleritis.[27,61] Filters on the FA camera provide useful information: For example, macular changes in AMN may be identified with red-free photos, and autofluorescence properties of optic nerve head drusen may be demonstrated without injecting fluorescein.[63,76]

In What Cases Is Ultrasonography Helpful?

Ultrasonography provides a cross-section of the globe and orbit. It is used for differentiating tumors by determining the internal patterns of reflectivity and measuring the cross-sectional height. Several estimations of the height and extent of a lesion are important in determining growth since the last examination. In addition, ultrasonography may be helpful when media opacities obscure clear visualization of the posterior segment.

The internal reflexivity of a choroidal mass can provide important diagnostic information. For example, a choroidal melanoma classically displays a high initial spike on A-scan with a medium to low internal reflectivity,[22] whereas a choroidal hemangioma demonstrates a high initial spike with medium to high internal reflectivity.[10] Guidelines for the acoustic characteristics are helpful, but these lesions should be evaluated by experienced specialists familiar with ocular oncology who can differentiate subtle differences.

The reflectivity of other lesions may be useful in identification. Optic nerve head drusen display high reflectivity on B-scan, even at low gain.[76] Lesions that contain calcium, such as choroidal osteoma, demonstrate a high initial spike with acoustic shadowing, or lack of acoustic waves, behind the lesion.[67] Eyes with posterior scleritis may have a diffusely thickened choroid and edema within the Tenon capsule, creating the "T-sign."[60]

Are There Other Tests That May Be Helpful?

Indocyanine green (ICG) angiography permits visualization of the choroidal and retinal vasculature, even in the presence of thin layers of blood. This technology may be useful in detecting CNVM, particularly occult CNVM. ICG is useful in evaluating conditions such as CSCR, idiopathic polypoidal choroidal vasculopathy, and inflammatory disorders of the choroid.[14]

Computed tomography (CT) scan may be helpful in evaluating scleral and choroidal thickening. In addition, disorders with calcification are readily visualized on CT scan images, such as choroidal osteoma and optic nerve head drusen. CT scanning also permits imaging of possible associated intracranial lesions, such as cerebellar masses in von Hippel–Lindau (VHL) syndrome.

Certain blood tests can be useful in diagnosing the cause of inflammatory retinal vasculitis or choroiditis. A sickle prep may identify a patient with salmon patch hemorrhage. A simple finger stick for blood sugar may help to diagnose a patient with diabetes mellitus and intraretinal hemorrhage. Orange–red intraretinal hemorrhages may develop from localized or diffuse retinal vasculitis. Appropriate laboratory testing may reveal the etiology of inflammatory, neoplastic, or infectious pathologies.

What Are Orange–Red and Gray Lesions of the Peripheral Retina?

Subretinal Origin (Fig. 10–1)

Subretinal lesions usually appear beneath the retinal vessels. Occasionally, associated bleeding into the inner retina may limit the ability to localize the lesion.

Choroidal Melanoma

Choroidal or uveal melanoma arises from the pigmented cells of the choroid. It is critical to differentiate a benign lesion, such as choroidal nevus, from choroidal melanoma. Examination and differentiation should be performed by an experienced specialist who is familiar with subtle differences in presentation.

Clinical Presentation

Choroidal melanoma typically appears as a dome-shaped, elevated, oval mass with variations in the degree of pigmentation. When the tumor reaches a large size, it typically assumes a mushroom shape as it passes through the Bruch's membrane. Smaller tumors may not be so readily recognized. Although choroidal melanomas are commonly seen as dark pigmented masses, they can have varying degrees of pigmentation and may even be amelanotic. Some are dark red or pale, nodular lesions. Their size also varies.[11]

When melanomas are confined to the choroid, or relatively soon after gaining access to the subretinal space through the Bruch membrane, they may demonstrate overlying patches of orange pigment, some with indistinct borders, and evidence of subretinal fluid. Evaluation of the thickness or height of the mass and determining whether there has been progression since a previous examination are critical in distinguishing a melanoma from a benign nevus. In general, lesions 2 mm or smaller are considered nevi, whereas those larger than 2 mm in height are suspicious for choroidal melanoma.[4–6]

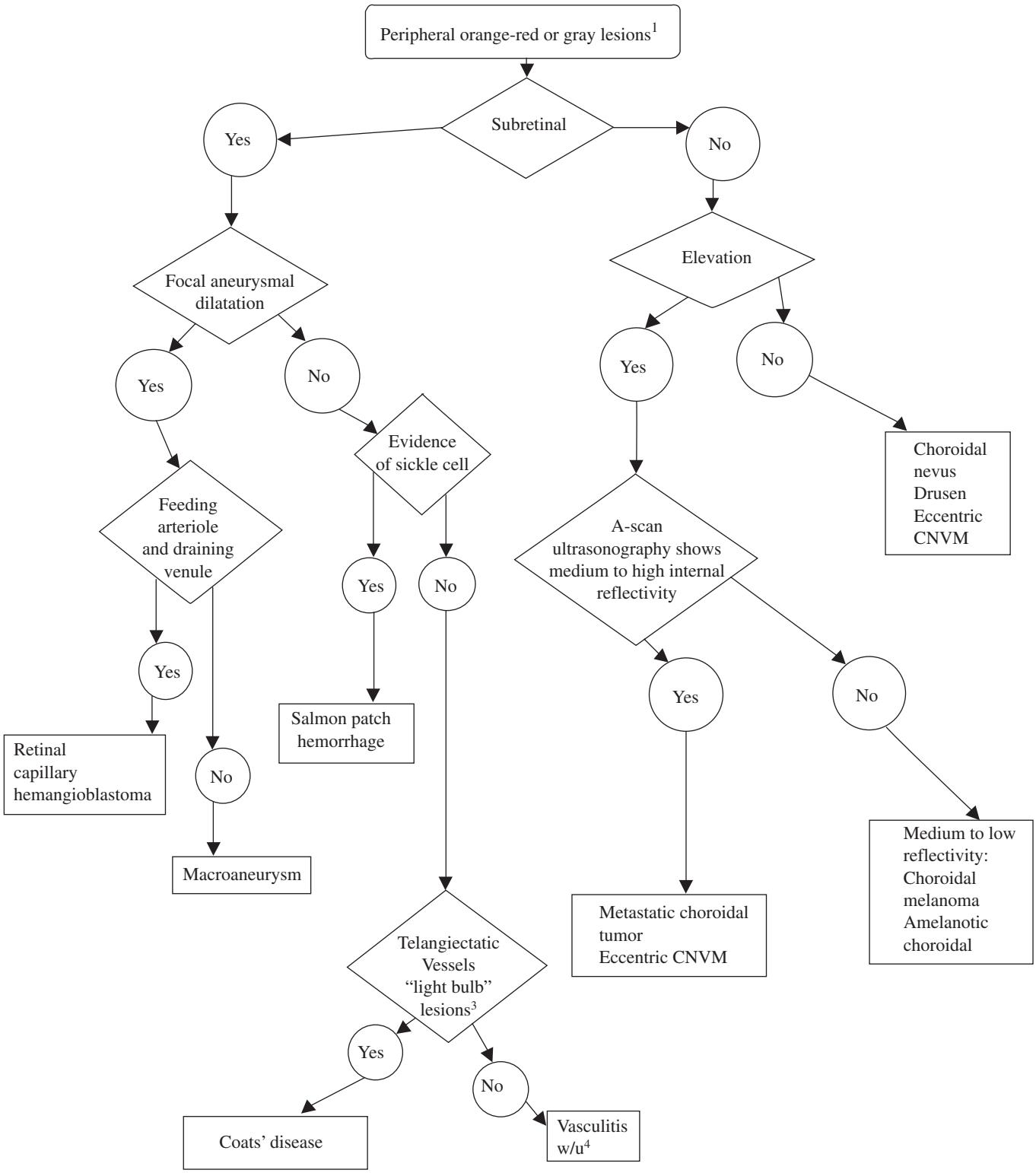

FIGURE 10–1. Clinical pathway: Peripheral orange–red or gray lesion. (1) Orange–red or gray lesion found inside the vascular arcades. (2) Differentiating subretinal versus deep retinal location may necessitate careful biomicroscopic examination. AMN, acute macular neuroretinopathy; CSCR, central serous chorioretinopathy.

Testing

Ultrasonography is used to measure the tumor height and to reveal its internal acoustic reflectivity. Choroidal melanoma has an initial steep spike with medium to low internal reflectivity.[11] In unclear cases, tumors are monitored for growth. Fluorescein angiographic characteristics have been described but are not pathognomonic.[4,15] Classic presentations include multiple pinpoint leaks on the surface of the tumor and an intrinsic or double circulation of the tumor. The orange pigment patches tend to appear as hypofluorescent spots.

Treatment

The definitive treatment for choroidal melanoma is controversial. Treatment involves eradicating the tumor's growth potential and, if possible, saving the vision and the eye. A large part of the treatment strategy is determined by the size and location of the tumor. Small tumors or suspected nevi in the periphery may be observed and measured with ultrasound to determine height and growth. Treatment options for melanoma include photocoagulation, radiotherapy, transpupillary thermotherapy, local resection, enucleation, and exenteration and are covered in greater detail in Chapter 15.[11,18–20]

Choroidal Nevus

Choroidal nevus is a benign growth within the choroid that may be confused with choroidal melanoma. In one series, it accounted for approximately one quarter of the lesions differentiated from choroidal melanoma.[21] A nevus occurs from a benign proliferation of melanocytes within the choroid.[9] As with choroidal melanoma, its presentation may be variable.

Clinical Presentation

The typical choroidal nevus, particularly when located in the peripheral retina, is discovered as part of a routine examination and is asymptomatic. It may be located anywhere in the fundus. The size is one to two disc diameters, but it may attain a larger size, simulating a medium to large malignant melanoma. There may be some elevation but usually less than 2 mm.[22] The nevus ranges in color from gray to the amelanotic orange–red. The surface characteristics may include a homogeneous color or an irregular mixture of orange and yellow pigment and small, drusen-like surface changes.[22,23] These clumps differ from melanomas that reveal larger patches of orange pigment. Variable amounts of RPE atrophy may surround the choroidal nevus, likely a reflection of the long-standing nature of this lesion. Subretinal fluid adjacent to the tumor is not a reliable distinguishing factor because other lesions may present with adjoining retinal detachment, including choroidal melanoma, choroidal osteoma, and others.[15,21,67]

Testing

As in choroidal melanoma, ultrasonography is used to measure the thickness and size of the nevus and detect growth in follow-up evaluations. FA plays a limited role but may demonstrate blockage of fluorescence with variable amounts of staining surrounding the lesion. If drusen are present on the surface of the lesion, these may also stain. At times, choroidal nevi are associated with choroidal neovascularization, and FA helps to detect this. Referral to a specialist for atypical or large lesions is advised.

Treatment

Nevi that do not develop into melanomas are followed up and need only treatment for visually threatening sequelae, such as adjacent choroidal neovascularization or exudative retinal detachment encroaching on the macula. These tumors should be followed up regularly because malignant transformation may occur.[22]

Metastatic Choroidal Tumors

Metastases to the choroid may occur due to its rich lobular vascular network. Metastatic choroidal tumors account for the most common intraocular malignancies.[26] The most common site of origin is the lung for men and the breast for women. At times, patients will be unaware of the presence of a primary tumor, and the ophthalmologist may be the first to identify evidence of neoplastic disease.

Clinical Presentation

Metastatic lesions may be multifocal or present as a single focus. Single metastatic tumors often are associated with an exudative retinal detachment. Metastatic lesions tend to have a creamy yellow to pale orange color and have indistinct borders. The size and location in the fundus are variable. Tumors may be bilateral. They do not grow to mushroom shape and may have an irregular elevation of the RPE. The surface of the tumor may present with coarse mottling and depigmentation of the RPE.[27] Sometimes they are difficult to differentiate from a choroidal melanoma.

Testing

As with all choroidal tumors, ultrasonography is important in the clinical evaluation. The ultrasound

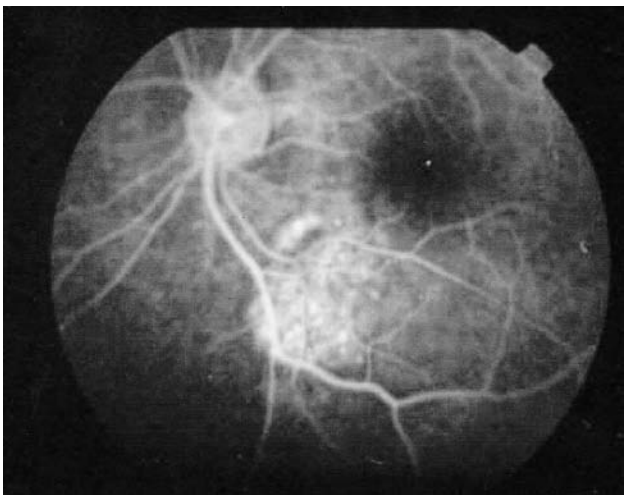

FIGURE 10–2. Late frame of the fluorescein angiogram demonstrates stippled hyperfluorescence in a metastatic choroidal tumor located along the inferior arcade.

characteristics of metastatic lesions are variable. Many present with a high initial spike and high internal reflectivity. Although not diagnostic, ultrasonography provides information about the size and characteristics of these lesions.

FA may be used, but there are no uniform fluorescein characteristics of these lesions. Many demonstrate hypofluorescence in the early transit frames with late hyperfluorescence (Fig. 10–2). Large choroidal vessels within the tumor are typically absent from the surface of the tumor.[28]

Both CT scan and magnetic resonance imaging (MRI) are useful in characterizing the extent of the primary tumor. Metastatic disease involving the central nervous system (CNS) can be detected with brain imaging.

Treatment

The prognosis for patients with metastatic choroidal tumors is poor. Median survival varies with the primary tumor, but most are on the order of months.[27] Treatment of metastatic tumors needs to be considered because, despite the poor prognosis, some patients do achieve long-term survival. Treatment involves systemic treatment of the primary tumor along with local treatment to the ocular tumor. Small peripheral tumors may be followed for response to systemic treatment. Radiation therapy, transpupillary thermotherapy (TTT), and photocoagulation are also treatment options. Enucleation is reserved for eyes with blind, painful symptoms.[26–28]

Choroidal Neovascularization (Extramacular Location)

Choroidal neovascularization may occur anywhere in the fundus. The most common location is in the macula where it interferes with vision. A choroidal neovascular membrane (CNVM) may form in the periphery of the fundus and result in an asymptomatic disciform scar (subretinal gliosis) with subretinal and/or intraretinal hemorrhage. However, sometimes these lesions bleed into the vitreous, resulting in reduced vision.

Clinical Presentation

Extramacular CNVM occurs rarely and usually is discovered on routine funduscopy. Because the location is away from the macula, vision is rarely affected. These lesions range in size from one to several disc diameters.[33] They may arise from old chorioretinal scars or the pars plana region or in the periphery without any apparent abnormality.[34] The amount of associated subretinal hemorrhage may vary, in part depending on how long the hemorrhage has been present. The surface of the lesion tends to have RPE mottling and may appear gray, with associated gliosis, or black, or dark orange with associated sub-RPE blood. Differentiating these lesions from choroidal melanoma is important.[33–35]

Testing

Fluorescein angiography is helpful in defining the extent of the lesion. In general, sub-RPE membranes will demonstrate early hyperfluorescence with pooling into the RPE detachment. Subneurosensory retinal membranes may demonstrate early hyperfluorescence with late leakage beyond the boundaries of the CNVM. When gliosis is present, the hyperfluorescence is associated with varying amounts of staining. Ultrasonographic findings vary. A-scan tends to show initially low reflectivity in early lesions and high reflectivity in older lesions. B-scan generally shows a broad, sessile thickening, with variable internal reflectivity.[10]

Treatment

Treatment is reserved for lesions that compromise vision. Laser photocoagulation or transscleral cryotherapy in peripheral lesions have been effective in reducing leakage that encroaches the macula.[9] Vitreous hemorrhage may be treated with pars plana vitrectomy if clearing does not occur spontaneously.[33]

Drusen

Drusen are subretinal deposits that increase in frequency with increasing age. Histopathologic studies have shown that drusen are localized collections of eosinophilic material between the basement membrane of the RPE and the Bruch's membrane.[36]

Clinical Presentation

Drusen typically are pale gray to yellow in color on funduscopy. They are often present in the posterior pole but may be seen in the periphery. There may be a symmetric appearance in both eyes. Drusen are usually multifocal, and the size of each individual druse ranges from a 63 μm or smaller diameter (hard drusen) to 250 μm or larger (soft drusen). Drusen may coalesce into larger lesions, and, as drusen enlarge, they become localized detachments of the RPE. Peripheral drusen usually are discovered on routine examination and have no affect on vision.[38]

Testing

Peripheral drusen do not affect vision, and so diagnostic testing is not routinely performed. FA, when performed in macular drusen, can reveal hyperfluorescence from RPE atrophy and hypofluorescence from hyperpigmentation or viscous subretinal fluid. The drusen, when large, may demonstrate early well-defined hyperfluorescence consistent with an RPE detachment.

Treatment

Treatment is reserved for complications that arise as sequelae to drusen, such as CNVM. Treatment for peripheral drusen is not indicated.

Retinal Origin

Retinal Arterial Macroaneurysm

Macroaneurysms are acquired localized dilatations of the retinal arteriolar vasculature usually occurring within the first three orders of retinal arteriolar bifurcations, but rarely they occur outside the posterior pole. Typically, macroaneurysms arise in patients in the sixth to seventh decade of life who have had systemic hypertension. Women outnumber men three to one. Histopathology demonstrates linear breaks in the vascular wall and thrombus formation within a thin-walled outpouching of the arteriole.[1–3,39]

Clinical Presentation

Peripheral macroaneurysms are discovered, most often as an incidental finding. Vision loss occurs as a result of leakage of blood and its constituents. When the macroaneurysm is located away from the macula, vision remains unaffected unless there is an associated breakthrough vitreous hemorrhage. Typical presentation is a variable amount of ring exudates, edema, and hemorrhage surrounding a gray or orange fusiform dilatation of a retinal arteriole. Often a distinct macroaneurysm may be difficult to find, leaving only the deposited lipoproteins (exudates) obvious. Variations in presentation will depend on the amount of leakage from the aneurysm. Bleeding may occur throughout all layers of the retina, subretinal space, and vitreous.[39]

Testing

FA is used to delineate the macroaneurysm. Blood may obscure the macroaneurysm, however, or it may be thrombosed and not appear on FA. Angiography delineates retinal microvascular abnormalities surrounding the lesion, such as capillary nonperfusion and cystoid edema of the retina.

Treatment

Photocoagulation is reserved for lesions threatening vision. Peripheral macroaneurysms may be observed. Pars plana vitrectomy for nonclearing vitrous hemorrhage affecting vision may be considered.

Retinal Capillary Hemangioma

Retinal capillary hemangiomas are congenital hamartomas that may be isolated or part of VHL syndrome associated with cerebellar hemangioblastoma. Patients with VHL are at risk for other organ involvement, such as tumors of the pancreas, adrenal glands, kidneys, liver, and epididymis. The familial disease has been mapped to chromosome 3.[40–42]

Clinical Presentation

Retinal capillary hemangiomas are typically red or orange–red, well-circumscribed tumors that may occur in the retina or optic nerve. Optic nerve hemangiomas appear different from the peripheral type and are discussed later. Peripheral hemangiomas are accompanied by two dilated vessels: a feeding arteriole and draining venule. The size of the angioma is variable and may range from less than a disc diameter to several disc diameters. Larger lesions have larger feeding arterioles and draining veins. The angiomas may be

single or multiple. There is often associated lipid or edema surrounding the angioma. Vitreoretinal traction may develop along the surface of the angioma or in the macula away from the angioma.

Testing

The funduscopic findings are typical so that diagnosis usually can be made on presentation. FA may help to identify smaller lesions undetected on clinical examination. Ultrasonography may help in larger lesions where the diagnosis is uncertain. MRI and CT scanning are critical to rule out tumors of the CNS and organs.

Treatment

Treatment of these vascular tumors is important for lesions that are posterior in location and large enough to affect vision. Some physicians advocated treating all tumors because they tend to grow. Small lesions are easier to treat than larger ones.[41] Photocoagulation for small lesions is accomplished by treating the vessels at the edge of the tumor and by direct tumor ablation. When treating the feeding vessels, it is important to treat the arteriole first to decrease the blood flow and the risk of bleeding. Larger lesions may require cryotherapy or radiation. Vitreoretinal complications, such as traction or rhegmatogenous retinal detachment, may need retinal detachment repair. Systemic involvement should be comanaged with appropriate specialists.

Coats Disease

Coats disease represents a spectrum of sporadic, unilateral, and congenital vascular telangiectatic and aneurysmal retinal vessels. Most cases present in males (3:1) before the age of 10 years. Patients with minimal changes in the macula often go unrecognized until adulthood, when the telangiectatic vessels are discovered on routine examination. Histopathologic studies have shown loss of retinal vessel endothelial integrity and lipid-laden macrophages in the subretinal space.[43–45]

Clinical Presentation

Presentation in children may take the form of leukocoria or strabismus. Red–orange lesions in the adult form of Coats disease may be either focal aneurysmal dilatation of the retinal vessels or intraretinal bleeding from incompetent vessels. Telangiectasia of the retinal vessels is found more often in the periphery than in the posterior pole and can have associated edema, exudates, or bleeding. Exudation from peripheral lesions may appear in the macula. Retinal vessel sheathing tends to be absent.

Testing

Fluorescein angiography delineates the extent of the retinal telangiectasia and corresponding retinal vessel nonperfusion. The classic "light bulb" lesion that represents a focal aneurysmal dilatation is pronounced on angiography. Fluorescein leakage from telangiectasia and aneurysms and hypofluorescence from the surrounding occluded microvasculature are features. In some childhood cases, CT scanning is used to distinguish Coats disease from retinoblastoma, which usually has calcification.

Treatment

Treatment is advocated for lesions that compromise or threaten vision. Visual loss usually occurs as a result of leakage of fluid or exudates into the macula. Photocoagulation or cryotherapy obliterates the incompetent vessels and aneurysms, permitting subsequent reabsorption of subretinal fluid. At times, extensive subretinal fluid may be drained to facilitate treatment. Multiple treatment sessions may be needed.

Salmon Patch Hemorrhage: Sickle Cell Retinopathy

Sickle cell retinopathy occurs from sickling of red blood cells within blood vessels as a result of abnormal hemoglobin molecules. The vessels become occluded and account for the clinical findings. Sickle cell retinopathy occurs almost exclusively in black patients. Most patients with retinopathy have the SC or S-thal variant.[46]

Clinical Presentation

A characteristic of sickle cell retinopathy is the salmon-patch hemorrhage, named for its characteristic orange–red appearance. It may be one to a few disc diameters in size and is often well circumscribed and circular to oval. These hemorrhages are located in the preretinal or superficial retina and frequently are found in the midperipheral and peripheral fundus. Rarely, they may be located in the posterior fundus. The blood may track into the vitreous, creating a vitreous hemorrhage, or into the subretinal space. Unless associated with a vitreous hemorrhage, they are generally asymptomatic.[46] They may be single or multiple. Other signs of sickle cell retinopathy include iridescent spots, remnants of blood products and macrophages within the retina, and black sunbursts that are reactions of the RPE to blood. Peripheral ghost vessels or sea-fan neovascularization may be present.

Testing

Confirmation of sickle cell disease by blood testing, specifically, a sickle prep or hemoglobin electrophore-

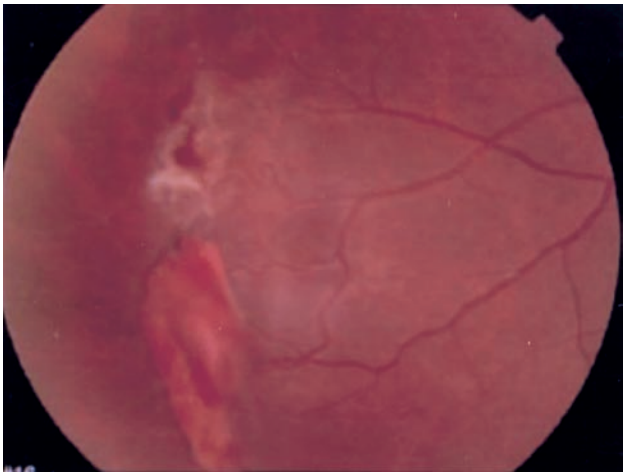

FIGURE 10–3. Sickle cell retinopathy; sea-fan neovascularization. The inferior aspect of the sea fan is partially obscured because of overlying hemorrhage. Note the absence of vascularization peripheral to the sea fan.

sis, is used to identify the presence of abnormal hemoglobin. FA may detect areas of nonperfusion in the periphery. Salmon-patch hemorrhages will block fluorescence. Sea-fan neovascularization leaks fluorescein (Figs. 10–3 and 10–4) and borders retinal capillary areas of nonperfusion.

Treatment

No treatment is necessary for salmon-patch hemorrhages because they resolve over time. If bleeding obscures vision because of a vitreous hemorrhage, observation is recommended. Sometimes surgical removal by vitrectomy is warranted. Rarely, bleeding tracks into the subhyaloid space. If this is premacular, yttrium–aluminum–garnet (YAG) laser or argon laser to the posterior hyaloid may allow the displacement of the hemorrhage into the vitreous and subsequent clearing.[49]

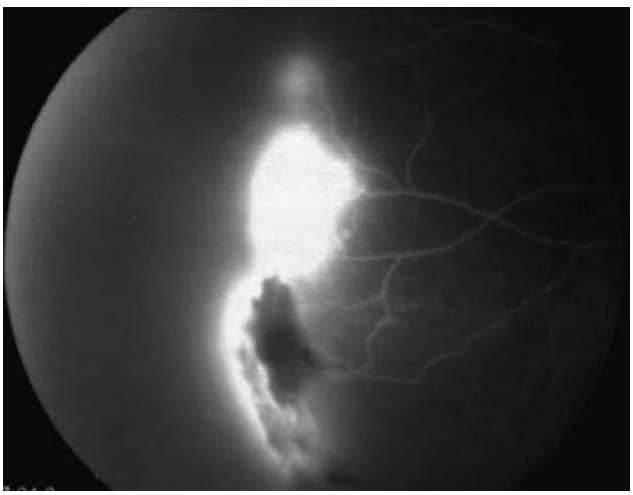

FIGURE 10–4. Fluorescein angiogram shows leakage of fluorescein from the sea fan and blockage due to overlying hemorrhage. Hypofluorescence peripheral to the sea fan reflects the vessel occlusion secondary to sickling of the red blood cells.

Retinal Vasculitis

Retinal vasculitis describes numerous conditions with inflammation of the walls of retinal blood vessels. Occlusion of retinal vessels can occur. Retinal hemorrhage or neovascularization may develop. These lesions appear red–orange if located within the retina or the posterior vitreous.

Systemic Disorders Associated with Orange–Red Lesions in the Retina

Hemorrhages occur from chronic and acute hypertensive retinopathy, diabetic retinopathy, neoplastic diseases, and intraretinal infections.

What Are Orange–Red and Gray Lesions of the Posterior Pole?

Subretinal Origin

Differentiating deep retinal from subretinal lesions (Fig. 10–5) is facilitated by magnified stereoscopic binocular examination using a contact lens.

Choroidal Neovascular Membrane

A choroidal neovascular membrane is thought to occur at sites where there is damage to the Bruch membrane and the RPE, allowing growth of new vessels from the choroid into the sub-RPE and subretinal space. CNVM has been divided into two groups based on the presumed location. Type 1 refers to membranes that grow within the Bruch's membrane, underneath the RPE. This is typical for age-related macular degeneration (AMD). Type 2 membranes are located in the subneurosensory space, between the RPE and retina. This is the more likely location for CNVM associated with ocular histoplasmosis syndrome (OHS) and idiopathic membranes. Submacular surgery to remove type 2 membranes yield better visual acuity results, likely because of the ability to preserve the RPE when removing the CNVM.[50] Causes of CNVM are listed in Table 10–1.

Clinical Presentation

Choroidal neovascularization in the posterior pole often causes symptoms of metamorphopsia, paracentral scotomas, or decreased central vision. Choroidal neovascularization in the posterior pole is most often,

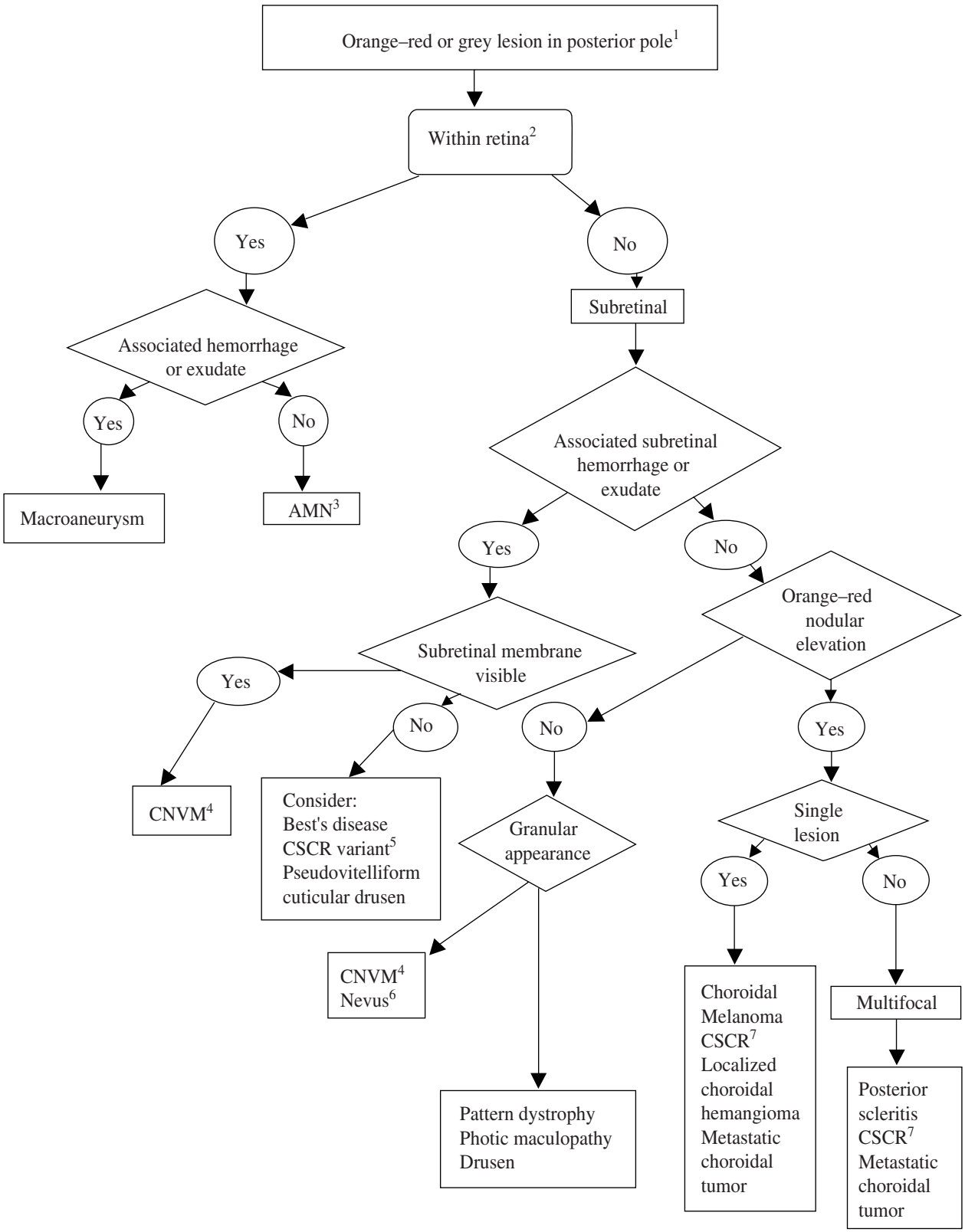

FIGURE 10–5. Clinical pathway: Orange–red or gray lesion in posterior pole. (1) Orange–red or gray lesion located within the vascular arcades. (2) Determination of the location of lesion as intraretinal or subretinal may take careful biomicroscopic examination. (3) Acute macular neuroretinopathy (AMN). (4) Choroidal neovascular membrane (CNVM). (5) Central serous chorioretinopathy (CSCR) may rarely be associated with exudates within elevation. (6) Choroidal nevus. (7) Central serous chorioretinopathy may be solitary or multifocal.

TABLE 10–1. Causes of Choroidal Neovascularization

Age-related macular degeneration
Angioid streaks
Multifocal choroiditis
Presumed ocular histoplasmosis
Myopia
Best's disease
Idiopathic
Serpiginous chorioretinopathy
Stargardt disease
Chorioretinal scar
Choroidal osteoma
Choroidal rupture
Pattern dystrophy
Localized choroidal hemangioma

but not always, associated with visual disturbances. Ophthalmoscopic findings include subretinal or intraretinal hemorrhage, subretinal exudates, and subretinal fluid. Subretinal gliosis may be present with older lesions. The lesions vary in size from pinpoint to multiple disc diameters. The color of the membrane may range from dark orange to gray. Most membranes have poorly defined borders on examination, and FA is needed to delineate the extent of the membrane. Often the borders are obscured by associated blood, exudates, or fluid.[52]

If the CNVM occurs as a result of chorioretinal scarring, it tends to be located adjacent to the edge of the scar. Often the membrane will grow along the foveal edge of the scar. In AMD, drusen will be present. Chorioretinal scars demonstrate areas of hyperpigmentation and hypopigmentation of the RPE with minimal elevation.

Testing

The most useful test to identify the presence and extent of a CNVM is FA. Membranes have been divided into two categories based on angiographic characteristics: occult and classic. Classic membranes demonstrate early hyperfluorescence with well-defined, lacy borders that leak later in the study. Occult membranes are of two types. Fibrovascular RPE detachment refers to a form of membrane that is believed to be underneath the RPE and shows a stippled hyperfluorescence early with persistence into the late study. Late leakage of undetermined source is the second type of occult membrane. Here, leakage late in the study is poorly defined and is not associated with early hypofluorescence. Serous RPE detachment represents a localized collection of fluid underneath the RPE, typically showing early hyperfluorescence on FA with slight blurring of the margins as the study progresses.[51] ICG angiography is helpful in selected cases where blood obscures the CNVM or when the CNVM is poorly defined with FA.

Treatment

Treatment for CNVM includes surgical excision, laser photocoagulation, and photodynamic therapy. Surgical excision of type 2 CNVM has shown benefit for some patients with idiopathic membranes and ocular histoplasmosis. Surgical removal of type 1 membranes, usually found in AMD, is associated with limited visual recovery because the RPE often is removed with the membrane. A National Eye Institute (NEI)-sponsored study is currently ongoing and will help to identify patients who are the best candidates for submacular surgery. Laser photocoagulation reduces severe visual loss from CNVM associated with AMD, OHS, and idiopathic and inflammatory membranes.[51] Recurrences are common, however, and overlying retina is destroyed with the treatment. Photodynamic therapy closes CNVM with relative preservation of the overlying retina and is recommended for certain subfoveal CNVMs.

Localized Choroidal Hemangioma

Localized or circumscribed choroidal hemangioma is a variant of choroidal cavernous hemangioma. Choroidal hemangiomas may be diffuse, involving the entire choroid, or localized, affecting a small portion of the choroid. It is a benign tumor classified as a hamartoma histologically, and it contains large choroidal vessels that blend with the surrounding choroidal vessels at the edge of the tumor.[29]

Clinical Presentation

Localized choroidal hemangioma usually is discovered on routine ophthalmoscopic evaluation; however, it may present with painless loss of vision, depending on its location. It is commonly seen in the fourth decade of life. The localized choroidal hemangioma is a well-circumscribed orange–red tumor arising from the choroid, with minimal elevation. The size of the tumor ranges from 2 to 10 disc diameters. Subretinal fluid, cystic edema of the retina, and RPE changes are present to varying degrees. Choroidal neovascularization has been reported infrequently.[30]

Testing

Localized choroidal hemangioma usually is diagnosed according to the classic funduscopic picture. There may be, however, varying degrees of RPE degeneration and associated subretinal fluid, making differentiation from choroidal melanoma difficult. Ultrasonography typically shows a high initial spike

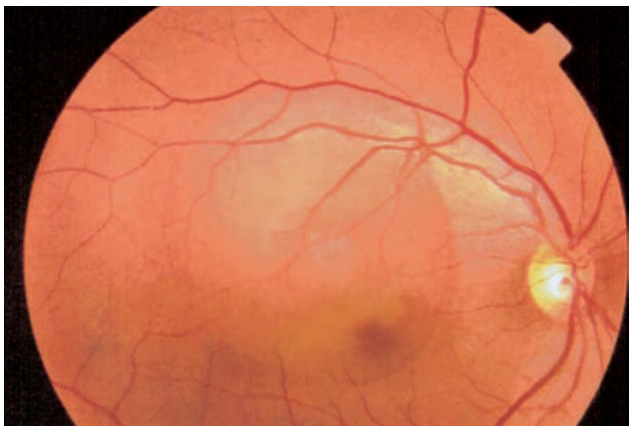

FIGURE 10–6. Idiopathic central serous chorioretinopathy.

with medium to high internal reflectivity on A-scan. FA reveals filling of the large vascular channels early with subsequent irregular spreading of the fluorescence through the transit frames, presumably from leakage of fluorescein from the surface of the tumor. Late frames reveal accumulation of fluorescein in the retinal cystic spaces. ICG angiography shows accumulation of the dye early with subsequent washout late in the study.[32]

Treatment

Treatment is reserved for tumors affecting vision. Observation is appropriate for tumors where vision is unaffected. When vision is reduced or threatened, photocoagulation is performed to areas of fluorescein leakage on the tumor surface. The goal of treatment is to create a chorioretinal scar and decrease the subretinal fluid leakage. Radiation therapy, transscleral cryotherapy, photodynamic therapy, and microwave thermotherapy also may be used in select cases.[31]

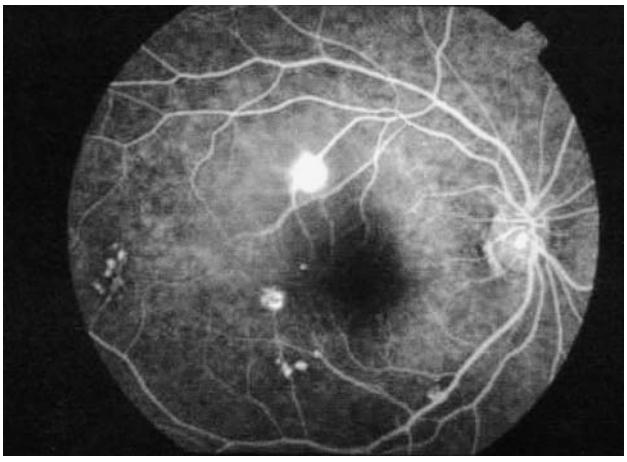

FIGURE 10–7. Early transit frame in the fluorescein angiogram demonstrates multiple focal retinal pigment epithelial detachments.

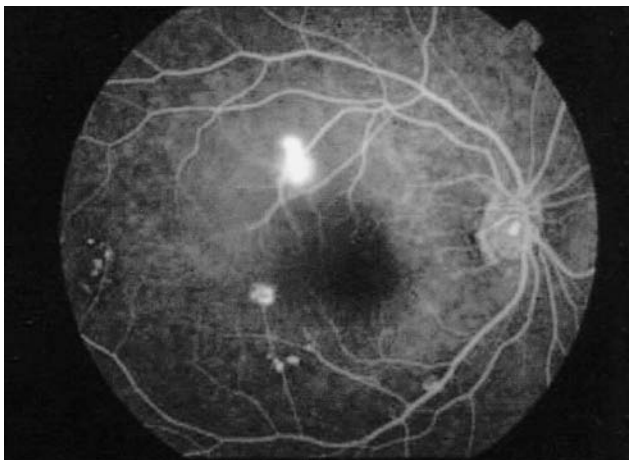

FIGURE 10–8. "Smoke-stack sign" located superior to the fovea showing leakage of fluorescein into the subretinal space that rises.

Best's Disease

Best's disease is a macular dystrophy that has a spectrum of findings. The classic "egg yolk" macular lesion can be associated with good visual acuity. In some stages, the macular lesion may take on a reddish hue, particularly in later stages.

Central Serous Chorioretinopathy

Central serous chorioretinopathy can appear as a red–orange elevation of the retina or RPE (Fig. 10–6). CSCR may be solitary or multifocal. The diagnosis is aided with FA (Figs. 10–7, 10–8, and 10–9) or ICG angiography.

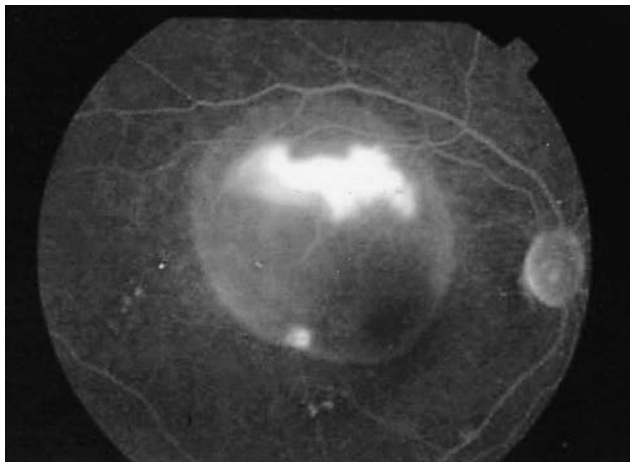

FIGURE 10–9. Late frames of the study demonstrate pooling of the fluorescein dye into the subretinal fluid.

Pseudovitelliform Cuticular Drusen

Cuticular drusen, also known as basal laminar drusen, are multiple small translucent, uniform drusen measuring 25 to 75 μ in size. In some cases, they are associated with the development of CNVM. More often, they become confluent and develop a detachment of the RPE that mimics Best disease. The drusen tend to be yellow but may appear reddish. In addition, the CNVM and pseudovitelliform lesion may appear reddish or gray.[54]

Choroidal Nevus

Choroidal nevi may occur anywhere in the fundus and have been described earlier.

Pattern Dystrophy

Pattern dystrophies of the macula are dominantly inherited conditions affecting the RPE. Although most of these conditions present with pigmented changes in the macula, some demonstrate red–orange geographic patterns. The changes are usually bilateral and symmetric. Visual loss tends to be mild or moderate and occurs during midlife. Choroidal neovascularization is a rare complication.[54,55]

Photic Maculopathy

Photic retinopathy encompasses injury from light that may occur as a result of iatrogenic light exposure (operating microscope), sun gazing (solar retinopathy), lightning, welding arc, or lasers. Light may cause injury by absorption of the light energy by pigments in the retina. There are three basic mechanisms responsible for retinal damage: photochemical, photocoagulative, and mechanical. *Photocoagulative changes* occur when light is absorbed and increases the retinal temperature by at least 10°C, resulting in coagulation of retinal proteins. *Photochemical effects* refer to damage caused by prolonged light at irradiances too low for photocoagulation. An example is the operating room microscope. *Mechanical effects* are related to transmission of shock waves after absorption of the light energy.[57–58]

Clinical Presentation

Patients may present with symptoms of decreased vision or paracentral scotomas soon after prolonged intraocular surgery, sungazing, or other types of light-induced injury. The acute fundus picture is variable but may range from a small yellow or gray lesion in the fovea or parafoveal area. The location is likely the deep retina or RPE. This lesion may become reddish over the next 2 weeks, eventually leaving a lamellar hole or RPE mottling.[57a] Iatrogenic photic maculopathy from operating microscopes generally presents with a lesion of variable sized diameter, one half to two disc diameters, that is oval or round yellow–white at the level of the RPE. The shape depends on the light source.[59] There may be associated retinal edema. Pigmentary changes usually remain. Patients often recover significant vision, depending on the degree of RPE damage and the location in the macula of the injury.

Testing

Fluorescein angiography shows intense staining of the RPE acutely. With resolution of the injury, angiography will show blockage from hyperpigmentation, staining, and transmission defects associated with loss of pigment or atrophy.

Treatment

Treatment is generally supportive; many patients experience visual improvement. Prevention has focused on educating the public about the dangers of sungazing during eclipses and laser pointer injuries and educating ophthalmologists about the risks of iatrogenic operating microscope macular damage associated with prolonged ocular surgery. During surgery, when possible, the macula should be protected from light.

Drusen

Drusen may occur anywhere within the fundus. Differentiation of drusen into hard drusen and soft drusen has been discussed. Although these usually appear yellow, at times they may appear red.

Choroidal Melanoma

See earlier section.

Metastatic Choroidal Tumor

See earlier section.

Posterior Scleritis

Posterior scleritis is uncommon and occurs behind the equator. There is a predilection for middle-aged women; however, this entity has been described in patients ranging from ages 8 to 87 years old. Posterior scleritis may present in association with anterior scleritis or as an isolated process. Although there may be a systemic association, often it presents as an isolated finding without systemic findings.[61]

Clinical Presentation

Patients typically present with symptoms of decreased vision, pain, photophobia, and often a red

eye. It is important to note that pain and redness may be absent. Examination reveals anterior segment inflammation with anterior chamber cells or scleral injection. Vitreous cells may be present, but the most typical finding is an exudative retinal detachment. Deep choroidal thickening or RPE detachment may appear as orange–red elevations. Optic nerve edema may be present. Extraocular muscle bellies may be involved, limiting gaze. Choroidal effusion with anterior rotation of the ciliary body and narrow angles have been reported.[62]

Testing

B-scan ultrasonography is used to demonstrate thickening of the choroid and sclera. The characteristic "T-sign" describes the echolucent posterior displacement of the Tenon capsule as a result of fluid within the Tenon space. The optic nerve, also echolucent, forms the vertical aspect of the "T" on ultrasonography. FA may show pinpoint areas of fluorescein leakage at the level of the RPE. In addition, there may be leakage from the optic nerve and staining of the retinal vessels. CT scan may demonstrate scleral thickening, orbital involvement, or intraocular muscle involvement.

Blood testing and systemic evaluation should be performed to search for a systemic association. Often an association is not found. Workup should include evaluation for inflammatory disease, such as systemic lupus erythematosus, rheumatoid arthritis, Wegener granulomatosis, inflammatory bowel disease, or relapsing polychondritis. Infectious causes, such as syphilis, also should be investigated. Evaluation with the aid of an internist is warranted to evaluate for rare conditions.

Treatment

Treatment relies on identifying the systemic condition; however, often no associated diagnosis is made. Empiric treatment with nonsteroidal antiinflammatory medications or oral prednisone 1 to 1.5 mg per kilogram of body weight is often effective in resolution of symptoms. The pain and subretinal fluid usually respond quickly to this therapy. Rarely, in refractory cases, pulse steroids or antimetabolites are necessary.[60,62]

Retinal Origin

Few conditions presenting as red–orange or gray lesions in the posterior pole are derived from within the retina. Most lesions tend to be beneath the retina. The two lesions presented here are the macroaneurysm and AMN.

Macroaneurysm

See earlier section.

Acute Macular Neuroretinopathy

This maculopathy is a rare condition that was first described by Bos and Deutman as a peculiar cloverleaf or wedge-shaped lesion in the macula associated with scotomata that develop in young persons often after a flu-like illness.[63] The pathogenesis has not been determined. Most patients are otherwise healthy women. Some reports described development of AMN after injections of sympathomimetics.[64]

Clinical Presentation

The typical patient is a young healthy woman who has a history of flu-like illness and then reports the rapid onset of central and paracentral scotomata. Patients usually can outline the field defects precisely on an Amsler grid. Ophthalmoscopic examination reveals wedge-shaped, petal-like, well-demarcated, deep retinal lesions approximately one to several disc diameters in size. The lesions are red and are believed to be in the deep retinal layers between the retinal vessels and RPE. One or both eyes may be involved. Other ophthalmic abnormalities are generally absent; however, rare flame-shaped hemorrhages have been described.[65,66]

Testing

The lesions tend to be well visualized with red-free photos. FA may show a mild hypofluorescence corresponding to the lesions. Macular field testing either with Goldmann perimetry or automated perimetry may help to define the scotoma and aid with determining progression or resolution.

Treatment

Most patients experience gradual improvement with disappearance or fading of the scotomata. The retinal lesions tend to fade with time as well. Currently, there is no known treatment and, given the benign natural history, observation is generally the preferred management option.[65,66]

What Are Orange–Red and Gray Lesions with a Peripapillary Location? (Fig. 10–10)

We define peripapillary lesions as those that occur within one disc diameter of the optic nerve head. These include some optic nerve head lesions where the adjacent retina is affected and appears red–orange

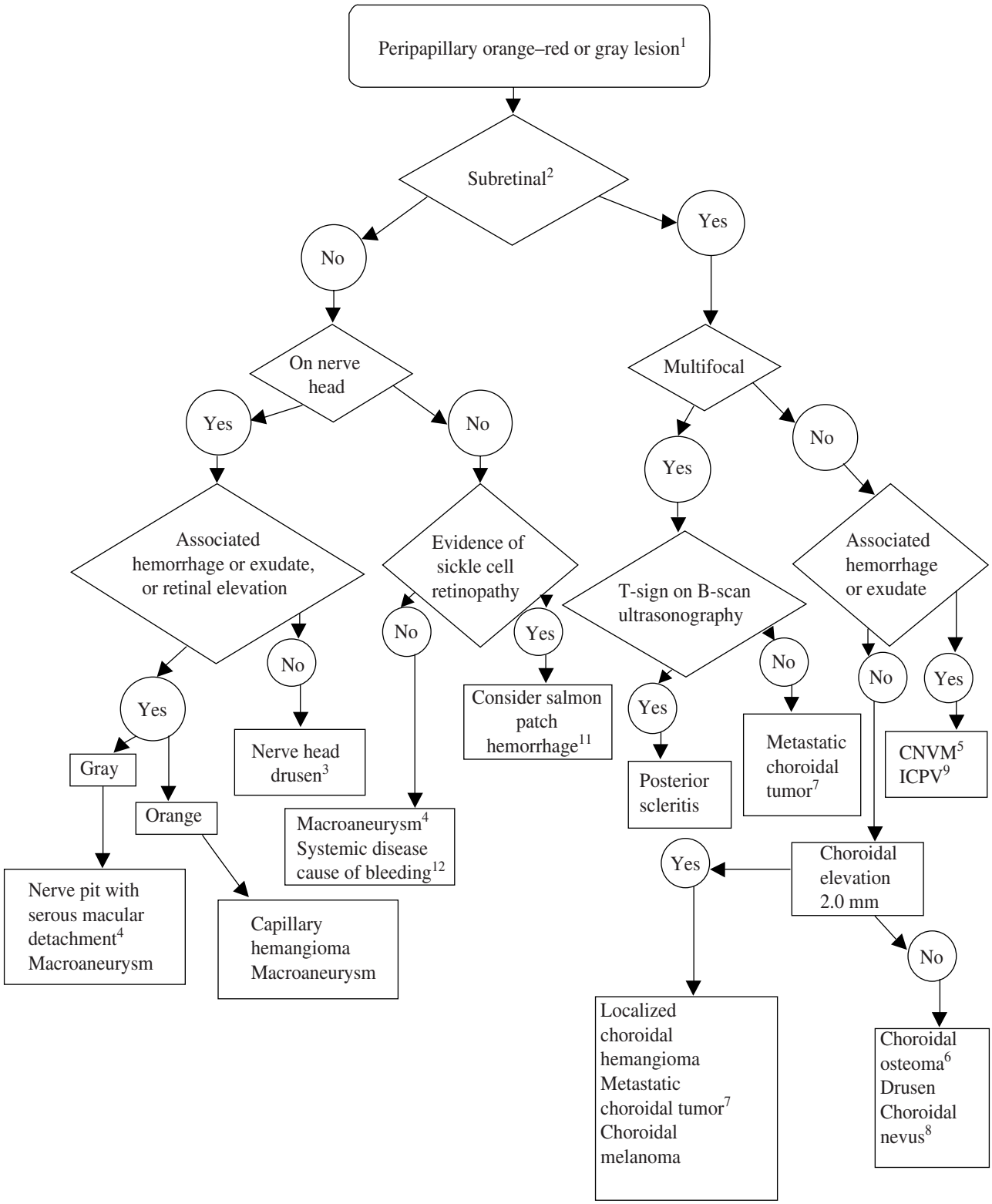

FIGURE 10–10. Clinical pathway: Peripapillary orange–red or gray lesion. (1) Lesion that is seen primarily surrounding the optic nerve. (2) At times, differentiating subretinal location from deep retina may need careful biomicroscopic examination. (3) Optic nerve drusen may be associated with CNMV and have variable amounts of blood, lipid, or retinal elevation. (4) Optic nerve pits are gray and located on the disc. They are often associated with serous retinal elevation adjacent to the pit. (5) Choroidal neovascular membrane (CNVM) may present with hemorrhage, exudates, or retinal elevation. At times, there may be none of these findings. (6) Choroidal osteoma may be elevated but not more than 2.5 mm. (7) Metastatic choroidal tumors may be multifocal or solitary. (8) Choroidal nevus may be elevated but not more than 2.0 mm. (9) Idiopathic choroidal polypoidal vasculopathy (ICPV) may be associated with hemorrhage, exudates, or retinal elevation. At times, there may be none of these findings. (11) Although sickle cell retinopathy is usually seen peripherally, bleeding may occur postoperatively. (12) Chronic and acute hypertensive retinopathy, diabetic retinopathy, neoplastic diseases, intraretinal infections and inflammations all can cause polar hemangiomas. Look for associated signs.

or gray. There is some overlap with posterior pole lesions described earlier.

Subretinal Origin

Lesions of subretinal origin include posterior scleritis, localized choroidal hemangioma, metastatic choroidal tumor, choroidal melanoma, choroidal nevus, drusen, choroidal neovascularization. For mention of these lesions see earlier section.

Choroidal Osteoma

Choroidal osteomas are rare tumors of the choroid that contain elements of bone and calcification. They are believed to be congenital choristomas, but low-grade choroidal inflammation also may play a role in the pathogenesis. Young, healthy females in their second or third decade of life are generally affected, but these lesions may present in men, young children, and older adults. Histopathology has shown the presence of cancellous bone located within the substance of the choroid, between the choriocapillaris and outer choroid.[67,68,70]

Clinical Presentation

Symptoms range from none to metamorphopsia or scotoma, depending on the location of the tumor and associated subretinal fluid. The lesion typically has a peripapillary location but may spread to involve the posterior pole. Some lesions have been described as isolated in the posterior pole without peripapillary involvement. The lesion can be yellow–white to orange–red and is sharply demarcated. The size ranges from one to several disc diameters and may be elevated, generally not more than 2.5 mm. These tumors have scalloped edges with pseudopod-like projections. The vasculature of the tumor may be seen on its surface and may appear as branching vessels that originate from within the substance of the tumor. Abnormalities of the retinal vessels, optic nerve, and vitreous are generally absent. Over time, there may be slow enlargement of the tumor. Subretinal fluid may be present. Choroidal neovascularization is a known association, and these patients must be followed for the development of it.[68–70]

Testing

As with any choroidal tumor, ultrasonography is valuable in assessing the thickness of the tumor and its acoustic behavior to differentiate it from tumors with malignant potential. A-scan typically shows a high initial spike followed by low reflectivity. B-scan shows a highly reflective minimally thickened structure with retrolesional shadowing that remains, even with low gain. CT scan will show calcification within the choroid consistent with bone. FA displays mottled hyperfluorescence of the lesion with late staining. The superficial vessels of the tumor do not leak. These are to be differentiated from CNVMs, which typically show characteristic early leakage.[67]

Treatment

Because of the benign nature of this tumor, treatment of the tumor itself is not indicated. Periodic examinations are recommended for development of CNVM. Laser treatment of CNVM may take several sessions because of the lack of pigment within these tumors.[67–70] Photodynamic therapy may offer a therapeutic option.

Polypoidal Choroidal Vasculopathy

Also known as *posterior uveal bleeding syndrome*, this entity presents most commonly in African-American women with blurred vision secondary to multiple irregular serous and hemorrhagic detachments of the RPE. The RPE detachments may resolve and recur. They are generally located around the optic nerve head. Bleeding may dissect into the subretinal space and vitreous. FA may show choroidal neovascularization or polypoidal hyperfluorescent lesions. ICG angiography may help to detect these abnormal choroidal vessels. These lesions tend to be self-limited, but overlying RPE changes may affect vision. Laser photocoagulation to the polypoidal lesions has been described.[71–73]

Optic Nerve Head Origin

Included in this section are some lesions that present on the optic nerve head. Orange–red or gray lesions typical on presentation will be discussed.

Macroaneurysm

Macroaneurysms of the retinal vessels may present near the optic nerve head and have been discussed in an earlier section.

Optic Nerve Pit with Serous Macular Detachment

Optic nerve pits are sporadic congenital anomalies that typically appear gray. They range in size from one tenth to two thirds disc diameter in size and usually are found along the temporal aspect of the nerve but may be located anywhere. Pits may be associated with a serous detachment of the retina, usually in a teardrop shape off the edge of the pit. The source of

the fluid is controversial. It may be from either cerebrospinal fluid or liquefied vitreous gaining access to the subretinal space through the pit. FA may show window defects and areas of hypofluorescence from RPE changes associated with long-standing detachments. Typically, no abnormal leakage is seen distinguishing it from CSCR. Treatment involves either pneumatic displacement with an intravitreal gas bubble or laser photocoagulation to the retina adjacent to the pit.[74,75]

Optic Nerve Head Drusen

Optic nerve head drusen may present as yellow or orange nodules on the surface of the disc. These represent hyaline bodies within the substance of the nerve head and may lead to the incorrect diagnosis of nerve head swelling. Optic nerve head drusen may be bilateral and may be associated with visual field defects due to compression of nerve fibers. They are rarely associated with subretinal hemorrhage.[76]

Peripapillary Capillary Hemangioma

These rare tumors are found on or within the substance of the nerve head and are a variant of the retinal capillary hemangioma described earlier. They display sessile exophytic structure unlike the classic endophytic growth pattern seen in VHL syndrome. Orange–red to yellow in color, they are associated with variable amounts of hemorrhage, edema, or exudates. The color depends on the location of the tumor, whether it is within the substance of the optic nerve or on the disc surface, and the degree of intratumor lipid deposition. Visual symptoms present when exudation or hemorrhage encroaches on the macula. Exophytic lesions do not demonstrate the dilated feeding vessels. Treatment with photocoagulation has shown variable success.[77]

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11

Linear and Curvilinear Streaks in the Fundus

SCOTT M. STEIDL AND ERIC JONES

Linear or Curvilinear Streaks Observed on or Near the Posterior Lens

Retrolenticular Membranes and Hemorrhage Associated with Hereditary and Acquired Vitreous Disease

Hemorrhage originating in the vitreous cavity may leave blood on the posterior lens surface, either clotted with a distinct edge or in streaks. This may occur in any situation where hemorrhage is retained in the vitreous cavity. Conditions predisposing to hemorrhage include vitreous hemorrhages, which are the result of systemic disease, such as diabetes,[1] retinopathy of prematurity, or sickle cell retinopathy,[2] or an old traumatic injury, such as from an air bag,[3] paint ball,[4] or other blunt or penetrating trauma injuries.[5–10] Vascular disease, such as central retinal vein occlusion[11] or macroaneurysms,[12] and age-related changes, like posterior vitreous detachment with retinal tears, also can lead to vitreous hemorrhage.[13] Figure 11–1 shows a clinical pathway that includes a method of approaching the diagnosis of lines or streaks seen on fundus examination.

Here we consider three conditions that can lead to anterior vitreous pathology in their advanced stages, manifesting as membrane formation, hemorrhage, or both. These are retinopathy of prematurity (ROP); persistent fetal vasculature (PFV), also known as persistent hyperplastic primary vitreous (PHPV); and proliferative vitreoretinopathy (PVR).

The first condition, ROP, commonly involves the anterior aspect of the eye in its severe stages. First reported by Terry in 1942,[14] ROP can result in both anterior retrolental membrane formation and vitreous hemorrhage as part of its spectrum of manifestations. Terry noted the formation of a V-shaped retinal detachment resulting in membrane growth behind the lens. It has since been documented that this condition is associated with premature birth, low birth weight, and neonatal oxygen use. Severe neovascular membranes grow on the retinal surface in advancing disease are thought to contribute to traction retinal detachments as well as to the development of vitreous hemorrhage. Over time, a localized vitreous hemorrhage may become dispersed within the vitreous cavity, and streaks of hemorrhage may be seen in the anterior vitreous. Cryotreatment has been used for treatment at the early signs of neovascularization and may result in an associated increase in hemorrhage shortly after treatment. It has been suggested that laser photocoagulation may produce less tissue destruction than cryotherapy and lessen the chance of vitreous hemorrhage.[15,16]

The second condition, PFV, is a congenital condition; when it occurs, it is most often noted during the first few days or weeks of life, usually in its anterior form.[17–19] It is usually unilateral in a microphthalmic eye and generally consists of a retrolental fibrovascular mass with dragged ciliary processes and a secondary cataract. It typically forms a posterior lens attachment with a distinct or feathery edge, around which one may obtain a posterior view of the retina. In this condition, effort should be made to avoid development of glaucoma or phthisis, the most common vision-threatening result of untreated PFV. A lensectomy usually prevents econdary glaucoma, typically the result of lens–iris diaphragm-induced secondary angle-closure glaucoma. Glaucoma also can be produced from recurrent hyphema. When hyphema occurs, outflow passageways in the angle may become blocked with blood. By removing a PHPV membrane and reducing the tractional forces on the ciliary body, one can lessen the risk of phthisis.[20]

The third condition, PVR, is a cause of retinal membrane development, but it also may involve contrac-

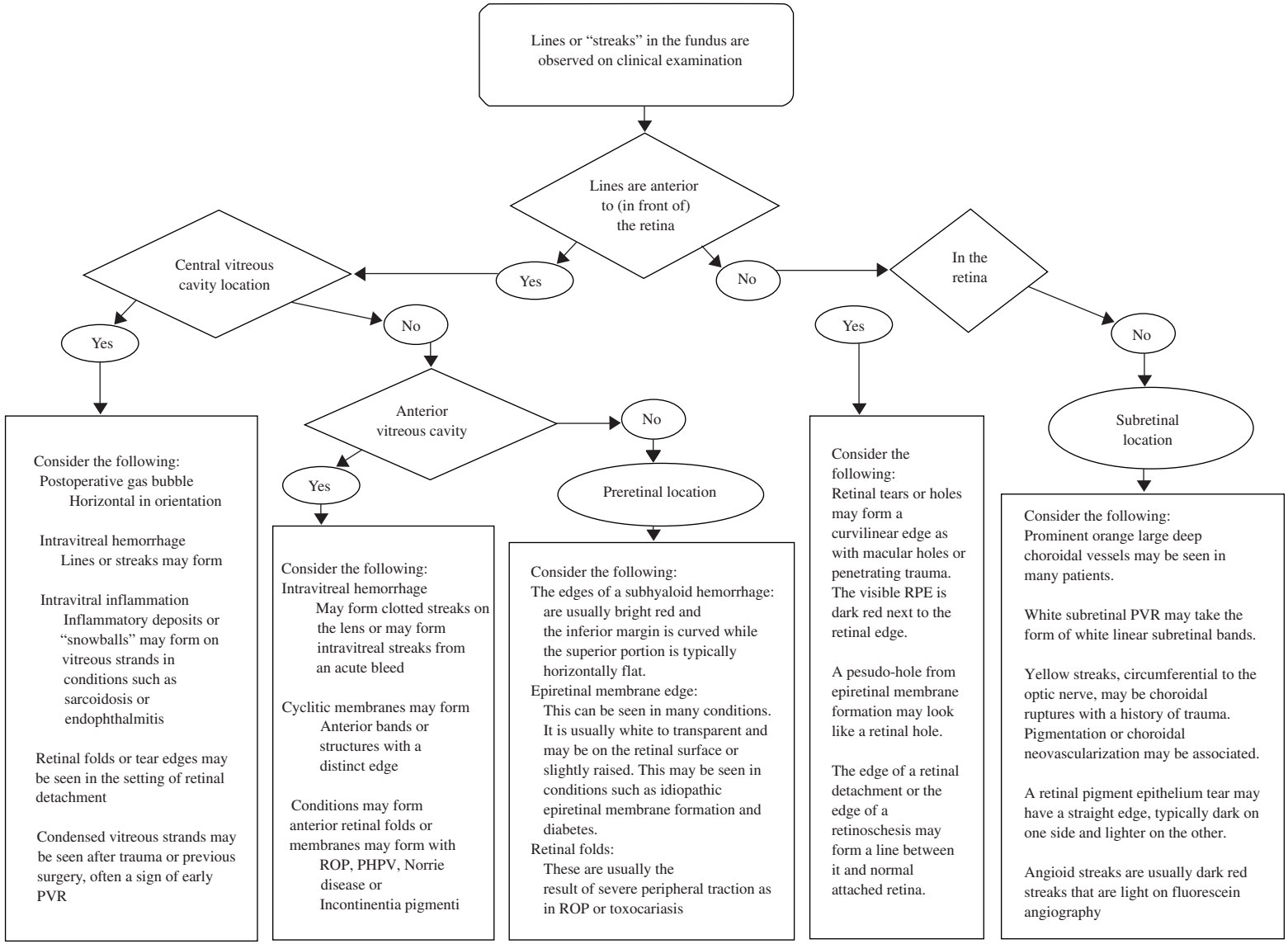

FIGURE 11–1. Diagnosis straight or curvilinear lines seen on fundus examination. PVR, proliferative vitreoretinopathy; ROP, retinopathy of prematurity; PHPV, persistent hyperplastic primary vitreous; RPE, retinal pigment epithelium.

ture of the vitreous. PVR is thought to result from mechanisms resulting from the presence of retinal breaks and retinal detachment. Complex retinal detachments may be caused by PVR, probably as a result of cellular changes, which occur in the vitreous cavity and on the retinal surface. These changes may include leukocytes in the vitreous and retinal pigment epithelium (RPE) cells passing through a retinal break, which can infiltrate the vitreous cavity and migrate onto the retinal surface, proliferate, and form a fibrous membrane.[21] These PVR membranes can contract and apply traction at the retinal surface. PVR is a complicating factor in 5 to 7% of rhegmatogenous retinal detachment cases.

Cyclitic Membrane Edges

A dense fibrovascular cyclitic membrane can develop after trauma[22] or after inflammatory insult. It may surround the lens or cover only a portion of the lens so that an edge is seen on either surface of the lens. Cyclitic membranes develop in the setting of prolonged uncontrolled inflammation, such as in juvenile rheumatoid arthritis,[23,24] trauma, or chronic proliferative conditions, such as persistent fetal vasculature.[25]

Linear or Curvilinear Streaks Observed in the Midvitreous

How Does a Vitreous Hemorrhagic Form Streaks?

When hemorrhages occur in the acute setting, they may form "string-like" streaks seen by the patient. Conditions that cause vitreous hemorrhage are mentioned in the first section of this chapter and in Chapter 12. Streaks of blood in the vitreous cavity may move or remain stationary based on the status of the vitreous. Because blood may be seen after a retinal tear, one should be suspicious of an occult tear when a hemorrhage occurs in the absence of other known predisposing conditions. Close observation is required to avoid a missed break and development of a retinal detachment when a vitreous hemorrhage limits the fundus evaluation. In rare cases, blood may break through into the vitreous from the suprachoroidal space in the setting of a suprachoroidal hemorrhage.[26]

Linear Inflammatory Debris

Inflammatory disease, such as endophthalmitis from bacterial infection or noninfectious inflammation such as sarcoidosis,[27–29] may cause opacification of vitreous strands through deposition of inflammatory debris on vitreous collagen strands. Localized collections of inflammatory cells are called *snowballs* and typically are seen in the inferior vitreous in sarcoidosis and pars planitis.[30] Intravitreal fibrin also may form under conditions of extreme inflammation. Fibrin membranes may form strands, sheets, or even encapsulating membranes. Fibrin formation can be extreme after extended vitrectomy for proliferative diabetic retinopathy or after inflammatory conditions such as endophthalmitis. When a fibrinoid syndrome occurs, fibrin deposition within the eye may produce pupillary block or even traction retinal detachment.[31,32]

What Findings Are Associated with Giant Tears

The edge of a giant tear may be seen as a curvilinear formation in the anterior vitreous. Giant tears are tears that have a circumferential length greater than three clock hours or 90 degrees.[33] Giant tear edges are seen when the tear flap inverts and it is displaced posteriorly. These tears are associated with high frequency of rhegmatogenous or complicated retinal detachment. The tear flap may be freely moving, or it may be semirigid if associated with PVR. When the flap is rolled over, either onto or close to the retinal surface, the whitened anterior rolled edge of the flap can be seen as a distinct border in relief against the dark red RPE. Also, the entire rolled flap itself may appear as a white strip or band, flanked with attached retina on one side and bare RPE on the other.

Why Are Streaks Seen with Retinal Detachment?

In some cases of retinal detachment with retinal tears (rhegmatogenous detachment), PVR may develop and contribute to surgical treatment failure (see preceding section entitled "Retrolenticular Membranes Associated with Hereditary and Acquired Vitreous Disease."). In such cases, it is thought that RPE cells migrate into the vitreous cavity and onto the retinal surface, where they proliferate and form contractile membranes. If the surface contraction is strong enough, these membranes may throw the retina into fixed folds.[34] These folds often first form in a "star"-shaped pattern.[35] With anterior PVR, circumferential retinal folds as well as peripheral radial folds may occur. The retina may take on a more curvilinear deeply folded pattern when folding is severe, often leading to a highly distorted vascular architecture. In the case of penetrating trauma, retinal incarceration into the wound site may cause deep radial folds centered at the wound site.

Linear or Curvilinear Streaks Observed in the Posterior Vitreous or Preretinal Space

Can Subhyaloid Hemorrhage Form Streaks?

Hemorrhage in the preretinal space, just under the posterior vitreous face (subhyaloid hemorrhage), may be seen in a variety of conditions. Some of these in-

clude diabetes, venous occlusion, retinal arterial macroaneurysm,[36] sickle cell disease, shaken-baby syndrome,[37] Terson syndrome,[38–40] Eale's disease,[41,42] and idiopathic retinal vasculitis with arterial macroaneurysms and neuroretinitis.

The inferior edge of a detachment of the vitreous may form a bright red, curved edge with hemorrhage pushing the posterior vitreous face forward. This is sometimes referred to as a "boat-shaped" hemorrhage with the inferior edge rounded and the superior edge flat horizontally. When blood is caught under the vitreous face in this way, neodymium:yttrium–garnet–aluminum (Nd:YAG) laser treatment directed at the inferior aspect of the detached vitreous surface can create a hole, possibly allowing a release of preretinal blood and clearing of the visual axis.

Do Diabetic Traction Detachment Membranes Form Linear Structures?

Diabetic preretinal membranes may form as part of the end-stage process of retinal neovascularization. When membranes form, contracture occurs, which can pull at multiple points on the retinal surface and cause retinal detachment.[43–48] Often, distinct edges are formed along these bands of preretinal membrane formation. They may create straight or curved structures, typically along the major vessels in the macular region. Also, organization of the vitreous may cause contracture and coalescence of its collagen fibers, which lead to linear bands within the vitreous cavity oriented either perpendicularly or obliquely to the retinal surface. These bands or membrane edges may be whitish, owing to their fibrotic nature, and they may collect blood on them if a vitreous hemorrhage is present.

Linear or Curvilinear Streaks Observed in the Retina

What Causes Retinal Folds?

Retinal folds are typically the result of some type of tractional force oriented along the retinal surface. Macular pucker resulting from localized preretinal membrane formation is a folding of the retina, as its name implies.[49–54] Preretinal membranes, also known as *epiretinal membranes*, are thought to form as the result of dehiscences in the inner limiting membrane, allowing retinal glial cells access to the retinal surface. The cells proliferate and form a membranous sheet, which contracts. A second possible mechanism of preretinal membrane formation involves contraction of vitreous cortex and proliferation of hyalocytes on the inner retinal surface (see Chapter 14). After a posterior vitreous detachment, this process may result in a contractile membrane that can cause retinal folding.[55,56]

Retinal folds can occur from distant points as a result of traction from peripheral granulomas in toxocariasis[57,58] or with peripheral areas of fibrovascular proliferation as in retinopathy of prematurity. In addition, choroidal neovascular membranes can cause retinal strial.

Linear or Curvilinear Streaks Observed in the Subretinal Space

Why Should Subretinal Proliferative Vitreoretinopathy Be Considered in the Differential of Linear Streaks?

When proliferative vitreoretinopathy develops in the subretinal space, the result is often development of a fibrous band. These bands may develop into linear structures, forcing the retina to drape over any elevated portion, much like a sheet drapes over a clothesline.[59]

Linear or Curvilinear Streaks Observed in the Retinal Pigment Epithelium or Bruch Membrane

What Are Angioid Streaks?

Angioid streaks are abnormal linear findings seen on fundus examination that may be associated with significant vision-threatening complications as well as significant systemic disease. These streaks offer a sometimes striking finding for the ophthalmologist and usually appear reddish brown and extend in a branching pattern for varying distances across the fundus. Angioid streaks are pigmented linear crack-like defects in the collagenous and elastic layers of the Bruch membrane,[60] and they radiate away from the optic nerve. These streaks are named *angioid* because of their resemblance to vessels; however, these streaks do not follow the retinal or choroidal vasculatures. These streaks have variable appearance on both fundus examination and angiography. Clinical examination can show a range of findings from subtle pigmentary change to more dramatic large branching bands. In the peripapillary area, the streaks can branch into circumlinear cracks that connect streaks. Streaks are variably seen with fluorescein angiography. In some cases where streaks are minimally evident with fluorescein angiography, infrared indocyanine green angiography can aid in the identification of streaks, whereas in other cases it does not.[61] In some cases of angioid streaks, a peau d'orange appearance occurs in the midperipheral fundus. The appearance results from multiple degenerative yellowish deposits in a

mottled RPE. Histologically, calcific degeneration of the Bruch membrane often is seen along the streaks.[62–65]

Complications of angioid streaks result from the defects in Bruch membrane. These include subretinal or sub-RPE exudation that can decrease vision. This exudation can result from choroidal neovascular (CNV) vessels into the subretinal space. Many of the CNV vessels in this disease are type 2 CNV that can become pigmented with proliferating pigmented epithelium cells and can be visualized on clinical inspection, although occult CNV can occur. Subretinal exudation also can occur from rupture of choroidal tissue along the angioid streak. This can occur with relatively insignificant trauma, and patients should warned of this possibility.[66] Fluorescein angiography can help identify CNV associated with angioid streaks. Laser photocoagulation can be used to treat CNV if the vessels spare the foveal avascular zone. The Bruch membrane in patients with angioid streaks can be regarded as brittle and prone to further defects and recurrent CNV membranes after laser therapy. If there is a CNV present, photodynamic therapy with intravenous injection of a photosensitive dye and a diffuse retinal laser application shows promise in the treatment of the type 2 CNV associated with angioid streaks.[67] If a CNV is not present, spontaneous regression of the subretinal exudate is more likely.

Angioid streaks may occur in association with a variety of systemic illnesses in addition to idiopathic cases and age-related degeneration of the Bruch membrane. In one study of the cause of angioid streaks, 50 consecutive patients underwent diagnostic workup; 25 patients (50%) demonstrated one of the disease associations listed subsequently.[68] For the patient, loss of vision with subretinal exudation can be the first significant manifestation of these diseases. An inspection of associated physical findings, history, and review of systems should be undertaken in cases when the cause is unknown. The presence of extracellular matrix changes present in pseudoxanthoma elasticum, Paget disease, and Ehlers-Danlos syndrome results in defects in the Bruch membrane and other tissues. In sickle cell disease, calcific accumulation at the levels of the Bruch membrane are thought to result from excessive breakdown of red blood cells and hemoglobin.[69,70] Related mechanisms of angioid streaks probably account for the association of angioid streaks with beta-thalassemia, hemoglobin H disease, hemoglobin C disease, hereditary spherocytosis, and abetalipoproteinemia.

Of the connective tissue diseases associated with angioid streaks, pseudoxanthoma elasticum is the most common. This disease is named for the skin changes that occur with confluent yellowish papules that gives the skin a "plucked chicken" appearance. This can be seen particularly in the antecubital fossae, neck, and periumbilical areas.[71–74] Vascular changes can cause gastrointestinal bleeding and calcification of larger arteries. Eye findings include orangish mottling of the RPE called peau d'orange for its orange-peel appearance and atrophic lesions from alterations in the pigmented epithelium,[75,76] hyaline drusen of the optic nerve,[77] crystalline bodies in the RPE,[78] and pattern dystrophy-like changes in the macula.[79] Inheritance is either autosomal dominant or recessive.

In the case of Ehlers–Danlos, abnormal skin findings with "webbing" of the neck can be seen. Associated eye findings variably include blue sclera and corneal ectasia. Paget disease can be a disfiguring disease with variable thickening and deformity of bones. When the disease is more generalized with skull involvement and hearing loss, angioid streaks are more commonly seen. Peau d'orange can be seen in the midperipheral fundus as in pseudoxanthoma elasticum and sickle cell disease.

What Findings Are Associated with Choroidal Rupture?

Traumatic disruption of the choroids, Bruch membrane, and RPE can result in curvilinear yellow streaks in the posterior pole. These streaks have tapered, pointed ends and are usually concentric to the optic nerve. Although in most cases a recent history of significant ocular trauma is obvious, in some cases, such as in the presence of angioid streaks, relatively minor trauma can result in choroidal rupture.[80] In most cases, acute hemorrhagic detachment of the retina obscures a portion of the choroidal and RPE rupture. Retinal changes with Berlin edema may occur initially as a result of trauma and then resolve with time. Fluorescein angiography can evaluate the extent of choroidal and RPE defects obscured by thin hemorrhage. With fluorescein angiography, larger choroidal vessels sometimes can be seen crossing the defect. Spontaneous resolution of the detachment can occur, leaving the appearance of the streaks and various RPE changes. Decreased vision can result despite resolution of the hemorrhage with hemoglobin-induced neuronal degeneration. Traumatic optic neuropathy can result in additional vision loss following trauma, with visual field defects greater than the area of hemorrhagic retina detachment. Choroidal neovascularization can develop through the defect in the RPE, resulting in the delayed reappearance of retinal exudative detachment. Treatment of CNV resulting from choroidal rupture can include focal laser photocoagulation if the fovea remains untreated. Displacement of subretinal hemorrhage with vitrectomy and

pneumatic retinopexy with a meticulous (filtered room air) air–fluid exchange and face-down positioning can allow visualization for laser and can limit irreversible damage to retinal neurons resulting from hemoglobin.

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12

Hemorrhage

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The presence of hemorrhage in the posterior segment may cause significant visual disturbance and may signify a serious ocular or systemic abnormality. For this reason, accurate diagnosis and appropriate care for the patient with hemorrhage of the posterior segment require a thorough medical history, review of systems, and careful and complete examination of both eyes. The clinical entities discussed in this chapter are common and important conditions most likely to be encountered in daily practice. The guidelines provided are intended as a framework for clinical evaluation and therapeutic considerations to be thought out carefully in the context of the individual patient.

Vitreous Hemorrhage

What Are the Sources of Vitreous Hemorrhage?

Blood in the vitreous cavity may be as mild as a suspension of pigmented cells or as severe as to cause complete obscuration of any fundus detail. The source of the blood can be (1) subretinal vessels (e.g., from choroidal neovascularization in age-related macular degeneration or from a choroidal tumor); (2) an avulsed, native retinal blood vessel (e.g., caused by a retinal break or direct trauma); or (3) fragile, proliferative preretinal new vessels.

Vitreous hemorrhage most often stems from bleeding from an area of preretinal or intraretinal neovascularization (Table 12–1). This neovascularization is most commonly seen as a sequela of diabetic retinopathy or retinal occlusive disease (see later discussion) but may occur as part of the body's compensatory response to any condition that produces retinal ischemia. Careful funduscopy often reveals the source of the bleeding, but in cases of dense vitreous hemorrhage, B-scan ultrasonography is valuable for visualizing the posterior segment. Ultrasound examination may disclose a retinal break, retinal detachment, or retinal or choroidal mass, or an elevated area of neovascularization. Treatment and timing of treatment are determined by the underlying condition causing the vitreous hemorrhage as well as by the patient's level of functioning and systemic health.

Terson Syndrome

Terson syndrome is the term used to describe the specific association of intracranial and vitreous hemorrhages[1] and has been found to occur in 3 to 8% of patients with subarachnoid hemorrhage.[2–4] Some type of intraocular hemorrhage (subretinal, intraretinal, preretinal, or vitreous) may be seen in up to 20% of patients with subarachnoid or subdural hemorrhage.[2,5]

The exact pathogenesis of Terson syndrome is still unknown. It is thought that intracranial hemorrhage leads to increased intracranial pressure, which is transmitted along the subdural space of the optic nerve. This acute rise in intraocular pressure in turn causes compression of the central retinal vein and blockage of retinal venous outflow, which leads to rupture of retinal capillaries.[6] Typically, multiple blot-shaped retinal hemorrhages are seen in the peripapillary and macular regions. Larger areas of hemorrhage beneath the internal limiting membrane or posterior hyaloid face, sometimes assuming an elevated or dome-shaped appearance, also may occur. Vitreous hemorrhage may be dense enough to obscure visualization of the posterior pole.

The presence of intraocular hemorrhages may have prognostic as well as diagnostic value. In one retrospective study of 320 patients with subarachnoid hemorrhage, those with associated intraocular hemorrhage had a significantly higher mortality rate (53.6%) than those without intraocular hemorrhage (19.7%).[5] Although mortality rates have diminished substantially in the 25 years since publication of that study, it remains likely that intraocular hemorrhage correlates

TABLE 12-1. Conditions Causing Retinal Neovascularization

Systemic diseases
Diabetic mellitus
Hemoglobinopathies
Sarcoidosis
Ocular ischemic syndrome
Hyperviscosity syndromes
Incontinentia pigmenti
Systemic lupus erythematosus
Antiphospholipid antibody syndrome
Retinal vascular diseases
Venous occlusion
Arterial occlusion
Radiation retinopathy
HIV retinopathy
Retinopathy of prematurity
Intraocular inflammation
Uveitis
Pars planitis
Eales disease
Behçet disease
Bird-shot chorioretinopathy
Acute retinal necrosis
Toxoplasmosis
Neoplasms
Choroidal melanoma
Choroidal hemangioma
Inherited retinal conditions
Familial exudative vitreoretinopathy
Retinitis pigmentosa
X-linked juvenile retinoschisis

HIV, human immunodeficiency virus.

with the severity of injury. In a recent prospective series of 100 patients with subarachnoid hemorrhage, patients with intraocular hemorrhage were much more likely to have experienced coma than those without ocular involvement (89% versus 46%).[2]

How Is Terson Syndrome Managed?

In most cases, these hemorrhages clear spontaneously, albeit slowly. Vitreous hemorrhage usually clears within 1 year but may remain for as long as 6 years.[7,8] Schultz and colleagues reported final visual acuity of 20/50 or better in 12 of 16 patients managed with observation alone.[8] The main complication following spontaneous clearing is epiretinal membrane formation, but cataract, macular pigmentary changes, retinal detachment, and proliferative vitreoretinopathy also have been reported.[9–11]

Vitrectomy has been successful in removing vitreous hemorrhage and accelerating visual recovery in patients with Terson syndrome, even in patients with initially dense hemorrhages.[2,12] Kuhn and colleagues reported on their results of vitrectomy performed as early as 1 month, and as late as 30 months following diagnosis of Terson syndrome. Vision was 20/30 or better in 21 of 26 eyes (81%) of adult patients. None of the seven eyes of five children, however, achieved vision of better than 20/60.[2] Whereas this worse result in children (four of whom were under 1 year of age) may have been a result of associated brain injury, earlier intervention should be considered in children for the prevention of deprivational amblyopia.

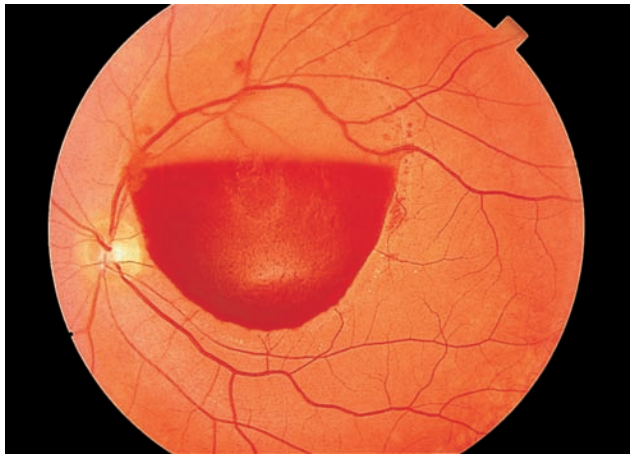

FIGURE 12–1. Valsalva retinopathy. A boat-shaped retinal hemorrhage is present, presumably located under the internal limiting membrane of the retina. (Courtesy of William Tasman, M.D.)

Valsalva Retinopathy

Activities such as lifting, straining, coughing, vomiting, childbirth, or similar exertion cause a sudden rise in intraabdominal or intrathoracic pressure (Valsalva maneuver). The concomitant acute elevation in ocular venous pressure may precipitate rupture of superficial retinal capillaries (termed *Valsalva retinopathy*).

The typical ophthalmoscopic finding is of one or more well-circumscribed, round or dumbbell-shaped hemorrhages beneath the posterior hyaloid or internal limiting membrane (ILM) within the macula of one eye (Fig. 12–1). Overlying striae, representing wrinkling of the ILM, also may be seen. Sudden and dramatic loss of vision is often caused by hemorrhagic detachment of the ILM, vitreous hemorrhage, or hemorrhage in the fovea.[1,13]

How Is Valsalva Retinopathy Managed?

The hemorrhages of Valsalva retinopathy typically resolve spontaneously over several weeks, with accompanying return of vision. In rare cases in which vision or physical function is impaired as a result of macular subhyaloid hemorrhage, blood may be drained into the vitreous by neodymium:yttrium-aluminum-garnet (Nd:YAG) laser disruption of the posterior hyaloid face.[14] The chance of complications of the procedure,

particularly macular hole and retinal detachment, must be considered seriously, however, if such a procedure is contemplated.[14]

Retinal Hemorrhage

What are the features that aid in the diagnosis of retinal hemorrhage? In the evaluation of retinal hemorrhage, various clinical features will aid in the formulation of a differential diagnosis (Fig. 12–2):

1. Topographical location (macular, posterior pole, anterior)
2. Intraretinal location (superficial, deep, or mixed) (Fig. 12–3)
3. Spatial distribution (sectorial or diffuse, unilateral or bilateral)
4. Number (few or multiple)
5. Shape and appearance (flame-shaped, dot/blot, white-centered, circumscribed, or irregular)
6. Appearance of vasculature (venous tortuosity or dilatation, arteriolar attenuation, sheathing, aneurysmal changes)
7. Associated ocular signs (anterior chamber reaction, vitreitis, papillitis, nerve fiber layer infarcts)

Diabetic Retinopathy

Diabetic retinopathy remains one of the leading causes of blindness in the United States. Large-scale epidemiologic studies have elucidated the natural history, prevalence, and progression of retinopathy and other ocular complications of diabetes, and randomized clinical trials have outlined recommendations for therapy (Fig. 12–4). Regular examination and timely treatment remain essential to preservation of vision for patients with diabetes.

What Are the Important Points Regarding the Epidemiology and Pathogenesis of Diabetic Retinopathy?

Microangiopathy is the fundamental abnormality in diabetic retinopathy. Disturbances in capillary function lead to retinal nonperfusion, which in turn leads to retinal ischemia. Elaboration of vasoproliferative factors (among them vascular endothelial growth factor, or VEGF)[15] induces proliferation of new blood vessels on the retina and optic nerve (proliferative diabetic retinopathy, or PDR), with subsequent contraction of these fibrovascular proliferations.[16]

The risk of developing retinopathy is directly related to the duration of disease and the extent of hyperglycemia.[17,18] In patients with the onset of type 1 insulin-dependent diabetes mellitus before the age of 30 years, few will show any change within 5 years of diagnosis. After 20 years, however, nearly all will have some retinopathy, and roughly half will have proliferative disease.[19] Among patients who are older than 30 at diagnosis, 67% will have some retinopathy after 10 years, and 10% will have proliferative change.[20] The risk of retinopathy in these patients is correlated with the requirement for insulin.

What Are the Clinical Features of Diabetic Retinopathy?

The initial ophthalmoscopic findings (nonproliferative, or background, retinopathy) are microaneurysms, which appear as minute red dots in the inner and middle retinal layers. Accompanying dot and blot hemorrhages (located in the outer plexiform and inner nuclear layers of the retina) may be indistinguishable from microaneurysms. Patent microaneurysms may be identified by fluorescein angiography because they leak fluorescein dye (Fig. 12–5). An increase in the number of microaneurysms may be an early sign of progression of diabetic retinopathy.[21] Klein and colleagues reported that patients with an increased ratio of microaneurysms at 4-year follow-up compared with baseline (greater than 3:1) were at three times greater risk for development of PDR by 10-year follow-up than patients with smaller change.[22]

The vascular permeability that accompanies microaneurysmal change allows leakage of fluid into the intercellular spaces of the retina. Clinically, this leakage appears as thickening of the retina and is appreciated biomicroscopically as decreased translucency of the retina and blurring of the normal background choroidal pattern. Lipid exudation may accumulate in the areas of leakage, often forming a ring around the leaking microaneurysms.[23] When such intraretinal edema occurs in the macula, vision is often affected. Macular edema is an important manifestation of nonproliferative diabetic retinopathy (NPDR) and is the leading cause of legal blindness among diabetic patients.

With worsening diabetes, the inner retina becomes more ischemic, with increases in hemorrhages, nerve fiber layer infarcts, and areas of capillary nonperfusion. Venous beading (focal dilatations likely representing areas of poor circulation) develops, along with intraretinal microvascular abnormalities (IRMAs, which are flat, dilated capillary channels that may serve as collateral circulation). IRMAs often resemble surface retinal neovascularization; angiographically, however, IRMAs retain fluorescein dye, whereas neo-

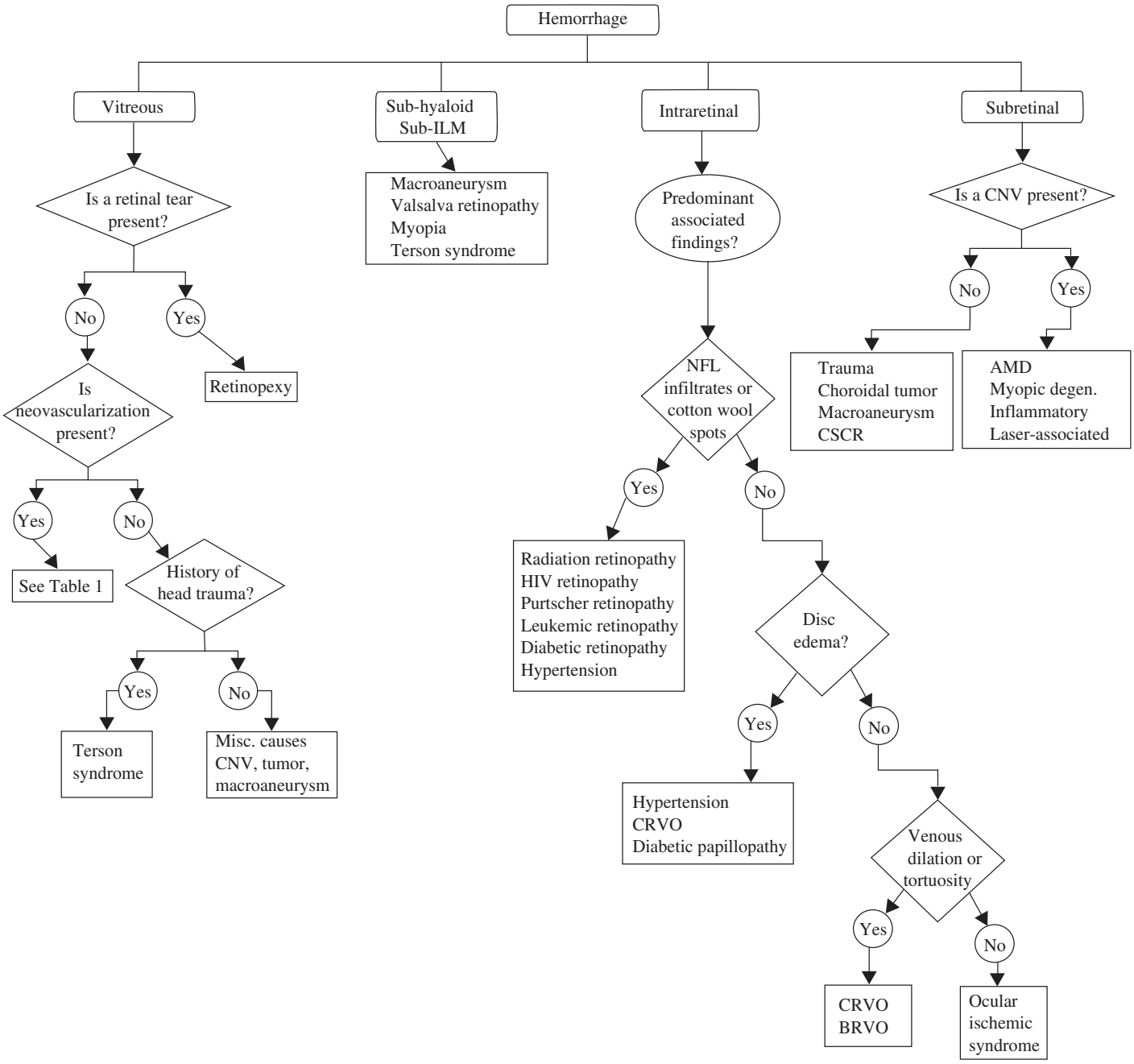

FIGURE 12–2. Diagnostic evaluation of hemorrhage of the posterior segment. ILM, internal limiting membrane; CNV, choroidal neovascularization; AMD, age-related macular degeneration; CSCR, central serous chorioretinopathy; CRVO/BRVO, central/branch retinal vein occlusion; NFL, nerve fiber layer.

vascularization leaks dye profusely. Advanced NPDR was defined by investigators in the Early Treatment Diabetic Retinopathy Study (ETDRS) as intraretinal hemorrhages in four quadrants, venous beading in two or more quadrants, or IRMA in one or more quadrants (the so-called 4:2:1 rule). The presence of one or more of these clinical signs was highly predictive of progression to PDR within 1 year.[24]

According to the ETDRS, nearly 50% of patients with very advanced NPDR (with two or more signs of the 4:2:1 rule present) developed PDR after one year.[24] Proliferative blood vessels tend to arise in the posterior pole in areas of severe retinal ischemia. When they arise at or within one disc diameter (1 DD) of the optic nerve, they are referred to as *neovascularization of the disc* (NVD). When they arise more than 1DD away

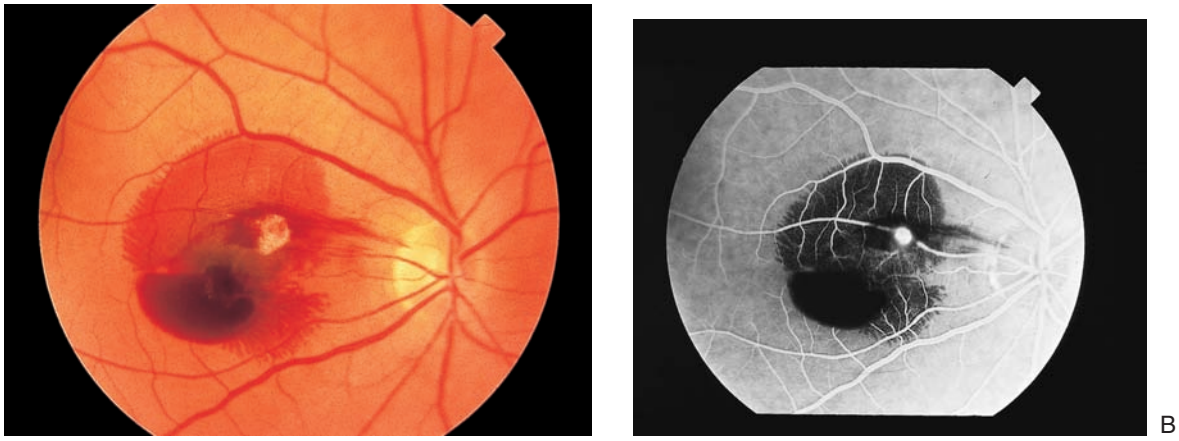

FIGURE 12–3. (A). Retinal arterial macroaneurysm with subretinal hemorrhage in the superior macular and a boat-shaped subhyaloid hemorrhage in the inferior macula. (B). Fluorescein angiogram at 23 seconds after injection. The macroaneurysm appears as a hyperfluorescent focus along a retinal artery. Retinal vessels are visible overlying the subretinal blood but are obscured inferiorly by the subhyaloid blood.

from the disc, they are termed *neovascularization elsewhere* (NVE).[24] These vessels grow more easily along a "scaffold" of connective tissue, such as the posterior hyaloid face, and may be pulled into the vitreous cavity. The new vessels gradually become surrounded with fibrovascular tissue. Vitreous contraction, coupled with intrinsic contraction from fibrovascular proliferation, transmits tension along the fragile new blood vessels, resulting in vitreous hemorrhage.[16] Tension along the retina may result in tractional retinal detachment.

Vitreous hemorrhage often occurs during sleep, possibly as a result of rapid eye movement, and is seldom induced by exercise.[25] If erythrocytes enter the vitreous cavity and become invested within the gel, they may take months to years to clear spontaneously. Superficial hemorrhages beneath the ILM may be seen as round, oval, or "boat-shaped" patches of bright red blood that obscure vessel detail. Tight sub-ILM hemorrhages may progress rapidly to tractional retinal detachment.

What Are the Relevant Issues Regarding Medical Management of Diabetic Retinopathy?

The most effective method for preventing diabetic retinopathy remains regular funduscopic examination and tight control of blood glucose. In a study of 1441 patients with type 1 diabetes mellitus in the Diabetes Control and Complication Trial (DCCT), those treated with "intensive" glycemic control (frequent monitoring to achieve a mean hemoglobin A_1C of 7.2) suffered significantly less progression in retinopathy and nephropathy than those treated "conventionally" (hemoglobin A_1C of 9.1).[26,27] These effects have remained after 10 years of follow-up.[28] Patients with good glycemic control and shorter duration of disease at baseline had the best prognosis. Whereas up to 13% of patients showed initial worsening of their retinopathy after 12 months of intensive therapy, recovery was achieved soon thereafter and the ultimate reduction in long-term risk remained significant.[29]

Reduction in blood pressure with the angiotensin-converting enzyme inhibitor lisinopril, even in normotensive patients with type 1 diabetes, slows progression of retinopathy.[30] Captopril and atenolol (a beta-receptor antagonist) appear to work equally well.[31] According to the ETDRS, treatment with aspirin did not affect the progression of retinopathy, visual loss, or risk of vitreous hemorrhage, but it did reduce morbidity and death from cardiovascular disease by 17%.[32,33] Because diabetic patients with high levels of cholesterol and lipids have higher risks of both PDR and macular edema from retinal exudation,[23] treatment of hyperlipidemia may be advisable. Clinical trials of drugs targeting angiogenic factors (i.e., VEGF, growth hormone) are also under way.[34,35]

When and in What Way Is Intervention with Laser Photocoagulation Appropriate for Diabetic Retinopathy?

Following its introduction in the late 1950s, laser energy was used to coagulate areas of blood vessels on the surface of the retina[36] and was found to have a beneficial effect on retinal neovascularization and macular edema. Data from the Diabetic Retinopathy Study (DRS), a multicenter trial of 1742 patients, iden-

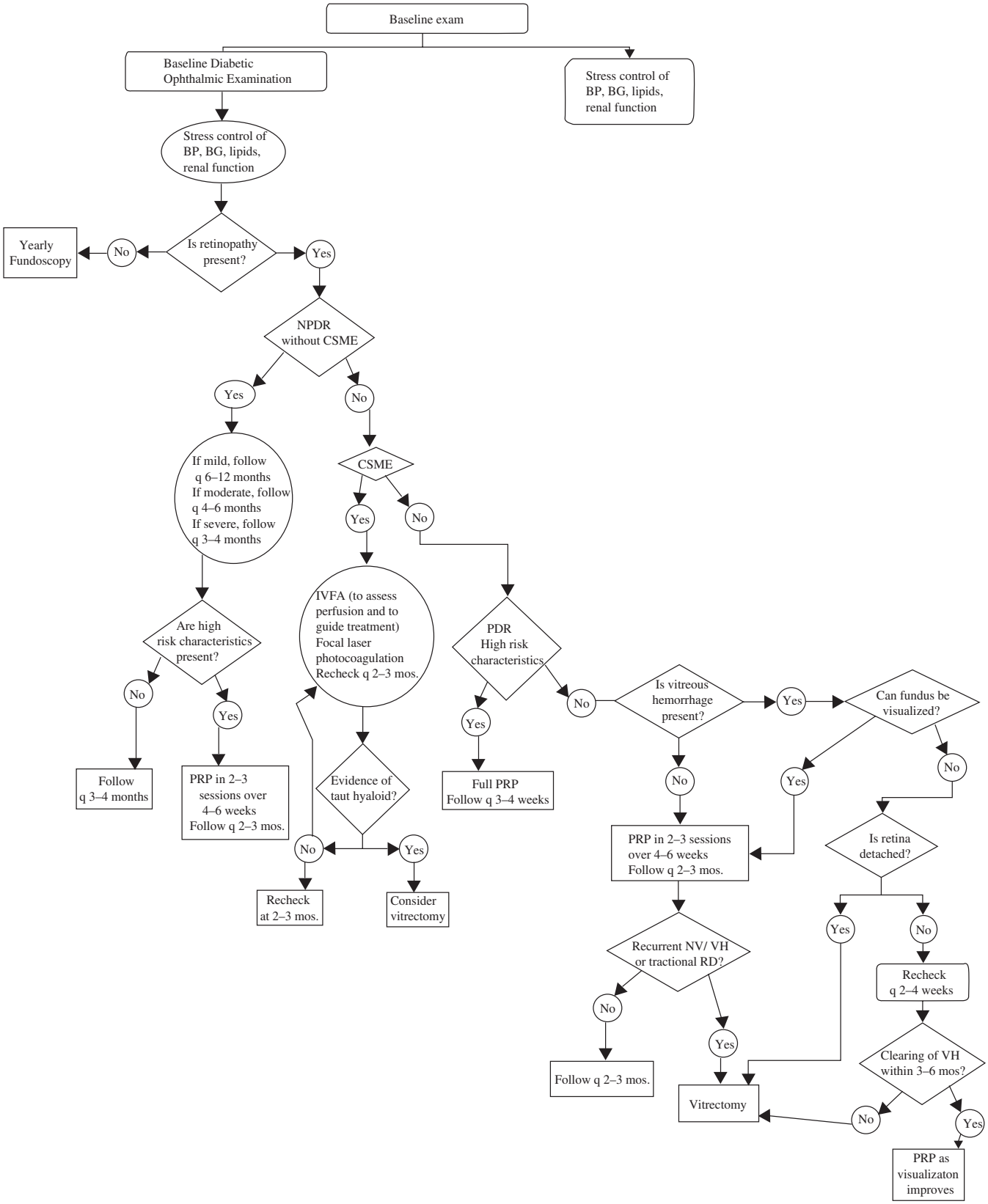

FIGURE 12–4. Ophthalmic management guidelines of the patient with diabetes mellitus. BP, blood pressure; BG, blood glucose; NPDR, nonproliferative diabetic retinopathy; CSME, clinically significant macular edema; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; NVI, neovascularization of the iris; NV, neovascularization; VH, vitreous hemorrhage; RD, retinal detachment.

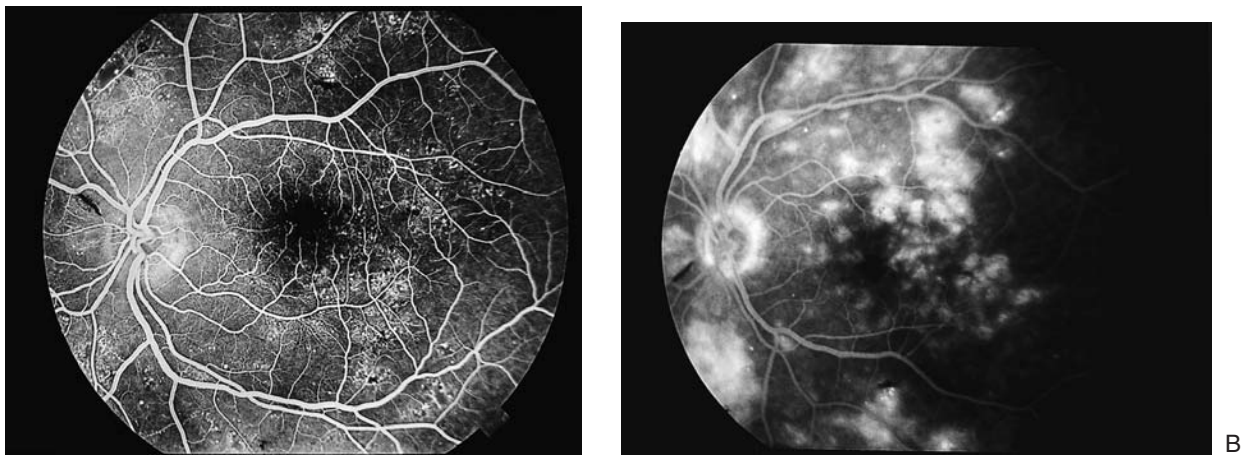

FIGURE 12–5. (A). Background (nonproliferative) diabetic retinopathy; fluorescein angiogram 17 seconds after injection. The retinal hemorrhages block the background choroidal fluorescence, but the numerous microaneurysms appear as multiple small hyperfluorescent foci. (B). Fluorescein angiogram 298 seconds after injection reveals intraretinal leakage of dye, primarily from the microaneurysms, in this eye with macular edema.

tified characteristics associated with a particularly high risk of visual loss (defined as 5/200). These so-called high-risk characteristics are NVD greater than one third disc area, any NVD with vitreous hemorrhage, and one half disc area of NVE associated with vitreous or preretinal hemorrhage.[37] The goal of panretinal photocoagulation (PRP) is to arrest retinal neovascularization and prevent visual loss. Treatment with xenon-arc or argon-laser PRP reduced the risk of severe visual loss by 50%.[37] The current standard of PRP uses 1200 to 2000 spots of argon green or blue green laser burns, 500 μm in width, of intensity sufficient to lightly whiten the overlying retina.

The ETDRS established that focal macular laser photocoagulation is effective in slowing progression of visual decline in patients with clinically significant macular edema (CSME). CSME was defined as retinal thickening involving the macula, hard exudates within 500 μm of the fovea if associated with retinal thickening, or an area of macular edema greater than one disc area but within 1 DD of the fovea. The goal of treatment is to treat all leaking microaneurysms 500 μm or greater from the center of the macula.[38,39] Alternatively, grid treatment to areas of diffuse capillary nonperfusion may be applied. Patients with macular edema with the best visual prognosis following focal treatment have circinate retinopathy of recent duration and good macular perfusion. Poorer prognosis is associated with foveal lipid exudation, diffuse edema, widespread nonperfusion, and systemic hypertension.[40]

Under What Conditions Should Vitrectomy Be Considered for Diabetic Retinopathy?

The main indications for surgical treatment of diabetic retinopathy include vitreous hemorrhage, retinal detachment, and intractable macular edema resulting from a taut posterior hyaloid face.[41,42] In the Diabetic Retinopathy Vitrectomy Study (DRVS), the efficacy of immediate vitrectomy, deferred vitrectomy, and observation in diabetic patients were analyzed in a randomized, prospective fashion.[41,43–45] On the basis of the DRVS reports, the following recommendations may be made:

1. The decision for vitrectomy must be weighed seriously, as 25% of patients who underwent immediate vitrectomy had a final visual acuity of no light perception.
2. Patients with moderate to advanced PDR and useful vision (defined as 10/200 or better) are more likely to benefit from early vitrectomy. This advantage was most clear-cut for patients with type I diabetes.
3. Patients with PDR and vitreous hemorrhage reducing vision to 5/200 or worse are more likely to regain vision (20/40 or better) with immediate vitrectomy (25% versus 15%). This advantage was again more pronounced for Type I diabetics (36% versus 12%).

In a recent study of patients with persistent macular edema unresponsive to laser photocoagulation, vitrectomy with stripping of the premacular posterior hyaloid face improved vision by at least two lines in half of the patients.[42] Vitrectomy remains a valuable therapeutic modality for preservation of vision in patients with end-stage diabetic retinopathy. Furthermore, clinical utility analysis has shown early vitrectomy in appropriate situations both to improve quality of life and to be highly cost-effective.[46]

Retinal Occlusive Disease

Occlusions of the retinal venous and arterial circulations are a significant cause of visual morbidity and may be associated with serious or even life-threatening systemic conditions (Fig. 12–6). Because such patients often present with abrupt visual changes, recognition of retinal occlusive disorders by the ophthalmologist and referral for appropriate medical evaluation are essential.

Central Retinal Vein Occlusion

The typical appearance of central retinal vein occlusion (CRVO) includes intraretinal hemorrhages in all four quadrants, optic disc edema, and dilation and tortuosity of the retinal venous system. Hemorrhages are clustered in the posterior pole and often are accompanied by nerve-fiber layer infarctions ("cotton-wool spots") and macular edema.[47,48] The occlusion is thought to arise from thrombus formation at the lamina cribrosa.[49]

What Are the Important Clinical and Epidemiologic Aspects of Central Retinal Vein Occlusion?

Central retinal vein occlusion can affect patients from 9 months to 92 years of age, but it occurs most often in patients 60 years or older; fewer than one sixth are under 45 years of age. Men are affected more commonly than women.[50–52]

On the basis of clinical and fluorescein angiographic features, two forms of CRVO have been identified.[47] This distinction is important because of the significant difference in visual prognosis, management, and patient counseling. The more severe, "ischemic" form (also termed complete, nonperfused, or hemorrhagic retinopathy) is characterized by poorer vision at presentation, copious intraretinal hemorrhages and nerve-fiber layer infarcts, electroretinographic abnormalities, and extensive capillary nonperfusion (more than 10 disc areas of capillary nonperfusion by fluorescein angiography) (Fig. 12–7). The milder, "nonischemic" form (also termed incomplete, perfused, or venous stasis retinopathy) generally presents with better vision and less widespread ischemia (Fig. 12–8). Patients with nonischemic CRVO have better visual prognosis and are less likely to develop intraocular neovascularization and neovascular glaucoma, a dreaded complication of retinal occlusive disease.[50,53,54]

Several case–control studies have identified a profile of risk factors, especially in older patients, similar to that seen in cardiovascular disease. CRVO is associated with systemic arterial hypertension, electrocardiographic abnormalities, diabetes mellitus, peptic ulcer disease, and thyroid disease.[51,55,56] Because there is often a history of glaucoma or ocular hypertension, *both* eyes should be examined carefully.[51,57]

What Is the Prognosis, and What Are the Management Options for Central Retinal Vein Occlusion?

Neovascular glaucoma has been recognized as a complication of CRVO for nearly a century. Numerous researchers have concluded that the risk of neovascularization is directly related to the extent of retinal ischemia.[53,54,58] Neovascularization is thought to be induced by increased levels of angiogenic factors (among them, VEGF) in the vitreous cavity and anterior chamber of eyes that have suffered ischemic injury.[15]

The Central Vein Occlusion Study (CVOS) was a prospective, multicenter clinical trial with several aims: (1) to describe the natural history of CRVO and to identify risk factors for development of intraocular neovascularization and vision loss; (2) to evaluate the efficacy and timing of PRP for the prevention of anterior segment neovascularization in cases of ischemic CRVO; and (3) to evaluate the efficacy of macular grid photocoagulation for visual improvement in patients with chronic macular edema.

In the CVOS, initial vision was a strong predictor of final vision as well as risk of neovascularization. Sixty-five percent of patients with initial vision of 20/40 or better maintained vision in that range, whereas patients with presenting vision of 20/200 or worse had only a 20% chance of visual improvement. Neovascularization of the iris (NVI) or of the iridocorneal angle (NVA) developed in 10% of eyes initially classified as "perfused" or nonischemic (fewer than 10 disc areas of capillary nonperfusion). By contrast, NVA/NVI developed in 35% of nonperfused ("ischemic") eyes within 3 months. Fewer than 5% of patients with initial vision of 20/40 or better developed neovascularization.[47,50]

On the basis of the CVOS findings, several recommendations can be made:[47,50,59,60]

1. The extent of retinal ischemia (capillary nonperfusion demonstrated by fluorescein angiography) and the patient's risk for developing neovascularization should be established; patients in whom fluorescein angiography is impossible should be treated as if they were ischemic.
2. All patients with ischemic CRVO and those at high risk for conversion to ischemic status should be followed up monthly for 6 months with undilated slit-lamp biomicroscopy, gonioscopy, and dilated funduscopy.
3. Patients with initial visual acuity of 20/40 or better are less likely to develop neovascularization

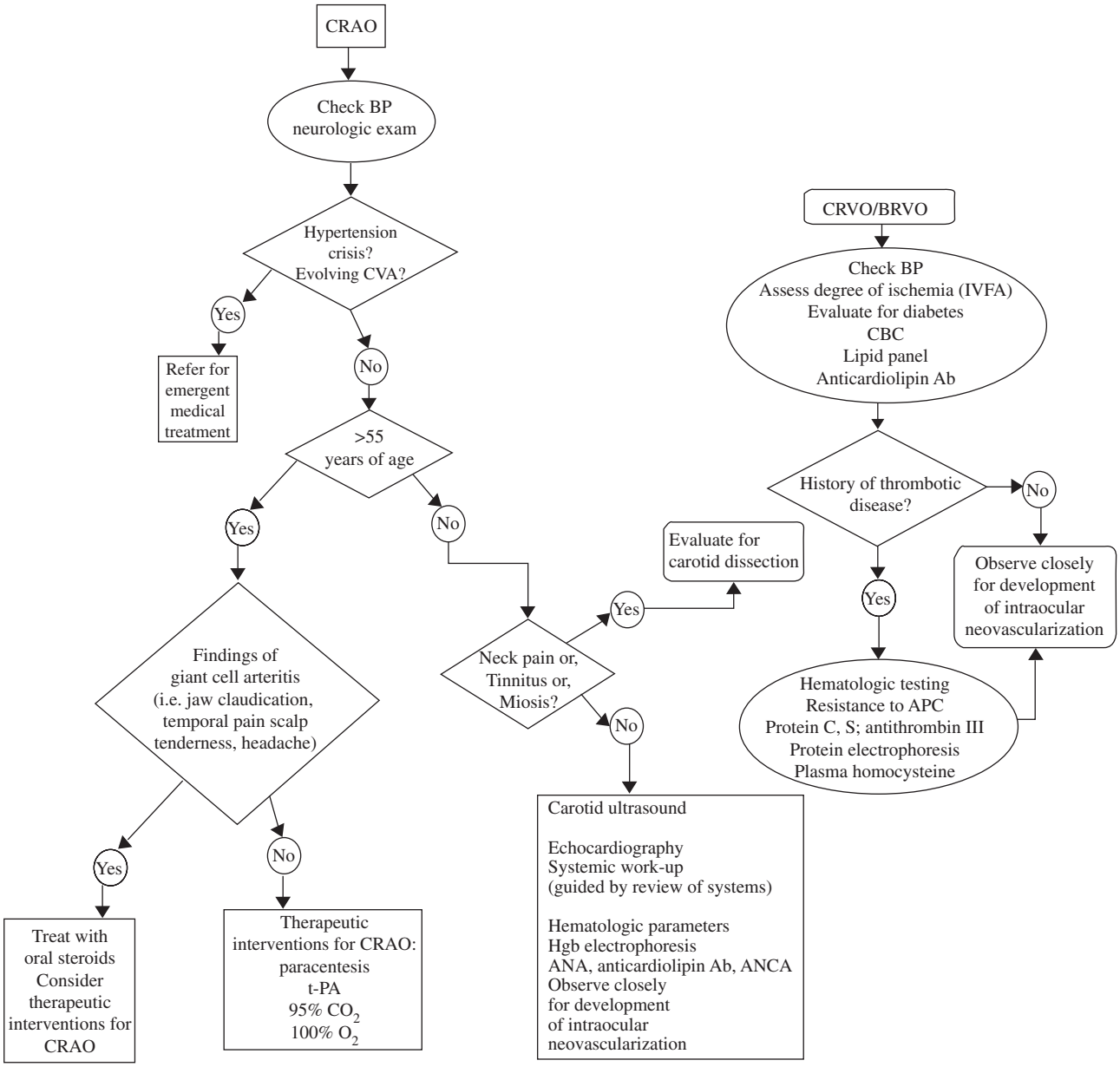

FIGURE 12–6. Evaluation and initial management of acute retinal vascular occlusion. CRAO, central retinal artery occlusion; CVA, cerebrovascular accident; CBC, complete blood count; t-PA, tissue plasminogen activator; APC, activated protein C; ANA, antinuclear antibody; BRVO, branch retinal vein occlusion; Ab, antibodies; ANCA, anti-neutrothir cytoplasmic antibodies; IVFA, intravenous fluorescein angiography.

and may be followed up every 1 to 2 months for the first 6 months and at longer intervals thereafter if stable.

4. PRP should be applied when two clock hours of NVI or any NVA develops. Treatment in the CVOS consists of 1000 to 2000 spots of argon-green or blue green laser (500- to 1000-μm spot size, 0.2 seconds in duration, spaced 0.5 to 1 burn-width apart, to produce a medium-white burn at the level of the retinal pigment epithelium, or RPE). PRP may be supplemented if neovascularization persists.
5. In patients younger than 60 years with vision of 20/50 or worse and good macular perfusion, grid photocoagulation may be considered. A trend toward visual improvement was seen in this subgroup of patients but because of small sample size did not achieve statistical significance.

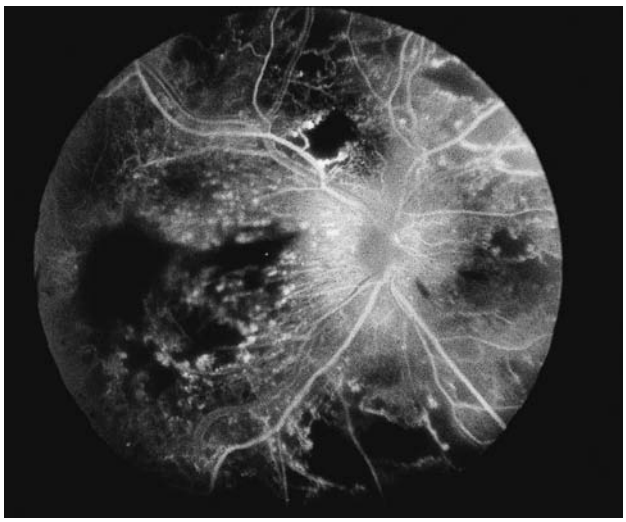

FIGURE 12–7. Ischemic central retinal vein occlusion. Fluorescein angiogram reveals multiple areas of gray/black retinal capillary nonperfusion.

What Newer Therapeutic Modalities Are Available for Central Retinal Vein Occlusion?

It has been noted that, during evolution of nonischemic CRVO, cilioretinal shunts may form in a compensatory attempt to bypass the thrombosis and allow blood to exit the retinal circulation via the choroid. McAllister and Constable first reported on the use of laser to create an anastomosis between the retinal venous and choroidal circulations. In their first series of 24 patients with nonischemic CRVO, successful anastomosis and improvement in visual acuity were achieved in one third of the patients.[61] In a follow-up study of 91 patients, in which the technique was modified, the rate of success rose to 54%.[62] Other researchers have reported comparable results.[63] Vitreous, intraretinal, or subretinal hemorrhage may occur in up to 20% of patients.[62,64,65]

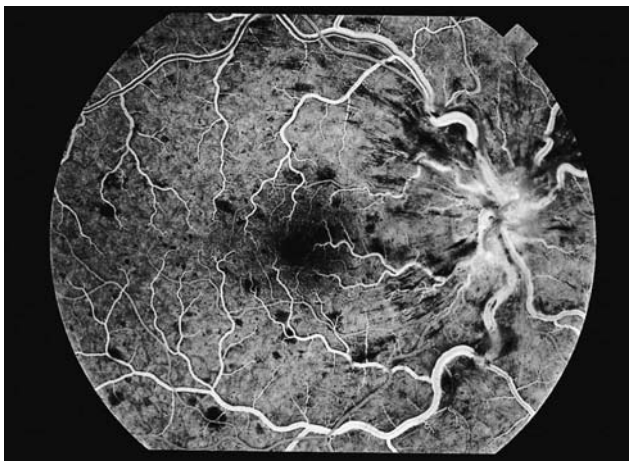

FIGURE 12–8. Nonischemic central retinal vein occlusion. Fluorescein angiogram reveals a perfused retinal capillary bed.

Additional techniques reported in small case series with modest successes include surgical creation of chorioretinal venous anastomosis,[66,67] the use of recombinant tissue plasminogen activator (either intravitreally[68] or deposited into a cannulated central retinal vein[69]), optic nerve sheath decompression, radial optic neurotomy and vitrectomy for treatment of macular edema.[70,71] Without a controlled, randomized trial, however, these preliminary successes may simply reflect spontaneous improvement.

Branch Retinal Vein Occlusion

Branch retinal vein occlusion (BRVO) is characterized by variable degrees of intraretinal hemorrhages, retinal edema, and nerve-fiber layer infarcts in a clearly identifiable sector of the retina. The extent of involvement corresponds to the area drained by a single, obstructed tributary of the central retinal vein.[72,73] The occlusion appears to be at an arteriovenous crossing, presumably because of compression of the vein by its adjacent, atherosclerotic arteriole.[74] Most BRVOs are diagnosed in the temporal retina, probably because of the increased number of arteriovenous crossings in that area or because visual symptoms resulting from macular involvement prompt patients to seek care.[72]

What Are the Epidemiology and Natural History of Branch Retinal Vein Occlusion?

The vast majority of affected patients are older than 50 years of age, and men are affected slightly more often than women. Systemic arterial hypertension is the risk factor most strongly associated with BRVO.[55,75] In white Americans, cerebrovascular disease, peptic ulcer disease, and thyroid disease appear to be associated as well.[56]

Hemorrhages may take 6 to 12 months to resolve, whereas retinal edema and nerve-fiber layer infarcts resolve more quickly. Roughly 50% of patients will recover visual acuity of 20/40 or better without treatment.[73,76,77] Neovascularization of the posterior segment is observed in about one fourth of patients. Clinically, this appears as fronds of fine, lacy blood vessels in the superficial retina and extending into the vitreous. New vessels may be located at the optic nerve head, at the border of perfused and nonperfused retina, and rarely in normal retina distant from the occlusion. In contrast to CRVO, neovascularization of the anterior segment and neovascular glaucoma are rare following BRVO (less than 2% in large

series).[53] The rate of occurrence of an occlusion in the fellow eye within 4 years of the first episode is 5 to 9%.[52,75]

What Are the Important Issues Regarding Management of Branch Retinal Vein Occlusion?

Two important vision-limiting complications of BRVO are macular edema and vitreous hemorrhage from posterior segment neovascularization. The Branch Vein Occlusion Study (BVOS) evaluated the efficacy of laser treatment to reduce visual debilitation associated with these events.[76,77]

On the basis of the BVOS, the following treatment guidelines can be made:

1. Vitreous hemorrhage should be allowed to clear sufficiently to permit adequate visualization and fluorescein angiography of the fundus.
2. Patients with vision better than 20/40 and no retinal neovascularization should be followed up every 4 to 6 months.
3. Patients with greater than five disc areas of capillary nonperfusion are at greater risk for neovascularization and should be evaluated every 2 to 4 months.
4. Patients who develop retinal neovascularization should be treated with scatter argon-laser photocoagulation of the involved retinal sector. Spots of 200 to 500 μ, of 0.1 to 0.2 seconds' duration, should be placed one burn width apart from the major arcades to the peripheral extent of nonperfusion.
5. In patients with BRVO of at least 3 months' duration and vision of 20/40 or worse, fluorescein angiography should be performed to evaluate macular perfusion:
   a. If visual decline is attributable to macular nonperfusion, observation alone is recommended because treatment will likely be of little benefit.
   b. If macular edema is present and appears to be the cause of visual decline, macular grid photocoagulation may be applied (100-μm spots, of 0.1-second duration, one burn width apart).

Pars plana vitrectomy and surgical lysis of the sheath ("sheathotomy") surrounding the arteriovenous crossing may relieve venous compression and reduce macular edema. In one prospective series of 15 patients, preoperative vision of 20/70 or worse was improved by an average of four lines in 10 patients.[78] The improvement may be long-standing. Shah and colleagues reported visual improvement (from 20/200 preoperatively to 20/30 to 20/70) in four of five patients followed for at least 5 years.[79]

Retinal Arterial Occlusion

Although typically not associated with hemorrhage, occlusion of the central retinal artery (CRAO) often gives rise to a bright red spot in the foveola, which may be confused with a dot hemorrhage. The retina is often diffusely whitened and swollen, especially in the macula. Because the retina overlying the foveola is thinner than in the neighboring perifoveal region, the underlying choroid and RPE are more visible, giving rise to the pathognomonic "cherry-red spot." Retinal arterioles are often attenuated, and, in about one fifth of cases of CRAO, a yellow-white, glistening embolus may be seen within the arterial circulation. Patients often report an acute and irreversible decline in vision, usually to the level of finger counting or hand motions. Central vision may be preserved, however, in about 10% of patients who retain foveolar perfusion via a cilioretinal artery.[80]

Occlusion of a branch of the central retinal artery (BRAO) will produce a sectorial pattern of retinal whitening in the area of circulatory compromise without hemorrhage. Visual acuity is usually 20/40 or better because the macula, although edematous, remains perfused. If hemorrhages are seen in association with a retinal arterial occlusion, one must consider a concomitant retinal venous occlusion or a systemic cause (e.g., hypertension, diabetes mellitus, anemia).

What Are Some Conditions Associated with Retinal Arterial Occlusion?

Several researchers have reported an increased incidence of cardiovascular disease, stroke, and mortality in patients with retinal arterial occlusions.[81,82] For this reason, systemic evaluation must include Doppler ultrasonography of the carotid circulation and echocardiography. Nearly one fifth of patients with acute RAO will have hemodynamically significant carotid stenosis warranting systemic anticoagulation or carotid endarterectomy.[83,84] Nearly one half will demonstrate echocardiographic abnormalities, and one tenth will require systemic treatment.[85,86] Numerous other conditions have been reported in association with RAO, among them coagulopathies, inflammation (particularly collagen vascular diseases), infection, and orbital trauma.[87] Often, an etiology can be ascertained by careful history, examination, and appropriate laboratory investigation.

Two conditions, although rare, merit special attention because of their potentially catastrophic threats to vision and to life: temporal ("giant-cell") arteritis (GCA) and internal carotid artery dissection. All patients with RAO who are 55 years and older should be questioned specifically for symptoms of GCA, including headache, scalp tenderness, jaw claudication, fever,

anorexia, and myalgias.[88] In patients without a visible retinal embolus, a Westergren erythrocyte sedimentation rate (ESR) should be performed immediately. Lastly, patients should be questioned about ipsilateral headache, neck pain, or tinnitus and examined carefully for evidence of ipsilateral ptosis or pupillary miosis; if these findings are present, magnetic resonance angiography or cerebral angiography may be needed to evaluate for carotid dissection.[89]

What Are the Issues Regarding Management of Retinal Arterial Occlusion?

Unfortunately, no consistently effective treatment is available for patients with CRAO. Attempts to dislodge an embolus by digital ocular massage or by acute lowering of intraocular pressure (either pharmacologically or with anterior-chamber paracentesis) have been anecdotally successful, as has inhalation of 95% CO_2 or 100% O_2.[90] Up to 18% of patients with CRAO may develop iris neovascularization as soon as 2 weeks after the event.[91] PRP is usually effective in inducing regression of the new vessels. Patients with BRAO are treated with observation only because the visual prognosis is usually quite good.

How Do Hypercoagulability States Relate to Retinal Vascular Occlusion?

Increasing attention has been directed toward thrombogenicity as a risk factor for retinal arterial and venous occlusions. Normally, the body maintains a complicated but well-regulated equilibrium between coagulation (clot formation) and fibrinolysis (clot dissolution). Factors leading to excessive thrombosis or inadequate fibrinolysis may predispose patients to increased risk of occlusion. As depicted in Figure 12–9, the balance may be shifted toward hypercoagulability through the following: (1) increased levels or activity of procoagulant compounds (prothrombin, factor Va, thrombin, fibrinogen), (2) decreased levels or activity of endogenous anticoagulants (protein C, protein S, antithrombin III), (3) decreased levels or activity of fibrinolytic compounds (plasminogen, plasmin), or (4) an increased level or activity of lipoprotein(a).

Isolated case reports and small case series implicating all these thrombophilic factors have been published.[92–97] On the basis of multiple case-control studies, however, no definite association with any of these variables has been clearly substantiated.[98–102] Because of the inconsistency of results and the low prevalence of these coagulation disorders, it is reasonable to screen only patients with a personal or family history of thrombotic disease.

An elevated level of the amino acid homocysteine, a normal metabolic intermediate, is now accepted as a risk factor for cardiovascular and cerebrovascular disease.[103,104] Several retrospective studies suggested its involvement in retinal vascular occlusive disease as well.[105–107] Homocysteine appears to have a deleterious effect on vascular endothelium and may induce increased platelet aggregation, lipid accumulation, and thrombosis.[104] Although no controlled study has documented a reduction in vascular disease after reduction of homocysteine levels, dietary supplementation of folic acid is reasonable in patients with hyperhomocysteinemia.

An additional mechanism for hypercoagulability appears to be the activity of circulating autoantibodies against membrane phospholipids and plasma proteins. These circulating immune complexes (e.g., lupus anticoagulant and anticardiolipin antibodies) may lead to thromboembolic arterial and venous occlusions with systemic complications: recurrent spontaneous abortions, deep venous thrombosis, chronic renal failure, and thrombocytopenia. The major ocular manifestation is retinal vasculitis, which leads to arterial occlusions and a Purtscher-like retinopathy.[108] In a recent prospective, case-control study of 40 patients with retinal vascular occlusions free of accepted risk factors for occlusive disease, Cobo-Soriano and colleagues found a significantly higher prevalence of anticardiolipin antibodies in affected patients (22.5% versus 5%) and made a diagnosis of primary antiphospholipid syndrome requiring systemic treatment in three patients. The prevalence of immunologic abnormalities was no different in the 14 younger patients (under the age of 50 years) compared with the 26 older patients.[109]

Hypertensive Retinopathy

Systemic arterial hypertension affects more than 50 million Americans and is a significant risk factor for such major debilitating diseases as coronary artery disease, stroke, renal failure, peripheral vascular disease, retinal venous occlusive disease, and age-related macular degeneration.[51,75,110,111] Although funduscopy never can replace the blood pressure cuff as the diagnostic test of choice for hypertension, the ophthalmologist nevertheless has the opportunity to alert patients with undiagnosed hypertension as well as to counsel patients with a known history on the need for good blood pressure control.

Historically, classification of hypertensive retinopathy has focused on changes in the ophthalmoscopic appearance of retinal arterioles.[112] Arteriolar narrowing, thought to be an early sign of hypertensive change, is seen in only 20 to 30% of hypertensive patients and may occur in older, normotensive persons, likely reflecting age-related arteriolosclerosis.[113]

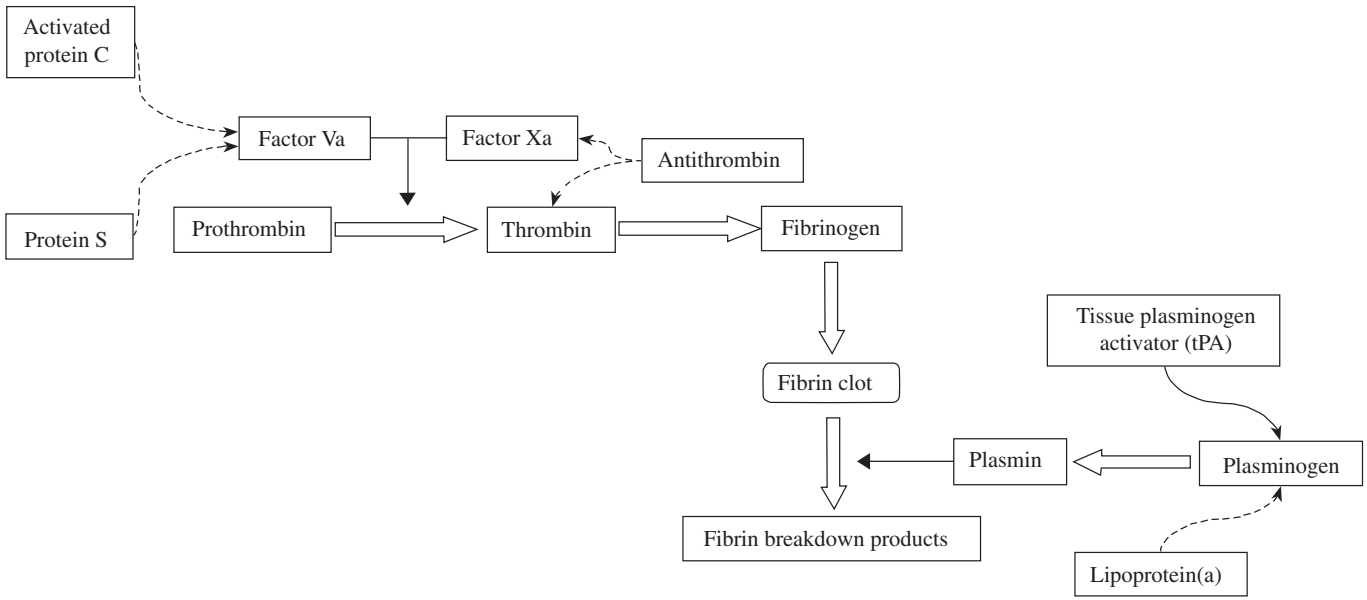

FIGURE 12–9. Coagulation cascade. Dashed line blocks, solid line enhances.

Retinal dot hemorrhages, lipid exudation, retinal edema, and nerve-fiber layer infarcts are considered signs of advanced disease. In a large, population-based study, Klein and colleagues found retinopathy (defined as microaneurysmal changes, nerve-fiber layer infarcts, and hard exudates as well as intraretinal hemorrhages) in 11% of hypertensive subjects compared with 6% of normotensive controls. The presence of retinopathy was by no means pathognomonic, however, because nearly 50% of patients with retinopathy did not have hypertension.[114]

Intraretinal hemorrhages are more likely to be seen in acute or accelerated episodes of hypertension. They tend to be flame shaped and located in the peripapillary region, and they often are associated with nerve-fiber-layer infarcts, retinal edema, and optic disc edema.[115] Unilateral or bilateral serous retinal detachment sometimes occurs. The ophthalmologist must be able to recognize the acute hypertensive episode and refer the patient to an internist for urgent systemic evaluation and treatment.

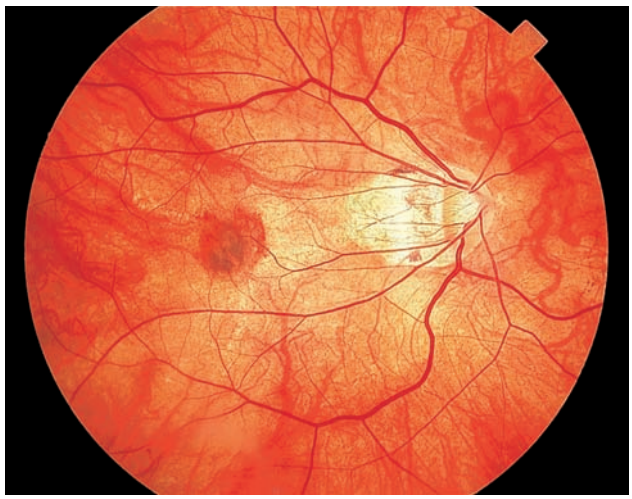

FIGURE 12–10. High myopia with temporal tilting of the optic disc, thinning of the retinal pigment epithelium, and a gray Fuchs spot (choroidal neovascularization) in the central fovea associated with surrounding subretinal blood.

Myopia

Pathologic myopia is defined as progressive elongation of the globe with associated degeneration and thinning of the choroid, Bruch's membrane, RPE, and retina, especially in the macular region[116] (Fig. 12–10). Patients with high degrees of myopia (greater than 5 diopters) or increased axial length (25 mm or greater) are at increased risk for these changes.[117] Hemorrhages in myopic eyes are usually isolated, subretinal, less than one disc diameter in size, and located in the perifoveal region.[1] They often occur in association with lacquer cracks. Lacquer cracks are linear breaks in the Bruch's membrane radiating outward from areas of RPE atrophy and may arise *de novo* at the site of previous hemorrhage.[118]

Cases of macular hemorrhage in high myopes within days following refractive surgery [either photorefractive keratectomy (PRK) or laser in situ keratomileusis (LASIK)] have been reported.[119,120] Most of these patients had preexisting evidence of myopic macular disease (i.e., pigmentary changes or so-called Förster-Fuchs spots, lacquer cracks, and choroidal neovascularization). It is theorized that the increase in intraocular pressure and the laser's acoustic shock wave associated with the LASIK procedure cause significant mechanical stress to already susceptible eyes.[120]

What Are the Important Issues Regarding Evaluation and Management of Myopia?

Fluorescein angiography is valuable in determining whether myopic subretinal hemorrhage is associated with choroidal neovascularization (CNV). CNV has been documented histopathologically in 5% of myopic eyes[118] and may lead to rapid visual decline by causing hemorrhagic macular detachment. The hemorrhagic detachment of myopia is similar to that seen in age-related maculopathy but can be differentiated angiographically by its propensity for pigment deposition and associated circumferential chorioretinal atrophy.[117] The CNV associated with myopia tends to be smaller than that of age-related maculopathy. If untreated, the disease has a course that is often self-limited, and it results in a nonexudative scar in most patients, with final visual acuity often better than 20/200 in younger patients.[121] Patients older than 50 years, however, tend to have poorer outcomes.[122]

Treatment of CNV in myopic patients has included laser photocoagulation and submacular surgery. Laser treatment of juxtafoveal lesions must be approached with caution because of the possibility of visual loss resulting from expansion of laser scars (so-called atrophic creep) or elongation of lacquer cracks.[123] Small series of surgical removal of submacular CNV have shown visual stabilization or improvement, but patients were generally younger (median age of 38 to 44 years). A recent report of 81 patients treated with photodynamic therapy suggested initial success in stabilizing vision.[124]

Purtscher Retinopathy

Purtscher originally described the constellation of multiple superficial white retinal patches, superficial retinal hemorrhages, and papillitis occurring in five

patients with head trauma.[1] Nearly identical findings, often occurring bilaterally, have been reported in numerous other conditions, the most common being acute pancreatitis, bone fractures, and renal failure.[125–127] Hemorrhages are located in the nerve-fiber layer close to the disc, but the predominant finding is widespread retinal whitening (Fig. 12–11). The common pathway of retinal damage appears to be retinal arterial embolization by aggregates of complement-activated leukocytes or other blood products.[128]

Hemorrhages and retinal infarcts usually resolve over several months, and complete return of vision is common. No ocular treatment is advocated, but administration of high-dose corticosteroids may accelerate visual recovery.[129]

Radiation Retinopathy

X-ray irradiation is a common therapeutic modality for intraocular and orbital neoplastic processes. Fundus changes result from radiation-induced ultrastructural damage to retinal and choroidal vascular endothelial cells and to the optic nerve.[130] Ophthalmoscopic findings consistent with vasoocclusive retinopathy include one or more of the following: hard exudates, micoraneurysms, intraretinal hemorrhages, nerve-fiber layer infarcts, vascular sheathing, and optic nerve head swelling (Fig. 12–12). Hemorrhages are located in both superficial and deeper retinal layers (flame, dot, and blot in appearance) and are most evident in the posterior pole. They may be seen most commonly in patients treated with external-beam irradiation (up to 85% of patients with retinopathy) and generally are distributed more diffusely in the fundi of these patients.[131] Peripapillary hemorrhages and subretinal fluid often accompany radiation optic neuropathy[132], which may evolve into optic atrophy. The underlying vasculopathy of radiation retinopathy is confirmed by fluorescein angiography, which shows capillary nonperfusion in the areas of retinal involvement. Intraocular neovascularization may develop and occurs more commonly (nearly 50%) in patients with retinopathy secondary to external-beam irradiation.[131]

The onset and extent of radiation retinopathy vary according to the source, type, and intensity of irradiation.[131,133,134] Changes attributable to external-beam radiotherapy, for example, are seen at mean of 19 months following treatment completion but may be seen as soon as 3 weeks and as late as 7 years later.[131,135] Retinopathy may develop after as little as 1500 cGy of exposure, but usually 3000 to 3500 cGy are required to produce visible changes. Increased doses are correlated with accelerated course of disease.[131] In a review of 1300 patients with uveal melanoma treated with local plaque radiotherapy, Gunduz and colleagues reported a cumulative incidence of retinopathy of 43%; proliferative retinopathy was seen in 8%. Development of retinopathy was correlated with tumor proximity to the fovea and a higher dose of radiation rate to the tumor base.[136]

Causes of visual decline attributable to radiation retinopathy include foveal exudation, macular edema, and optic neuropathy. In the original series of Brown and colleagues, with mean follow-up of 26 months posttreatment, none of 20 patients with local treat-

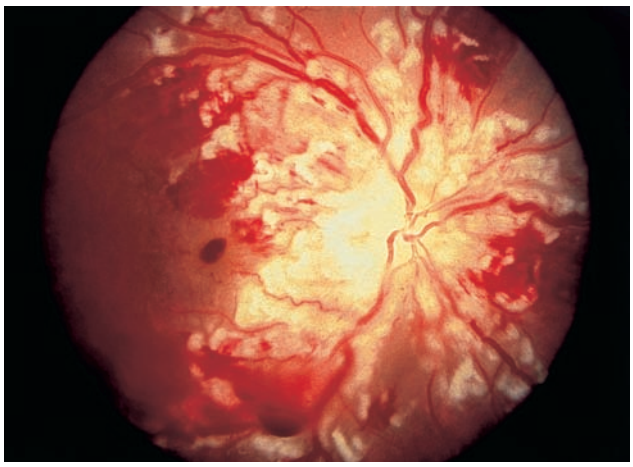

FIGURE 12–11. Purtscher retinopathy occurring after a blunt injury to the abdomen. Numerous cotton-wool spots and retinal hemorrhages are present. The visual acuity in the eye was light perception.

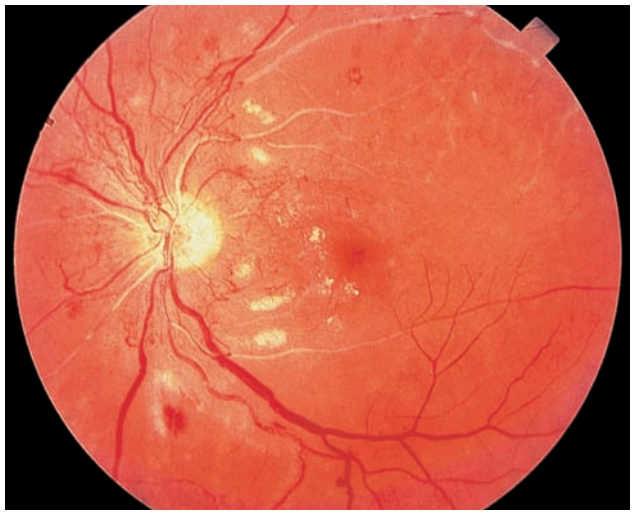

FIGURE 12–12. Radiation retinopathy. Cotton-wool spots are present, as are retinal vascular sheathing and retinal hemorrhages.

ment developed vision worse than counting fingers; 5 of 16 eyes of patients treated with external radiation had no light perception.[131] Other causes of visual decline that must be considered include retinal damage from the intraocular tumor itself (such as macular edema, retinal detachment, or CNV) as well as toxicity from adjuvant chemotherapeutic agents.

Hemoglobinopathy Retinopathy

What Are the Important Points Regarding Epidemiology and Pathogenesis of Hemoglobinopathy Retinopathy?

Hemoglobin (designated HbA in adults) is the polypeptide, consisting of two alpha- and two beta-globin chains, that is responsible for the binding and transport of oxygen by red blood cells. Genetic mutations at the sixth amino acid position of the beta-globin chain of hemoglobin result in abnormal structure and function of the hemoglobin molecule. Depending on the amino acid substitution, the mutant hemoglobin molecule is designated HbS or HbC. Particularly under conditions of oxidative stress or acidosis, these mutations induce a conformational change in erythrocytes, from their normal biconcave shape to an elongated, crescentic, or "sickled" shape. This abnormal shape results in aggregation of erythrocytes, intravascular stasis, and tissue hypoxia. The heterozygous condition (one abnormal beta-globin chain) is designated HbAS, or "sickle trait," and is prevalent in roughly 8% of African Americans. Classic sickle cell anemia (HbSS) afflicts about 0.5%, and the double heterozygous condition (HbSC) is found in about 0.1 to 0.3%.[137] Inadequate production of either globin chain is referred to as *thalassemia*. Ultimately, characterization and diagnosis are made by hemoglobin electrophoresis.

Patients with HbSS disease suffer from multiple systemic abnormalities, including anemia, infarctions of bone marrow and visceral organs, and recurrent infections. Other hemoglobinopathies result most commonly in mild anemia. For unclear reasons, patients with HbSC and HbS-Thal disease have the most severe ocular manifestations.[138]

What Are the Important Retinal Findings of Hemoglobinopathy Retinopathy?

The pathophysiology of sickle cell retinopathy is one of chronically inadequate microvascular perfusion and consequent retinal ischemia. Sludging of erythrocytes may be seen as small dark spots in the peripapillary capillaries. Macular ischemia and infarction may be seen angiographically as enlargement and irregularity of the foveal avascular zone.[139] Nonspecific signs of venous tortuosity and arteriolar narrowing are commonly seen. The disease is typically classified as either nonproliferative or proliferative.[140]

Characteristic findings of nonproliferative sickle retinopathy include "salmon patch" hemorrhages and "black sunburst" lesions.[141] Bright-red superficial or preretinal hemorrhages may occur in the equatorial region from rupture of an ischemic, sclerotic arteriole. Within weeks, the hemorrhage may lighten to a light orange–red or salmon color. Deep retinal hemorrhages, usually one to two disc diameters across, may be seen at the equator or more anteriorly. These hemorrhages often penetrate the subretinal space, allowing retinal pigment epithelial cells to migrate intraretinally to form a hyperpigmented lesion with spiculated borders. The resulting hyperpigmented (brown–black) lesion is termed a black sunburst.

Severe vision loss in patients with sickle hemoglobinopathy is most often a result of proliferative sickle retinopathy (PSR). This progression usually occurs in the third or fourth decade of life. Goldberg classified PSR into five stages: (1) peripheral arteriolar occlusions, (2) arteriovenous anastomoses, (3) neovascular and fibrous changes (Fig. 12–13), (4) vitreous hemorrhage, and (5) retinal detachment.[140] This progression is similar to the pathophysiologic response observed in other ischemic retinopathies, such as diabetes and venous occlusive disease, and likely evolves through similar cellular mechanisms.

The hallmark finding of PSR is the "sea-fan" configuration of peripheral retinal neovascularization growing circumferentially along the border of perfused and nonperfused retina. These new vessels may extend into the vitreous and may bleed with little or no trauma. Fibrovascular tissue may grow along the sea fan and cause peripheral tractional retinal detachments. Rhegmatogenous detachment may arise from stretching of a hole in atrophic, nonperfused retina.[140]

What Is Important to Know Regarding Treatment and Prognosis of Hemoglobinopathy Retinopathy?

Roughly 12% of untreated patients with PSR will lose vision entirely.[138] Prevention of retinal detachment necessitates adequate treatment and arrest of retinal neovascularization. Peripheral cryotherapy, diathermy, and laser photocoagulation all have been used. Laser treatment may be directed at the vessel feeding the sea fan[142] in a sector pattern to areas of nonperfusion or in a 360-degree scatter PRP pattern. The last technique appears to be most effective in reducing vitreous hemorrhage and recurrence of sea fans.[143]

Surgery for retinal detachment can be challenging. Apart from the patient's anemia, immunosuppression, and higher risk of thromboembolic events, specific

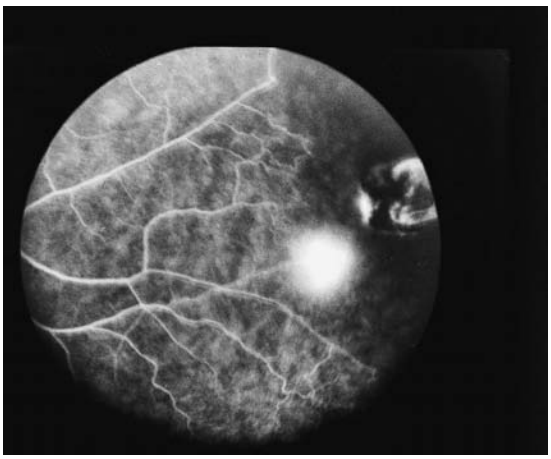

FIGURE 12–13. Hemoglobin SC disease; fluorescein angiogram at 106 seconds after injection reveals marked hyperfluorescence resulting from the retinal neovascularization as well as retinal capillary nonperfusion peripheral to the area of neovascularization. The area of the black sunburst manifests with hyperfluorescence due to a retinal pigment epithelial window defect.

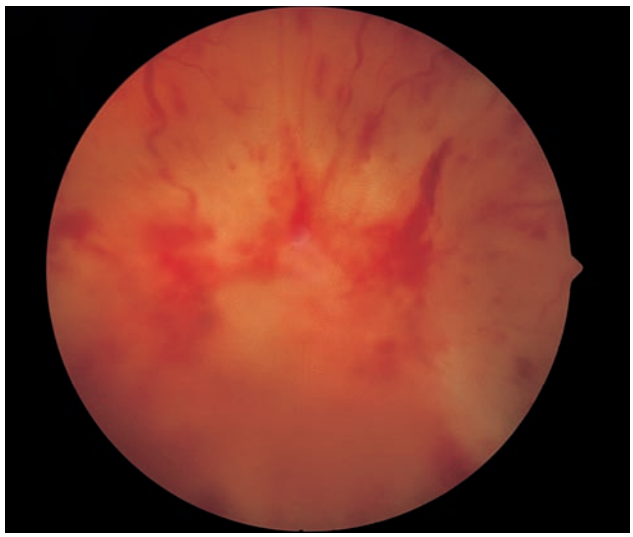

FIGURE 12–14. Retinopathy of leukemia. Retinal hemorrhages are present, there is diffuse infiltration of the optic disc (located in the center of the photograph) by leukemic cells, and a peripapillary neurosensory retinal detachment can be seen. (Courtesy of Dr. Jerry Shields)

ocular complications must be considered. These include the higher risk of optic nerve and macular ischemia associated with fluctuations and elevation in intraocular pressure[144] and the possibility of anterior segment ischemia, particularly if a scleral buckle is used over the long posterior ciliary arteries.[145]

Leukemic Retinopathy

What Are the Clinical Features of Leukemic Retinopathy?

Ocular abnormalities are seen in 35 to 50% of patients with leukemia at diagnosis and are more common in adults than in children.[146–149] Intraretinal hemorrhages are the most common finding and are often multifocal and bilateral. White-centered retinal hemorrhages may be seen in up to one third of patients.[149] Other findings include cotton-wool spots, vascular sheathing, optic disc edema, hypopyon, retinal neovascularization, and exudative detachments of the neurosensory retina, RPE, and choroid[146,150–152] (Fig. 12–14). The true leukemic infiltrate, a flat, whitish, irregular lesion in the neural retina often associated with retinal hemorrhages and overlying vitreous cells, is seen in fewer than 5%.[148] These whitish lesions also may represent infection with opportunistic organisms (e.g., *Candida*, *Nocardia*, and others), especially in patients immunosuppressed as a consequence of either their malignancy or chemotherapy.

Guyer and colleagues suggested that the presence of intraretinal and white-centered retinal hemorrhages are manifestations of concomitant anemia and thrombocytopenia rather than of the leukemia itself.[148] Others proposed a correlation between leukocytosis and nerve-fiber layer infarcts.[149]

How Should Patients Suspected of Having Leukemic Retinopathy Be Evaluated?

All patients with retinal findings suspicious for leukemia should be evaluated thoroughly. In cases of optic nerve involvement, concurrent central nervous system involvement is probable, and neuroimaging and lumbar puncture for cytological analysis should be performed. In cases of vitreitis associated with retinal infiltrates, fine-needle aspiration biopsy or vitrectomy may be necessary for diagnosis.

What Is the Treatment and Prognosis For Leukemic Retinopathy?

Intraocular leukemia is best treated with chemotherapy appropriate for the type and stage of leukemia. External-beam radiation may be applied to lesions of the optic nerve or orbit. The presence of retinopathy in general is a poor prognostic sign for survival. Patients with infiltrative lesions have a median survival of less than 6 months.[153]

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13

Abnormal-Appearing Retinal Vessels

MITRA AYAZIFAR AND LORY SNADY-MCCOY

Congenital Tortuosity of the Retinal Vessels (Nonaneurysmal Congenital Anomalies)

What Are Arterial Vascular Anomalies?

The arterial circulation of the retina, with the exception of the cilioretinal artery, is supplied by the central retinal artery. The quadrantal branches divide upon leaving the optic disc and extend toward the periphery; at the ora serrata, they turn back toward the optic disc to form venules. In 1977, Awan conducted a study on the incidence of nonaneurysmal and noncommunicating anomalies of the retinal arteries in 2100 normally functioning eyes of healthy subjects. Unusual anomalies included triple branching, anomalous course, arteriolar–arterial crossing, unusual tortuosity, prepapillary loops, aberrant macular arteries, unusual supply of the optic disc, presumed total ciliary arterial supply of the retina, anomalous relationship with the central retinal vein at the optic disc, and pseudoaneurysm of a major retinal artery (Fig. 13–1).[1]

What Is the Most Common Congenital Vascular Anomaly of the Retina?

In one study, the incidence of cilioretinal artery was found to be as high as 49.5%. It is considered the most common congenital vascular anomaly of the retina.[2]

What Is Idiopathic Juxtafoveal Retinal Telangiectasis?

Retinal telangiectasis is a retinal vascular anomaly characterized by irregular dilation and incompetence of the retinal vessels.[3] These vascular anomalies may be confined to the juxtafoveal area, a condition termed idiopathic juxtafoveal telangiectasis. Central vision loss may result because of exudation or diffusion abnormalities from ectatic and incompetent juxtafoveal retinal capillaries. The condition may be congenital or of unknown cause and may be bilateral or unilateral. Idiopathic juxtafoveal retinal telangiectasis is classified into several groups.[3]

What Is the Classification System for Idiopathic Juxtafoveolar Retinal Telangiectasis?

In 1982, Gass and Blodi[4] proposed a classification system of idiopathic juxtafoveolar retinal telangiectasis based on biomicroscopic and fluorescein angiographic findings. There were subsequent revisions in 1987 and 1992 (Table 13–1).

What Are the Characteristics of Group 1 of Gass and Blodi's Classification?

Patients are divided into three groups and are further subdivided into group 1A and 1B. Group 1A has visible and exudative idiopathic retinal telangiectasis. Most of these patients are males with unilateral disease. The temporal macula is typically involved with exudation present. The size of the involved area is two disc diameters (DD) or greater. This is considered a mild form of Coats disease that may progress to the entire retina and cause massive exudation. Telangiectasis involves the superficial and deep capillary plexus of juxtafoveolar retinal capillaries. Vision loss occurs secondary to the extension of exudation into the foveolar area. Laser treatment to these telangiectatic capillaries is effective in reducing the foveolar exudation and in improving or preserving visual acuity. No systemic disease is associated with this category.

Group 1B is identical to group 1A in patient characteristics. The difference between group 1A and 1B is in the size of the affected area, less than 2DD. Visual acuity is rarely affected.

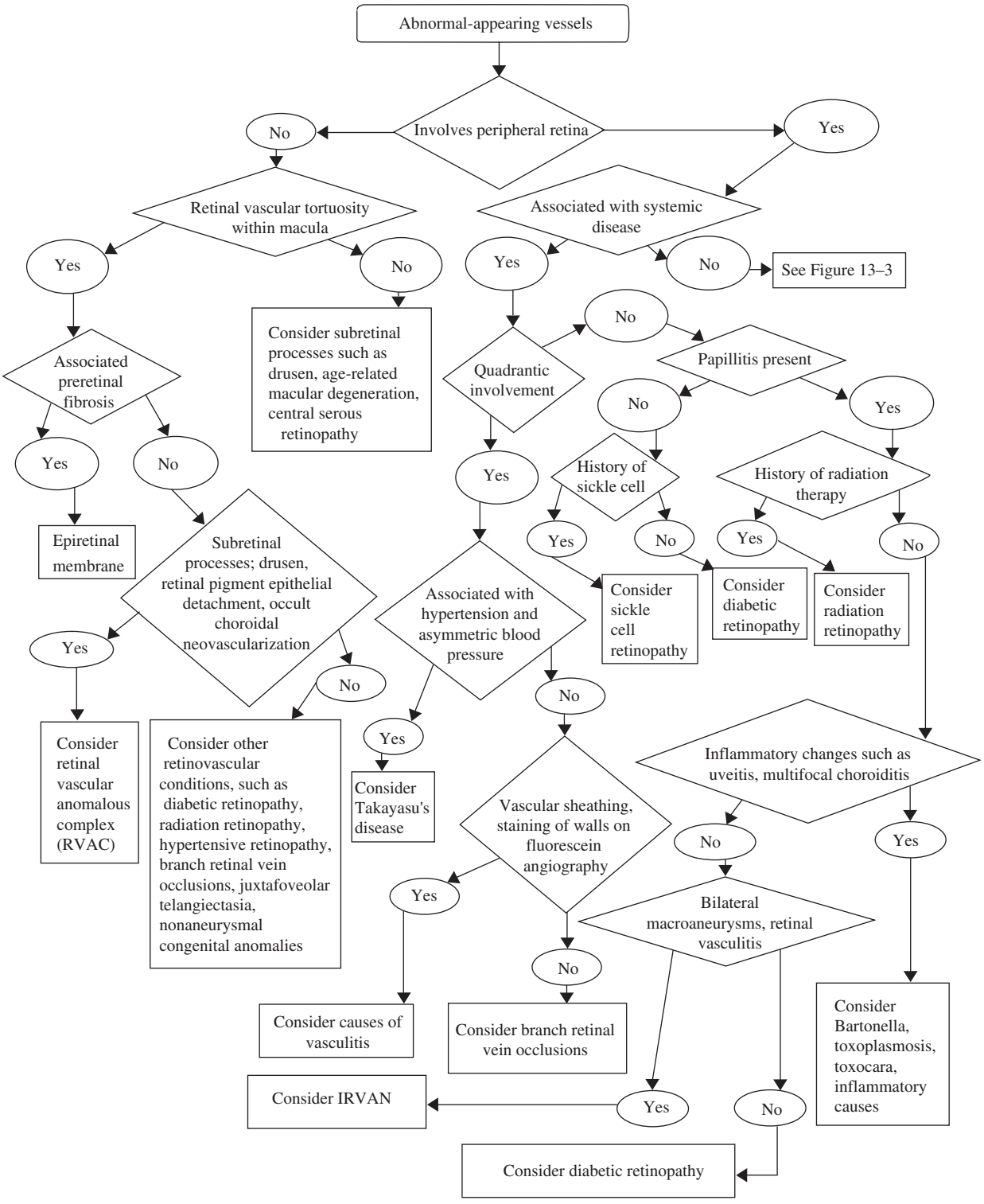

FIGURE 13–1. Clinical pathway: Abnormal-appearing retinal vessels. RVAC, retinal vascular anomalous complexes; IRVAN, idiopathic retinal vasculitis, aneurysms, and neuroretinitis.

TABLE 13–1. Idiopathic Juxtafoveolar Retinal Telangiectasis (JRT) Classification

Group 1A	Visible and exudative idiopathic JRT	Male predilection	Often unilateral
Group 1B	Visible and exudative and focal idiopathic JRT		
Group 2A	Occult and nonexudative idiopathic JRT	No gender predilection	Usually bilateral
Group 2B	Juvenile, occult familial idiopathic JRT		
Group 3A	Occlusive idiopathic JRT	No gender predilection	Usually bilateral
Group 3B	Occlusive idiopathic JRT associated with central nervous system vasculopathy		

What Are the Characteristics of Group 2 of Gass and Blodi's Classification?

Group 2 is subdivided into group 2A and 2B. The telangiectasis is acquired during middle age, has no sex predilection, and presents bilaterally in 98% of cases. Group 2A has occult and nonexudative idiopathic juxtafoveolar retinal telangiectasis, the most common form of the disease. In many patients, slight loss of retinal transparency is the only biomicroscopic clue to the presence of these capillaries. Fluorescein angiography is the best method to detect the telangiectatic vessels. The temporal parafoveolar area is involved in all cases, within 1 DD of the center of the fovea. Minimal loss of vision is secondary to foveolar atrophy and rarely is due to subretinal neovascularization. Forty-five percent of these patients have golden refractile deposits near the inner retina surface in the juxtafoveolar area. The cause of these deposits is unknown. The findings in group 2A eyes are further subdivided into five stages of development (Table 13–2).

Group 2B patients have a juvenile onset of occult familial idiopathic juxtafoveolar retinal telangiectasia. Gass and Blodi included the case of two brothers with bilateral subretinal neovascularization and subtle retinal juxtafoveolar telangiectasis in this category. These patients differ from group 2A patients in that they lack right-angle venules, superficial retinal refractile deposits, and stellate pigmented plaques.

What Are the Characteristics of Group 3 in Gass and Blodi's Classification?

Group 3 is subdivided into 3A and 3B. Patients in group 3A have extensive capillary occlusion associated with juxtafoveolar telangiectasis. Given the large capillary-free zones (greater than 1 DD in size), the reason for continued good visual acuity is unclear. Systemic disease (hypertension, diabetes, or cardiovascular disease) is present in all described cases.

Group 3B consists of patients with occlusive idiopathic juxtafoveolar retinal telangiectasis associated with central nervous system vasculopathy. All have loss of central vision associated with the telangiectasis, capillary closure, and minimal exudation. A specific central nervous system lesion was never identified. Gass and Blodi suspected that these patients may have had an autosomally dominant cerebroretinal vasculopathy.[4–7] Overall, visual loss in Group 3 is presumed to be caused by ischemia from the capillary occlusion rather than from exudation.

TABLE 13–2. Group 2A Stages of Development in Juxtafoveal Retinal Telangiectasis

Stage	*Biomicroscopy*	*Fluorescein Angiography*
Stage 1	No abnormality	Early: no capillary dilation Late: mild staining at the outer temporal parafoveolar area
Stage 2	Perifoveolar graying Minimal or no telangiectasia	Early: telangiectasia of the outer temporal capillary network
Stage 3	Dilated/blunted retinal venules extending into parafoveolar retina	Capillary dilation and permeability changes
Stage 4	Foci of hyperplastic RPE beneath Right-angle venules leading to an irregular or stellate plaque	Capillary dilation and permeability changes
Stage 5	Subretinal neovascularization in the temporal parafoveolar area associated with intraretinal pigment epithelial migration	

RPE, retinal pigment epithelium.

How Is Idiopathic Juxtafoveolar Telangiectasia Treated?

In patients in group 1, this condition is considered nonfamilial and predominantly exudative. Laser photocoagulation is recommended to stabilize and prevent further visual loss. In groups 2 and 3, the condition is nonexudative, obstructive, and occasionally familial, and patients benefit little from laser photocoagulation treatment. Most patients have a good long-term prognosis for retaining reading vision in at least one eye.

What Are Retinal Vascular Anomalous Complexes (RVAC)?

Retinal vascular anomalous complexes (RVACs) are angiomatous lesions within the deep retina that are derived from the retinal circulation and associated with age-related macular degeneration (AMD).[8] When first described, they were identified with pigment epithelial detachments,[9] but subsequent studies have shown this to be uncertain.[10,11] Over time, they may become chorioretinal anastomoses.

Takayasu Disease

What Is Takayasu Disease?

Takayasu disease, or occlusive thromboaortopathy or pulseless disease, is an idiopathic, inflammatory disease of the large arteries, including the aorta and its branches, that leads to arterial narrowing and obliteration. The four major complications include Takayasu retinopathy, secondary hypertension, aortic regurgitation, and aortic or arterial aneurysm.[12] Studies of retinal hemodynamics suggest that carotid artery involvement leading to diminished ocular perfusion is the mechanism of Takayasu retinopathy.

In Japan, women account for 90% of the cases of Takayasu arteritis. The female-to-male ratio decreases, however, as one moves toward the West.[13] Genetic studies have revealed a strong human leukocyte antigen (HLA) association with the HLA A24-B52-DR2 haplotype. Patients with this haplotype are thought to be more likely to develop accelerated inflammatory progression and resistance to steroid therapy.[14]

What Are the Signs and Symptoms of Takayasu Disease?

The clinical manifestations will vary depending on the site and severity of the affected vessels. The aorta and its tributaries, including the braciocephalic, carotid, subclavian, vertebral, renal, coronary, and pulmonary arteries, are narrowed.

Patients may present with complaints of dizziness, syncope with or without headache, and visual disturbances. More commonly, weak or absent radial pulses are demonstrated. A comparison of the blood pressure in each arm is classically asymmetric. On examination, patients may have an associated systolic vascular murmur (aortic regurgitation secondary to dilatation of aortic valve root); this may lead to congestive heart failure and arrhythmia. Patients at risk of developing Takayasu retinopathy will have a prolonged arm-to-retina circulation time.

On laboratory evaluation, patients may have elevated acute-phase reactant markers, including erythrocyte sedimentation rate (ESR) and elevated C-reactive protein.

What Is the Pathogenic Mechanism Involved in Takayasu Disease?

Takayasu disease is a chronic vasculitis of unknown cause. On pathologic examination, Takayasu disease is a panarteritis involving the intima, media, and adventitia; this finding produces an array of ischemic clinical symptoms attributable to stenosis or secondary thrombus formation within the vasculature. Its various clinical manifestations are due mainly to insufficient perfusion of the tissues caused by progressive narrowing and obliteration of their vascular supply.[15]

The retinal vascular changes in Takayasu disease occur in response to a gradual decrease in the central retinal artery pressure below a critical level. The retinal vessels react to diminished perfusion by generalized vasodilation, microaneurysm formation, and hyperpermeability of the vessel wall. A further decrease in arterial pressure peripheral to the shunt vessels accelerates vascular nonperfusion, leading to vessel occlusion with secondary neovascularization of the iris, chamber angle, and retina.

What Are the Ocular Findings Associated with Takayasu Arteritis?

Retinal vascular changes occur secondary to chronic decrease in the central retinal artery pressure. These retinal changes include progressive small vessel dilation, microaneurysm formation, retinal arteriovenous anastomoses, vitreous hemorrhage, proliferative retinopathy, vitreous hemorrhage, anterior ischemic neuropathy, and retinal emboli.[16–18] Retinal arteriovenous (AV) shunt formation is a unique retinal finding in moderate to advanced stages of Takayasu disease[19]

and may be followed by capillary nonperfusion in the midperipheral retina.

There are three reported types of retinal AV shunts. One type forms at AV crossings; the other develops consequent to capillary dilatation followed by preferential channel formation. In the more advanced cases of Takayasu disease, peripapillary vascular loops have been reported; however, the midperipheral retina remains the major site of AV shunt formation.[20]

Patients also sometimes demonstrate dilated episcleral vessels with intravascular sludging and signs of anterior and posterior uveitis with anterior chamber cells. Dilation is noted in the retinal veins with impressive intravascular sludging of blood. This is more prominent on fluorescein angiography, which highlights numerous capillary microaneurysms seen as dot hemorrhages on indirect ophthalmoscopy.

How Is Takayasu Disease Diagnosed?

Imaging studies, including magnetic resonance imaging (MRI), computed axial tomography (CT), or digital subtraction angiography, may demonstrate narrowing of the aorta and its tributaries. Decreased central retinal artery pressure with increased arm-to-retina circulation time confirms the diagnosis.

On examination, patients may have absent or faint radial pulses and asymmetric blood pressure with possible systolic murmur on cardiac auscultation.

What Is the Visual and Systemic Prognosis of Takayasu Disease?

If diagnosed and treated at an early stage, before ischemic symptoms develop, the prognosis is positive. The high incidence of cerebrovascular accidents due to renovascular hypertension has been reported as the main cause of death in some Asian countries, including China, Thailand, and India.

Takayasu retinopathy regresses with resolution of carotid artery stenosis, leading to a gradual increase in the central retinal artery pressure.

How Is Takayasu Disease Treated?

Initially, Takayasu arteritis is managed with high-dose steroids, followed by maintenance with low-dose steroids and aspirin. In cases of steroid resistance, immunosuppressive drugs are used as supplementary treatment.

In cases of Takayasu retinopathy, once the retinal artery pressure rises above a critical level, the AV shunts and other retinal findings slowly regress. Early diagnosis and treatment prior to ischemic manifestations is primary in management of the disease.

Eales Disease

What Is Eales Disease?

Eales disease is associated with idiopathic obliterative peripheral retinal vasculopathy and retinal periphlebitis. It is uncommon in North America but is a major cause of widespread visual loss on the Indian subcontinent. Healthy young adult males in their second to third decade of life are primarily affected. In most patients, ocular findings are bilateral. Although there is no evidence of a hereditary tendency, studies have shown a statistically significant higher phenotype frequency of HLA B5 (B51), DR1, and DR4 among patients with Eales disease compared with controls.[21]

What Is the Pathogenesis of Eales Disease?

Eales disease is also known as periphlebitis retinae; evidence suggests that the inflammatory aspect of this disease affects the arterioles as well as the venules.[22] Sheathing of peripheral retinal vessels occurs secondary to the leukocytic infiltration of the vessel wall, with a resultant perivascular cuff of lymphocytes and plasma cells. Early capillary closure of the temporal peripheral retina is followed by retinal ischemia, leading to neovascularization between areas of the perfused and nonperfused retina. In most patients, there is a strong fibroglial component to this neovascular tissue that may lead to recurrent vitreous hemorrhages and tractional retinal detachment.

What Are the Retinal Manifestations of Eales Disease?

In the early stages of Eales disease, patients develop ocular inflammation, manifested by vascular sheathing of varying degrees. On fluorescein angiography, areas of sheathing demonstrate hyperfluorescence; however, the intensity of this hyperfluorescence does not correlate with the intensity of inflammation. Ocular inflammation may also present as keratic precipitates, anterior chamber cell and flare, vitreous cells, and cystoid macular edema. Intraretinal hemorrhages with microvascular occlusion lead to vascular tortuosity and retinal ischemia, mainly in the temporal retina. Fluorescein angiography highlights venous beading, microaneurysms, and AV shunts at the junction of the perfused and nonperfused retina.

What Are the Systemic Manifestations of Eales Disease?

Eales disease can affect the vestibuloauditory system, with resultant sensorineural hearing loss in up to 50%

of patients.[23] In several reports, Eales disease has been associated with cerebrovascular accidents.[24]

How Is Eales Disease Diagnosed?

Although Eales disease is distinct, its diagnosis remains one of exclusion. Patients should be evaluated for other systemic diseases leading to retinal vascular abnormalities, such as sickle cell disease, diabetes, sarcoidosis, and connective tissue disorders such as systemic lupus erythematosus. The presence of active pulmonary tuberculosis should be excluded, and the tuberculin hypersensitivity status should be determined. Patients should be questioned extensively with regard to hearing and balance problems. According to a recent study, Eales disease may be associated with factor V Leiden mutation and previous thrombotic events. This finding has caused the standard evaluation of Eales disease and other causes of peripheral retinal neovascularization to include factor V Leiden testing and further coagulopathy evaluation.[25]

Branch retinal vein occlusion (BRVO) is commonly confused with Eales disease. The distinguishing feature in Eales is the involvement of multiple retinal quadrants without respect to the retinal midline.

What Is the Relationship between Eales Disease and Tuberculosis?

Many studies have shown a higher than normal incidence of tuberculin hypersensitivity in patients with Eales disease.[26,27] In one study, this incidence was as high as 48%.[28] Tuberculin hypersensitivity may play a role in the pathogenesis.

What Is the Visual Prognosis for Eales Disease?

Eales disease affects mainly the peripheral retina while sparing the macular vasculature. Therefore, many patients retain good central visual acuity that is interrupted by periods of blurred vision and floaters caused by vitreous hemorrhage. Vitreous hemorrhage remains the most common cause of visual loss. Complications such as persistent vitreous hemorrhage, traction retinal detachment, neovascular glaucoma, cystoid macular edema, macular holes, retinal telangiectasia, or epiretinal membrane formation may cause long-term visual loss.

How Is Eales Disease Treated?

Retinal neovascularization is very responsive to peripheral laser photocoagulation. In patients with persistent vitreous hemorrhage, pars plana vitrectomy is recommended and yields good results.[27,28] Retinal detachments in Eales disease are treated with standard scleral buckle and vitrectomy techniques. If possible, preoperative laser to areas of attached peripheral avascular retina should be performed prior to vitrectomy. There are no treatment modalities to prevent or reverse the initiating retinal ischemia.

Idiopathic Retinal Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) Syndrome

What is IRVAN Syndrome?

Originally described by Kincaid and Schatz,[29,30] this syndrome is characterized by the presence of bilateral retinal vasculitis, multiple macroaneurysms, neuroretinitis, and peripheral capillary nonperfusion. More recently, Chang and colleagues[31] proposed the acronym IRVAN to highlight the most prominent clinical features of this syndrome (idiopathic retinal vasculitis, aneurysms, and neuroretinitis). It typically affects young, healthy persons and appears to have a female predilection. Family history and extensive systemic investigations are negative. Patients are frequently asymptomatic at the time of presentation despite the impressive fundus appearance on clinical examination.

What Are the Retinal Findings in IRVAN?

Reported cases show focal areas of vascular sheathing. Numerous aneurysmal dilatations of the retinal arterioles are noted at the optic nerve head, on the macular branch arteries, and at branching sites of the first- and second-order retinal arteries. These vascular abnormalities typically have a "Y-shaped" configuration and also have been described as "knots" tied onto the arteriolar tree.[32–34]

Patients may have bilateral optic nerve head edema with surrounding peripapillary exudates extending to the macula. Areas of peripheral capillary nonperfusion may be associated with retinal neovascularization and vitreous hemorrhage (Table 13–3).

What Are the Fluorescein Angiographic Findings in IRVAN?

Fluorescein angiography reveals prominent vascular dilatation with evidence of late staining of macroaneurysms and retinal arteriole walls. The peripheral retina demonstrates extensive areas of capillary nonperfusion. The optic nerve head commonly appears hyperfluorescent with extensive leakage in the late stages of the angiogram.

What Is the Visual Prognosis for IRVAN?

Exudative retinopathy and peripheral capillary nonperfusion may threaten vision. Exudative retinopathy is typically concentrated in a peripapillary area adjacent to the retinal and optic nerve head aneurysms.

TABLE 13–3. Ocular Findings in IRVAN Syndrome

Anterior segment	Mild anterior uveitis
Anterior vitreous	Cellular debris
Lens	Posterior subcapsular cataract
Retina	Tortuous, telangiectatic retinal arteries, aneurysms
	Retinal edema and circinate exudation
	Serous retinal detachment
	Tractional band detachment
Macula	Macular exudates
Peripheral retina	Marked vessel attenuation
	Extensive retinal ischemia
Optic nerve	Optic nerve head edema
	Optic nerve head aneurysms "hairpin loops"
	Tufts of neovascularization
Vitreous	Recurrent vitreous hemorrhages

IRVAN, idiopathic retinal vasculitis, aneurysms, and neuroretinitis.

Extensive retinal ischemia secondary to peripheral capillary nonperfusion often leads to retinal neovascularization with subsequent vitreous hemorrhage. In rare cases, ischemia leads to iris neovascularization with neovascular glaucoma.

How Is IRVAN Treated?

Despite the presumed inflammatory component of this syndrome, patients do not benefit from oral or intravenous high-dose steroids. Given the adverse side effects of systemic steroids, this therapy is not recommended. One case report noted the disappearance of retinal aneurysms over a 7-year interval without surgical intervention.[33]

The role of panretinal photocoagulation in treating other ischemic retinopathies may be applied to IRVAN. Although the timing of laser photocoagulation in treating the associated retinal ischemia is not well defined, it is beneficial in stabilizing anterior segment and retinal neovascularization.

In cases with recurrent vitreous hemorrhage, pars plana vitrectomy with supplemental endolaser may be required to stabilize the disease. At present, proposed treatments for this syndrome are recommended for symptomatic patients.

How Is IRVAN Different from Eales Disease?

Although both IRVAN and Eales disease are characterized by vasculitis, Eales tends to affect venules more commonly than arterioles. Eales also occurs in young healthy males with associated tuberculin hypersensitivity, vestibuloauditory deficits, and rare cerebral infarction.

Sickle Cell Disease

What Is Sickle Cell Disease?

Heterozygous and homozygous forms of sickle cell disease involve mutations in the hemoglobin gene resulting in the production of defective or abnormal peptide chains of the hemoglobin molecule.

Normal hemoglobin, HbA, has two alpha and two beta chains. In HbS, or sickle hemoglobin, valine replaces glutamic acid on the beta chain. HbC has lysine substituting for glutamic acid on the beta chain. HbSS is the homozygous form of sickle cell disease; the heterozygous states are HbAS, HbSC, and alpha or beta thalassemia with failed or defective production of one peptide chain in the hemoglobin molecule.

About 8% of black Americans are heterozygous for HbS. The gene frequency is highest in central Africa, particularly in areas where malaria is endemic. Heterozygotes gain mild protection against falciparum malaria.

What Is the Pathogenic Mechanism Involved in Sickle Cell Disease?

Genetic mutation produces hemoglobin molecules that polymerize under acidic or hypoxic conditions, causing the formation of sickled erythrocytes. These sickled red blood cells have rigid membranes, leading to difficulties in the microcirculation. Vasoocclusions in all organ systems are possible.

The erythrocyte polymerization rate depends on the intracellular concentration of HbS and the extent of deoxygenation. Factors such as acidosis or increased red blood cell 2,3-diphosphoglycerate lower the oxygen affinity of red blood cells and enhance polymerization and sickling.

What Are the Signs and Symptoms of Sickle Cell Disease?

Patients with HbSC and thalassemia demonstrate the most severe ocular manifestations, whereas HbSS patients exhibit the most dramatic systemic complications. Heterozygotes for sickle cell require a much lower oxygen tension for sickling than homozygotes. Overall, heterozygotes have a higher life expectancy and lower morbidity compared with sickle cell disease patients.

The constitutional manifestations of sickle cell anemia include failure to thrive and susceptibility to infections (especially due to encapsulated organisms). The vasoocclusive manifestations caused by microinfarcts affect various parts of the body, particularly the abdomen, chest, back, and joints.

Recurrent macroinfarcts lead to anatomic and functional damage of various tissues and organ systems. The most common organs include the spleen, lungs, kidney, liver, skeleton, and skin.

In homozygote SS patients, anemia becomes severe if erythropoiesis is suppressed. Aplastic crises in these patients may be caused by folic acid deficiency and infection (especially with parvovirus).

Nonocular signs and symptoms, including musculoskeletal and joint pain, abdominal discomfort, cholelithiasis, and episodic anemia seen commonly in HbSS patients are rare in those with HbSC disease.

What Are the Ocular Complications of Sickle Cell Disease?

The *comma sign of the conjunctiva* refers to changes in the conjunctival vessels' appearance that occur secondary to microvascular occlusions. The *disc sign of sickling* refers to intravascular occlusions of the small surface vessels of the optic nerve that do not result in visual impairment and do not appear to impede perfusion substantially. Neovascularization of the disc is rare.

Patients also demonstrate an enlarged foveal avascular zone, macular vascular occlusion, branch retinal artery occlusion (BRAO), and, rarely, spontaneous central retinal artery occlusion (CRAO). These manifestations may lead to central, paracentral, or even complete loss of vision[34,35] (Table 13–4).

Nonproliferative and proliferative retinal changes occur in sickle cell disease. A nonproliferative change is the occurrence of a salmon-patch hemorrhage, a focal intraretinal and subretinal hemorrhage that develops after an acute arteriolar occlusion, typically in the midperipheral retina, with subsequent ischemic necrosis and hemorrhage through the vessel wall. The term *salmon patch* comes from the orange discoloration that develops in this area after several days. Over time, the hemorrhage is resorbed from the intraretinal space and a schisis cavity remains. Iridescent spots within the schisis cavity are thought to represent collections of macrophages responsible for resorption and breakdown of the preretinal hemorrhage.

Black sunbursts are black chorioretinal scars that represent focal areas of hyperplastic retinal pigment epithelium (RPE) in areas of previous ischemia and hemorrhage. These scars are characteristically perivascular in location and do not produce clinical symptoms. They are sometimes mistaken for focal areas of chorioretinitis.

Proliferative sickle cell retinopathy primarily tends to affect the temporal aspect of the peripheral retina. It may be more progressive in children and adolescents than in adults.

Angioid streaks occur more commonly in patients with HbSS disease compared to patients with HbSC disease. Rarely, angioid streaks may be associated with choroidal neovascularization occurring as a result of trauma.

Choroidal vascular occlusions may result from posterior ciliary artery occlusions and appear as triangular, hypopigmented patches at the level of the RPE. These are not thought to be visually significant.

TABLE 13–4. Ocular Manifestations of Sickle Cell Disease

Conjunctiva	Comma sign
Optic nerve	Intravascular occlusions of small surface vessels of the optic nerve ("disc sign" of sickling)
Macula	Enlarged foveal avascular zone (FAZ)
	Macular arteriolar occlusions (infrequent)
	Epiretinal membranes
	Macular holes
Retina	Venous tortuosity
	"Salmon-patch" hemorrhage
	Iridescent spots
	Schisis cavity
	"Black sunburst"
	Angioid streaks
	Central retinal artery occlusions
	Branch retinal artery occlusions
	Neovascularization in the periphery
	Arteriovenous shunts in periphery
Choroid	Choroidal vascular occlusion

How Is Sickle Cell Anemia Diagnosed?

The diagnosis of sickle cell anemia should be considered in patients with African heritage and hemolytic anemia. Similarly, any patient with African heritage who presents to the ophthalmologist with a hyphema should be tested for sickle cell disease.

The peripheral blood smear reveals normochromic normocytic red blood cells with some target cells. The presence of Howell–Jolly bodies, siderocytes, and occasional normoblasts suggests defective splenic function.

The diagnosis of the sickle cell trait or any sickle cell syndrome depends on demonstration of sickling under lowered oxygen tension in the sickle prep test. If the sickle prep is positive, hemoglobin electrophoresis is performed to distinguish between the homozygous and heterozygous forms of the disease.

How Is Sickle Cell Disease Treated?

Before birth, fetal hemoglobin or HbF, is the predominant form of hemoglobin. At birth, the switch from fetal to adult hemoglobin is not complete such that normal adults have about 1% HbF. It has been proven that HbF interferes with HbS polymerization.[36]

Understanding this pathophysiology has led investigators to treat sickle cell disease by increasing the

distribution and concentration of fetal hemoglobin in sickle erythrocytes. Drugs such as hydroxyurea (HU) have laboratory and clinical efficacy in HbSS disease, and a recent study demonstrated its therapeutic benefits in pediatric patients with severe HbSC disease.[37] Larger clinical trials of HU therapy in HbSC disease are warranted.

What Is the Pathogenesis of Sickle Cell Retinopathy?

Early forms of angiogenesis are seen in 40% of HbSS disease compared with 80% of HbSC disease.[38] Sickle cell retinopathy is a disease that affects primarily the peripheral retinal vasculature. Peripheral vascular occlusion secondary to sickled erythrocytes results in a nonperfused and ischemic peripheral retina.[39] Neovascularization develops at the junction of the perfused and nonperfused retina.

Vasoocclusions and subsequent vascular remodeling causes formation of AV anastomoses. It is at these anastomotic channels that preretinal neovascular formations, called sea fans, form. Several studies have also reported formation of sea fans at hairpin loops and AV crossings.[40] The most common sites of sea-fan formation are in the superotemporal and inferotemporal peripheral retina. With time, most sea fans autoinfarct and regress; rarely, they lead to vitreous hemorrhages, and produce traction retinal detachments. Sea fans are the predominant causes of blindness in sickle cell disease.

Occlusive disease of the perifoveal arterioles is known to occur in sickle cell disease.[41] An enlargement of the foveal avascular zone and ischemic maculopathy may result.

What Is the Classification System for Proliferative Sickle Cell Retinopathy?

Proliferative sickle retinopathy is most prevalent in patients with HbSC and S-thalassemia disease. In general, sickle cell trait and HbAS do not cause systemic disease or retinal neovascularization.

In 1971, Goldberg proposed a classification system for the development of proliferative sickle retinopathy (Table 13–5). Stage I refers to peripheral arteriolar occlusions seen as "silver-wire" vessels with an avascular zone of retina anterior to the occluded vessels on fluorescein angiography. Stage II is the vascular remodeling that takes place with the formation of AV anastomoses at the junction of vascular and avascular retina. On fluorescein angiography, these AV anastomotic channels do not leak.

TABLE 13–5. Classification of Proliferative Sickle Cell Retinopathy

Stage I	Peripheral arteriolar occlusion
Stage II	Peripheral arteriolar–venular anastomoses
Stage III	Neovascular proliferation
Stage IV	Vitreous hemorrhage
Stage V	Retinal detachment

Stage III represents the appearance of neovascularization from the AV anastomotic channels at the border of the perfused and nonperfused retina. These neovascular tufts demonstrate dye leakage on fluorescein angiography and have a characteristic fan-shaped appearance. With time, these sea fans may acquire surrounding fibroglial tissue.

Stage IV refers to the vitreous hemorrhage that occurs from peripheral neovascular fronds secondary to minor ocular trauma or vitreous contraction. Previous studies found that the associated risk factors for vitreous hemorrhage are HbSC disease, more than 60 degrees of perfused sea fans, and the presence of old hemorrhage in the vitreous that can lead to vitreous band formation, secondary vitreous traction, and subsequent vitreous hemorrhage.

Stage V represents tractional retinoschisis or tractional retinal detachment secondary to vitreoretinal traction bands and membranes. These bands may cause rhegmatogenous retinal detachments from full-thickness retinal break formation.

More commonly, the neovascular tufts tend to involute and regress with time and rarely lead to severe visual impairment.[42] Autoinfarction is thought to occur when the feeder vessel occludes. The mechanism for involution is possibly due to ischemia from fibroglial tissue strangulation of the feeder vessels.[43]

What Are the Local and Systemic Angiogenic Factors Associated with Proliferative Sickle Cell Retinopathy?

A study by Cao and colleagues demonstrated that autocrine production of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are associated with sea-fan formation.[44] This finding supported the previous hypothesis that local rather than systemic angiogenic factors are responsible for neovascular changes in sickle cell patients.

How Is Proliferative Sickle Cell Retinopathy Treated?

The more severe stages of proliferative sickle cell retinopathy are more common in children and adolescents, especially those with HbSC and S-thalassemia. Hence, the goal of treatment is early detection of neovascularization and eradication of new vessels before progression to more advanced stages of proliferative sickle cell retinopathy.

Treatment is not recommended for stage I and stage II disease. In the past, various treatment options, in-

cluding diathermy, cryotherapy, xenon-arc photocoagulation, and argon-laser photocoagulation have been used to treat peripheral retinal neovascularization. Today, laser photocoagulation to the area of peripheral neovascularization is most commonly used. Techniques vary widely and include feeder vessel photocoagulation, direct treatment of the neovascular frond, and treatment of the nonperfused ischemic retina anterior to neovascularization (Fig. 13–2). Ease of administration and fewer complications following scatter laser photocoagulation led Jampol and coworkers to recommend this approach as the initial therapy in most cases.[45–47]

Retinal occlusive events may be treated by exchange erythrocyte transfusion in patients with bilateral retinal vascular occlusion.[48] A follow-up case report in a 9-year-old boy with extensive perimacular arteriolar occlusions, however, did not demonstrate visual improvement, possibly secondary to treatment delay.[49] Therefore, further studies regarding the role of exchange erythrocyte transfusion and visual outcomes in the setting of macular and retinal occlusive change are warranted.

Wyburn–Mason Syndrome

Arteriovenous Malformations of the Retina

What Are Arteriovenous Malformations of the Retina?

Arteriovenous malformations (AVMs) result from the persistence of an embryonic vascular pattern in which arteries or arterioles communicate directly with veins or venules. Numerous terms have been used to describe this lesion, including racemose aneurysm, racemose angioma, AV aneurysm of the retina, retinal arteriovenous fistula, racemose hemangioma, cirsoid aneurysm, aneurysma racemosum retinae, congenital AV anastomosis, and aneurysmal varix.

The vascular malformation may range in size from one AV communication to a complex anastomotic system with indistinct arterial and venular components. There is a predilection for the papillomacular bundle and the temporal quadrants of the retina. AVMs differ from von Hippel-Lindau disease, which has an autosomal-dominant pattern.

What Are the Ocular Complications Associated with Retinal Arteriovenous Malformations?

Arteriovenous malformations may cause macular, preretinal, and vitreous hemorrhages, as well as central retinal vein occlusion (CRVO) and BRVO. Venous occlusive disease is thought to be associated with the spontaneous regression or remodeling of the AVM. Rare cases of secondary neovascular glaucoma have also been reported.[50,51]

What Is the Classification System of the Various Arteriovenous Malformations in the Retina?

In 1973, Archer and associates classified retinal AVMs into three groups.[52] Group 1 is characterized by an intervening abnormal capillary bed between the communicating artery and vein. The AVM is localized to one sector of the retina, often the macular area, and is usually an incidental finding on ophthalmoscopic examination. These anomalous communications rarely decompensate, and there is no fluorescein leakage; rarely, they involve the peripapillary structures. Association with other ocular anomalies or significant cerebrovascular malformations is uncommon, and visual acuity is not normally affected. There is no indication for treatment, and further evaluation for cerebral AVMs should not be pursued.

Group 2 describes AVMs with direct communication and without intervening capillary plexus or arteriolar elements. These may be single end-to-end junctions or multiple anastomoses with channels that are intermediate (100 to 200 μ) or large (200 to 300 μ) size. The afferent vessels may demonstrate beading and multiple fusiform dilatations within their walls with occasional aneurysm formation. Surrounding capillary beds may show dropout or nonperfusion.

These anomalous communications commonly remain stable over time, with rare instances of regression, thrombosis, and remodeling. Decompensation of the AVM may demonstrate fluorescein leakage, retinal edema, intraretinal exudates, and hemorrhage. In some instances, photocoagulation may be used to decrease the caliber of the afferent artery. Association with cerebral AVMs is uncommon. Carotid or cerebral angiography is not advisable unless adequate clinical suspicion exists.

Group 3 refers to AV communications that are extensive, complex, and have secondary retinal complications leading to severe visual impairment at an early age. The arterial and venous components of these AVMs are difficult to separate. The anastomosing channels are large in caliber (500- to 600-μ diameter) and cover most of the fundus; they develop fibromuscular coats within the media of the vessel, with a surrounding adventitial covering. The intervening retina may be attenuated with cystic degeneration.

Various degrees of vascular decompensation occur. Cerebral AVMs, the most common of these malformations, are part of this group.[52]

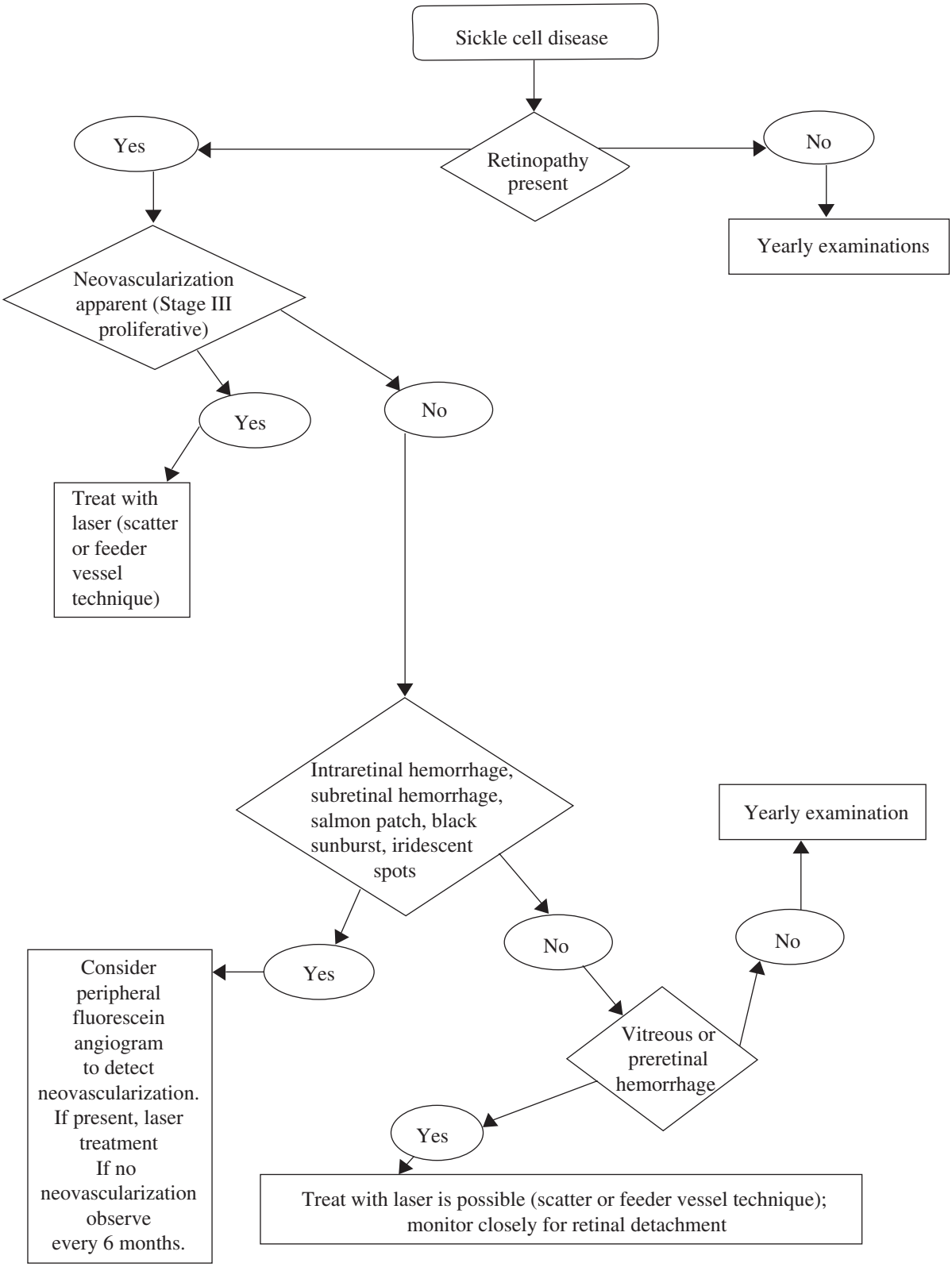

FIGURE 13–2. Clinical pathway: Sickle cell disease.

Is There an Association between the Retinal Arterio-Venous Malformation Group and Cerebral Arterio-Venous Malformation and Visual Prognosis?

Patients with group 1 or 2 retinal AVM tend to have a late presentation. Usually the lesion is an incidental finding on ophthalmoscopic examination with little or no visual deficit. There is rarely an association with cerebral AVMs.

Patients with group 3 retinal AVMs present at an earlier age and can have high degrees of visual deficit due to large lesions. They may be symptomatic from associated systemic AV communications. One study by Mansour and colleagues followed up on 88 cases with retinal AVM and found that the location of the systemic AV communications associated with retinal AVM included central nervous system (25%), orbit (8%), oronasopharyngeal area (7%), eyelid (2%), skin (1%), lung (1%), and spine (1%).[53]

Wyburn–Mason Syndrome

What Is Wyburn–Mason Syndrome?

Wyburn–Mason syndrome belongs to a rare group of disorders known as the phakomatoses, defined by AVMs affecting the visual pathways, midbrain, and subcutaneous facial structures. Extensive studies have failed to show an inheritance pattern, despite initial reports by Wyburn–Mason (Fig. 13–3). The disease is mainly unilateral[53] and does not appear to have a sex predilection. Patients become symptomatic in the second to third decade.

Are There Cutaneous Manifestations Associated with Wyburn–Mason Syndrome?

Facial angiomas in the distribution of the trigeminal nerve ipsilateral to the affected eye and cerebral lesion have been reported. These vascular nevi may be dramatic, as in those of Sturge–Weber syndrome, or may be subtle, presenting as erythematous skin lesions. Deeper structures of the face, including the frontal and maxillary sinuses and the mandible, may be involved, leading to severe epistaxis or gingival hemorrhage.[54]

What Are the Central Nervous System Manifestations of Wyburn–Mason Syndrome?

Typically, AVMs occur ipsilateral to the retinal lesion, most commonly in the midbrain. Patients may present with headache, seizures, or loss of consciousness resulting from the subarachnoid hemorrhage arising from the cerebral AVM. The severity of neurological signs and symptoms depends on the location and extent of the AVM.

Expansion of these intracranial vascular lesions may lead to intermittent hydrocephalus with elevated intracranial pressure, marked enlargement of the ventricles, headache, vomiting, and papilledema. On clinical examination, patients also may exhibit hemiparesis, hemiplegia, and Parinaud syndrome. In previous studies, these vascular malformations were not typically associated with seizures, and this was thought to be secondary to the greater depth of the AVMs.[55]

What Are the Ocular Findings Associated with Wyburn–Mason Syndrome?

Patients may complain of acute or gradual loss of vision. On fundus examination, there may be incidental findings consisting of direct AV communications between an enlarged and tortuous artery and vein. The lesions can vary widely in size, some presenting as large masses of tortuous and dilated vessels covering an extensive area of the retina. There may be cystic retinal degeneration between the vessels, causing impaired vision. These lesions typically affect the temporal retina and are characterized by a lack of pulsations.

On pathologic examination, the retinal vascular lesions have been shown to extend through the optic nerve, chiasm, and optic tract to the midbrain and cerebellum. There may be no visual impairment, or vision may regress to light perception. Retinal hemorrhages, vitreous hemorrhages, and mechanical compression of the optic nerve or the visual pathway may be responsible for the visual deficits.

Other orbital manifestations include optic nerve atrophy and enlargement of the optic foramen on imaging studies, proptosis, orbital bruits, and third-nerve signs with ptosis and ophthalmoplegia. The most common neuroophthalmic sign of intracranial AVMs is a homonymous hemianopia field defect.

How Is Wyburn–Mason Syndrome Diagnosed?

The signs and symptoms described, including the retinal lesion in combination with a patient presenting with headache, seizure, loss of consciousness, and focal neurologic deficits, is highly suspicious for the presence of unstable intracranial AVMs and mandates a complete evaluation.[56,57]

Patients with retinal AVMs should undergo visual field testing and a complete neurologic evaluation. Neuroimaging studies such as CT or MRI of the brain and orbits are recommended to rule out an intracranial AVM, primarily in patients with group 3 retinal AVMs. Digital subtraction angiography can be used to confirm the findings. Limited neurosurgical treatment may be indicated, depending on the results of these

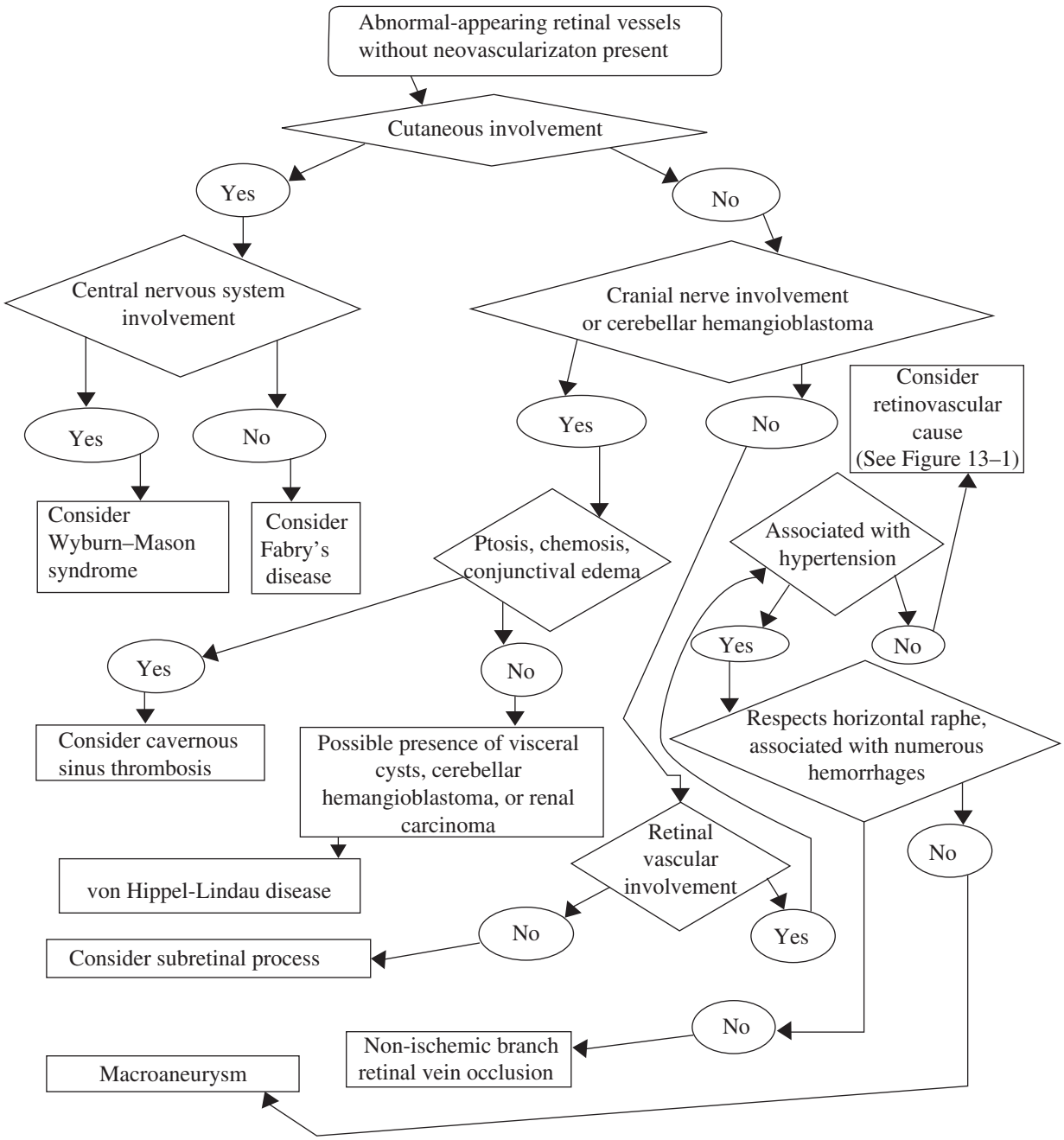

FIGURE 13–3. Clinical pathway: Abnormal-appearing retinal vessels without neovascularization.

studies. It is important to note that retinal involvement is not essential for the diagnosis of Wyburn–Mason syndrome.

How Is Wyburn–Mason Syndrome Treated?

Some AVMs remain stationary; however, most are dynamic structures that undergo substantial remodeling over time. Atrophy of some vessels concurrent with expansion and dilation of others may occur within the same lesion.

The high morbidity and mortality associated with these lesions is secondary to complicating subarachnoid hemorrhage. Patients may suffer from significant neurologic deficits and death, depending on the extent of hemorrhage. Because of their deep location within the brain, these vascular lesions are not amenable to neurosurgical resection. The visual

prognosis depends on the extent of retinal involvement and the presence of retinal or vitreous hemorrhage as well as the degree of optic nerve or visual pathway involvement secondary to mechanical compression from the AVM.

Fabry Disease

What Is Fabry Disease?

Fabry disease, or angiokeratoma corporis diffusum universale, is the second most prevalent metabolic storage disorder of humans following Gaucher disease.[58] Fabry disease is an inborn error of glycosphingolipid metabolism caused by defective activity of the lysosomal hydrolase, alpha-galactosidase A. This deficiency leads to accumulation of globotriaosylceramide, the glycolipid substrate of this enzyme, in cellular lysosomes.

Is There an Inheritance Pattern Associated with Fabry Disease?

Fabry disease is an X-linked recessive disorder with a reported incidence of 1:40,000 to 1:117,000 live births.[59,60] Based on genetic studies, it has been mapped to the Xq22.1 locus.[61] Men are predominantly affected, but many female carriers have similar clinical involvement.

What Is the Pathogenesis of Fabry Disease?

The deficiency of alpha-galactosidase A leads to lysosomal accumulation of the neutral glycosphingolipid globotriaosylceramide (Gb3) within vascular endothelium and smooth-muscle cells. It is also found in the renal epithelium, myocardium, dorsal root ganglia, autonomic nervous system, and brain.[62] This accounts for the symptoms and clinical findings associated with Fabry disease.

What Are the Systemic Manifestations of Fabry Disease?

Hemizygous males tend to be severely affected, whereas heterozygous female carriers appear to be minimally affected. Patients as young as 5 years of age may present with intermittent episodes of burning, aching pain in the hands and feet. These painful acroparesthesias are sometimes accompanied by elevated body temperature. On routine physical examination, neurologic abnormalities are not detected.

Cutaneous manifestations include dark red macules and papules known as angiokeratomas seen in a "bathing suit" distribution; however, these lesions may also involve the eyelids, oral mucosa, arms, fingertips, and abdomen. These develop in the first to second decade of life.

Fabry disease is potentially fatal. It can lead to renal failure as well as cardiovascular, gastrointestinal, and central nervous system disturbances. These organ systems are generally affected starting in the third decade of life (Table 13–6).

What Are the Ocular Manifestations of Fabry Disease?

Ocular manifestations do not tend to impair vision but are recognized as one of the distinctive hallmarks and earliest clinical manifestations of Fabry disease (Table 13–7). Aneurysmal dilatation of conjunctival veins is commonly seen. Whorl-like corneal opacities are seen in almost all hemizygotes and heterozygotes. These cream-colored opacities, corneal verticillata, are inferiorly located and appear to be in the subepithelial or Bowman layer of the cornea.

Two types of lenticular changes have been noted. The first is a granular, bilateral inferoanterior capsular opacity with a "propeller-like" distribution primarily in the inferior aspect of the capsule. This is noted

TABLE 13–6. Systemic Manifestations of Fabry Disease

Skin	Angiokeratoma
Cardiovascular	Myocardial infarction
	Valvular insufficiency
	Conduction defects
	Myocardial hypertrophy
Renal system	Renal insufficiency
	Renal failure requiring transplantation
Central nervous system	Ischemic seizures
	Ischemic strokes
	Transient ischemic attacks
Peripheral/autonomic nervous system	Acroparesthesias
	Vasomotor instability
	Gastrointestinal symptoms

TABLE 13–7. Ocular Manifestations of Fabry Disease

Conjunctiva	Venous aneurysmal dilatation
Cornea	Whorl-like opacity (verticillata)
Lens	Anterior "propeller" cataract
	Posterior "Fabry" cataract
Retina	"Corkscrew-like" diffuse vascular tortuosity
	Diffuse distribution
	No neovascularization
	Central retinal artery occlusion (rare)
	Anterior ischemic optic neuropathy (rare)

mainly in the male hemizygotes. Another posterior capsular opacity, known as the Fabry cataract, is best seen by retroillumination. These opacities appear to radiate from the posterior sutures and have the appearance of spokelike or dendritic projections.[63]

Studies have shown that retinal vascular changes are more prevalent in hemizygous males (70% versus 25% in the heterozygous females). Retinal findings consist of varying degrees of venous vascular tortuosity commonly seen at AV crossings. The more severe form has been described as having a "corkscrew-like" appearance. Retinal changes have a diffuse distribution. There have been reported cases of CRAO as a complication of Fabry disease.[64–67] There are no reported cases of neovascularization, and there has been a reported case of anterior ischemic optic neuropathy in association with cilioretinal artery occlusion in a Fabry patient.[68]

How Is Fabry Disease Diagnosed?

The ocular and cutaneous findings of Fabry disease are among the earliest clinical manifestations. A positive family history and a marked decreased activity of alpha-galactosidase A within white blood cells or cultured skin fibroblasts confirm the diagnosis. Also, immunofluorescent staining can be used to detect glycosphingolipid in exfoliated renal tubular cells obtained from a urine specimen.[69]

How Is Fabry Disease Treated?

Visual acuity is not typically affected in Fabry disease, except in cases of CRAO or anterior ischemic optic neuropathy. Renal failure and cardiac and nervous system defects are managed medically.

Currently, etiology-based therapies are under development; these include enzyme replacement therapy, gene therapy, and substrate deprivation. A recent double-blind, placebo-controlled clinical trial of intravenous infusions of alpha-galactosidase A in patients with Fabry disease demonstrated promising results.[70,71] By correcting the metabolic defect via infusion of exogenous lysosomal enzymes, the function of individual cells may be improved, thereby preventing further deterioration of organ function and possibly reversing the disease process.

Cavernous Sinus Thrombosis

What Is Cavernous Sinus Thrombosis?

In the modern antibiotic era, a septic cavernous sinus thrombosis (CST) arises from a dural AVM or carotid cavernous fistula thrombosis. The most common cause of CST formerly was considered to be an infection of the sphenoid and ethmoid sinuses. The second most common cause was otitis media followed by maxillary dental infections, which accounted for 10% of the dural infections. Rarely, CST may arise from the hematogenous spread of a systemic infection. Prior to the use of antibiotics, the mortality from CST was 100%. Now, with appropriate therapy, mortality has decreased to below 30%. Morbidity remains in the 50% range due to blindness, cranial nerve palsy, coma, and neurologic sequelae.[72]

What Are the Signs and Symptoms of Cavernous Sinus Thrombosis?

Symptoms of CST result from the congestion of the orbital venous system. CST may be difficult to distinguish from orbital cellulitis. Patients classically present with proptosis, eyelid edema, conjunctival injection, chemosis, ophthalmoplegia, and pupillary palsy. Complete loss of vision occurs in about 10% of cases. In cases of septic CST, patients also may have an elevated white blood cell count with a left shift, elevated ESR, and possible increased C-reactive protein. Advancement of symptoms to the contralateral eye is due to an extension of the clot and is considered pathognomonic.

Bacterial orbital apex syndrome (OAS), orbital cellulitis, and orbital inflammatory syndromes are often difficult to distinguish from CST, given the similar presentations of proptosis, chemosis, and injection. OAS classically presents with visual loss, optic nerve dysfunction, and ophthalmoplegia. These signs and symptoms are not proportional to the apparent orbital inflammation; they often precede other signs of orbital inflammation, such as lid edema and chemosis. Unilateral and bilateral symptoms and the amount of optic nerve dysfunction distinguish OAS from CST.[73] The preceding diagnoses must be excluded early to ensure proper and timely treatment of CST.

What Is the Visual Prognosis in Cavernous Sinus Thrombosis?

Visual loss is uncommon in CST. In rare cases, nonarteritic anterior ischemic optic neuropathy is associated with CST, secondary to decreased perfusion through the posterior ciliary arteries resulting from elevated intraorbital and intraocular pressures.[74] A case of a 60-year-old woman with CST with secondary BRAO and anterior ischemic optic neuropathy has been reported. Presumably, the BRAO was caused by an embolic occlusion following septic CST. Vision

decreased to light perception 2 days later due to embolic or vasculitic ischemic optic neuropathy. An embolus from a focus of carotid arteritis within the CST could have been responsible for further visual loss due to anterior ischemic optic neuropathy in such cases.[75] Another case of a patient with CST and bilateral visual loss due to CRAO and anterior ischemic optic neuropathy has also been reported.[76]

Overall, visual loss may result from corneal ulceration secondary to poor lid closure, mechanical pressure at the orbital apex producing occlusion of the central retinal vein, emboli to the retinal arteries, arteritis of the internal carotid artery causing impaired perfusion of the ophthalmic artery, and ischemic optic neuropathy. The main factors affecting visual outcome in CST remain early recognition, appropriate selection of empirical antibiotic therapy, and the awareness of associated complications.

How Is Cavernous Sinus Thrombosis Diagnosed?

The diagnosis may be made clinically, but radiologic studies are more definitive. Patients often have the classic presentation, with eyelid edema, ptosis, chemosis, and injection. Funduscopy may demonstrate generalized, bilateral increased venous tortuosity. Findings consistent with secondary CRAO, BRAO, or anterior ischemic optic neuropathy may or may not be present. These findings can be confirmed with fluorescein angiography.

The best neuroimaging study to establish the diagnosis of CST is MRI. A main advantage is its ability to highlight various stages of thrombosis.[77] CT cannot establish the diagnosis of CST but can rule out intracranial abscess.

Carotid angiography can demonstrate areas of attenuation along the intracavernous portion of both internal carotids consistent with focal inflammation. This inflammation and its secondary changes may lead to subsequent ophthalmic artery ischemia. The venous phase of selective internal carotid arteriography may demonstrate a reversal of normal venous drainage at the skull base with poor filling of the cavernous sinus. These findings confirm the diagnosis of CST. In a critically ill patient, a venogram may be more beneficial and appropriate than an arteriogram.

How Is Cavernous Sinus Thrombosis Treated?

The underlying cause must be determined and, when indicated, appropriate antibiotic therapy must be quickly initiated. Patients should receive anticoagulation with heparin in most cases. This is thought to prevent both further thrombosis of the venous sinus and multiple septic infarcts in the lungs, brain, orbit, and kidneys. Blood cultures should be obtained as soon as the diagnosis is suspected. In immunocompromised patients, fungal infections must be considered, and treatment should include antifungal therapy with necessary surgical debridement.[78] In appropriate cases, steroid therapy may decrease orbital inflammation and possibly prevent vascular collapse secondary to pituitary dysfunction.[79]

Coats' Disease

What Is Coats' Disease?

Coats' disease is a sporadic, nonhereditary condition characterized by idiopathic retinal telangiectasia and intraretinal or subretinal exudation without appreciable signs of vitreoretinal traction.[80–82] Coats' disease is commonly unilateral, and there is no genetic, familial, racial, or ethnic predisposition. Coats' disease has a predilection for gender, 76% of patients being males. Birth history, medical history, and family history are nearly always negative. Most patients are diagnosed in the first or second decade of life.

What Are the Signs and Symptoms of Coats' Disease?

In children, the common presenting sign is leukocoria or strabismus. Some patients present with complaints of decreased vision. Other presenting signs include pain, heterochromia (due to iris neovascularization), and nystagmus. The anterior segment findings are usually normal with the occasional findings of corneal edema, iris neovascularization, and anterior chamber cholesterolosis. A considerable percentage of patients are asymptomatic.

What Is the Pathogenesis of Coats' Disease?

The etiology of Coats' disease is unknown. The retinal manifestations are thought to be due to abnormal permeability of the vascular endothelium, leading to a breakdown of the blood–retinal barrier. There is subsequent leakage of lipid-rich exudates and a formation of an exudative retinal detachment.

What Are the Retinal Findings Associated with Coats' Disease?

These findings include one or more localized foci of retinal telangiectasia (Fig. 13–4) with variable amounts of surrounding retinal edema and lipid exudates within and beneath the neurosensory retina. Most telangiectasias are located in the inferior and temporal

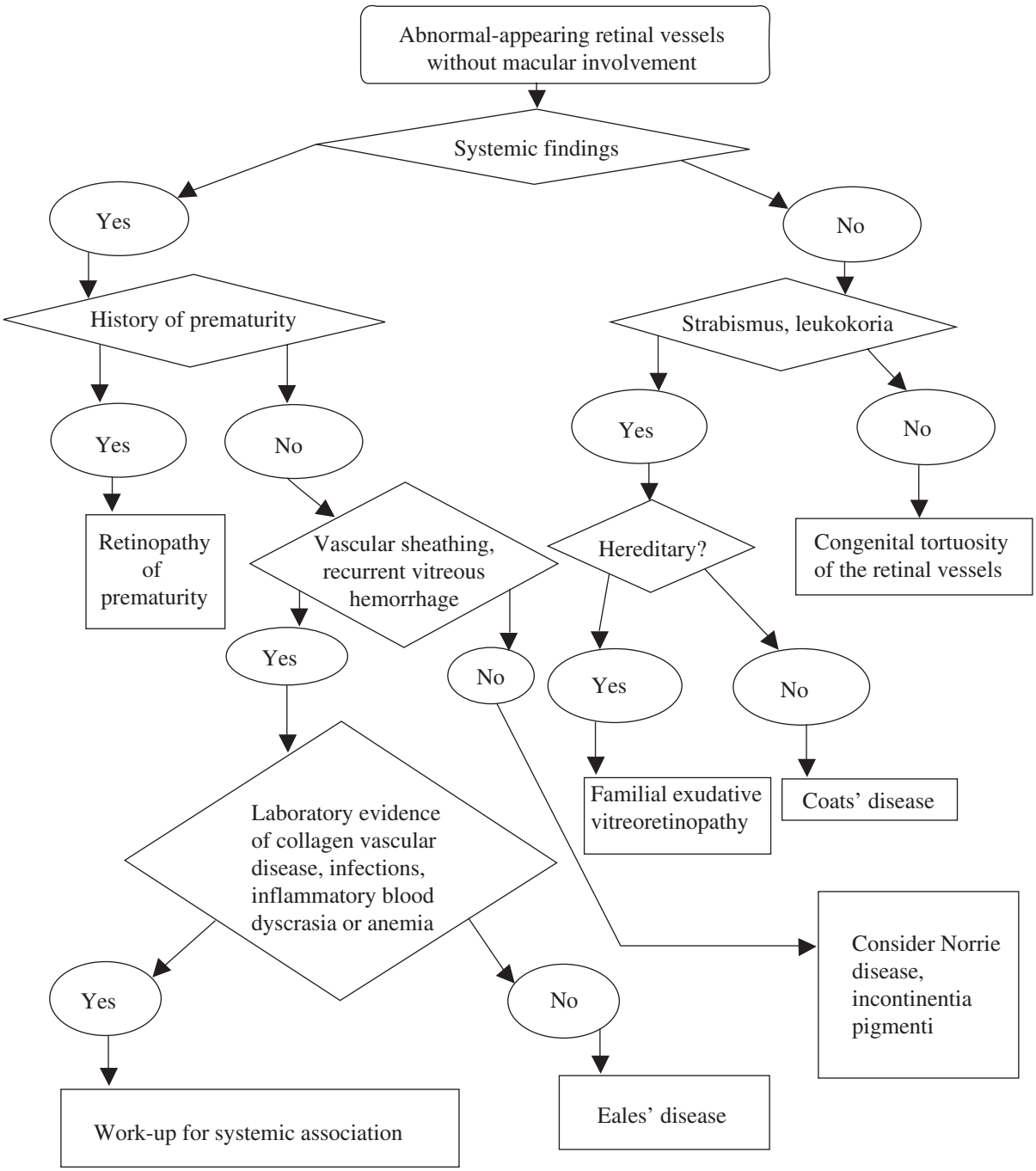

FIGURE 13–4. Clinical pathway: Abnormal-appearing retinal vessels without macular involvement.

quadrants between the equator and ora serrata, with about one third extending posterior to the equator toward the vascular arcades.[80] Microaneurysms, areas of capillary nonperfusion, and light-bulb dilatations of retinal venules are also noted.

Lipid exudation involves the retina diffusely with preferential involvement of the macula. When macular exudation has a dense consistency or a gray intraretinal fibroglial component, poor visual prognosis is expected. Preretinal fibrosis is also associated with Coats' disease. Although Coats' disease is characterized by areas of capillary nonperfusion in the telangiectatic quadrants, neovascularization of the disc and periphery is uncommon.

TABLE 13–8. Coats' Disease Staging Classification

Stage 1	Retinal telangiectasia only
Stage 2	Telangiectasia and exudation
	A. Extrafoveal exudation
	B. Foveal exudation
Stage 3	Exudative retinal detachment
	A. Subtotal detachment
	a. Extrafoveal
	b. Foveal
	B. Total retinal detachment
Stage 4	Total retinal detachment and glaucoma
Stage 5	Advanced end-stage disease

What Are the Fluorescein Angiographic Findings in Coats' Disease?

Early hyperfluorescence of the telangiectasia, hypofluorescence of the exudation, and late, mild hyperfluorescence of the subretinal fluid are characteristic. Areas of capillary nonperfusion are seen in telangiectatic areas. Retinal neovascularization is rare.[83] Late angiograms can demonstrate central hyperfluorescence from macular edema.

What Is the Classification System for Coats' Disease?

In the past, some researchers classified Coats' based on age at presentation and severity of clinical findings. Recently, Shields and colleagues proposed a staging classification for Coats' disease applicable to treatment selection and ocular prognosis[81] (Table 13–8).

How Is Coats' Disease Diagnosed?

Clinical findings and the results of fluorescein angiography, ultrasonography, CT, and sometimes MRI aid in the diagnosis. Some studies suggest aspiration of the subretinal fluid and cytologic diagnosis in cases presenting with a subretinal mass.

The differential diagnosis involves a vast differential that includes diabetes, hypertension, hyperlipidemia, AMD, retinal capillary hemangiomatosis, arterial macroaneurysm, familial exudative vitreoretinopathy, primary vasoproliferative tumor, retinitis pigmentosa with exudative retinopathy, BRVO, juxtafoveal telangiectasia; inflammatory or infectious retinal vasculitis, and angiomas (such as von Hippel-Lindau syndrome).

The most common misdiagnosis is retinoblastoma. Young males are commonly referred for evaluation of a subretinal mass thought to be retinoblastoma. Ultrasonography findings commonly demonstrate a retinal detachment but no solid mass or calcification. In advanced Coats' disease, osseous metaplasia of the RPE can induce high echogenicity that may simulate calcium in a retinoblastoma. Its curvilinear pattern differentiates it from the more random distribution of calcified foci in retinoblastoma. Cytopathologic evaluation of subretinal fluid by sclerotomy or fine-needle aspiration biopsy may demonstrate the presence of lipid-laden macrophages and cholesterol crystals, aiding in the diagnosis.[84]

Other common diagnoses submitted by referring physicians include retinal detachment, retinal hemorrhage, toxocariasis, choroidal melanoma, choroidal hemangioma, choroidal coloboma, endophthalmitis, cytomegalovirus (CMV) retinitis, retinopathy of prematurity (ROP), traumatic retinopathy, and toxoplasmosis.

What Is the Visual Prognosis in Coats' Disease?

Recent studies have shown several factors associated with poor visual outcome in patients with Coats' disease. These risk factors include nonwhite race; diffuse, postequatorial, and superior location of the telangiectasias and exudation; failure of exudation to resolve after treatment; and presence of retinal macrocysts[82] (Table 13–9).

The natural history of the disease is the development of an exudative retinal detachment progressing to total retinal detachment if no treatment is given. Some patients undergo enucleation for severe angle-closure glaucoma or a blind, painful eye without glaucoma. In one study, the most significant risk factors predictive of enucleation were elevated intraocular pressure, iris neovascularization, and heterochromia (usually secondary to iris neovascularization).[82] Overall, the extent, severity, and prognosis of the secondary retinal detachment are worse if diagnosed in younger children, particularly those under 3 years of age.

How Is Coats' Disease Treated?

The primary goal of treatment should be eradication of abnormal retinal vessels to facilitate resolution of exudation and salvage the globe and vision. Treatment in-

TABLE 13–9. Risk Factors for Poor Visual Outcome in Coats' Disease

Nonwhite race
Location of telangiectasia and exudation
Diffuse
Postequatorial
Superior
Persistent exudation posttreatment
Presence of retinal macrocysts

cludes observation, laser photocoagulation, cryotherapy, and surgical approaches to reattach the retina. It is important to realize, however, that patients undergoing treatment may continue to develop telangiectasias up to 10 years after the start of therapy. These patients mandate close monitoring and may require additional treatment based on clinical presentation.

Observation may be used in selected cases of Coats' disease. The first group is those with stage 1 and 2A disease with mild exudation. The second group is those with blind but comfortable eyes without hope of visual recovery (stage 3B and stage 5 disease).

Laser photocoagulation to the telangiectasia can be performed in cases of retinal exudation without retinal detachment. Cryotherapy, using a double freeze–thaw method, is used in cases of shallow retinal detachment. The patient should be reevaluated 3 months after laser photocoagulation or cryotherapy. If vascular changes persist and exudation does not resolve, a second treatment should be given. Drainage of subretinal fluid may facilitate the treatment of telangiectasia in selected cases. Enucleation is recommended for patients with stage 4 disease (total retinal detachment with glaucoma) to relieve severe ocular pain.

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14

Macular Membranes and Holes

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Macular Holes

What Is a Macular Hole?

A *macular hole* is a central retinal hole that may be the end stage of an evolving full-thickness macular dehiscence, a contracting premacular membrane, macular trauma, or macular cyst formation either with or without associated macular edema. Idiopathic macular holes are more common than macular holes associated with trauma, inflammation, edema, or myopia. As a result, attention is focused here on idiopathic macular hole development and management. Because treatments for macular holes may be quite involved, they must be differentiated from macular-hole–like lesions, such as a macular cyst or macular pseudohole. Epiretinal membranes (ERMs) can mimic macular holes and may be idiopathic or the result of surgical intervention or inflammatory insult. Both ERMs and macular holes share some common pathogenic mechanisms, but the resulting structural changes and treatments are distinct and therefore are described separately.

What Are the Symptoms of a Macular Hole?

Patients note a unilateral decrease in central vision with or without metamorphopsia (Fig. 14–1). Some patients report an increase in floaters and a central scotoma. Often symptoms are noticed when a patient covers the fellow eye. A fully developed macular hole typically causes vision loss to the level of 20/60 or worse.

What Are the Signs of a Macular Hole?

Macular holes are full-thickness holes in the retina generally involving the central foveal tissue. They are usually easily diagnosed with a contact lens or with indirect slit-lamp biomicroscopy (typically using a 78- or 90-diopter lens). A cuff of retinal detachment surrounds a dark, round defect in the fovea. Macular holes must be distinguished from the masquerading condition of the pseudomacular hole, which is a hole in a premacular membrane. Both may benefit from surgery if there is associated vision loss. Features associated with idiopathic macular holes include a yellow central macular spot or ring in the case of a premacular hole. Once a full-thickness defect has developed, a pseudooperculum may be seen. This is not a true operculum but rather a cellular condensation of the posterior vitreous that has detached from the retinal surface. With time, intraretinal cysts may form at the edge of the hole, and fine striae or associated ERMs of variable size may be seen in association with the edge of the macular hole. In the end stage of a mature full-thickness macular hole, fine yellow deposits are seen on the retinal pigment epithelium surface (RPE) (Table 14–1).

What Are the Historical Concepts of Pathogenesis of Macular Holes?

There are three basic concepts of macular hole formation: trauma, cyst development, and vitreous or retinal surface traction.

In the *traumatic theory* of macular hole development, it is postulated that forces are transferred to the macula via the vitreous body along various attachment points, one of which is at the foveola. Abrupt rotation of the globe can affect tangential traction at the vitreomacular interface. The vitreous is most strongly attached to the retina at the vitreous base, along the major arcades, the optic nerve, and at 1500-μ diameter rim surrounding the fovea and the 500-μ diameter foveola. In addition, stretching of the globe during impact causes stretching of the retina. The foveal retina may be more susceptible to damage because it is relatively thinner. If tractional forces become

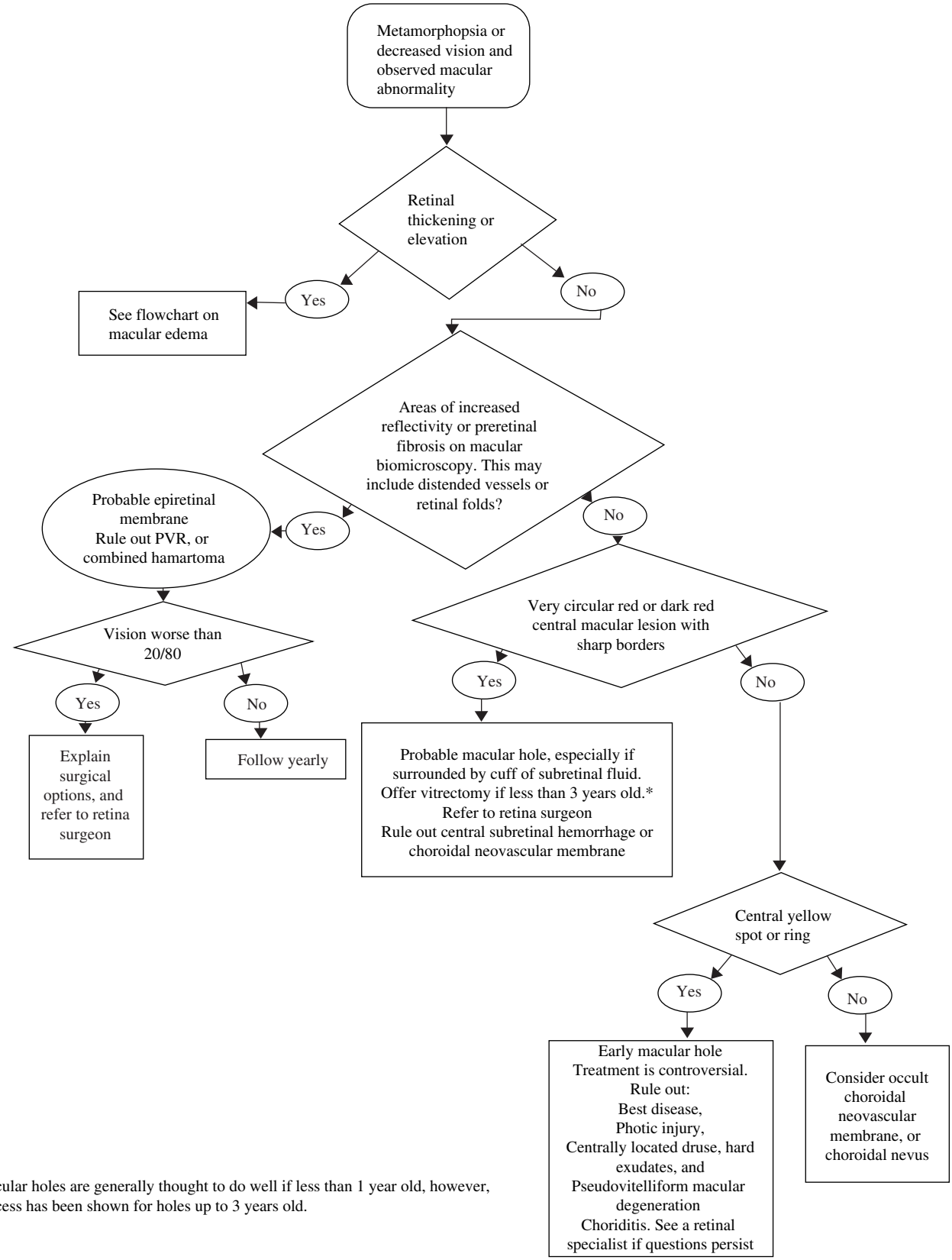

FIGURE 14–1. Management of metamorphopsia or decreased vision associated with an observed macular abnormality. PVR, proliferative vitreoretinopathy.

TABLE 14–1. What Features Can Help Differentiate Vitreomacular Traction (VMT) Syndrome from an Epiretinal Membrane (ERM)?

	ERM	*VMT*
Age (yr)	60–70	60–70
Surgical anatomy	Complete PVD (80%)	Incomplete PVD
Pathology	RPE cells, glial cells, new collagen	Glial cells, new collagen
Traction vector	Tangential	Anteroposterior, tangential

PVD, posterior vitreous detachment; RPE, retinal pigment epithelial.

greater than the cohesive forces, macular holes can result.[1]

The *cystoid theory* holds that aging causes cystoid changes within the fovea. The coalescence of these cystoid spaces is implicated in the formation of macular holes.[2] The relatively weak associations between most macular holes and cystoid macular edema (CME) or epiretinal membranes argue in favor of newer theories involving the vitreous.

What Are the Current Ideas Regarding the Pathogenesis of Macular Holes?

Gass suggested that tangential tractional forces along the retinal surface from a shrinking cortical vitreous are a possible cause of macular holes.[3] This theory is incorporated into his widely accepted staging of macular holes. Both the "tangential traction theory" and the staging of macular holes are discussed in a separate section in this chapter. Recent work with optical coherence tomography (OCT) has shed new light on the initial stages of macular hole formation. It appears that, in many cases, the inciting event is an incomplete posterior vitreous detachment (PVD) with residual vitreous attachment at the fovea. During this event, radial retinal striae and cystoid formations at the foveola are seen. Complete PVD results in one of the following events: (1) the cystoid spaces resolve; (2) unroofing of a cystoid space occurs, and a lamellar macular hole forms; or (3), if there has been a dehiscence of the floor of the cystoid space, a full-thickness macular hole develops (Fig. 14–2).[4,5]

Because of variations in local foveal anatomy, most eyes do not develop full-thickness macular holes or early premacular hole findings. Some associated factors in the formation of macular holes include the relative tensile strength and health of the native fovea (foveal susceptibility), the strength of the vitreofoveal attachments, and the nature of the PVD.[5]

What Is the Histology of Macular Holes?

Microscopically, macular holes are seen as round or oval retinal defects surrounded by rounded retinal edges and a cuff of detached neurosensory retina with subretinal fluid present. In one report, intraretinal cystoid edema and variable amounts of photoreceptor atrophy were present in most eyes (78%), especially near the edge of the hole.[6] An ERM was present in 68% of these eyes.

The role of ERMs in the development of macular holes is not clear. Although ERMs may be associated with CME, most eyes with ERMs do not develop macular holes. The presence of ERMs on histologic specimens may represent a local inflammatory response to macular hole formation.[6]

Studies of removed pseudoopercula show that they are composed of contractile glial elements and RPE cells and do not contain displaced neurosensory photoreceptor cells. Fibrous astrocytes and Muller cells are the predominant components.[7]

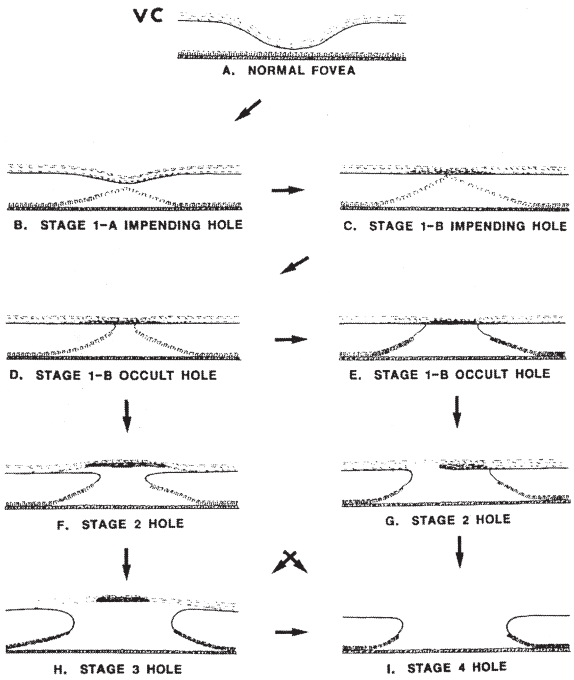

FIGURE 14–2. The Gass classification for macular hole staging.

What Is the Gass Classification for Macular Holes?

Gass and Joondeph are credited with recognizing the yellow spot and ring as the initial presentation of macular holes.[3,8] They described a classification scheme that categorizes the development of a macular hole into several stages. This system of macular hole classification is widely used and correlates well with clinical observations (Fig. 14–2).

Stage 1 macular hole (foveolar detachment) is characterized by a central yellow spot (stage 1A, impending hole) or a yellow ring (stage 1B, occult hole) and loss of the foveal depression. These are not true holes because there is no full-thickness dehiscence of the retinal tissue. The cortical vitreous is attached to the fovea, and the yellow spot that develops is thought to be the result of xanthophyll pigment that has become more visible because of retinal detachment from the RPE. In a stage 1B occult hole (yellow ring), an occult dehiscence may occur under the contracted prefoveolar vitreous cortex and may be kept closed by the overlying vitreous. Visual acuities are in the range of 20/25 to 20/40. Most stage 1 holes do progress, although some show resolution with completion of the PVD.[9]

Stage 2 macular holes (early full-thickness macular hole) result from continued vitreous traction and enlargement of the yellow ring with the formation of a foveal hole or dehiscence associated with a cuff of subretinal fluid (Fig. 14–3). The posterior vitreous cortex is still attached to the retina, and radial striae may be seen around the edges of the hole at the level of the inner retina and the internal limiting membrane. The retinal defect inside the yellow ring may be oval, crescent, or horseshoe shaped. The full-thickness tear may begin at the center of the fovea and expand in a symmetric manner. Alternatively, a full-thickness tear may begin in an eccentric location in the fovea and extend in a can-opener manner to form a crescent-shaped hole. Visual acuity is in the range of 20/40 to 20/100. Most stage 2 holes gradually enlarge and progress to stage 3 holes within several months.

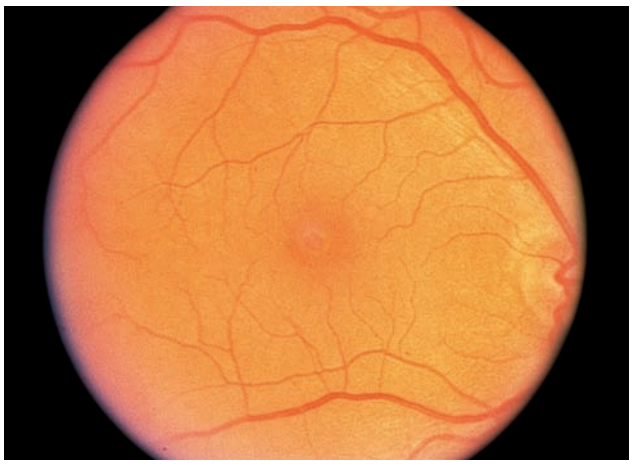

FIGURE 14–3. Early full-thickness macular hole (stage 2 by Gass classification).

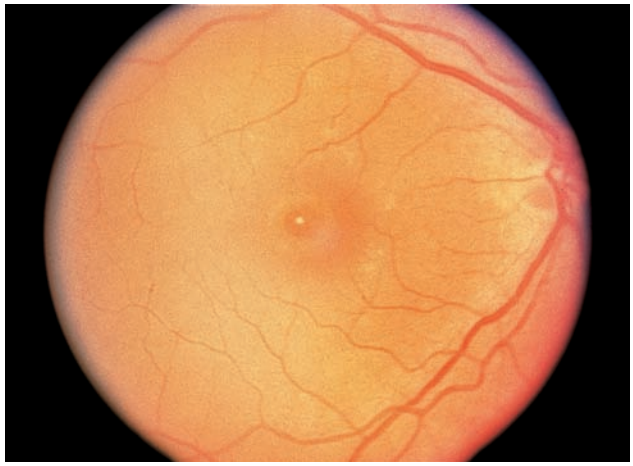

FIGURE 14–4. A stage 3 macular hole is shown with a white nodular deposit at the base of the hole.

Stage 3 macular holes (fully developed macular holes without complete PVD) are characterized by further enlargement of the retinal defect to 400 μ or more in diameter. A localized PVD overlying the hole may be detected if there is a pseudooperculum. As the hole enlarges, discrete white nodular deposits are seen at the base of the hole, representing RPE reaction (Fig. 14–4). Vision is in the range of 20/60 to 20/400.

Stage 4 macular holes (full-thickness macular hole with complete PVD) are round retinal defects with a rim of elevated retina. The presence of a Weiss ring confirms the completed PVD. The size of the hole and the level of vision loss will stabilize at this stage for most patients. If progressive, visual loss occurs, it is likely to be due to photoreceptor atrophy, cystoid changes at the border, or accumulation of subretinal fluid under the hole. A prefoveolar opacity may or may not be seen in the case of stage 3 or 4 macular holes. The presence of the pseudooperculum indicates a good prognosis because it indicates separation of the cortical vitreous from the fovea.

What Is a Lamellar Macular Hole?

A *lamellar* macular hole is a partial-thickness loss of the foveal retina. It resembles a round or petal-shaped red depression in the inner retinal surface. Lamellar macular holes may be due to the unroofing of a foveal cyst secondary to vitreous traction on the fovea. The floor of the cyst remains attached to the RPE; hence, it is a partial-thickness defect in the neural retina.[4]

What Are the Risk Factors for Developing Macular Holes?

The Eye Disease Case Control Study Group studied the risk factors for development of full-thickness macular holes and compared 198 subjects with macular holes with 1023 normal controls. Although the study group did not look at vitreomacular relationships or involutional macular thinning as factors, they found that older age and female sex were risk factors.[10] Seventy-two percent of patients with macular holes were female, whereas fewer than 3% of macular holes were found in patients less than 55 years old. Data from recent studies suggest that an abnormally strong vitreomacular attachment combined with impending PVD substantially increases the risks for developing macular holes.[5]

What Is the Risk in the Fellow Eye?

Risk of development of a macular hole in the fellow eye ranges from no risk to 28%, depending on the study. The normal fellow eye without a PVD in patients with a unilateral full-thickness macular hole has a 10 to 20% risk of developing a macular hole within 5 years. The presence of a complete PVD seems to confer protection and lowers the risk to less than 1%. In fellow eyes with an impending macular hole, the risk is much higher, in the range of 40 to 60%.[9,11,12]

What Should Be in the Differential Diagnosis for Impending Macular Holes?

The differential diagnosis should include lamellar holes and pseudomacular holes. In these cases, a raised retinal edge will not be seen. Alternate diagnoses that must be ruled out include central serous retinopathy, solar and inflammatory maculopathy, pigment epithelial detachment, a centrally located druse, CME with central macrocyst, subfoveal choroidal neovascularization, and vitreomacualar traction (VMT) syndrome.[8,13] In VMT syndrome, the entire foveola may be elevated above the plane of the retina, visible on slit-lamp biomicroscopy or with the aid of OCT. In solar retinopathy and a centrally located druse, there will be preservation of the foveal depression. Although a yellow spot could be seen from other disease processes, the change from a yellow spot to a yellow ring is quite specific to patients developing a macular hole.

Some entities that mimic macular holes can be distinguished by fluorescein angiography (FA), including choroidal neovascularization, CME, and central serous retinopathy. In early central areolar choroidal dystrophy, mild atrophy of choriocapillaris under the fovea can give the appearance of a full-thickness macular hole, a round red lesion. Careful examination will reveal an intact neurosensory retina without the typical rim of subretinal fluid surrounding the red circular lesion.

How Can Epiretinal Membranes Mimic Macular Holes?

Epiretinal membrane contraction can cause foveal detachment, mimicking an impending macular hole. ERMs with a central round opening and pseudoholes have been mistaken for macular holes.[8,13] The presence of a crinkled reflex from the inner retinal surface surrounding the hole and the absence of a perifoveal ring of retinal detachment, operculum, or yellow deposits at the level of the pigment epithelium centrally are the features of a hole in an ERM. If the hole is in a membrane rather than in the retina, visual acuity is often better than 20/40.

How Do You Differentiate a Lamellar Macular Hole from a Full-Thickness Hole?

Inner retinal lamellar (partial-thickness) holes typically have vitreofoveal separation and often are accompanied by an operculum, the presence of a foveal depression, and one sharply demarcated round, oval, or petal shaped depression in the inner retinal surface. In contrast, stage 1 lesions will have loss of foveal depression. Angiographically, lamellar holes are differentiated from stage 2 or 3 holes by minimal or a complete lack of hyperfluorescence, whereas full-thickness holes typically show moderately intense early hyperfluorescence in the area of the hole. Lamellar holes do not have a rim of detached retina, unlike full-thickness macular holes. The key to proper diagnosis and staging of macular holes is contact fundus biomicroscopy through an adequately dilated pupil. This will allow for better delineation of flat versus elevated structures and preretinal membranes as well as vitreous condensation. OCT may be a helpful test to correlate the physical findings.

What Are Some Conditions That Have Been Associated with Macular Holes?

Macular holes have been reported in association with other conditions. Some of these include proliferative diabetic retinopathy, pan-retinal photocoagulation for diabetic retinopathy, high myopia, choroidal neovascularization, Best disease, adult vitelliform macular degeneration, trauma, topical pilocarpine, scleral buckle operations, and pneumatic retinopexy for retinal reattachment.[9,11]

What Diagnostic Tests Would Be Appropriate?

Fluorescein angiography is nonspecific for stage 1 macular holes. FA may or may not demonstrate hyperfluorescence. When there is a defect in the

neuroretina, as in stage 2 and beyond, early transmitted fluorescence may be seen in the area of the hole. Sometimes the early transmitted fluorescence may be blocked by the pseudooperculum, showing hypofluorescence. Although it is a nonspecific test for diagnosing macular holes, FA is useful to rule out other macular entities that have classic findings such as CME, choroidal neovascularization, and central serous chorioretinopathy. Other modalities, such as OCT, are more sensitive in defining the anatomic relationships between the cortical vitreous and retina and in showing intraretinal detail; however, OCT is not always available.

Perhaps the simplest test is the Watzke-Allen test.[14] This is especially helpful in differentiating between impending or full-thickness macular holes and masquerade syndromes. A narrow beam of light from a slit lamp is shone passing through the foveola, and the patient is asked to describe what he or she sees. If the patient reports that he sees a break in the white line (positive Watzke sign), it can be assumed that a defect in the retina exists. Patients with impending macular holes and their mimickers will either report a straight line or a line with thinning in the middle.

Alternatively, a 50-μ aiming beam can be aimed at the lesion. Patients with macular holes will not see the aiming beam as it passes over the macular hole. The beam will seem to disappear once it passes over the lesion.

What Is the Management of Macular Holes?

Standard treatment of macular holes is pars plana vitrectomy with complete cortical vitreous detachment and injection of a nonexpanding mixture of long-acting intraocular gas with prone positioning for at least 1 week.[15] Silicone oil can be used as the tamponade agent if the patient is unable to tolerate face-down positioning.[16] Because about half of stage 1 lesions resolve with relatively good vision, most clinicians wait until the lesion has progressed to stage 2 before considering repair.[17]

The 1990s saw the development of adjuvant use in the treatment of macular holes. Usually, the adjuvant is added in the area of the macular hole at the end of vitrectomy in hope of either providing tamponade or acting as tissue adhesive by promoting wound healing. Anatomic closure rates range from 64 to 100%, with functional success from 33 to 100%. A recent meta-analysis showed a greater than 80% chance of success for macular hole surgery in general. Postoperative vision of greater than 20/40 has been reported in up to 49% of patients.[17]

Recently, internal limiting membrane removal in addition to the standard treatment has been shown to have slightly improved anatomic success.[26,27] Good outcomes were obtained for repair of traumatic macular holes without use of adjuvants.[18] It is interesting to note that patients' vision can continue to improve beyond one year after successful anatomic repair.[19]

What Is the Stability of the Repair?

In a series of 390 operated eyes, there was a 4.8% rate of reopening of macular holes. In this series, the reopening occurred spontaneously. Ten of the 17 eyes had a history of cataract surgery, but only one cataract surgery case was thought to be directly responsible for macular hole reopening.[20] Another study reported a reopening rate of 9.5% in a series of 116 patients.[25] Reoperation resulted in good results for most patients.

What Can Complicate Macular Hole Repair?

The rates of anatomic and functional success after macular hole repair are very promising; however, posterior segment complications, such as endophthalmitis, rhegmatogenous retinal detachment, phototoxicity, enlargement of the hole, and RPE derangements have been reported. In addition, development of cataract or worsening of preexisting lens opacities is common. Secondary glaucoma, CME, visual field defects, and choroidal neovascular membranes also can complicate otherwise successful surgery.[21]

What Is the Natural History of Macular Holes?

Unoperated macular holes typically slowly enlarge, and the adjacent RPE atrophies. The vision stabilizes at a level of 20/200 to 20/400. The presence of an operculum, PVD, and ERM do not appear to be correlated with the visual morbidity.[22]

What Is the Prognosis for a Failed Macular Hole Repair?

For a macular hole that has reopened, the rates of success of a second operation are similar to that of the first operation. If the hole detaches a second time, 75% of patients can be expected to obtain anatomic improvement and 56% can be expected to attain both anatomic and functional improvement.[23] If the initial two surgeries for repair have been unsuccessful, a third attempt at repair showed no benefit. For long-standing macular holes (longer than 6 months), anatomic closure was still effective in improving vision. Rates of anatomic closure are slightly less than repairs made for holes of less than 6 months' duration. Alternatively, up to 98% achieve anatomic closure if repaired before 6 months. Long-standing cases are limited to about 70% closure rates by standard techniques.[24]

Epiretinal Membranes

What Are Epiretinal Membranes?

Different cells types can gain access to the inner surface of the retina and proliferate to form fibrocellular tissue, which forms thin membrane sheets that cover the retinal surface. Numerous and overlapping terms have been used to describe such proliferative membranes: *ERM, premacular membrane, preretinal macular fibrosis, surface-wrinkling retinopathy, cellophane maculopathy,* and *macular pucker.*[28,29] ERM can be secondary to many ocular conditions, such as ocular inflammatory disease, retinal vascular disease, rhegmatogenous retinal detachment, and accidental or surgical trauma, particularly after retinal cryotherapy or photocoagulation. RPE cells are observed to be the primary cell type in this condition.[30,31] ERM may also be idiopathic, unassociated with any ocular disorder. The primary cell type recognized in idiopathic ERM is the fibrous astrocyte.[32]

What Are the Symptoms of an Epiretinal Membrane?

Patients affected with ERM may be asymptomatic in most cases. Membranes that are asymptomatic do not cause distortion of underlying foveal photoreceptors or are eccentric to the fovea. If retinal distortion occurs, patients may recognize variable degrees of vision loss, metamorphopsia, and micropsia (Fig. 14–1). Some may complain of an acute loss of vision with accompanying distortion over a period of a several weeks, although the actual onset and duration of symptoms are difficult to ascertain.[28,33]

What Are the Signs of an Epiretinal Membrane?

The clinical features of an ERM vary, depending on the severity of the membrane, membrane thickness, membrane location, and degree of contraction. An irregular or glistening light reflex from the retinal surface may be the only sign in asymptomatic patients. This may be seen only with careful slit-lamp biomicroscopy. In some cases, the membrane may appear to cover the entire macula. In more advanced cases, in symptomatic patients with actual contraction or shrinkage of the membrane, distinct retinal findings can be appreciated, such as retinal striae radiating from the center of the ERM, retinal vessels straightened toward the membrane center, or tortuosity of retinal vessels and dilated retinal veins.[28,34] Macular dragging and foveal ectopia can occur if the membrane is centered distal to the center of the fovea. Inner retinal punctate hemorrhages also can be seen and may be associated with retinal thickening resulting from retinal vessel leakage and retinal edema secondary to the tractional effects of the ERM. Such traction also may produce stasis on axoplasmic flow resulting in cotton-wool spots. Pseudoholes or lamellar holes also may be associated with ERMs and may simulate full-thickness macular holes.[35] A PVD is present in the most eyes (75 to 90%) with idiopathic ERMs, although it is not a necessary prerequisite.[34,36,37]

What Techniques and Diagnostic Tests Are Helpful in the Diagnosis?

Traditionally, slit-lamp biomicroscopy with a contact lens evaluation has been considered the best method for evaluation of an ERM. It remains the most important diagnostic tool in such cases.

Fluorescein angiography is also a useful tool in the diagnosis of ERM. Anatomic features of retinal distortion may be better seen on FA, such as straightened retinal vessels, retinal vascular tortuosity, foveal ectopia, and macular dragging. Fluorescein leakage and macular edema secondary to ERM traction-induced vascular leakage also may be assessed. FA also may help to distinguish between a full-thickness hole and a pseudohole caused by an ERM or because transmitted fluorescence is not usually present in a pseudohole. Another important role of FA would be to detect the presence of other retinal pathology, such as a choroidal neovascular membrane.

Optical coherence tomography may be helpful in evaluating patients with ERM. OCT provides good visualization of the vitreoretinal juncture and actually may show the membrane on the retinal surface. It also may be helpful to distinguish a pseudohole from a full-thickness hole. OCT also may play a role in preoperative and postoperative evaluation of surgery for ERMs.[38]

How Are Epiretinal Membranes Classified?

There are many classification schemes for ERM. A commonly used method of classification is by severity of retinal distortion proposed by Gass.[39] Another method of classifying ERM is according to associated biomicroscopic findings. Secondary ERM may be classified by their associated disorders.

What Is the Gass Classification?

Grade 0: Cellophane Maculopathy

This stage is characterized by a cellophane-like light reflex from the inner retinal surface when viewed ophthalmoscopically because the ERM may be transparent with no associated retinal distortion. Visual acuity is generally normal with minimal to no symptoms.

Grade 1: Crinkled Cellophane Maculopathy

In this stage, the inner retinal surface may be contracted into small irregular folds resulting from shrinkage of the ERM. Biomicroscopically, an important sign is the presence of fine superficial radiating retinal folds extending outward from the edge of the ERM. Details of underlying retinal vessels may be obscured; the retinal vessels may show tortuosity. The visual acuity is usually better than 20/40 primarily because of distortion in the outer retinal layers with symptoms of metamorphopsia.

Grade 2: Macular Pucker

The degree of retinal distortion and wrinkling of the retinal surface is marked in this stage. Gross puckering of the macula may be present with a distinct gray membrane on the inner retinal surface. Other associated findings in this stage are intraretinal hemorrhages, retinal edema, cotton-wool spots, and localized serous retinal detachment with a PVD found in more than 90% of such cases. Visual acuity may be reduced to less than 20/200 in severe cases with prominent metamorphopsia.

What Is the Foos Classification of Epiretinal Membranes?

Simple ERM are incidental without contraction features or associated ocular disease.[40] *Intermediate* ERM are thicker than simple ERMs and contain contraction features and pigment.[41] *Complex* ERM are present after retinal detachment surgery or after trauma and may be secondary to other ocular conditions. Traction retinal detachments may develop as a result of contraction of such membranes.[41]

What Are the Risk Factors for Developing an Epiretinal Membrane?

Age is a risk factor for the development of ERMs.[42,43] Idiopathic ERMs occur in eyes of patients older than 50 years of age.[44] There is no sex predilection, with males and females affected equally. A PVD is present in 90% of patients.[37] Idiopathic membranes have been reported in children and adolescents but are generally nonprogressive.[45] Diabetes has a significant association with idiopathic ERM with or without the presence of diabetic retinopathy but with minor effects on vision.[43]

What Is the Risk to the Fellow Eye?

In large population-based studies such as the Beaver Dam Eye study, bilateral involvement was reported to occur in 20% of patients.[42] The Blue Mountains Eye Study from Australia reported a 31% incidence of bilateral ERMs.[43]

What Is the Pathophysiology of Epiretinal Membranes?

The forces generated by the movement of the vitreous gel, particularly the premacular bursa, have been implicated in the formation of ERM and macular holes.[46] Although stimuli for the formation of ERM are not fully understood, Gass proposed two mechanisms for the development of ERM. The first mechanism involves dehiscences in the inner limiting membrane (ILM) caused by vitreous separation from the macular surface, which allows retinal glial cells entry onto the retinal surface that then proliferate and contract. The optic-nerve head and sites along the major vessels are the most common sites of dehiscences because the ILM is noncontiguous or attenuated at these sites. A second proposed mechanism of ERM formation involves contraction of vitreous cortical remnants and proliferation of hyalocytes on the inner retinal surface after a PVD.[47,48] The cortical remnants may act as a scaffold for cellular elements composing the membrane. This hypothesis may be more applicable to membranes confined to the central macular area.[32,48]

What Is the Histology of an Epiretinal Membrane?

In histopathologic studies, ERMs consist of a layer or multiple layers of abnormal cells with variable thickness on the retinal surface.[49] These cell types have been characterized by ultrastructural studies as belonging to one of the following four morphologically distinct cell types: fibrous astrocytes (glial cells), RPE cells, fibrocytes, and macrophages.[50] The collagenous component of the membranes can be derived from any of the cellular groups. Categorization of cell types is difficult because of their ability to transform into cells with similar appearance and function. The ability of each cell type to develop myofibroblast-like properties gives rise to a fifth group of cells, the myofibroblast-like cells.[50] The myofibroblastic property of all the cell types mentioned is important in that it may account for the contractile ability of ERMs and allow the membranes to exert tractional forces on the retina.[30,50,51]

What Is the Management of an Epiretinal Membrane?

Most idiopathic ERMs remain stable both anatomically and visually over time.[37,52] Surgical intervention with pars plana vitrectomy (PPV) and epiretinal membrane peeling is indicated only if vision is

markedly reduced and distortion is symptomatic. Although infrequent, spontaneous resolution can occur. PPV with membrane peel has been shown to remove ERM successfully; more than 80% of eyes have visual improvement.[53,54] Favorable prognostic factors for visual improvement are good preoperative vision and short duration of symptoms preoperatively.[54,55] Although eyes with preoperative visions of less than 20/200 or long duration of visual symptoms have been associated with worse overall visual improvement, these eyes often improved the greatest number of lines after surgery.[55]

What Complications Are Associated with Surgical Management of Epiretinal Membranes?

A common complication of PPV for ERM is the development or progression of nuclear sclerotic cataract up to 31%.[53,56] Although much less common, other complications are associated with surgery for ERM, including posterior and peripheral retinal breaks, retinal detachment, and phototoxic retinal burns from endoillumination.[53]

What Is the Chance of Recurrence after Surgery?

Recurrence of the membrane after PPV is uncommon. Reported recurrence rates are near 5%.[57] Repeat vitrectomy and membrane peel can offer visual improvement in these cases.

Vitreomacular Traction Syndrome

The firmest attachment of the vitreous to the retina is at sites where the ILM is thinnest: the vitreous base, along retinal vessels, the optic-nerve head, a 1500-μ rim surrounding the fovea, and the 500-μ-diameter foveola.[58] Normal aging changes in the vitreous gel lead to separation of the posterior vitreous cortex from the retinal ILM, termed a PVD.[59] If this separation is incomplete with persistent vitreous attachment on the posterior retina, traction on the macula may occur resulting in the syndrome of VMT.[60,61]

What Are the Symptoms of Vitreomacular Traction Syndrome?

Traction on the macular region can result in decreased vision, metamorphopsia, photopsia, and micropsia.[60,63,74] Symptoms in VMT syndrome may be a result of cystoid changes in the macular region.

What Are the Signs of Vitreomacular Traction Syndrome?

The clinical findings in VMT syndrome may be seen with careful slit-lamp biomicroscopy using a contact lens. The most common morphologic configuration involves a partial PVD with adherence of the posterior vitreous cortex to the macula and optic-nerve head.[60,64] The site of vitreomacular adherence may have a distinct curvilinear or horizontal border in the macula, or it may be less sharply demarcated with a dense irregular pattern. In studies that evaluated intraoperative vitreoretinal relationships in VMT syndrome, two distinct patterns were found, one in which the cortical vitreous was detached in all four midperipheral quadrants with only macular adherence remaining, and the second in which one or more quadrants of vitreous remained attached in the periphery with residual attachment to the macula.[60,61] Other possible findings in VMT include a thickened posterior hyaloid, radiating retinal striae, retinal distortion, and a focal traction retinal detachment. In addition, an ERM may also be present. Peripapillary vitreous traction may occur, resulting in the appearance of a ring of fibrous tissue atop the optic-nerve head, referred to as a "fleshy doughnut" sign by McDonald and associates.[61]

What Techniques and Diagnostic Tests Are Helpful in the Diagnosis of Vitreomacular Traction Syndrome?

The traditional method for identifying VMT syndrome remains careful slit-lamp biomicroscopy with contact lens examination. Nevertheless, even with careful biomicroscopic examination, a diagnosis of VMT syndrome may be missed. Other techniques such as FA, ultrasonography, and OCT can help to elucidate this diagnosis. FA can help to demonstrate cystoid macular leakage, retinal vascular leakage, and optic-nerve head edema. Ultrasonography is a noninterventional method for viewing vitreomacular relationships and can aid in the diagnosis of VMT syndrome. An alternate method for viewing the vitreoretinal interface is OCT, which can acquire high-resolution, cross-sectional images of the retina.[65] OCT can image the partially detached posterior hyaloid exerting traction on the macula and also may show secondary cystic spaces and intraretinal thickening[66,67] (Fig. 14–5).

What Is the Pathogenesis of Vitreomacular Traction Syndrome?

Direct anteroposterior traction on the retinal surface secondary to changes in the vitreous gel can lead to macular distortion. The etiology of this traction is an incomplete vitreous separation in which the vitreous maintains a focal attachment to the retinal surface. This can occur as a part of normal aging or secondary to ocular inflammation, vascular disorders, or trauma

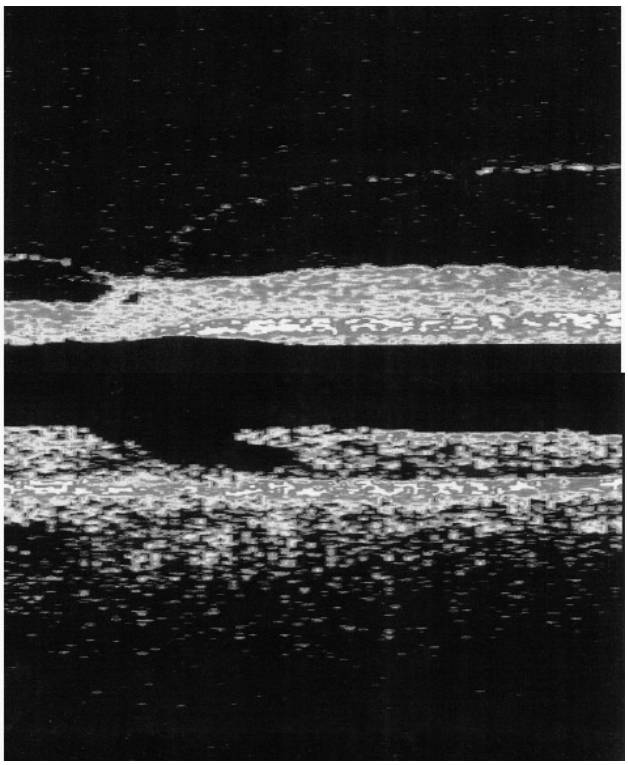

FIGURE 14–5. Optical coherence tomography. *Above*, posterior hyaloid traction on the macula is causing secondary cystic spaces and intraretinal thickening. *Below,* the fellow eye has a partial-thickness inner hole, thought to be due to similar posterior hyaloid traction with cyst formation and inner layer retinal dehiscence.

causing condensation and shrinkage of the vitreous gel.[68]

What Are the Risk Factors for Developing Vitreomacular Traction Syndrome?

Increasing age is an important factor for developing VMT syndrome; the chance of developing a PVD increases with age. Secondary causes of vitreous gel shrinkage, such as retinal vascular disease, ocular inflammation, and accidental or surgical trauma also can yield an increased risk for development of VMT syndrome.

What Is the Histopathology of Vitreomacular Traction Syndrome?

A commonly held theory suggests that vitreous traction caused by a PVD can lead to fine breaks in the retinal ILM, allowing glial cells access to the retinal surface.[69] These preexisting glial cells may cause an area of firm posterior vitreoretinal adhesion and prevent the completion of a PVD.[70] A study of the ultrastructure of VMT syndrome revealed the predominance of fibrous astrocytes but no retinal pigment epithelial cells, which normally predominate in cases of proliferative vitreoretinopathy.[60] The predominance of fibrous astrocytes and the finding of ILM fragments in samples from cases of VMT syndrome suggest that, in the absence of retinal breaks, migration and proliferation of these glial cells may be a secondary response to vitreoretinal traction.[60] The vitreoretinal traction itself may predate and influence cellular migration rather than breaks in the ILM being the primary stimulus.

What Is the Natural History of Vitreomacular Traction Syndrome?

Spontaneous resolution of VMT syndrome and associated retinal edema have been reported and documented by OCT.[66] Jaffe reported 50% of eyes with VMT syndrome having visual improvement after completion of posterior vitreous separation.[62] A retrospective study of the natural history of VMT syndrome reported that eyes with persistent cystoid changes had worsened visual acuity with a median follow-up of 60 months.[71] This study concluded the following: that cystoid macular changes may develop secondary to VMT syndrome and may persist; that these cystoid changes can cause a further decline in vision; and that spontaneous vitreomacular separation can occur with resolution of cystoid changes and visual improvement or stabilization, although infrequently, in the VMT syndrome.[71]

What Is the Role of Surgery in the Management of Vitreomacular Traction Syndrome?

Patients with VMT syndrome in whom visual acuity declines suddenly or remains poor after a period of observation may be candidates for surgical intervention. PPV is indicated in such patients, and many reports have documented favorable visual results. Smiddy and colleagues reported a two Snellen-line visual improvement in 63% of eyes after PPV for VMT syndrome.[72] Subsequent studies have reported visual improvement in 75 and 89% of eyes after PPV.[61,73] Although surgical reattachment of the macula may be successful, visual improvement may be limited by factors such as chronicity of detachment, CME, or epiretinal fibrosis.[64]

What Complications Are Associated with Surgical Management of Vitreomacular Traction Syndrome?

Complications in PPV for VMT syndrome are similar to those encountered in surgery for ERM. A significant intraoperative complication is the formation of peripheral retinal breaks, which can occur with attempts

at stripping the posterior hyaloid peripherally out to the vitreous base.[61] Other frequent complications involve the development or progression of nuclear sclerotic lens changes and the development of ERMs.[60,61,73]

Cystoid Macular Edema

Macular edema is the nonspecific reaction of the macula to surgical and metabolic insults. CME represents a specific entity in the continuum of macular edema. It is characterized by accumulation of intraretinal fluid in the macula, with accompanying cystoid changes seen ophthalmoscopically or angiographically. It may be a complication of surgical procedures, or it may accompany other metabolic diseases of the retina (Fig. 14–6). Because it may present as a result of a comorbid condition, it is important that CME is recognized.

Since being first reported by Irvine and later by Gass after extracapsular cataract extraction (ECCE), various definitions of CME have been used in the literature.[74,75] *Clinical CME* refers to ophthalmoscopically detectable retinal thickening with cystoid spaces in the fovea. *Angiographic CME* refers to leakage of fluorescein into the fovea in a distinct petalloid pattern. *Clinically significant CME* implies angiographic CME, yielding a best-corrected vision of less than 20/40. *Histologic CME* refers to the presence of cysts in the outer plexiform and inner nuclear layers of the retina. It is important to note that many patients with angiographic CME and vision better than 20/40 may report qualitative disturbances in vision.

The various definitions of CME reflect varying thresholds. For example, more patients will have angiographic CME than clinically significant CME. This reflects the varying susceptibility of the individual retina to edema. Clinically significant CME will be more prevalent than clinical CME because FA is more sensitive for detecting CME.

Clinical Presentation and Course

The CME that follows cataract surgery (ECCE) typically presents 2 to 3 months after the procedure. Patients' vision is initially unaffected after surgery. As edema develops, patients will have a gradual decline in visual acuity (Fig. 14–1). With the faster visual recovery rates seen with clear corneal phacoemulsification of cataracts, symptoms of CME may be reported sooner. The vision will be decreased to the range of 20/40 to 20/100.[79]

Clinical examination may reveal a mild anterior chamber cell and flare, although this may be variable. Vitreitis is rarely seen. The hallmark of CME is macular thickening associated with the formation of cystoid spaces in the fovea.

The incidence of postoperative CME is variable, depending on the type of surgery and the definition of CME. The rate of angiographic CME is 50 to 70% following intracapsular cataract extraction (ICCE) and 20 to 30% following uncomplicated ECCE.[80] The incidence of angiographic CME following uncomplicated ECCE using phacoemulsification and posterior chamber lens insertion was reported to be 19% at 2 months postoperatively in one study.[79] Cell and flare readings between patients with CME and without CME as measured by a laser cell-flare meter were not statistically significant.[79] The incidence of clinically significant CME is approximately 2% in uncomplicated cataract surgery with implantation of intraocular lenses.[81] The incidence of angiographic CME was higher in retinal detachment surgery.[78]

The natural history of CME following ECCE/posterior chamber lens insertion follows a favorable course. Of the patients who develop clinically significant CME, 90% achieve resolution within 1 year. Resolution of macular edema has been associated with vision better than 20/40.[81] Most cases of drug-induced CME resolve with the discontinuation of the offending agent.[82,83]

What Diagnostic Tests Are of Value with Cystoid Macular Edema?

The clinical appearance of macular edema associated with cystoid spaces in the fovea is suggestive for CME. FA showing a "petalloid pattern" of hyperfluorescence in the fovea will confirm the diagnosis in most cases. Other FA features of CME include telangiectasis of the parafoveal capillaries, progressive hyperfluorescence due to leakage from these vessels, and late accumulation of hyperfluorescence surrounding the cystic spaces in the fovea.

Other modalities, such as OCT and scanning laser ophthalmoscopy (SLO), have been used to evaluate CME.[104] The amount of retinal edema is correlated strongly with the level of vision. Advantages of these diagnostic modalities lie in their ability to quantify the amount of retinal edema and to document its change over time. In addition, it is noninvasive. Because retinal edema can be due to many causes, however, an initial FA is needed to confirm CME. OCT and SLO can be used subsequently to monitor the patient.

What Is the Histology and Pathophysiology of Cystoid Macular Edema?

The initiating event in the formation of CME is thought to be a breakdown in the blood–retinal barrier. The inner blood–retinal barrier is maintained by the endothelial cells of the retinal arteries. The outer

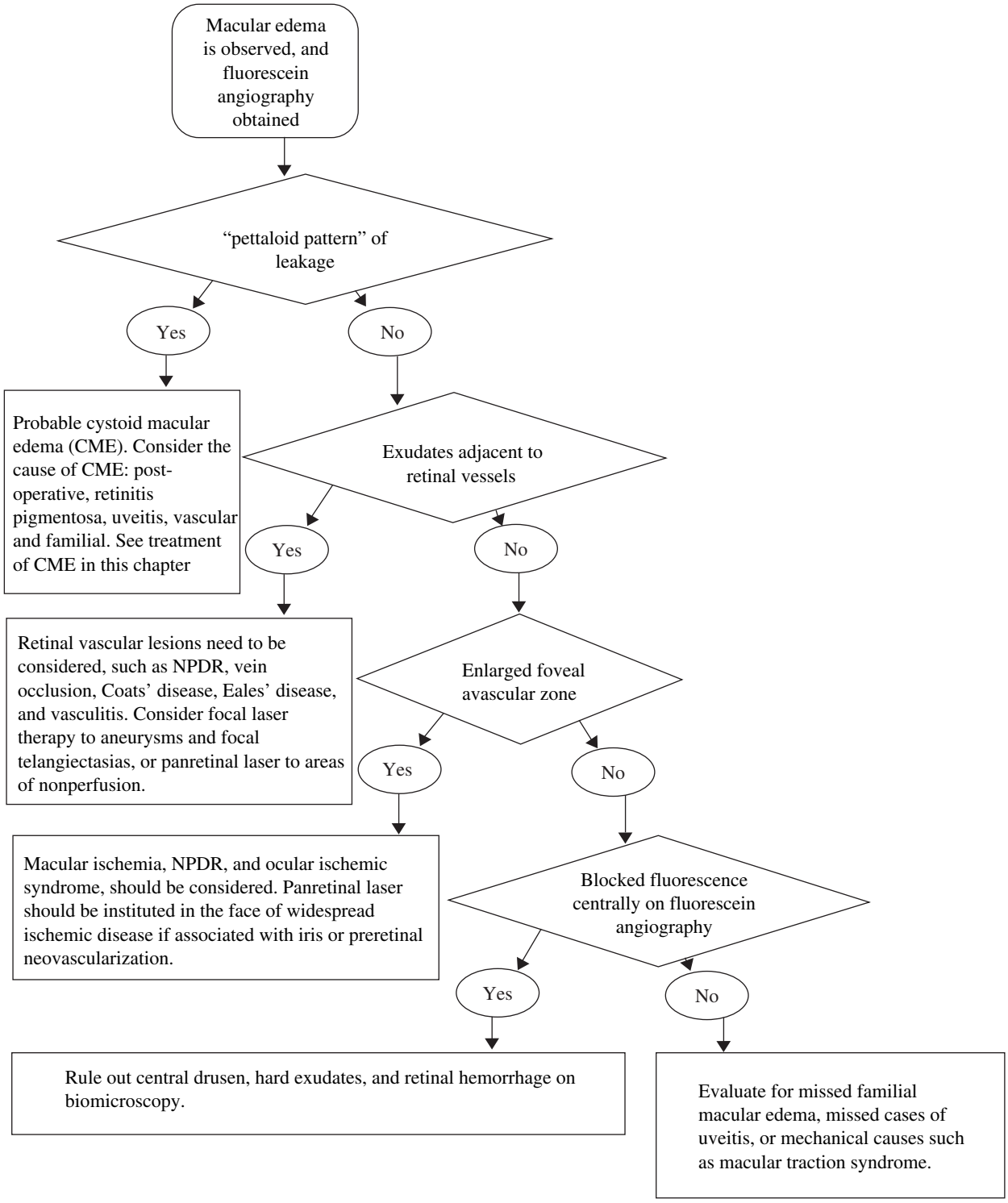

FIGURE 14–6. Evaluation of macular edema. FA, fluorescein angiography; NPDR, nonproliferative diabetic retinopathy.

blood–retinal barrier is maintained by the RPE as it monitors the fluid transport between the photoreceptor outer segments and the choriocapillaris. CME results when the inflow of fluid into the fovea overcomes the ability of the RPE to pump fluid out. The formation of cystoid spaces (surfaces not lined by epithelium) and appearance of the characteristic FA pattern are due to the arrangement of the photoreceptors and ganglion cells in the fovea.

The blood–retinal barrier can be compromised by a variety of mechanisms, including mechanical means, as in the case of macular holes, ERM, VMT syndrome, and vitreous wick from the iris or cataract wounds. It can also be compromised by overaction of the inflammatory pathway as in postoperative CME and uveitis. Lastly, the blood–retinal barrier can become incompetent due to vascular compromise as in diabetic or radiation retinopathy, toxic drug interaction, and retinitis pigmentosa (RP). Development of CME is often due to a combination of these mechanisms.

In histologic studies of eyes with CME due to various causes,[76] the location and the contents of the cystoid spaces in the retina varied, depending on the primary cause of CME. In most cases, the intraretinal cystoid spaces were seen in the inner nuclear layer and the outer plexiform layer. A general dropout of photoreceptors was seen. For CME from diabetes and retinal vein occlusion, the cystoid spaces were filled with a proteinaceous material. In CME secondary to pseudophakia and trauma, the cystoid spaces were filled with "watery" material. Varying degrees of damage to the microvasculature was present in all the cases. In addition, in CME due to trauma, damage to RPE was seen.[76]

The macular swelling is thought to be due to intracytoplasmic swelling of the Muller (glial) cells. Extravasation of the Muller cell contents into the extracytoplasmic place represents the endstage of this process-forming the cystoid spaces observed clinically.[77] The formation of the cystoid spaces disrupts cellular connections within the retina, leading to cell dropout.

Histologic studies of CME are limited by the fact that most eyes being enucleated are the end-stage of various disease processes. In the specimens obtained for histology, the CME is probably more chronic in nature and does not necessarily reflect the acute, postoperative CME seen clinically. The study of the varied pathophysiologic mechanisms allows clinicians to tailor the therapy of CME.

What Are the Guidelines to Treating Cystoid Macular Edema?

Therapies must be consistent with the mechanism initiating CME because CME is the final common reaction of the macula to stressors with varying mechanisms. For CME secondary to inflammatory process, antiinflammatory therapy is begun. For CME caused by mechanical traction, the release of the traction is attempted. For CME owing to malfunction of the components of the blood–retinal barrier, therapy is directed toward the malfunction.

How Is Postoperative Cystic Macular Edema Diagnosed and Treated?

Usually, CME is the result of complicated cataract surgery—rupture of the posterior capsule with vitreous loss, incarceration of the vitreous in the surgical wound, or a poorly positioned intraocular lens. In addition, scleral buckle procedures for repair of retinal detachment, glaucoma-filtering procedures, penetrating keratoplasty, laser iridotomy, and neodymium: yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy all have been associated with CME (Fig. 14–6).

For clinically significant CME following uncomplicated surgery, antiinflammatory drugs are the first choice. Various studies have proven the efficacy of perioperative nonsteroidal antiinflammatory drugs (NSAIDs) in preventing the development of angiographic CME. They are also useful in prolonging the effect of mydriatics. Both ketorolac and diclofenac are U.S. Food and Drug Administration (FDA) approved for treating postoperative CME and seem equally effective.[84,85,86] Some studies have found diclofenac to be equal in efficacy to a similar dose of prednisolone acetate in controlling postoperative inflammation. Anecdotal reports of corneal melt have been reported with prolonged use of NSAIDs, and controlled studies are in the process of evaluating this unfortunate side effect. It must be noted that visual improvements owing to the use of NSAIDs are minimal in most studies even in light of significant decrease in the incidence of angiographic CME.[87,88]

Postoperative CME unresponsive to NSAIDs usually requires the addition of topical steroids such as prednisolone acetate or fluorometholone. Rarely, depot injections of steroids are necessary to control the CME, which has become chronic at this time. Some have advocated the use of NSAIDs, topical steroids, and Daimox to control resistant CME.

For CME from vitreous adhesions to the surgical wound, Nd:YAG vitreolysis seems to be a logical first step. Studies suggest that half of patients treated in this manner have improved vision.[89,90] The most common complication is a transient rise in intraocular pressure immediately after the procedure. CME resistant to conservative management with clear anatomic disruption, such as a poorly positioned lens or strong

vitreous adhesions to the cataract wound, benefit from surgical intervention. Lens repositioning or vitrectomy is a viable option in medically resistant cases.[92] Vitrectomy has shown benefit in eyes without obvious evidence of vitreous incarceration into the cataract wound or vitreous–cornea contact.[91]

What Are the Results for Vitrectomy or Steroid Use for Cystoid Macular Edema Associated with Uveitis?

Uveitis represents the imbalance of the immune response leading to disruption of the blood–retinal barrier at various levels. As opposed to the self-limiting nature of postoperative inflammation, endogenous uveitis represents an ongoing derangement of immune mediators. CME must be suspected in reduced visual performance in patients with uveitis. Medical therapy of CME in uveitis is aimed at controlling the ocular inflammation.

Intermediate and posterior uveitis is more likely to lead to the development of CME. Uveitis in this setting can become chronic in nature with irreversible damage to the macula. Vitrectomy, in combination with epiretinal membrane peeling, has shown favorable results. In a small study, 78% of patients with sarcoid uveitis had resolution of CME after vitrectomy.[93] Patient selection criteria and other factors related to favorable outcomes need to be further identified.[93,94] In addition, intravitreal triamcinolone has improved chronic CME in this setting.[95] Formation of cystoid spaces returned in 3 to 6 months.

Immune Recovery Congenital Macular Edema—Highly Active Antiretroviral Therapy

In the era of highly active antiretroviral therapy (HAART), a new syndrome of cytomegalovirus (CMV) retinitis reactivation associated with the rise of CD4+ T-lymphocyte levels in patients with acquired immunodeficiency syndrome has been reported.[97,98] These patients had quiescent CMV retinitis initially. The initial presentation of vitreitis and CME was associated with a rise in CD4+ cells. In most cases, treatment with corticosteroids improved vision and was not associated with reactivation of the retinitis. It is hypothesized that increasing competency of the immune system is related to the recurrent retinitis.

Cystoid Macula Edema and Retinitis Pigmentosa

Retinitis pigmentosa represents a spectrum of clinical entities as a result of a pan-retinal degeneration with characteristic "bone spicule formation" in the midperiphery, waxy pallor of the disc, and a depressed electroretinogram. Clinically significant CME has been reported to be around 26% and was associated strongly with presence of antiretinal antibodies and aqueous flare.[99–101] Anti-enolase and anti-carbonic anhydrase antibodies have been found in up to 60% of patients with RP.[98] Conversely, up to 90% of patients with RP presenting with CME were found to have antiretinal antibodies.[100,101] About 6% of controls will have antiretinal antibodies. It is unclear whether the autoantibodies are the cause of CME in RP. Systemic and topical carbonic acid inhibitors have been tried with varying success.[29–31,102,103]

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SECTION III

Intraocular Mass, or Lesions Associated with an Elevated Retinal Surface

15

Intraocular Mass

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Retinoblastoma

What Are the Incidence and Epidemiology of Retinoblastoma?

Retinoblastoma is the most frequent intraocular tumor in children.[1,2] It affects between 1 in 15,000 to 1 in 20,000 live births annually, resulting in 200 to 300 children in the United States being affected by the disease.[2,3] Retinoblastoma accounts for 12% of infant cancers.[3] There is no sexual or racial predilection for the development of this disease.[3] There is a higher incidence of retinoblastoma in the developing world.[4–6] Uveal melanoma is uncommon in black populations; thus, retinoblastoma is the most common intraocular tumor in Africa.[6]

What Are the Underlying Genetics of Retinoblastoma?

The retinoblastoma gene occupies 200 kilobases on chromosome 13 in region 13q14.[7] The product of the retinoblastoma gene acts as a tumor suppressor and plays an important role in regulating cell growth and differentiation.[8] Both alleles must be mutated at the RB1 locus for retinoblastoma to develop.[7–11] These two genetic mutations correlate with the "two-hit hypothesis" proposed by Knudson.[12] In 1971, Knudson evaluated epidemiologic data in 48 cases and concluded that retinoblastoma likely results from either a germinal or somatic mutation. He hypothesized that in heritable retinoblastoma the first "hit" occurs in the germline and is inherited or develops spontaneously in all cells of the body. The second "hit" is a somatic mutation that develops within retinal cells. In patients with sporadic unilateral retinoblastoma, both hits are somatic mutations within a single retinal cell, and there is normal chromosomal composition elsewhere in the body.[12] Subsequent to Knudson's hypothesis, Comings proposed that mutations responsible for the phenotype could inactivate both alleles of a single responsible gene.[13] The cloning of the retinoblastoma gene and subsequent detailed genetic analysis confirmed the validity of these scientific proposals.[7–14]

Approximately one third of children affected by retinoblastoma will have bilateral disease. Bilateral retinoblastoma results from a germline mutation at the retinoblastoma locus or mosaicism affecting primordial cells in the retina. Bilateral disease is associated with an underlying mutation that is transmissible in the germline to offspring. In these patients there is a risk for midline brain tumors, primitive neuroectodermal tumors, and second malignancies such as osteogenic or soft-tissue sarcomas.

Unilateral retinoblastoma usually develops due to a mutation occurring somatically within a single retinal cell at the retinoblastoma locus. Although most unilateral patients have sporadic, somatic mutations, up to 19% of children who present with unilateral disease have an underlying germline retinoblastoma mutation. These patients are also at risk for second tumors and midline brain tumors.[15,16]

The retinoblastoma gene was the first tumor suppressor gene to be identified. Deletion or mutation in a tumor suppressor gene results in deregulated cell growth and proliferation. Children with germline mutations at the retinoblastoma locus demonstrate a lifelong tumor predisposition. Treatment of the primary ocular tumors in these children can increase this already elevated risk of second tumor development.[17–20] Therapy aims for cure primary disease while minimizing the risk for second tumors.

What Are the Pathologic Features of Retinoblastoma?

On light microscopic examination, viable retinoblastoma cells are basophilic, whereas necrotic retinoblastoma tumors are eosinophilic. In areas of necrosis,

foci of calcification are typically seen. Another characteristic finding is the presence of basophilic material deposited in the walls of blood vessels; this represents precipitated DNA and chromatin. The tumor is composed of neuroblastic cells that can develop from any nucleated retinal layer. Poorly differentiated tumors are composed of small, round cells with a high nuclear-to-cytoplasmic ratio and hyperchromatic nuclei. More differentiated tumors contain rosettes or florets. The Homer–Wright rosette consists of radially arranged cells surrounding a central tangle of neurofilaments. These rosettes are observed in tumors such as neuroblastoma, medulloepithelioma, sinonasal undifferentiated carcinoma, and medulloblastoma. The Flexner–Wintersteiner rosette is composed of cells arranged in a circular fashion around a central empty lumen. An internal limiting membrane separates the cells' borders from the central lumen. Retinocytoma and the most well-differentiated forms of retinoblastoma contain florets composed of benign-appearing tumor cells demonstrating photoreceptor differentiation. Pear-shaped eosinophilic processes extend along one side of the tumor cells; these cells are bound together by terminal bars that represent the outer limiting membrane of the retina.[21]

How Does Retinoblastoma Present Clinically?

Retinoblastoma occurs very early in life. Germline retinoblastoma mutations likely develop prenatally. Patients with a known family history of retinoblastoma should be examined shortly after birth and followed carefully thereafter. All siblings and offspring of retinoblastoma patients should be evaluated at the earliest possible opportunity and followed with serial examinations under anesthesia (EUA).

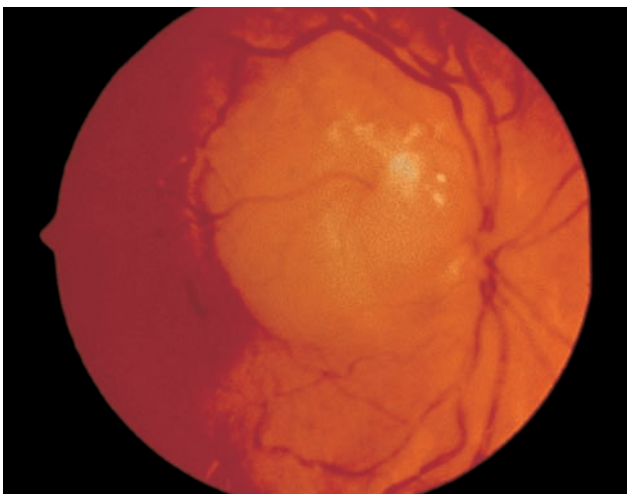


FIGURE 15–1. Untreated peripapillary retinoblastoma. Lesion demonstrates the pinkish white gelatinous appearance typical of active tumor. Bright white flecks represent intrinsic tumor calcification.

Patients with small tumors and no family history may present with strabismus or decreased visual acuity, depending on the location of the tumor. Pediatric patients should receive full retinal evaluations to exclude retinoblastoma or other retinal pathology as the etiology of their strabismus. Such complete evaluations are important because early diagnosis and treatment may spare the patient systemic toxicity associated with radiation or chemotherapy.

Early retinoblastomas are round, slightly elevated, gray–white intraretinal masses. These tumors frequently demonstrate an intrinsic vasculature that appears as a fine network of pink vessels within the main tumor mass. Flecks of intrinsic calcification may be present within larger tumors, appearing as dense, white opacifications (Fig. 15–1). Substantial subretinal fluid may be associated with active retinoblastoma. Larger tumors may seed the subretinal or vitreous space, and tend to present as unilateral or bilateral leukokoria. The retrolental tumor mass may enlarge in an endophytic pattern toward the vitreous cavity or in an exophytic pattern toward the choroid and sclera.

A diffuse infiltrating pattern is less common but more likely to be misdiagnosed. Retinoblastoma rarely grows diffusely within the retina without producing a discrete mass. Patients who present with presumed endophthalmitis resulting from the appearance of pseudohypopyon are likely to have the diffuse form of retinoblastoma.[22–24]

Neovascularization of the iris occasionally occurs in retinoblastoma associated with posterior segment ischemia,[25] which can lead to neovascular glaucoma and spontaneous hyphema without a history of trauma. Patients with endophytic tumors may have vitreous seeding; seeds may also be shed into the anterior chamber, giving a clinical appearance similar to iritis. The tumor may infiltrate the iris, producing heterochromia iridis. Preseptal cellulitis is an uncommon manifestation of retinoblastoma and is associated with secondary periocular inflammation. In the developing world, retinoblastoma frequently presents with corneal perforation, buphthalmos, proptosis due to posterior orbital extension, or a prolapsing orbital mass.[26]

What Is the Appropriate Diagnostic Approach for Retinoblastoma?

The initial evaluation of suspected retinoblastoma requires a detailed medical history. The prenatal history should address any maternal history of rubella infection or other prenatal exposures and any medical complications that arose during pregnancy. Eliciting a perinatal history of prematurity, oxygen therapy, and labor and delivery complications is helpful in exclud-

ing retinopathy of prematurity in the differential diagnosis. History of pica and contact with puppies or cats should be elicited to evaluate the possibility of toxocariasis. The child's physical and mental development should be assessed. A detailed family history should be taken and a detailed family tree recorded. Family history of retinoblastoma, blindness in any generation, eye loss in family members, and a history of osteosarcoma or other cancer should be noted. A review of systems should focus on symptoms of weight loss, cachexia, failure to thrive, or other manifestations of systemic malignancy.

Physical examination initially should focus on the child's general appearance and behavior. Dysmorphic features and developmental delay suggest 13q minus syndrome, which occurs in association with retinoblastoma in a small percentage of patients.[27] Visual acuity should be assessed in each eye. A slit-lamp examination and indirect ophthalmoscopy may narrow the differential diagnosis and determine which additional tests are necessary.

Definitive examination is performed under anesthesia. The EUA should include external eye examination, intraocular pressure recording, and anterior segment evaluation with a portable slit lamp or under the operating room microscope. Indirect ophthalmoscopy with scleral depression and fundus photography should be performed. Simulating lesions, such as toxocariasis, Coats' disease, or retinopathy of prematurity (ROP), can usually be distinguished through clinical evaluation.

Ultrasonography should be performed to narrow the differential diagnosis. Retinoblastoma is suggested on A-scan by highly reflective internal echoes consistent with intrinsic tumor calcification. Rapid attenuation of the normal orbital pattern presents as dampening of echoes posteriorly. B-scan ultrasonography characteristically demonstrates a dome-shaped mass within the vitreous space. A low-gain setting is useful to demonstrate highly reflective echoes corresponding to calcium within this intraocular mass. Calcification within the tumor produces attenuation and reflection of the sound wave, resulting in soft-tissue shadowing in the orbit.

Computed axial tomography (CT) scan of the orbit should be obtained in all patients with confirmed retinoblastoma on EUA. This study confirms intrinsic tumor calcification and delineates tumor extension into the orbit. Magnetic resonance imaging (MRI) is the most sensitive study to evaluate for pinealoblastoma, optic nerve disease, or intracranial extension.

Retinoblastoma may be diagnosed clinically. Invasive intraocular techniques such as fine needle aspiration are never indicated because they produce a high associated risk for retinoblastoma dissemination.[28] Any child who presents with retinal detachment, hyphema, or other conditions which preclude view of the posterior pole, should have retinoblastoma excluded by imaging studies (ultrasound, CT, or MRI) before any surgical procedure is performed. Retinoblastoma should always be considered carefully in the differential diagnosis of pediatric ocular disease.

How Is Retinoblastoma Treated?

The most frequent treatment for retinoblastoma is enucleation; this procedure is required in 90 to 95% of unilateral patients (Fig. 15–2). Chemoreduction with application of local therapies, such as cryotherapy, laser ablation, or plaque radiotherapy, provides an alternative to enucleation in some patients. External-beam radiation therapy is highly effective in curing primary disease but may be associated with disfiguring midface hypoplasia and an increased risk of a second tumor development.[17] The choice of therapy must consider the visual potential of each eye, the age of the patient, the stage of disease at presentation, and the location of tumors. Patients with asymmetric disease, with one eye having greater than 50% of ocular volume occupied by the tumor, may benefit from enucleation of the more involved worse eye and local therapy applied to the better eye. In relatively symmetric disease, treatment such as external-beam radiation or chemoreduction should be considered.

Patients with retinoblastoma may have recurrent tumors throughout the first years of their lives. Any systemic therapy has the potential to increase the bilateral retinoblastoma patient's already elevated predisposition for a second tumor. Patients should be followed prospectively for second tumor development by knowledgeable pediatric oncologists.

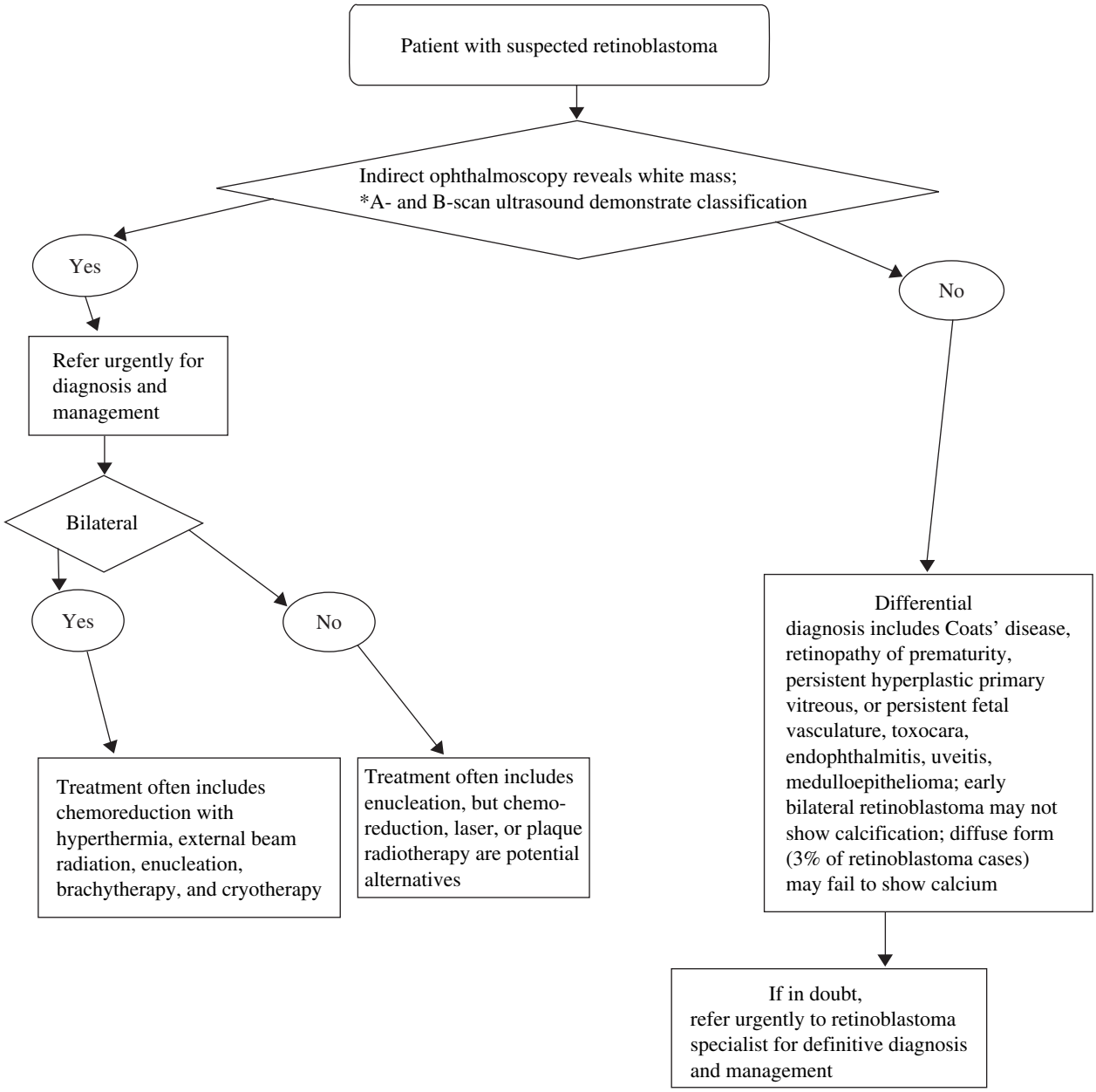
Retinocytoma

What Are the Epidemiology and Incidence of Retinocytoma?

Retinocytoma or retinoma are spontaneously regressed retinoblastomas. These lesions have the clinical appearance of treated retinoblastoma. In a series of 920 consecutive retinoblastoma patients, the incidence of retinocytoma was estimated at 1.8%.[29] Others have estimated this incidence to be as high as 10% among all retinoblastoma patients.[30] On average, retinocytoma presents at a later age than retinoblastoma. The median age at diagnosis for retinocytoma is 15 years, with a range from 4 to 45 years.[29]

What Are the Pathologic Features of Retinocytoma?

A small number of retinocytomas have been evaluated histopathologically; most of these tumors are clinically observed. Eagle described the histopathologic



*An alternative to ultrasound for diagnosis of intraocular calcification is computed axial tomography (CT)

FIGURE 15–2. Clinical pathway: Evaluation of suspected retinoblastoma.

appearance of a retinocytoma followed for 3 years with no clinical change until a rapid growth phase in the third year indicated enucleation. Histopathology revealed a poorly differentiated retinoblastoma within the region of rapid growth. The remainder of the tumor demonstrated features more characteristic of retinocytoma, including bland nuclear morphology, a complete absence of mitoses, fibrillar eosinophilic stroma, occasional calcific foci, and dispersed florets. Immunohistochemical analysis confirmed that positivity for S-100 protein, glial fibrillary acidic protein, and retinal S-antigen was confined to the more differentiated, basal portion of the tumor.[31] Other histopathologic reports describe retinocytomas as tumors composed of normal photoreceptor cells, bipolar cells, Muller cells, and astroglia.[32]

Spontaneously regressed retinoblastoma also has been described in phthisical eyes.[32–34] In these cases,

the tumors display coagulative necrosis and dense calcification. Only the outlines of fossilized tumor cells are visible by light microscopy. Secondary hyperplasia of the retinal pigment epithelium, glial cells, and ciliary epithelium may be observed.[33]

How Does Retinocytoma Present Clinically?

Retinocytomas are frequently asymptomatic and diagnosed by routine ophthalmologic examination. These tumors may be discovered in asymptomatic family members of retinoblastoma patients. Retinocytomas resemble treated retinoblastoma in that they are frequently small tumors with intrinsic calcification. The tumors may be slightly elevated, gray, homogeneous, and translucent.[34] A surrounding halo of chorioretinal atrophy may be observed, suggesting previous tumor regression.[29]

What Is the Appropriate Diagnostic Approach for Retinocytoma?

Malignant degeneration is possible in retinocytomas. The diagnostic approach parallels that of retinoblastoma. A complete medical history, family history, and physical examination with indirect ophthalmoscopy and imaging studies should be undertaken. Fundus photos and A and B-scan ultrasound should be obtained serially to document stability. Years of observation may be required to distinguish retinoblastoma from retinocytoma.

How Is Retinocytoma Treated?

A series by Singh and colleagues suggested that the risk for malignant transformation in retinocytomas is about 4%.[29] Thus, patients with a presumed diagnosis of retinocytoma require close serial observation. Fundus photography is useful in documenting tumor stability. Ultrasound evaluation of basal dimensions and tumor thickness should be obtained, and repeat indirect ophthalmoscopic examinations should evaluate the tumor for any signs of activity. A presumed retinocytoma with documented growth in basal dimension, increase in thickness, development of associated fluid, or signs of seeding should be treated as a retinoblastoma.[31]

Melanocytoma

What Are the Epidemiology and Incidence of Melanocytoma?

Melanocytoma is a nevus usually observed in the region of the optic disc but also observed elsewhere in the choroid. These congenital, nonhereditary lesions are composed of proliferations of pigmented melanocytes. Over time, the tumors generally remain stationary in clinical appearance and demonstrate very limited malignant potential. Melanocytoma occasionally is confused with choroidal melanoma or choroidal nevi.[35]

The incidence and prevalence of melanocytoma are not precisely known. Although these tumors are most likely present at birth, the age of diagnosis is variable, ranging from 14 to 80 years. Melanocytomas are usually unilateral. The incidence in women is slightly higher than the incidence in men, with 58% of cases reported in females. Around 50% of melanocytomas occur in patients of African heritage, in contrast to melanoma, which occurs in fewer than 1% of African-American patients.[35–37]

What Are the Pathologic Features of Melanocytoma?

On light microscopy, melanocytoma is composed of plump polyhedral cells with bland nuclei. Melanocytoma cells are densely pigmented, and bleaching is required to visualize cellular details. Cells have an oval to round shape with abundant cytoplasm, small nuclei, and few nucleoli. These tumors are frequently composed of two cell types: Type I cells are large, round, and deeply pigmented, with large melanosomes, and type II cells are smaller, spindle-shaped, and less pigmented, with small melanosomes. Type II cells are less metabolically active and have a slower pattern of growth, and cystic spaces may be observed within the main tumor mass. There is no chromatin margination, and mitotic figures are not observed. These tumors may be associated with overlying drusen and attenuation or hyperplasia of the retinal pigment epithelium (RPE).[38]

How Does Melanocytoma Present Clinically?

Melanocytomas of the optic-nerve head are generally asymptomatic.[25] These tumors may enlarge slowly and infiltrate locally, resulting in afferent pupillary defects or visual fields defects.[39] The melanocytic cells that constitute these tumors can produce compression of the axons of the optic nerve with optic disc edema and occasional progressive vision loss.[39] Retinal vascular obstruction is not frequently observed in association with melanocytoma but has been associated with the development of severe neovascular glaucoma.[40]

On indirect ophthalmoscopy, melanocytomas present clinically as elevated, dark brown to black masses. They frequently show a fibrillated tumor margin that recapitulates the peripapillary nerve-fiber layer of the retina. These pigmented tumors may be eccentric, straddling one edge of the optic nerve, or they may

involve the entire surface of the optic-nerve head. Other clinical features include overlying RPE changes, drusen, and sheathing of retinal vessels. The optic disc may appear anomalous in configuration or may have an edematous appearance.

Melanocytomas also occur in the iris, ciliary body, and choroid. These deeply pigmented tumor cells generally produce sharply circumscribed masses.[25] A diffuse growth pattern with involvement of the majority of the uveal tract has also been observed.[41]

What Is the Appropriate Diagnostic Approach for Melanocytoma?

The indirect ophthalmoscopic features of melanocytoma are frequently diagnostic. Serial fundus photos are indicated to monitor these tumors for growth. Visual field changes associated with melanocytoma of the optic disc include enlargement of the blind spot and nasal step and are related to absolute nerve-fiber bundle defects. Visual fields may be monitored to confirm clinical stability.[39] Progressive growth or progressive loss of vision suggests malignant transformation.

Fluorescein angiographic studies of melanocytoma demonstrate hypofluorescence throughout all phases of the angiogram; this is associated with blockage by the intense pigmentation of densely packed melanocytoma cells, with little associated vascularity. Hyperfluorescence of the disc may be associated with optic nerve edema. Ultrasonography may be helpful in distinguishing melanocytoma from choroidal melanoma. Melanocytomas are characteristically smooth, dome-shaped, minimally elevated lesions that are highly reflective, with regular internal structure and minimal internal vascularity.[42]

Melanocytomas may progress to malignant transformation into malignant melanoma, although such transformation is infrequent. Extrapapillary melanocytoma is more likely to undergo malignant transformation than a tumor that overlies the optic-nerve head. In juxtapapillary melanocytoma, the choroidal component is more likely to undergo malignant transformation.[25]

How Is Melanocytoma Treated?

Melanocytoma is managed with close observation and careful follow-up. If progressive growth and visual loss are clearly documented, treatments appropriate for uveal melanoma should be considered. A melanocytoma is normally managed in the same manner as a choroidal nevus, with observation and serial fundus photography. In cases of documented growth and suspected malignant transformation, all tests used in the diagnosis of uveal melanoma are indicated. Fluorescein angiographic (FA) features and ultrasound characteristics will frequently demonstrate a melanoma pattern; this is helpful in forming an accurate diagnosis and in choosing the appropriate therapy.

Choroidal Melanoma

What Are the Epidemiology and Incidence of Choroidal Melanoma?

Choroidal melanoma is the most common primary intraocular malignancy in adults; it is extremely rare in children. The incidence of choroidal melanoma in the United States is six cases per one million population[43,44]; it increases with age, from about 2.5 per million between the ages of 15 and 44 to 25 per million after the age of 65.[43–46] The diagnosis is more frequent in white populations.[43,44] Asian and African-American populations are rarely affected.[43–46]

What Are the Pathologic Features of Choroidal Melanoma?

Choroidal melanoma characteristically produces a dome-shaped subretinal mass with variable pigmentation ranging from mostly amelanotic to heavily pigmented. Clumps of orange pigmentation at the level of the RPE represent lipofuscin. Localized serous retinal detachment is frequently observed.[47] The size of the tumor in largest basal dimension and the predominant cell type are the two most important pathologic variables in the prognosis.[47] Uveal melanomas are classified according to the modified Callender classification as predominantly spindle cell type, epithelioid, or mixed cell type.[48] Spindle-cell tumors can be classified as spindle-A or spindle-B. Spindle-A cells have low nuclear-to-cytoplasmic ratio. In these cells, nucleoli are absent, intranuclear vacuoles may be observed, and a chromatin strip may extend centrally through the nucleus. Tumors composed entirely of spindle-A cells are considered to be nevi. Spindle-B cells have higher nuclear-to-cytoplasmic ratio, open chromatin, and more prominent nucleoli. Tumors composed of a mixture of spindle-A and spindle-B cells are classified as *spindle cell melanomas*. Epithelioid melanoma cells resemble epithelium, with abundant cytoplasm and large oval to round nuclei. These cells have large nucleoli and very coarse chromatin. A tumor is *epithelioid* according to the Callender classification if it is composed of more than 50% epithelioid cells. Tumors composed of less than 50% epithelioid cells are *mixed cell tumors*.[48]

How Does Choroidal Melanoma Present Clinically?

Choroidal melanoma located in the posterior pole may present with decreased vision. Flashes, floaters, or photopsias may narrow the differential diagnosis,

especially when there is associated exudative detachment or hemorrhage caused by rupture of the tumor through Bruch's membrane. There may be a scotoma corresponding to the tumor or visual field changes associated with exudative detachment. Large or anterior tumors may produce angle-closure glaucoma and pain as a result of elevated intraocular pressure. Rarely, choroidal melanoma may present with orbital discomfort associated with scleritis.[49] Frequently, choroidal melanomas are completely asymptomatic and diagnosed on routine ophthalmologic examination.[25]

What Is the Appropriate Diagnostic Approach for Choroidal Melanoma?

Choroidal melanoma is frequently diagnosed through indirect data because biopsy is rarely required. Intraocular biopsy can be external through fine-needle aspiration or internal by a vitrectomy with a biopsy approach. Careful application of indirect methods, including indirect ophthalmoscopy, fundus photography, FA, and A and B-scan echography assures an accurate diagnosis (Fig. 15–3). The Collaborative Ocular Melanoma Study (COMS) reported a 99.7% accuracy of diagnosis following indirect diagnostic testing in 1532 cases.[50,51]

Disciform scar, large choroidal nevi, choroidal metastases, choroidal hemangioma, choroidal detachment, granuloma, and melanocytoma can simulate choroidal melanoma. Appropriate testing is necessary to narrow the differential diagnosis (Fig. 15–4).

On indirect ophthalmoscopy, choroidal melanoma is characteristically elevated, dome-shaped, pigmented (although amelanotic melanoma can show minimal pigmentation), and associated with subretinal fluid. Orange pigmentation may be associated with the main tumor mass. Tumors that have broken through the Bruch's membrane display a characteristic, although not pathognomonic, collar-button configuration.[52] These tumors may be associated with overlying vitreous or subretinal hemorrhage. Retinal invasion may be velvety brown and adjacent to the primary mass. Infrequently, choroidal melanoma may demonstrate a diffuse pattern; these forms tend to be large in basal dimension and relatively thin. Diffuse tumors can extend extraocularly.[53–55]

Fundus photographs may demonstrate the clinical features and establish a baseline for serial comparison. FA frequently demonstrates "hot spots" or point sources of leakage. An intrinsic tumor vasculature may be observed[56,57] and may be particularly evident in the apical collar button area. FA is also useful in the diagnosis of similar lesions, such as eccentric disciform scar, arterial macroaneurysm, choroidal hemangioma, or choroidal detachment.

A and B-scan ultrasound studies are particularly useful in narrowing the differential diagnosis. Compared with other intraocular masses, choroidal melanoma demonstrates characteristically low to moderate reflectivity on A-scan evaluation. B-scan demonstrates choroidal excavation, internal sound attenuation, and the presence of intrinsic vascularity. A break through Bruch's membrane with a characteristic collar button configuration may be confirmed by echography.[42]

How Is Choroidal Melanoma Treated?

A careful history and physical examination are important in the initial evaluation. Questions should be directed to the patient's state of overall health. Recent weight loss, cachexia, malaise, abdominal discomfort, breathing difficulties, or shortness of breath should be explored during the review of symptoms.

Initial history should also focus on the patient's visual symptoms and should explore other causes of decreased vision such as glaucoma, diabetic retinopathy, or age-related macular degeneration. Chemotherapy for treatment of a previous malignancy should be discussed because this exposure may aggravate radiation-associated retinopathy. The patient's occupational and recreational visual needs must be addressed because these could impact on the chosen therapy. It is particularly important to assess the visual potential of both the involved and uninvolved eye.

Treatment of primary intraocular melanoma is not indicated if the patient has already developed systemic metastases. Although choroidal melanoma patients usually do not present with metastases, these should be excluded by liver function tests and chest radiography. If liver function tests are elevated, an imaging study of the liver, including ultrasound, MRI, or CT imaging should be obtained. Less common sites of metastasis are the lungs, skin, bones, and brain.[58] Once metastatic disease is eliminated as a possibility, the patient's treatment may be determined. Accurate diagnosis and treatment of choroidal melanoma require informed consent from the patient with knowledge of all potential treatments and available outcomes data.[50,51,53,59–67]

Enucleation

Enucleation is a standard therapy in the treatment of large and medium-sized choroidal melanomas. The COMS compared preenucleation external beam radiation followed by enucleation to enucleation alone for large uveal melanoma.[50,51,59] There was no statistically significant difference in five year survival.[60] Enucleation is the best treatment option for eyes with very large choroidal melanomas or with very limited

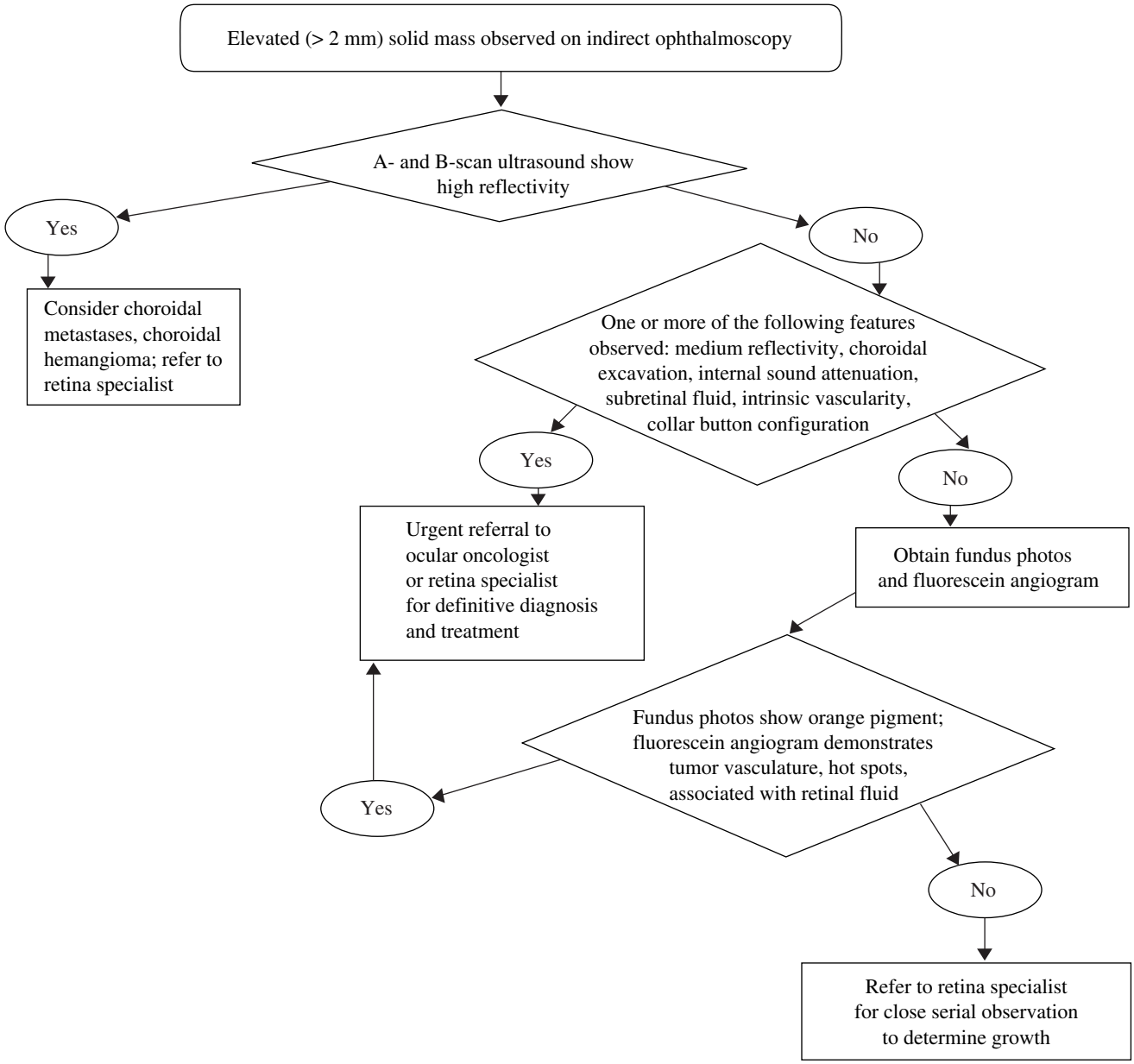


FIGURE 15–3. Clinical pathway: Evaluation of suspected choroidal melanoma.

visual potential. An ocular implant is usually placed at the time of enucleation.

Radioactive Plaque (Brachytherapy)

Radioactive plaques may be applied to administer high-dose radiotherapy (brachytherapy). A variety of isotopes have been used effectively, including ruthenium 106, iridium 192, iodine 125, and cobalt 60.[25] Iodine 125 is the most frequently used isotope in the United States. Complications of brachytherapy are dose dependent. Vision loss is generally more pronounced for tumors involving the macula or optic nerve. Late complications can include optic neuropathy and radiation retinopathy. During brachytherapy, the maximum dose of radiation is delivered in the region contiguous to the plaque; thicker tumors require more radiation delivered to the tumor base to assure that the tumor apex receives adequate irradiation.[25] The COMS Medium Tumor Trial demonstrated that radiation delivered by plaque radiotherapy (Fig. 15–5) and enucleation are equally effective in controlling primary disease at up to 12 years of follow-up.[61,63]

Charged Particle Radiation

For this treatment, tantalum marker clips are surgically placed at the margins of an uveal melanoma be-

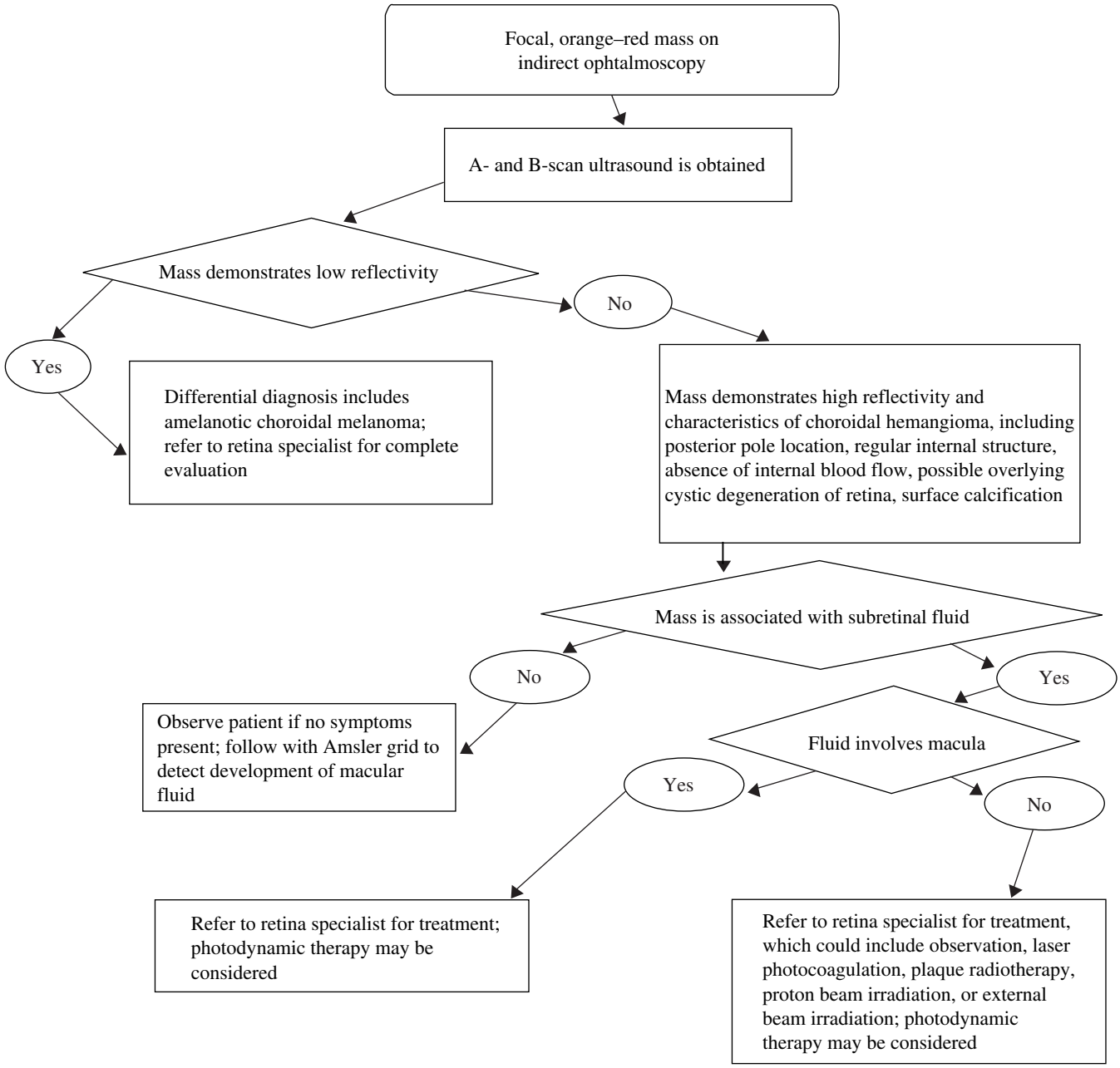


FIGURE 15–4. Clinical pathway: Evaluation of circumscribed choroidal hemangioma.

fore radiation, providing for beam localization.[68] High-energy radiation is delivered with charged particles (protons or helium ions) in an accelerated linear beam. The energy is delivered in a homogeneous fashion; there is no gradient in dose between tumor apex and base. The lateral spread of radiation from the charged particle beam is considerably less than from brachytherapy; the dose of radiation drops from 100 to 0%, 2.3 mm from the beam edge. This method may be advantageous in tumors that have a peripapillary or macular location. Charged particle radiation, like brachytherapy, may result in radiation-associated retinopathy or optic neuropathy.[69,70] Although this method of radiation delivery has not been assessed in prospective, multicenter, randomized trials, it has been used for many years and is considered as effective as radiation delivery by brachytherapy.[71–82]

Transpupillary Thermal Therapy

Small trials have reported efficacy for transpupillary thermal therapy delivered by diode laser.[67,83–93] Follow-

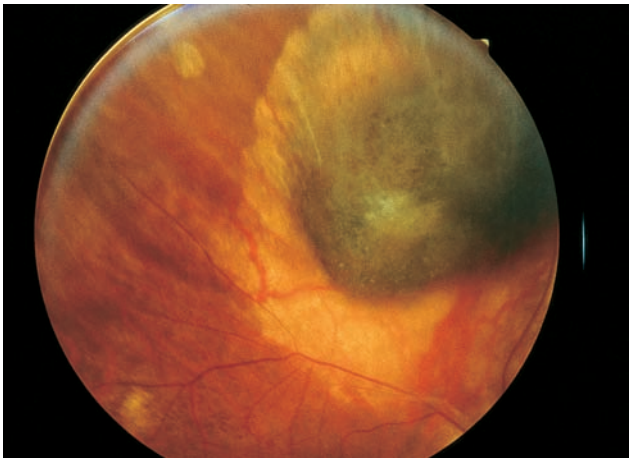


FIGURE 15–5. Treated choroidal melanoma. Tumor exhibits a slate gray regression pattern with surrounding choroidal atrophy.

up for this relatively new mode of therapy is short, and large, prospective, randomized trials have not compared this treatment with more established methods of treatment such as enucleation or radiation. Diode therapy may be indicated for tumors that threaten vision in uniocular patients. This method may also reduce the thickness of the tumor, allowing a reduction in radiation dose following the application of heat.[67,83–93] Until long-term clinical outcomes data are available, this treatment must be considered investigational.[8]

Eye-Wall Resection

Eye-wall resection and endoresection have been recommended for iris or ciliary body melanoma and occasionally in patients with choroidal melanoma. The outcomes from eye-wall resection have been reported in single center case series only. The technique is difficult, and the tumor often is not eradicated in the operative margins.[94–97]

Choroidal Metastases

What Are the Epidemiology and Incidence of Choroidal Metastases?

Choroidal metastases occur most often as manifestations of breast cancer in women and lung cancer in men. Carcinomas are the most frequently observed ocular metastases, whereas sarcoma and melanoma are less frequent. Carcinoma of the gastrointestinal tract, kidney, thyroid gland, pancreas, and prostate occur with even lower frequency. In published series, 74 to 94% of uveal metastases involve the choroid.[98–100]

The incidence of choroidal metastases has increased with the prolongation of survival in cancer patients. Choroidal metastases represent the most frequent malignancy observed in the eye.[98] Over one third of breast cancer patients have choroidal metastases.[101] Metastases to the choroid are observed most frequently in middle-aged or older patients, and, with the exception of metastatic choroidal disease in leukemia patients, choroidal metastases are rare in children.

What Are the Pathologic Features of Choroidal Metastases?

Choroidal metastases diffusely involve the choroid, are frequently multifocal, and are associated with exudative retinal detachment. The histopathologic appearance of metastases often corresponds to the primary malignancy, particularly when the metastatic lesion is well differentiated. Metastatic carcinoma of the breast may demonstrate glandular structures, whereas metastatic oat cell carcinoma may show an alveolar pattern. Metastatic tumors can be less differentiated and may not resemble the primary tumor; in these cases, special stains and ultrastructural analysis may be informative.[21]

How Do Choroidal Metastases Present Clinically?

Choroidal metastases that involve the posterior pole present with decreased vision. These lesions are characteristically creamy yellow at the level of the choroid. Metastatic tumors may be multiple and frequently are associated with substantial subretinal fluid. Choroidal metastatic tumors can grow dramatically over time; thus, early treatment should be undertaken to maintain vision. These tumors frequently produce reactive RPE changes referred to as *peau d'orange*. When retinal detachment is extensive and bullous, subretinal fluid may shift dramatically. Large metastatic tumors, particularly those involving the anterior uvea, may result in secondary glaucoma.

What Is the Appropriate Diagnostic Approach for Choroidal Metastases?

Patients with suspected choroidal metastases require an immediate medical history and physical examination. Urgent referral to a medical oncologist is indicated. If the primary tumor is unknown, then appropriate medical evaluation, imaging studies, and appropriate tissue biopsy should be undertaken. The metastatic choroidal lesion should generally be treated with external-beam radiation therapy.

Fluorescein angiography reveals initial hypofluorescence in the laminar venous phase with late hyperfluoresence of the mass.[102] Echographically, metastatic choroidal tumors usually show moderate elevation, although high elevation occasionally is observed (Fig.

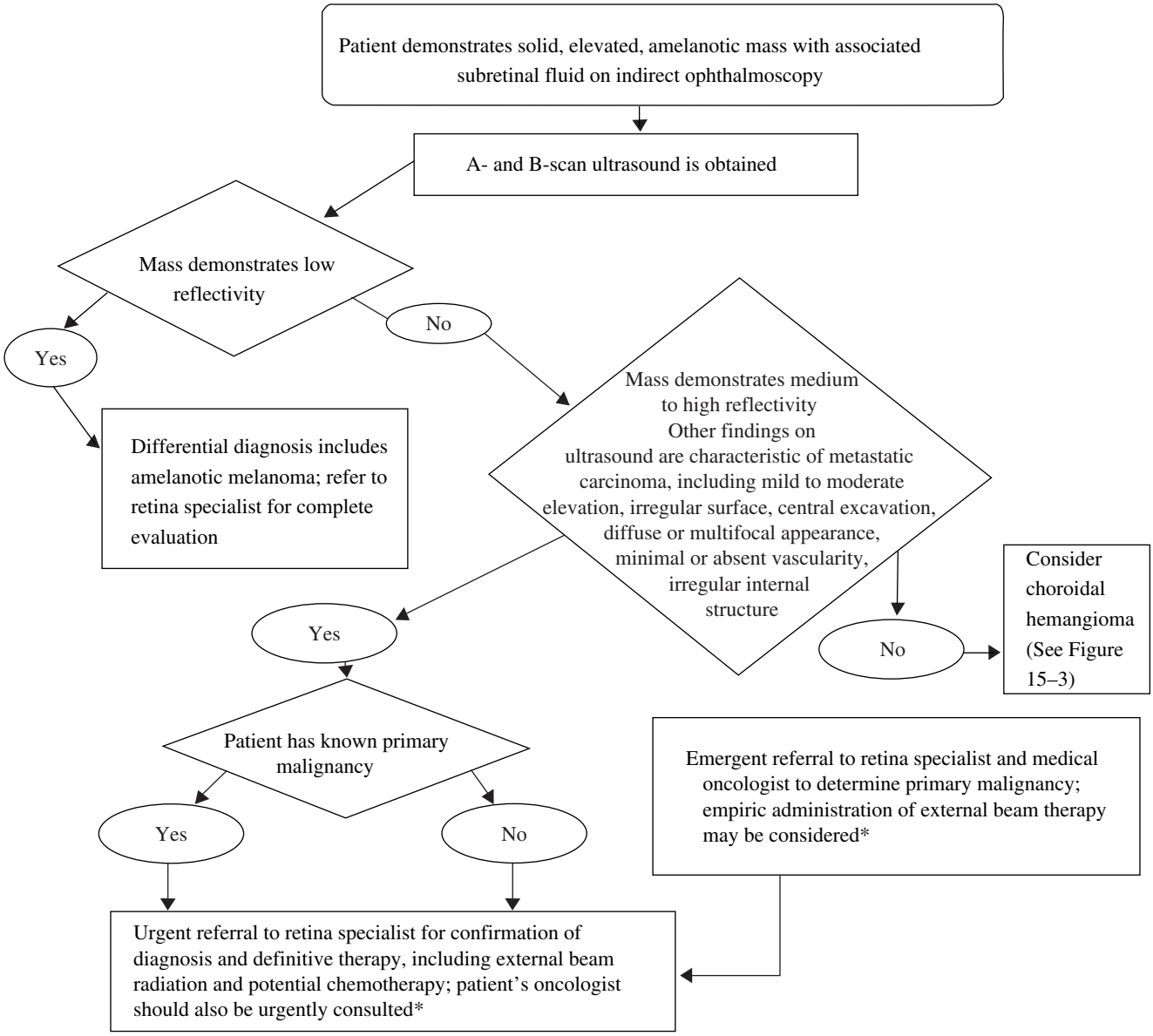


FIGURE 15–6. Clinical pathway: Evaluation of suspected metastases to choroid from systemic malignancy.

15–6). Differentiation between suprachoroidal effusion or hemorrhage should be made (Fig. 15–7). Multifocality, an irregular anterior surface and central excavation are frequently observed. B-scan demonstrates a diffuse, subclinical thickening of the choroid. A-scan demonstrates moderate to high reflectivity with an irregular internal structure.[42] Choroidal metastases require urgent imaging of the brain and orbits to exclude concomitant central nervous system (CNS) metastases; these must be considered in planning ports for subsequent radiation therapy.

How Are Choroidal Metastases Treated?

Treatment with external-beam radiation therapy should begin as soon as possible to prevent progres-

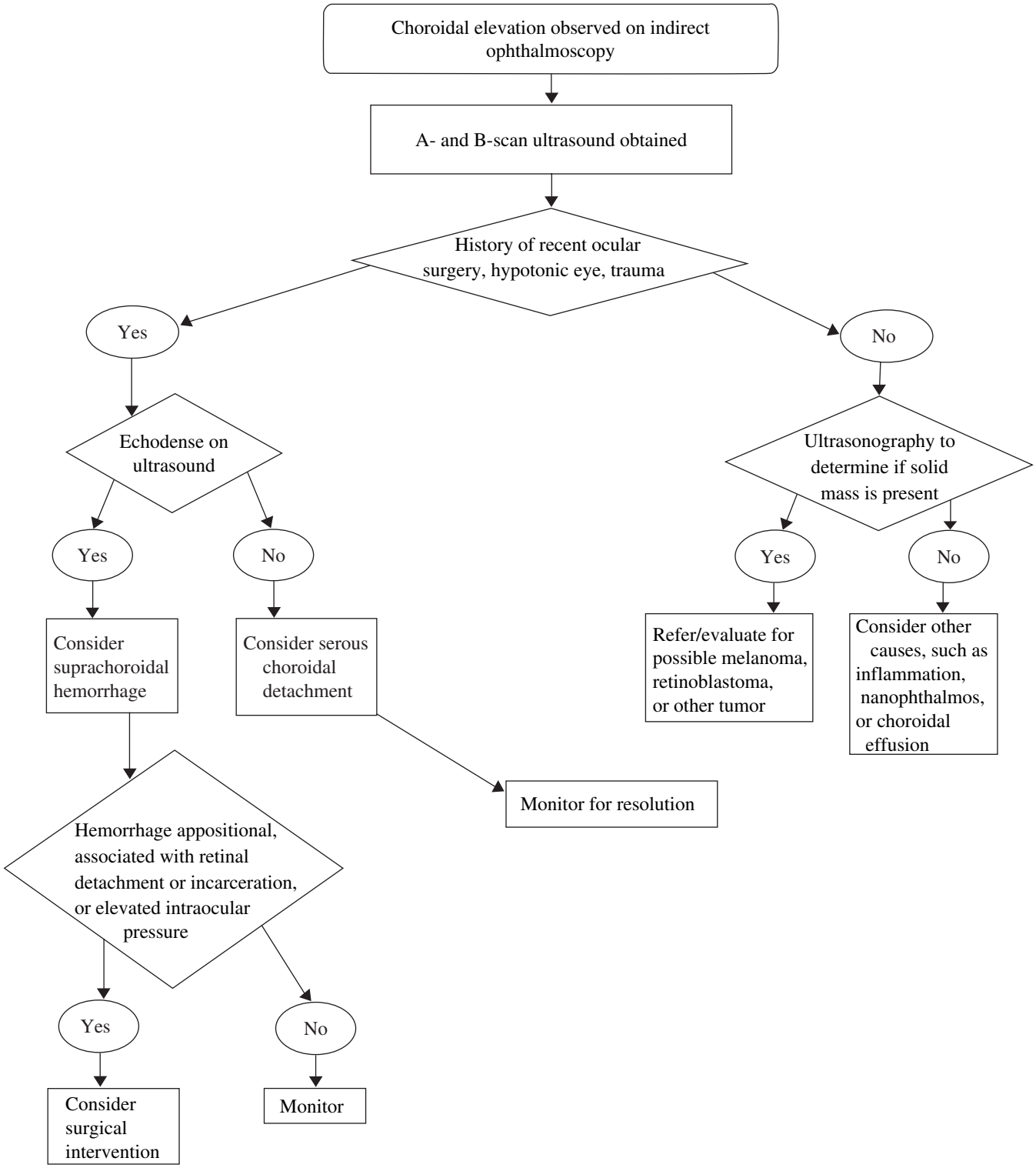


FIGURE 15–7. Clinical pathway: Evaluation of suprachoroidal effusion or hemorrhage.

sive visual loss.[103,104] Definitive chemotherapy or radiation therapy for the primary lesion and treatment of the ocular lesion may be simultaneous. In some cases, radiation therapy may be avoided if chemotherapy is advanced.[105] Careful consultation with the treating medical oncologist is necessary. Patients with choroidal metastases have a poor prognosis overall. Breast cancer patients with choroidal metastases may have a more favorable prognosis compared with patients with lung cancer or metastatic choroidal melanoma.[106]

Medulloepithelioma

What Are the Epidemiology and Incidence of Medulloepithelioma?

Medulloepithelioma is an embryonal tumor arising from the primitive medullary epithelium.[107] It is the most common congenital tumor of the nonpigmented epithelium within the ciliary body,[108] and it rarely occurs in the retina or in the optic nerve.[109] Medulloepithelioma is also known as *diktyoma*, a descriptive term alluding to the net-like arrangement of primitive neuroepithelial cells occasionally observed.[107,108]

Medulloepithelioma usually is diagnosed in the first decade of life,[109] although there are occasional reports of adult occurrence.[109–112] The tumor shows no predilection for sex, race, or laterality.[113] Although the precise incidence of this tumor is unknown, it is much less frequently observed than retinoblastoma.

What Are the Pathologic Features of Medulloepithelioma?

Medulloepitheliomas contain elements of the medullary epithelium, RPE, nonpigmented and pigmented ciliary epithelium, vitreous, and neuroglia.[113] Medulloepitheliomas often contain rosettes similar to, but larger than, those seen in retinoblastoma, including Homer–Wright and Flexner–Wintersteiner rosettes. The proliferating medullary epithelium is arranged in cords and sheets with intervening cystic spaces filled with hyaluronic acid.[113]

There are two histologic types of medulloepithelioma: nonteratoid and teratoid.[114,115] Both types may be benign or malignant.[114–116] The nonteratoid variant, frequently referred to as diktyoma, consists of cells reminiscent of the ciliary epithelium.[107,108,114] The teratoid variant, also termed *teratoneuroma*, demonstrates heteroplasia, with cartilage, rhabdomyoblasts, undifferentiated mesenchymal cells, and neuroglial cells resembling brain within the main tumor mass.[117–122] Malignant medulloepithelioma demonstrates tightly packed neuroblastic cells with numerous mitotic figures.[123–129]

How Does Medulloepithelioma Present Clinically?

In Broughton and Zimmerman's series of 56 patients with medulloepithelioma, the most common presenting sign was reduced vision.[113] About one third of patients described ocular pain in association with this tumor.[113] Leukocoria and an iris or ciliary body mass were also frequent. Less frequently, the tumor was associated with globe enlargement, pupillary abnormalities, acquired heterochromia, hyphema, exophthalmos, strabismus, or epiphora.[113] Very small tumors may be entirely asymptomatic.

Shields and co-workers described 10 patients who presented with medulloepithelioma. In this series, all patients had a discernible nonpigmented ciliary body mass.[109] A characteristic lens notch was observed, with a lens coloboma in the quadrant of the tumor; this finding may result from the absence of zonular support in the region of this congenital tumor. In most patients, there was a delay in the diagnosis ranging from 3 to 8 months.[109] Neovascular glaucoma was observed in most patients.[109,122] Several patients in this series underwent surgical procedures for treatment of glaucoma, cataract, or other secondary conditions before diagnosis of the ciliary body mass.

On presentation, medulloepitheliomas are typically pinkish white, cystic masses within the ciliary body.[109,113] They may produce lens subluxation initially. With time, a cataract may develop, precluding a view of the posterior pole. At this stage, the tumor may be confused with persistent hyperplastic primary vitreous (PHPV) now referred to as fetal vasculature (PFV) or an anterior retinoblastoma. Neovascular glaucoma may be a late manifestation, and occasionally cystic seeds may separate from the main tumor mass and be visible in the anterior chamber or vitreous space.

Medulloepithelioma also may involve the optic disc, the optic nerve, or the retina.[114–116] These tumors, located in the posterior pole, likely are derived from the primitive pluripotent medullary epithelium that lines the invaginated optic vesicle. Posteriorly located tumors are aggressive, with frequent orbital extension, resulting in proptosis and disc edema.

Broughton and Zimmerman described PFV coexisting with medulloepithelioma,[113] suggesting that this tumor occasionally derives from persistent tunica vasculosa lentis. Medulloepithelioma occasionally extends over ocular surfaces, resembling a cyclitic membrane rather than a discrete mass. The observed delays in diagnosis are likely due to this variation in clinical presentation.[117–124]

What Is the Appropriate Diagnostic Approach for Medulloepithelioma?

The clinical appearance of medulloepithelioma on slit-lamp examination and indirect ophthalmoscopy provides the most useful clinical information.[125] The tumor is characteristically unilateral, although bilateral disease has been described.[126] FA may demonstrate an intrinsic tumor circulation, but this does not distinguish medulloepithelioma from other ciliary body tumors.[125,127–130] A- and B-scan ultrasound may demonstrate tumors that are located posterior to the iris plane. Cystic areas within the main tumor mass may be better differentiated by echography than by clinical examination.[131] Other echographic features suggestive of medulloepithelioma include high internal reflectivity, irregular tumor surface, the presence of internal vascularity, and tumor molding to intraocular surfaces.[132] CT scan with 1-mm cuts through the orbit may be a useful imaging study. On MRI scan, the tumor is hyperintense on T1-weighted images and hypointense on T2-weighted images.[132] Medulloepithelioma must be considered in the differential diagnosis of intraocular tumors of the ciliary body as well as in the differential diagnosis of atypical tumors at other intraocular locations.

How Is Medulloepithelioma Treated?

Small, localized medulloepitheliomas are treated with local excision. Lesions confined to the iris or ciliary body may be treated with iridocyclectomy or cyclectomy. Retinoblastoma is frequently high in the differential diagnosis, and when this is a possibility, eyewall resection is not indicated, even for anterior tumors. Most medulloepitheliomas are treated by enucleation, and exenteration may be indicated if extrascleral extension is observed.[123] The efficacy of irradiation and chemotherapy is not well established but should be considered for recurrent tumors.

Neurilemoma

What Are the Epidemiology and Incidence of Neurilemoma?

Neurilemoma (schwannoma) most commonly presents as a benign peripheral nerve sheath tumor.[133] These tumors have been described in the orbit and rarely on the bulbar conjunctiva.[134] Intraocular neurilemomas have been described in the ciliary body[133] and choroid.[135–139] These last tumors are encapsulated and arise from ciliary nerves within the uveal tract. Neurilemomas of the uvea occur as solitary tumors, and three published cases report an association with neurofibromatosis.[138] Age at diagnosis in reported cases is 4 to 40 years. Average age at diagnosis is 38 years, a younger average age than in uveal melanoma patients.[125] Intraocular neurilemomas are extremely rare, although the precise incidence and prevalence are not defined.

What Are the Pathologic Features of Neurilemoma?

Neurilemomas are neuroectodermal and composed of spindle cells with vesicular nuclei but no prominent nucleoli. These cells form a palisading pattern (Antoni A) in solid cell growth areas that alternate with looser myxoid stroma and stellate or ovoid cells (Antoni B).[140] The Antoni B pattern represents cell degeneration within the tumor. The palisading nuclei in Antoni A cells may form Verocay bodies, oval-shaped collections of picket-fence nuclei with imbricated cytoplasmic processes. The capsule surrounding the tumor derives from the perineurium of the originating nerve. Transmission electron microscopy demonstrates features of Schwann cell origin. Findings include scattered mitochondria, short segments of rough endoplasmic reticulum, linear amorphous basement membrane formation, and long spacing collagen. On immunohistochemistry, neurilemomas are positive for S-100 protein.

How Does Neurilemoma Present Clinically?

Intraocular neurilemoma occurs as a solitary, nonpigmented mass of the choroid or ciliary body. Neurilemoma appears similar to amelanotic melanoma.[139] In rare instances, neurilemomas may become pigmented and may be difficult to distinguish from pigmented choroidal melanoma.[141] Neurilemomas are benign lesions but may enlarge; enlargement prompts enucleation with the presumed diagnosis of choroidal or ciliary body melanoma.[134–138]

What Is the Appropriate Diagnostic Approach for Neurilemoma?

Fluorescein angiography and ultrasound findings for choroidal neurilemoma may be quite similar to those of choroidal melanoma. On FA, neurilemomas show linear hyperfluorescence of the choroidal vessels during the arterial phase and mottled hyperfluorescence of the mass in the late phase. This pattern also may be observed with choroidal hemangioma and amelanotic choroidal melanoma.[125]

A-scan echography in choroidal neurilemoma produces a high initial spike and homogeneously low internal reflectivity. On B-scan, the tumor characteristically has a dome shape with an internal acoustic quiet zone, choroidal excavation, and orbital shadowing. These findings should exclude metastatic lesions

and choroidal hemangioma from the differential diagnosis.

How Is Neurilemoma Treated?

Intraocular neurilemoma is a rare tumor that may be misdiagnosed as choroidal or ciliary body melanoma. Observation is indicated for small tumors because they are likely to demonstrate a benign clinical course. Malignant degeneration, described rarely in the orbit,[125] has not been described in choroidal neurilemomas.[125,138] Photographic documentation and serial observation are indicated.

Astrocytic Hamartoma

What Are the Epidemiology and Incidence of Astrocytic Hamartoma?

Astrocytic hamartoma is a benign retinal and optic nerve tumor composed of glial cells and astrocytes. These lesions are typically congenital but rarely are acquired. They occur in about 50% of patients with tuberous sclerosis.[142,143]

Astrocytic hamartomas presenting in tuberous sclerosis occur with intracranial astrocytoma, cardiac rhabdomyoma, renal angiomyolipoma, skin lesions typical of adenoma sebaceum, or cutaneous angiofibromas and periungual angiofibroma of the fingernail.[144,145] The adenoma sebaceum skin lesions occur in the malar region of the face in a butterfly distribution. Other skin manifestations include large hypopigmented macules (ash-leaf sign) over the trunk and buttocks and elevated discolored areas with the texture of orange peel or pigskin (shagreen patches) in the lumbosacral region.[146] Genetic mutations on chromosomes 9 (9q34) and 16 (16p13.3) have been identified in tuberous sclerosis patients.

What Are the Pathologic Features of Astrocytic Hamartoma?

Astrocytic hamartomas are composed of elongated astrocytes with interlacing cytoplasmic processes. Nuclei are small and oval, and larger tumors may contain more pleomorphic large, round astrocytes. Regions of calcification may be observed; calcified astrocytic tumors have also been described in patients with retinitis pigmentosa.[147–149]

How Does Astrocytic Hamartoma Present Clinically?

Patients with astrocytic hamartomas are frequently asymptomatic. These patients may be referred for retinal evaluation when the diagnosis of tuberous sclerosis is suspected. Tumors located in the posterior pole or at the optic disc may produce reduced vision or visual-field defects. Tumors occasionally produce reduced vision through associated vitreous hemorrhage or retinal detachment.[150]

On indirect ophthalmoscopy, early retinal astrocytic hamartomas are minimally elevated and translucent. Some tumors are well defined, whereas others are diffuse. As the tumors enlarge, they develop a dome shape and may be calcified. Older tumors tend to show extensive calcification and may be mistaken for retinoblastoma. The calcific form of astrocytic hamartoma is usually elevated and multinodular, with glistening yellow calcified spherules described as tapioca clumps or salmon eggs.[142] The noncalcified tumors are frequently sessile and indistinct, occupying the inner aspect of the sensory retina. Tumors may be semitransparent to gray–yellow.

Other tumors in the differential diagnosis include retinal capillary hemangioma, myelinated nerve fibers, drusen of the optic nerve, and massive gliosis of the retina. Astrocytic hamartomas are characteristically a glistening yellow compared with the more chalky white calcifications seen in retinoblastoma. Also, astrocytic hamartomas rarely show intrinsic tumor circulation or tortuous retinal blood vessels. Retinal hemangiomas may be distinguished from astrocytic hamartoma because hemangiomas are usually pink rather than yellow–white.[149] Myelinated nerve fibers do not become calcified, and they show a characteristically fibrillated margin. Drusen of the optic nerve may be confused with astrocytic hamartoma; drusen are usually bilateral and are posterior to the lamina sclerales, whereas astrocytic hamartomas are usually unilateral and anterior to the lamina sclerales.[151] Astrocytic hamartomas also may be bilateral in one third to one half of patients.

What Is the Appropriate Diagnostic Approach for Astrocytic Hamartoma?

On indirect ophthalmoscopy, astrocytic hamartoma is a dome-shaped intraretinal mass with a peripapillary location. On FA in the arterial phase, the lesion is hypofluorescent, and within the main tumor mass, a characteristic reticular pattern of fine, leaking blood vessels is apparent. Late recirculation phases of the angiogram show hyperfluorescent staining.

On B-scan echography, astrocytic hamartomas demonstrate a dome shape and occasionally a mulberry configuration adjacent to the optic-nerve shadow. Orbital shadowing, particularly with more calcified tumors, may be present. On A-scan, these lesions demonstrate medium to high reflectivity. Patients who present with astrocytic hamartomas may

develop tuberous sclerosis. A complete physical examination with appropriate imaging studies should be undertaken.

How Is Astrocytic Hamartoma Treated?

Management of astrocytic hamartoma includes a systemic workup to diagnose any underlying systemic disorders, such as tuberous sclerosis or neurofibromatosis. Astrocytic hamartomas are benign, generally stationary lesions that may be observed with fundus photography. In cases of associated exudative retinal detachment, argon laser may produce chorioretinal adhesions that prevent leakage into the subretinal space. Peripheral lesions may be treated with cryotherapy to reduce subretinal fluid.

How Does Acquired Astrocytic Hamartoma Differ from Congenital Astrocytic Hamartoma?

Acquired astrocytic hamartoma may develop at any age. These acquired tumors are not associated with tuberous sclerosis or other underlying systemic syndromes.[152] They have the appearance of a pedunculated, amelanotic, and vascular solitary mass and lack the extensive calcification that occurs in many astrocytic hamartomas.[153] FA and ultrasonographic features are similar to those of congenital astrocytic hamartoma.[153,154] Treatment for these lesions is identical to treatments applied to congenital astrocytic hamartoma.

Von Hippel–Lindau Syndrome

What Are the Epidemiology and Incidence of von Hippel–Lindau Syndrome?

Von Hippel–Lindau syndrome (VHL) is characterized by retinal and CNS angiomas and predisposition to systemic cancer.[155,156] The associated visceral lesions include renal and pancreatic cysts, renal cell carcinoma, pheochromocytoma, and epididymal cystadenoma.[157,158] Cerebellar hemangioblastoma is the most frequently observed CNS lesion in VHL and is best diagnosed by an MRI scan of the brain. The presence of visceral lesions, such as renal or epididymal cysts, is not sufficient to diagnose VHL. If there is no family history of VHL, the presence of two or more retinal or cerebellar hemangioblastomas or one hemangioblastoma with one visceral tumor is required for diagnosis.[159,160] Clear cell carcinoma of the kidney occurs in up to 70% of VHL patients and is a frequent cause of mortality.[158]

According to Neumann and Wiestler, the prevalence of VHL syndrome was 1 in 40,000 residents of the Freiburg district of Germany.[156] Before this study, the prevalence of the syndrome had not been investigated.[156] The disease is autosomal dominant with high penetrance. There is no sexual, racial, or ethnic predominance. Twenty-five percent of patients have a familial form of the disease; the remainder likely represent new germline mutations at the VHL locus.[161–163]

What Are the Underlying Genetics of von Hippel–Lindau Syndrome?

This syndrome is caused by deletions or mutations in a tumor suppressor gene mapped to the short arm of chromosome 3 (3p25).[161–163] The gene coding sequence contains three exons and two isoforms of messenger ribonucleic acid (mRNA).[160] Loss or inactivation of the wild-type allele in a cell results in tumor formation. Initial studies suggest that large germline mutations are present in 20% of affected patients. Twenty-seven percent of VHL patients have missense mutations, and 27% have nonsense or frameshift mutations.[159,160] Type 1 VHL is not associated with pheochromocytoma, whereas type 2 disease is characterized by the presence of this tumor. Also, most type 2 families have missense mutations, while type 1 families have large deletions or mutations, resulting in premature terminations.[159,160,164] Patients with no family history of VHL may be new sporadic germline mutation carriers or may demonstrate mosaicism in their VHL gene.[164,165] Epigenetic modification of the VHL gene by methylation may result in loss of the expression of the VHL gene product (pVHL) in the absence of mutation.[166]

Normally, pVHL, a component of an ubiquitin ligase, degrades the hypoxia-inducible factor (HIF) in the presence of sufficient oxygen. Tumors lacking functional pVHL overproduce HIF and its target products, such as vascular endothelial growth factor (VEGF) and transforming growth factor alpha, resulting in the uncontrolled proliferation of hamartomatous blood vessels in patients carrying VHL mutations. Additional pVHL roles may include cell-cycle control, induction of differentiation, extracellular matrix formation and turnover, and angiogenesis.[159,160,164–166]

What Are the Pathologic Features of von Hippel–Lindau Syndrome?

The retinal tumors associated with VHL are benign, vascular, and similar to cerebellar hemangioblastoma. On light microscopy, full-thickness retina is replaced by a fusiform mass composed of capillary-like blood vessels. Larger lesions show vessels lined by endothelium and a fine reticulum, with vacuolated cells within the stroma. These vacuolated cells demonstrate features of lipidized fibrous astrocytes ultrastructurally.[155,167] The endothelium of tumor vessels

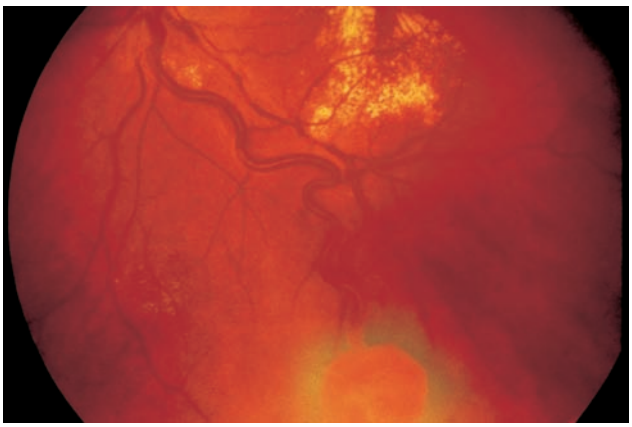


FIGURE 15–8. Retinal angioma in von Hippel–Lindau syndrome. Dilated feeding and draining vessels are shown with leakage manifested as macular lipid exudates.

fenestrates, resulting in extravasation of fluid and exudate, cystic degeneration of the retina, and exudative retinal detachment. Discontinuities in the internal limiting membrane of the retina may be associated with vitreous condensation, producing proliferative vitreoretinopathy.[155,167–169]

How Does von Hippel–Lindau Syndrome Present Clinically?

This syndrome may present with floaters, metamorphopsia, strabismus, or decreased visual acuity. Retinal hemangioblastomas are frequently multiple and bilateral in 50% of cases. Early tumors are red to gray and are not associated with abnormal feeder vessels. As these tumors enlarge, the feeding and draining vessels become dilated (Fig. 15–8). Larger tumors are frequently associated with exudative retinal detachment. Retinal angiomas often are located in the temporal periphery but may also be within the macula, in the peripapillary region, or overlying the optic disc. Vision is reduced initially by exudative retinal detachment. Lipid exudation, vitreous, intraretinal, or subretinal hemorrhage and rhegmatogenous retinal detachment eventually may develop, further reducing vision.[167–169]

What Is the Appropriate Diagnostic Approach to von Hippel–Lindau Syndrome?

On indirect ophthalmoscopy, the VHL tumor is red with tortuous vessels, and a characteristic appearance on FA aids in the diagnosis. A dilated feeder vessel usually leads to a small round angioma associated with a draining venule. These hemangiomas typically show profuse dye leakage in the late phases of the angiogram. VHL tumors may grow markedly over time; the feeder vessels may enlarge, and leakage may result in hemiretinal detachment with substantial subretinal exudate. The development of large serous retinal detachments can produce severe reduction in vision.

Five stages of disease progression have been described.[157] In stage 1, retinal lesions are small, comparable in size to a diabetic microaneurysm. These lesions do not demonstrate dilated feeder vessels, but the angiomas are visible on FA. In stage 2, the retinal lesions appear as red, elevated nodules with draining veins and pronounced leakage on FA. In stage 3, neovascularization and exudation associated with retinal hemangioma may cause vitreous hemorrhage. Exudative or tractional retinal detachment is present in stage 4. A total retinal detachment is observed in stage 5.

How Is von Hippel–Lindau Syndrome Treated?

Treatment for VHL lesions includes laser photoablation or cryotherapy for small lesions and radiation therapy for more extensive tumors. Small tumors of 1 to 2 disc diameters respond to laser photocoagulation.[167–169] Larger tumors of 2 to 2.5 disc diameters or more may require multiple sessions of laser photocoagulation and possible adjunctive cryotherapy; cryotherapy is especially useful for peripheral tumors.[169] Feeder-vessel occlusion with argon laser is controversial; it may be effective for small to medium sized arterioles but is ineffective for larger tumors and may result in retinal detachment or infarction.[167,168] Proton-beam irradiation is required in cases where other treatment has failed.

Management of VHL includes periodic examinations and serial imaging to screen for other malignancies. The Cambridge Screening Protocol recommendations for VHL are (1) an annual physical examination with urine analysis and 24-hour urine collection for vanillylmandelic acid (VMA), (2) an annual renal ultrasound, (3) an annual ophthalmoscopy with FA, and (4) an MRI or CT of the brain every 3 years until the age of 50 and every 5 years thereafter.[157]

Ocular Toxocariasis

What Are the Epidemiology and Incidence of Ocular Toxocariasis?

Ocular toxocariasis is caused by infestation of the eye with *Toxocara canis*, a nematode causing visceral larva migrans. Less frequently, ocular toxocariasis may be caused by the *Toxocara cati* worm.[170–173] It is transmitted by the oral ingestion of toxocara eggs from the environment.[174] The disease most frequently affects children between the ages of 5 and 10 years old[175] but occasionally presents in adulthood.[176]

What Are the Pathologic Features of Ocular Toxocariasis?

Wilder provided the first description of nematode retinitis, chorioretinitis, and endophthalmitis associated with *T. canis* migration into the eye.[173] In these patients, infection was associated with filamentous endophthalmitis, retinal detachment, and a retrolental mass. Granulomas containing the nematode were observed within the inflamed vitreous.[173]

Ashton described four patients with solitary retinal tumors involving the macula. Vitritis was limited to the region adjacent to the main retinal mass.[172] Histopathology demonstrated replacement of normal retina by an inflammatory mass containing nematode larvae. The larvae possibly had migrated from the choroid into the overlying retina. The adjacent choroid demonstrated chronic inflammation with eosinophils.[172]

More recently, several reports describe migration of nematode larvae into the vitreous and subsequent organism survival for a period of time. The death of the larvae results in the development of retinitis. On histopathology, a fibrous subretinal mass with chronic inflammation and eosinophils appears to contain the necrotic larvae. The adjacent retina is exudatively detached and atrophic with neovascularization and fibrosis of the overlying vitreous.[171,174]

How Does Ocular Toxocariasis Present Clinically?

A history of pica or contact with puppies or kittens is suggestive. If patients present with fever, pneumonitis, and hepatosplenomegaly, toxocariasis should be considered in the differential diagnosis.[175]

Ocular findings in toxocariasis include leukocoria and strabismus. Other clinical presentations are chorioretinitis, peripheral inflammatory mass, and chronic endophthalmitis.[177] Ophthalmoscopy frequently reveals a white chorioretinal mass, usually in the retinal periphery. This mass is associated with vitreous cells and, in more chronic cases, the formation of tractional bands, gliosis, and RPE proliferation. These advanced inflammatory changes are not observed with retinoblastoma and are helpful in narrowing the differential diagnosis. Ocular toxocariasis presenting as an isolated granuloma in the posterior pole may be easily confused with retinoblastoma.[175,178]

What Is the Appropriate Diagnostic Approach to Ocular Toxocariasis?

A- and B-scan echography reveal a moderately elevated mass without high-intensity echoes. These granulomatous retinal lesions occasionally show intrinsic calcification on ultrasound. Retinal detachment and vitreous bands are frequently present and are well demonstrated by B-scan echography.[42] A serologic test for *T. canis*, such as enzyme-linked immunosorbent assay (ELISA), is positive at a 1:8 dilution in a high percentage of patients with ocular involvement.[174] Anterior chamber paracentesis for ELISA[179] and cytology may be helpful in cases with uncertain diagnoses.[180,181] Cytologic examination of the aspirate demonstrates eosinophils in ocular toxocariasis.[180,181]

How Is Ocular Toxocariasis Treated?

Treatment of ocular toxocariasis depends on the stage of disease at diagnosis and the secondary retinal and vitreal changes. Treatment with antihelminthic has been recommended in selected cases but may be associated with enhanced inflammatory reactions.[174] A recent report evaluated the effect of albendazole in combination with systemic steroids in five patients and reported a mean visual acuity improvement from 20/40 to 20/20.[182] In eyes with pronounced inflammation, cycloplegics and topical steroids are indicated. More severe cases require periocular corticosteroid injection or high-dose oral steroid administration. Scleral buckle with or without vitrectomy and membrane peel are required in selected cases with retinal detachment developing secondary to ocular toxocariasis.[183] A case report where pars plana vitrectomy with removal of the epiretinal and subretinal components of the granuloma was performed demonstrated excellent clinical results.[184] Laser therapy has been used to eradicate motile subretinal worms.[175]

Coats' Disease

What Are the Epidemiology and Incidence of Coats' Disease?

Coats' disease is an idiopathic condition with massive subretinal exudates and associated telangiectatic retinal vessels and aneurysms.[185,186] It can simulate retinoblastoma because it produces leukocoria and generally occurs in the first decade of life.[186] The disease is usually unilateral (90%),[187,188] and more than two thirds of patients affected by Coats' disease are males. Affected patients are otherwise healthy, and there is no genetic, familial, ethnic, or racial predisposition associated with the disease. Pericentric inversion of chromosome 3 in a patient with Coats' disease has been reported.[189] The retinal vascular abnormalities characteristic of Coats' disease also can be seen in a variety of other illnesses, including Turner syndrome,[190] facioscapulohumeral dystrophy,[191–193] and familial renal–retinal dystrophy.[194] The precise incidence and prevalence of this disease are unknown.

What Are the Pathologic Features of Coats' Disease?

Coats' disease is associated with congenital abnormalities in retinal vessels that result in leakage of plasma and blood cells into and beneath the retina. On electron microscopy, it appears that an abnormality exists in endothelial cells, permitting plasma leakage into the vessel walls.[195] This leakage produces wall disorganization, aneurysms, and telangiectasia.[195,196] Plasma eventually escapes into the retina, producing characteristic intraretinal and subretinal exudates,[195–198] and exudation also may result in retinoschisis and retinal degeneration. Leakage of red blood cells into and beneath the retina produces intraretinal and subretinal hemorrhages. As these hemorrhages resolve, fatty deposits and accumulations of fibrin remain behind. Fibrous nodules composed of RPE cells and disorganized fibrovascular tissue can involve the macula, even when regions of leakage predominantly involve the peripheral retina.[195]

How Does Coats' Disease Present Clinically?

Coats' disease presents with mild to severe abnormalities. The milder manifestations of this disease initially were regarded as a separate entity and termed Leber miliary aneurysms. Currently, it is regarded as a single entity with variable expression.[190]

The distinguishing clinical features are the associated retinal vascular abnormalities. Outpouchings of retinal veins, or "light-bulb dilations," microaneurysms, and regions of capillary nonperfusion are characteristic.[195] As these abnormal vessels leak, they produce retinal edema and lipid exudation. Exudative retinal detachment, hard exudates in the fovea, and cystoid macular edema may eventually lead to vision loss. Fibrous disciform scars may develop, with choroidal neovascular membranes increasing the probability of vision loss. As more lipid and subretinal fluid accumulates, solid yellow subretinal masses form. The exudative detachment progresses and retinal nonperfusion and ischemia result in proliferative vitreoretinopathy, vitreous hemorrhage, tractional retinal detachment, neovascular glaucoma, cataract, and phthisis. Patients present clinically with some or all of these manifestations.[196–202]

What Is the Appropriate Diagnostic Approach for Coats' Disease?

Patients who present with early vascular abnormalities and lipid exudation should be evaluated for other forms of retinal vascular disease. An appropriate diagnostic evaluation would exclude diabetic retinopathy as etiologic.[203] Other processes to consider in the differential diagnosis include branch retinal vein occlusion,[204] radiation retinopathy,[205] systemic vasculitis,[206] juxtafoveal telangiectasis,[207–209] Eales disease,[210] and ROP.

Patients who present with more advanced Coats' disease will have subretinal masses and often bullous exudative retinal detachment. The differential diagnosis includes retinoblastoma, choroidal melanoma, medulloepithelioma, choroidal hemangioma, angiomatosis retinae, and familial exudative vitreoretinopathy. In this group of patients, ancillary testing is particularly important.

Fluorescein angiography is a useful ancillary test. Abnormal saccular outpouchings, dilation of the adjacent capillary bed, and retinal nonperfusion may be clearly demonstrated. The abnormal vessels in Coats' disease show early leakage with pooling of fluorescein in the subretinal space.[211]

In early Coats' disease,B-scan echography may demonstrate dome-shaped exudative retinal detachment. A-scan will demonstrate multipeaked spikes in areas of retinal thickening and medium reflectivity in regions of subretinal cholesterol deposition. With more advanced Coats' disease, B-scan will document funnel-shaped retinal detachment, marked thickening of the detached retina, and low to medium reflectivity from cholesterol deposits in the subretinal space.[42]

How Is Coats' Disease Treated?

Management of early Coats' disease should include therapy that produces ablation of abnormal vessels and resorption of lipid exudates; laser ablation using indirect delivery to abnormal vessels accomplishes this most precisely. FA or angioscopy may highlight leaking vessels. Repeat sessions are frequently necessary to ensure complete vascular closure. In areas of retinal thickening where abnormal vessels are less distinct, or when laser insufficiently effects vascular closure, transscleral cryotherapy may be particularly effective. When therapy is effective, gradual resorption of lipid exudates and subretinal fluid will occur. Careful serial examination with retreatment is always necessary because new telangiectatic vessels may develop for as long as 5 years after the initial diagnosis.[201] Successful management requires the fastidious application of ablative therapies to every area of abnormal vascularity. Failure to treat new vessels will result in recurrent exudation, retinal detachment, and the need for more invasive surgical procedures.

Patients who present with advanced Coats' disease may require surgical drainage of subretinal fluid and lipid exudate. Drainage may be accomplished externally with scleral buckling or internally by pars plana vitrectomy with endolaser. Patients who present with advanced disease tend to have poor visual recovery;

surgical procedures are undertaken to prevent severe retinal nonperfusion, neovascular glaucoma, and phthisis.[212,213]

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16

Thickened or Elevated Macular Retina

BYRON S. LADD AND MICHAEL J. COONEY

Thickened or Elevated Macular Retina

What Are the Symptoms of a Thickened or Elevated Macular Retina?

Multiple symptoms are commonly experienced, including decreased vision (a decline in central visual acuity affecting distance and near vision), *metamorphopsia* (image distortion, the most sensitive symptom for macular elevation) (Table 16–1), *micropsia* (objects appear smaller than normal), *dyschromatopsia* (colors appear faded), and loss of contrast sensitivity. These symptoms can be unilateral or bilateral and are often asymptomatic when the pathology is unilateral with normal vision in the unaffected eye or when the fovea is uninvolved. A systematic approach to the evaluation of these symptoms is outlined in Figure 16–1.

How Do You Differentiate the Causes of Metamorphopsia?

Determining the morphology of the macula is crucial in determining the cause of metamorphopsia. A thorough fundus examination with biomicroscopy and utilization of a fundus contact lens is necessary to appreciate the subtle changes that may be present. The most obvious sign of a thickened or elevated macular retina is often the loss of the foveal light reflex. This occurs when the normal concavity of the fovea is disrupted; however, changes can occur in the macula that are extrafoveal and therefore do not affect the foveal light reflex.

Five areas can be involved in producing an elevated or thickened macula. These include, from outer to inner layers, suprachoroidal space, choroid, subretinal pigment epithelial (RPE) space, subretinal space, and intraretinal space. Most of the changes at these levels are caused by abnormal accumulation of fluid, blood, or other substances, like lipofuscin. Elevation of the choroid from suprachoroidal hemorrhage or thickening of the choroid due to choroidal effusions can secondarily elevate the macular retina and produce metamorphopsia (Fig. 16–2). Common causes of choroidal effusion include ocular hypotony, uveitis, and scleritis.

The sub-RPE area is another location where pathology can occur and produce elevation of the macula. A change in this location will result in a pigment epithelial detachment (PED). These elevated areas will often appear as a small, rounded, yellowish gray elevation of RPE underneath an otherwise normal retina. A serous PED results from a collection of fluid beneath the RPE; whereas an ingrowth of choroidal neovascularization is categorized as a fibrovascular PED. Transillumination of the lesion with a slit beam will often differentiate a serous and fibrovascular PED. Other forms of PEDs develop from bleeding or large drusen formation beneath the RPE, termed *hemorrhagic* or *drusenoid* PEDs, respectively (Fig. 16–2B,C). A fluorescein angiogram is instrumental in differentiating between the various types of PEDs. These lesions most commonly are caused by age-related macular degeneration or other causes of choroidal neovascularization and can be present with central serous chorioretinopathy.

The subretinal location is the next potential space internal to the RPE. Again, the most common substances that accumulate in this area are fluid and blood. Other materials, like lipid and lipofuscin, also collect in this position. Choroidal neovascularization and macroaneurysms are common causes of subretinal fluid, hemorrhage, and lipid (Fig. 16–2A). The presence of lipofuscin in the subretinal space produces a yellowish color that is seen with Best's disease and pseudovitelliform macular dystrophy. Occasionally, the appearance of a pseudohypopyon can develop with layering of the subretinal fluid and lipofuscin[1] (Fig. 16–3). Central

TABLE 16–1. Common Symptoms of an Elevated or Thickened Macular Retina

Decreased vision
Effects both near and distance acuity
Metamorphopsia
Image distortion
Evaluate with an Amsler grid
Micropsia
Image minification
Results from increased separation of photoreceptors
Dyschromatopsia
Poor color vision
Colors appear desaturated
Decreased contrast sensitivity

serous retinopathy is characterized by leakage from an incompetent RPE layer and can produce localized neurosensory detachments. Fluorescein angiography (FA) is helpful in differentiating between the various causes of a localized macular neurosensory detachment of the retina. The specific characteristics are discussed later in this chapter.

The ability to determine whether the disturbance of the macular retina is secondary to elevation of more outer layers or thickening of the retina can be difficult. A ring of light reflex that replaces the normal foveal light reflex may outline the involved retina. Further examination of this abnormal retina with a slit beam positioned at an oblique angle of incidence will highlight a neurosensory detachment from the underlying RPE with an increased separation of the light reflexes between the surfaces of the RPE and retina. In addition, a localized detachment of the macular retina will appear more diaphanous due to the transparency of the retina than when elevated RPE is also present.

A thickening of the macular retina can be present with or without a neurosensory retinal detachment from the RPE. The most common causes of retinal thickening are vascular abnormalities that lead to macular edema from accumulation of intraretinal fluid. Therefore, the presence of microaneurysms or telangiectasias within the retina can be helpful in determining the cause. These most commonly are associated with diabetic retinopathy and venous occlusive disease. Intraretinal cysts also can develop from fluid accumulation in the foveal area. A characteristic petal configuration of cysts can form as a result of the architecture of the outer plexiform layer, that is, the Henle layer, within the perifoveal area. This results in cystoid macular edema, which is most often due to diabetic macular edema, the Irvine–Gass syndrome[2,3] or other inflammatory conditions. Large foveal cysts often have the appearance of a macular hole and are considered a pseudohole. Referral to a retinal specialist is often necessary for differentiation with the assistance of optical coherence tomography (OCT) or FA.

Macular Retinal Detachment

Central Serous Chorioretinopathy and Its Common Risk Factors

Central serous chorioretinopathy (CSC) is most commonly identified in young males between the ages of 30 and 50 years. There is a male preponderance, with a ratio of approximately 9:l.[4–6] The incidence in women, however, doubles between the second and third decades of life[7] and in persons over the age of 50 years, the male-to-female ratio is 2.6:1.0.[8] There may be a racial predisposition for whites, Hispanics, and Asians; the incidence in blacks is very low.[9,10] Stress and other psychological factors also have been linked with a causal relationship to this disorder.[11,12]

What Are Clinical Signs Indicative of Central Serous Chorioretinopathy?

A focal area of neurosensory retinal detachment is often present in the macula (Fig. 16–4). The small area of elevation appears as a well-defined blister filled with transparent fluid. When the fovea is involved, the foveal light reflex is not present. The area of neurosensory elevation can be associated with an underlying PED, or a PED can exist without separation of the overlying retina. These features are best appreciated by using a fundus contact lens with the slit beam at an oblique angle to highlight any increased separation between the surfaces of the pigment epithelium and retina. Occasionally, the outer surface of the retina contains whitish yellow fibrin precipitates. Other manifestations in the RPE can range from subtle pigmentary changes with areas of pigment atrophy and pigment clumping. Perivascular pigment clumping in the form of bone spicules has been termed pseudoretinitis pigmentosa-like atypical *CSC* presentation.[13] Severe or chronic leakage can produce RPE atrophic tracts that extend inferiorly and cause localized exudative retinal detachments.[14,15]

What Causes Central Serous Chorioretinopathy?

Although the exact cause of CSC is not known, dysfunction at the level of the RPE or choroid is commonly implicated. The normal RPE functions both as a barrier between the retina and choroid[16] and as a pump that moves fluid in a retinochoroidal direction.[17] Therefore, several investigators have suggested that defective RPE can lead to hyperpermeability and secondary accumulation of subretinal fluid.[17,18] Others have described widespread choroidal abnormalities seen with indocyanine green (ICG) green angiography and conclude that hyperpermeability of the choroid leads to abnormalities of the RPE.[8,19] The trigger that ultimately causes CSC may be a combination

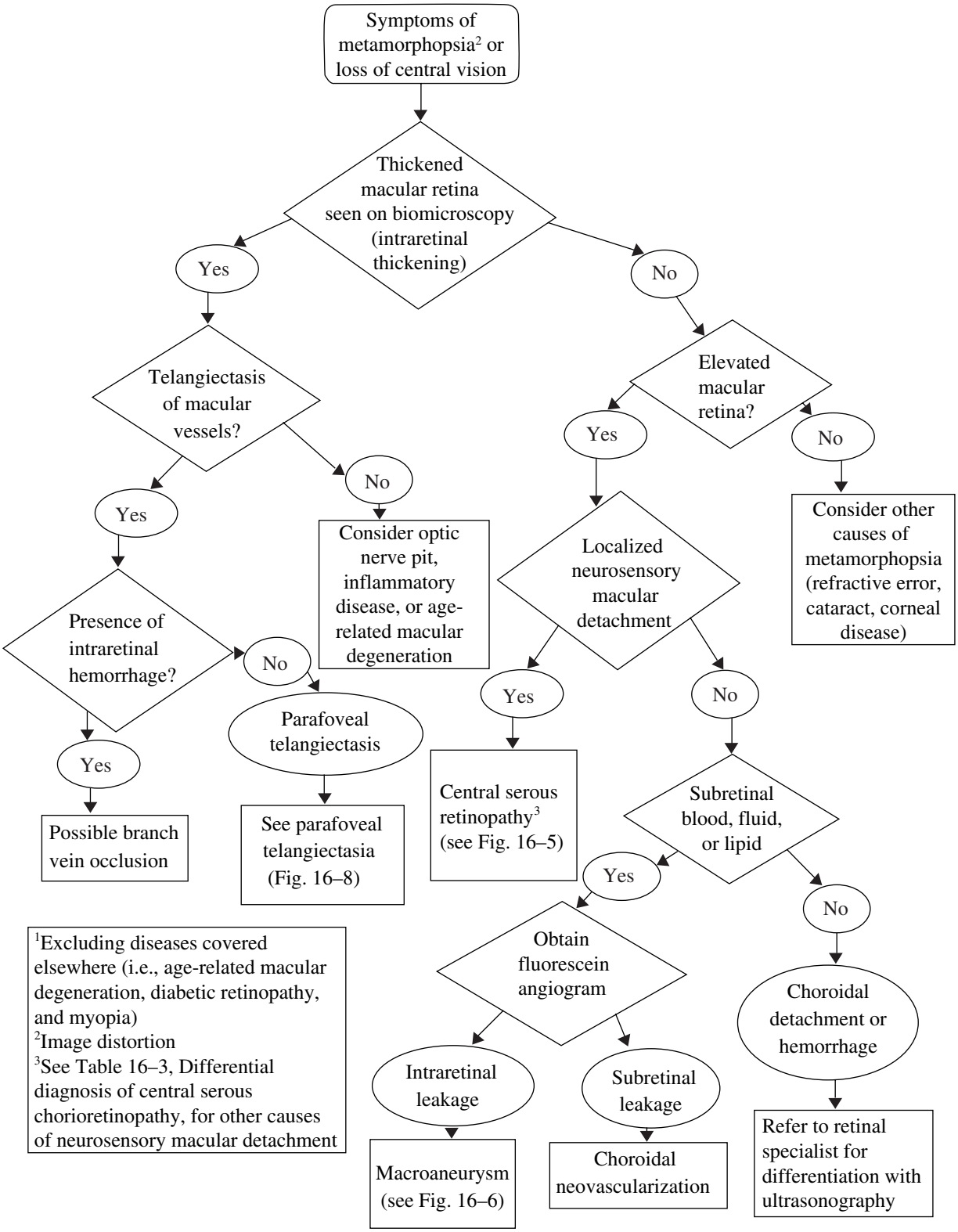


FIGURE 16–1. Evaluation of metamorphopsia secondary to elevated or thickened macular retina.

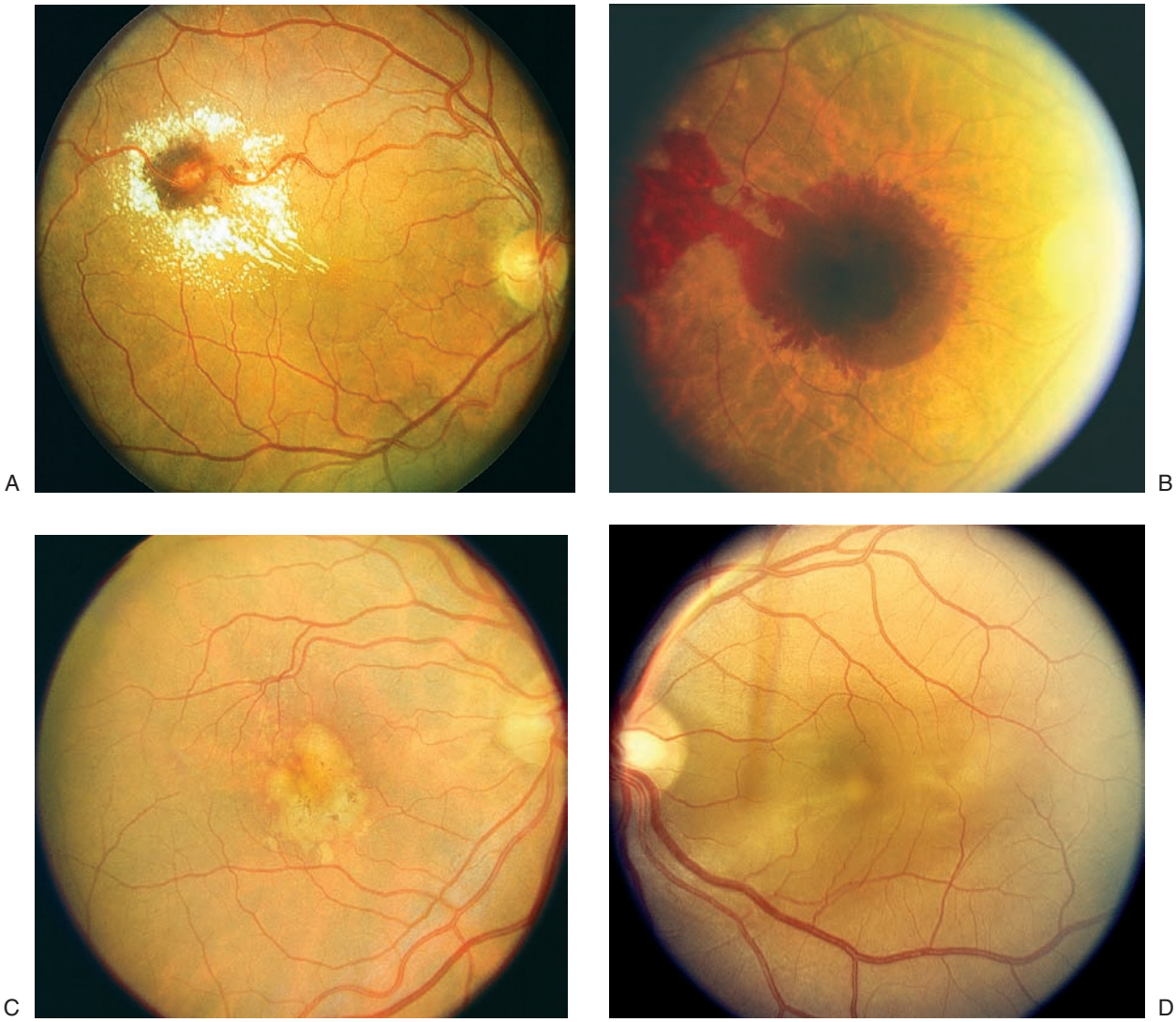


FIGURE 16–2. Causes of thickened or elevated macula. (A). Retinal arteriolar macroaneurysm surrounded by retinal edema and circinate lipid deposits. Subretinal fluid with a neurosensory retinal detachment extending into the fovea. (B). Subretinal hemorrhage in the macula extending temporally in a patient with age-related macular degeneration. (C). Large, confluent drusen causing a subfoveal drusenoid pigment epithelial detachment in a patient with age-related macular degeneration. (D). Localized choroidal detachment in a patient with acute myelogenous leukemia (AML). Whitish subretinal deposits from leukemic infiltrate.

of environmental, genetic, and behavioral factors[12] (Table 16–2).

What Are the Findings of Central Serous Chorioretinopathy with Angiography?

The early descriptions of CSC using FA revealed an area of leakage at the level of the RPE that accumulates within the neurosensory detachment[20,21] (Fig. 16–4). In about 95% of cases, there is usually one focal point of leakage, but up to seven leakage points have been documented.[5,22] Rarely, a diffuse area of leakage is present instead of a focal point of leakage. The classic smokestack phenomenon[23] of leakage is present in only a minority of cases, about 7[24] to 20%.[5,6] In the typical smokestack presentation, the fluorescein dye rises from a leakage point to the upper limit of the neurosensory detachment and then spreads laterally.

Although the blister of neurosensory detachment often involves the fovea, only about 10% of cases have the leakage point within the foveal area. Most cases contain the leakage source within 1 mm of the fovea, with the superonasal quadrant the most frequent location.[22] In prolonged cases of CSC, dependent neurosensory detachments may develop that extend inferiorly. These "gutter" formations are often seen on FA as tracts of atrophic RPE with mottled hyperfluorescence.

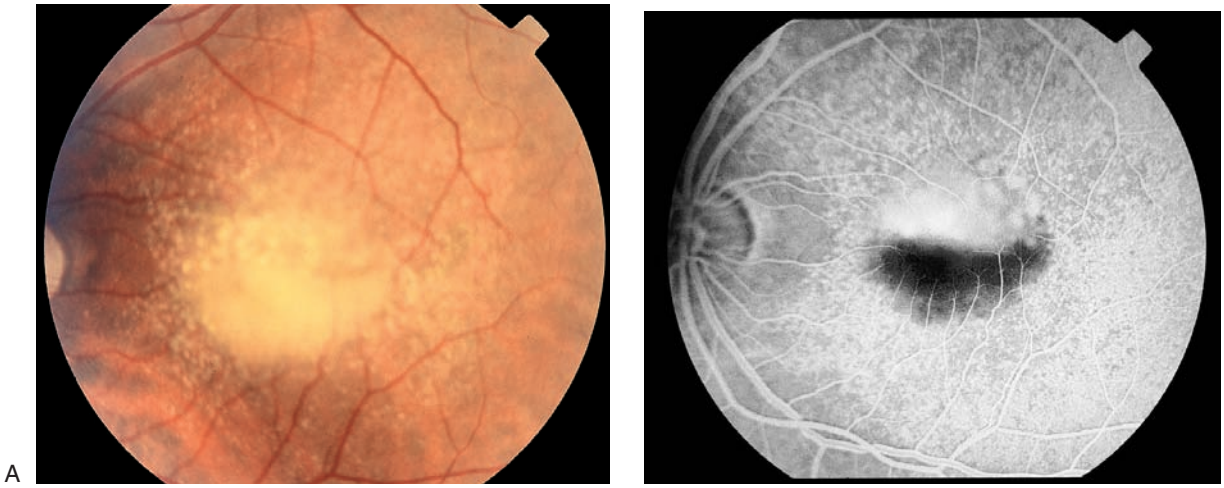


FIGURE 16–3. Pseudovitelliform disease. (A). Color fundus photograph with pseudohypopyon in macular neurosensory detachment with inferior layering of yellowish, lipofuscin material surrounded by drusen. (B). Early phase fluorescein angiogram with hyperfluorescence in superior portion of neurosensory detachment and inferior blockage by lipofuscin. Numerous punctate areas of hyperfluorescence from surrounding basal laminar drusen.

The use of ICG angiography has provided evidence that supports the theory of diffuse choroidal or RPE dysfunction leading to CSC. With ICG, multiple areas of early and midphase hyperfluorescence are apparent throughout the fundus; these areas fade in the late phase. Often these abnormal spots are not associated with areas of leakage on FA and can be present in normal fellow eyes lacking neurosensory retinal detachments.[19,25,26]

What Is the Prognosis of Central Serous Chorioretinopathy?

Central serous chorioretinopathy is usually a self-limited disease with reports of 100% recovery without treatment.[5,7] Patients usually recover within 3 to 4 months with visual acuities better than 20/40 in all cases, most achieving 20/20. Recurrences are reported in almost 50% of cases in these series, however, with half of the recurrences present in the first year but some up to 10 years after initial presentation.[7]

Fewer than 5% of patients have secondary complications from CSC that lead to a poor visual outcome. These can include peripheral atrophic tracts,[14] choroidal neovascularization,[27] macular RPE atrophy,[28] and cystoid macular edema.

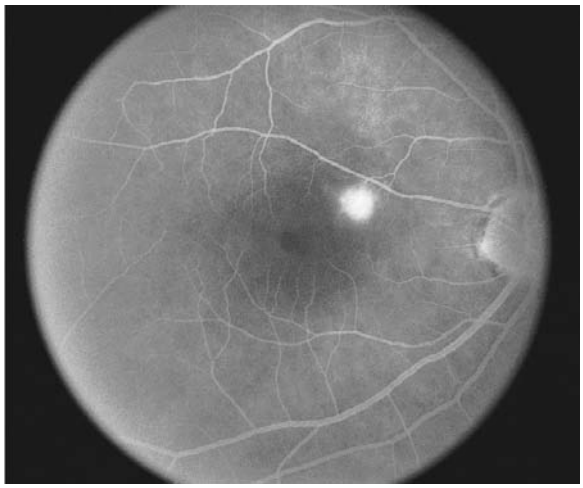


FIGURE 16–4. Central serous chorioretinopathy. Late-phase fluorescein angiogram with leakage from retinal pigment epithelium defect.

What Is the Treatment for Central Serous Chorioretinopathy?

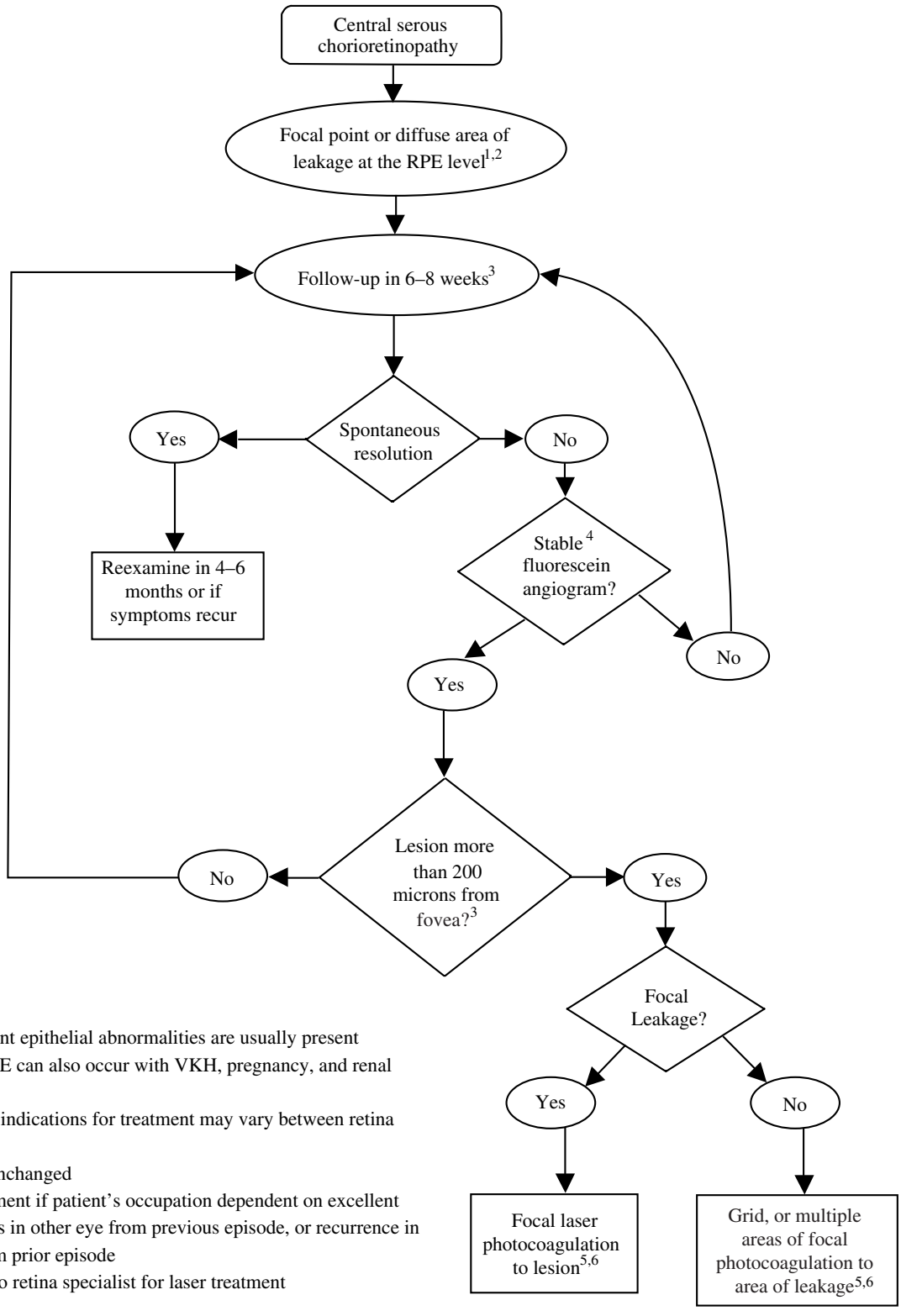
Almost all cases of CSC will resolve spontaneously without the need for treatment. In cases with chronic leakage from a persistent source, however, photocoagulation can hasten the resolution of the leakage and reduce the recurrence rate, but it does not improve final visual acuity.[29]

Most patients should be observed for spontaneous resolution for 6 months (Fig. 16–5). FA at the initial

TABLE 16–2. Clinical Signs of Central Serous Chorioretinopathy

Serous detachment of the macular retina
Serous retinal pigment epithelial detachment
Hyperpigmented and atrophic RPE changes
Subretinal precipitates
Inferior, atrophic RPE tracts (gutter)
Dependent exudative retinal detachment

RPE, retinal pigment epithelium.



[1]Bilateral retinal pigment epithelial abnormalities are usually present
[2]Diffuse leakage of RPE can also occur with VKH, pregnancy, and renal disease.
[3]Follow-up period and indications for treatment may vary between retina specialists
[4]Location of leakage unchanged
[5]Consider earlier treatment if patient's occupation dependent on excellent stereoacuity, visual loss in other eye from previous episode, or recurrence in an eye with deficit from prior episode
[6]Recommend referral to retina specialist for laser treatment

FIGURE 16–5. Management of central serous chorioretinopathy.

visit is helpful in identifying the leakage source, and if the same source is the cause of persistent leakage after 6 months, laser photocoagulation to that area may be considered. When a patient has an occupational need for prompt recovery of visual acuity, or the lesion is greater than 500 μ from the fovea, earlier treatment is feasible.

When treatment is recommended, a recent FA is required to determine the location of the source of leakage. Green, yellow, or red lasers are effective, but the krypton red is recommended for treatment within the foveal avascular zone or papillomacular bundle.[30] A light gray reaction with a 200-μ spot over the area of leakage is often sufficient. A low intensity delivered over a moderate duration (0.2 to 0.3 seconds) with slow titration of power to reach the desired endpoint is recommended. In areas of diffuse leakage, multiple burns may be necessary to cover the entire lesion.

Multiple complications can arise from laser treatment, including choroidal neovascularization,[31] gradual enlargement of the laser scar into the fovea, and accidental photocoagulation of the fovea.

What Is the Differential Diagnosis for Central Serous Chorioretinopathy?

Any disorder that causes a serous neurosensory detachment of the macula can be confused with CSC. Diseases associated with choroidal neovascularization like age-related macular degeneration, pathologic myopia, and ocular histoplasmosis syndrome must be considered. Posterior scleritis, multifocal choroiditis, Harada disease, and Eales' disease are inflammatory conditions that can be associated with elevation of the macula. Other disorders include primary ocular or metastatic tumors, lymphoma, uveal effusion syndrome, optic nerve pits, or retinoschisis (Table 16–3).

TABLE 16–3. Differential Diagnosis of Central Serous Chorioretinopathy

Disorders with choroidal neovascularization
Age-related macular degeneration
Pathologic myopia
Ocular histoplasmosis syndrome
Inflammatory disorders
Posterior scleritis
Multifocal choroiditis
Harada disease
Eales' disease
Ocular tumors
Metastatic tumors
Lymphoma
Posterior uveal effusion syndrome
Optic-nerve pit

Macroaneurysm

A *macroaneurysm* is an acquired degeneration of a retinal artery causing a round or fusiform dilation that most often occurs on one of the four major branch retinal arteries. Macroaneurysms occur within the first three orders of retinal arterial branching. A macroaneurysm is most commonly present on the superotemporal arcade and often is associated with an arterial bifurcation or arteriovenous crossing[32] (Fig. 16–2A).

What Causes Macroaneurysms?

Macroaneurysms are most commonly observed in the sixth and seventh decades of life,[33] which signifies that aging is a predisposing factor. There is also a large predisposition for macroaneurysms to occur in females, and they are commonly associated with hypertension, arteriosclerosis, elevated serum lipids, and lipoprotein abnormalities.[33–35] Histopathologic studies of macroaneurysms reveal linear breaks in the arterial wall surrounded by a laminated fibrin-platelet clot, hemorrhage, exudates, lipid-laden macrophages, hemosiderin, and a fibroglial reaction.[32,36]

How Does a Macroaneurysm Cause Loss of Vision?

Frequently, macroaneurysms are asymptomatic and diagnosed on routine funduscopic examination. When a patient does notice visual changes related to a macroaneurysm, the symptoms may be a gradual decrease or sudden visual loss that correlates with the location of the macroaneurysm and the presence of macular edema, hemorrhage, or both. Macroaneurysms are susceptible to chronic exudation, which can lead to macular edema with a secondary circinate retinopathy from deposition of lipid exudates. In addition, persistent leakage can cause a shallow, serous neurosensory retinal detachment (Fig. 16–2A). This results from the amount of exudation exceeding the clearing capacity of the retina and gravitating toward the fovea. The symptoms therefore depend on the proximity of the macroaneurysm to the macula and the extent that the secondary complications extend into the macular region. Thus, a decline in vision related to leakage from a macroaneurysm is usually mild to moderate with a gradual and chronic onset, but severe vision loss can result from chronic deposition of lipid in the fovea.

The other frequent cause of visual loss related to macroaneurysms is hemorrhage. Bleeding from a macroaneurysm usually results in acute, severe loss of vision. These hemorrhages can be subretinal, intraretinal, or preretinal. Often simultaneous bleeding into all three potential spaces results in an "hourglass"

configuration. Extensive accumulation in the preretinal space can result in a significant vitreous hemorrhage.

Acquired retinal arterial macroaneurysms have been studied according to their morphologic characteristics and classified into two groups.[37,38] Group I macroaneurysms are predisposed to developing hemorrhage from acute aneurysmal decompensation. These macroaneurysms are usually located on larger arterioles closer to the optic nerve and have a larger average diameter. Group II macroaneurysms are more susceptible to chronic exudation that often involves the macula. These exudative macroaneurysms tend to be located within 3 mm of the fovea and are smaller in diameter.

What Are the Characteristics of a Macroaneurysm on Fluorescein Angiography?

A macroaneurysm may cause partial, complete, or no obstruction of the associated arteriole on FA.[39] There is usually complete filling of the macroaneurysm in the early phase, but partial filling occurs when an intraluminal thrombosis is present. Also, associated lipid or hemorrhage can block the hyperfluorescence of the aneurysm. Other secondary microvascular abnormalities may develop near the macroaneurysm, including attenuation of the proximal and distal arteriole, areas of capillary dilation or nonperfusion, microaneurysms, and intraarterial collaterals. Leakage often occurs from the macroaneurysm and occasionally from the associated microvascular abnormalities.[32] In some cases, a Z-shaped kink has been described at the site of the microaneurysm following closure.[40] The use of ICG angiography can help to identify a macroaneurysm when there is significant hemorrhage.[41]

How Is a Macroaneurysm Treated?

Although most macroaneurysms will resolve spontaneously with preservation of good vision,[33] treatment has been recommended in cases where the vision is compromised (Fig. 16–6) by chronic exudation or hemorrhage involving the fovea[39,40] (Fig. 16–2A). Different techniques for treatment have used laser photocoagulation indirectly to the microvascular abnormalities surrounding the macroaneurysm and directly to the macroaneurysm. These treatments are performed with xenon-arc, argon-green, and krypton-yellow lasers.[35,40,42] The beneficial absorption of the krypton-yellow laser by hemoglobin and oxyhemoglobin has popularized the direct treatment of macroaneurysms.[43–45] The natural history of these lesions is usually benign, however, and treatment with laser photocoagulation is controversial,[46] especially because complications of the direct laser photocoagulation can include bleeding from rupture of the macroaneurysm, development of a distal branch arteriole occlusion,[44] and visual loss secondary to photocoagulation from treatment of macroaneurysms close to the fovea.

When laser photocoagulation is indicated, a slow burn with a large spot size is used. Careful consideration needs to be taken with macroaneurysms that are within 500 μ of the fovea because the laser treatment may be more harmful than the natural history. An argon-green or krypton-yellow laser with a 500-μ spot size and duration of 0.5 seconds is used to treat the microaneurysm directly with enough power to whiten the lesion.[32] The patient should be monitored every 3 months for persistent or recurrent exudation or hemorrhage or until these substances resolve.

In cases where significant subretinal, preretinal, or vitreous hemorrhage is limiting the vision, other treatment modalities may be indicated. Submacular surgery for removal of subretinal blood may provide a better outcome than allowing the hemorrhage to resolve on its own.[47] When preretinal bleeding is trapped under the internal limiting membrane or posterior hyaloid, the neodymium:yttrium–aluminum–garnet (Nd:YAG) laser has been used to puncture the membrane and allow the hemorrhage to escape into the vitreous.[48] Finally, non-clearing vitreous hemorrhages of unknown cause may be due to an underlying macroaneurysm, and a pars plana vitrectomy for removal of the blood can be both diagnostic and therapeutic.[49]

Choroidal Detachment (Uveal Effusion)

Choroidal detachment is synonymous with several clinical terms like *uveal effusion* or *ciliochoroidal effusion*. In these conditions, *detachment* and *effusion* have the same meaning. These terms are anatomic descriptions of a pathologic condition that has several etiologies. An *effusion* describes an abnormal accumulation of serous fluid in the choroid or outer layer of the ciliary body, which more accurately describes the clinical situation than a detachment. Occasionally, the fluid collects in the suprachoroidal space and causes disruption of the fine connective tissue fibers in this layer, leading to an actual detachment of the choroid.

What Is the Clinical Appearance of a Choroidal Effusion?

A typical choroidal effusion appears as a brownish orange, lobular elevation with smooth, convex surfaces. These effusions have a solid appearance and do not undulate with eye movements, like a rhegmatogenous retinal detachment; however, a serous retinal detachment can develop from a choroidal effusion. Transillumination of the globe is helpful in differentiating a serous collection from hemorrhage or a solid tumor.

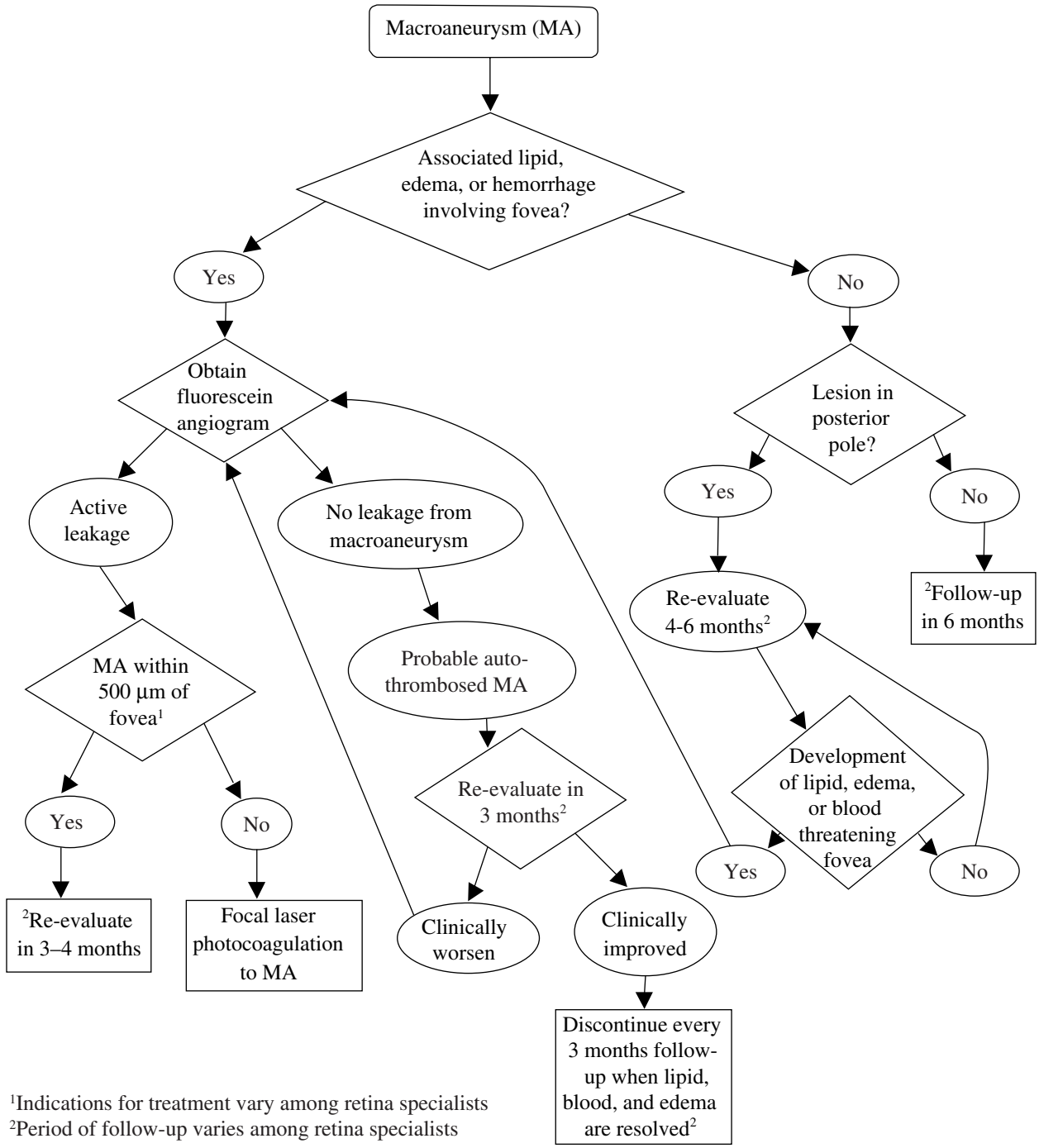


FIGURE 16–6. Management of macroaneurysm.

These elevations can occur anywhere in the posterior segment, but they are more commonly present at the pars plana or peripheral choroid and often allow visualization of the ora serrata without scleral depression. The anterior predisposition results from the connective tissue fibers in the suprachoriodal space being tangentially oriented and longer anteriorly compared with the shorter, perpendicular connections posteriorly. A characteristic four-lobed configuration occurs in large effusions as a result of the choroid–scleral attachments at the vortex vein ampullae.[50]

What Are the Symptoms of Choroidal Effusion?

A serous choroidal effusion can be asymptomatic or associated with decreased vision if large detachments

are present and the macula is involved. Decreased vision also can be caused by anterior displacement of the lens–iris diaphragm with an acute myopic shift. Hemorrhagic choroidal detachments most commonly are associated with redness, decreased vision, and severe eye pain.

What Causes a Choroidal Effusion?

Although choroidal effusions have multiple causes, there are four basic underlying mechanisms. These pathophysiologic categories include hydrodynamic, inflammatory, neoplastic, and scleral abnormalities.[50] The choroidal fluid dynamics are dependent on blood pressure, intraocular pressure, and the osmotic pressure gradient.[51] The osmotic pressure gradient relates to the intravascular and extravascular concentrations of albumin.[52] The extravascular albumin concentration is determined by its exudation from the choroid and diffusion through the sclera, which is influenced by the intraocular pressure.[53] Therefore, ocular hypotony, increased uveal venous pressure, inflammation, and scleral abnormalities all can lead to development of choroidal effusions. The various causes of choroidal effusions can be categorized according to the underlying pathophysiology[50,54]

Choroidal effusions can be secondary to any cause of ocular hypotony and can lead to exacerbation of the hypotony. Low intraocular pressure intraoperatively can cause choroidal detachments that range from mild to expulsive.[55,56] Postoperative hypotony is most commonly associated with overfiltration after glaucoma surgery or a persistent wound leak.[57,58] In addition, a cyclodialysis cleft or persistent wound leak after ocular trauma can cause choroidal effusions. Finally, decreased aqueous production from ciliary body dysfunction can result from tractional forces, like a cyclitic membrane or from anterior segment ischemia.

Elevation of the uveal venous pressure may cause an increased transudation from the choroid and lead to uveal effusion. This can occur from an arteriovenous fistula[59] and usually is associated with headache, orbital pain, proptosis, and arterialization of the conjunctival vessels. Scleral buckling often precipitates a choroidal detachment by compromising venous outflow. Risk factors that increase the incidence of choroidal effusion after a buckling procedure include cryotherapy, diathermy, intraoperative hypotony after drainage, and older age.[60,61] The presence of idiopathic prominent episcleral vessels or Sturge–Weber syndrome can result in significant intraoperative choroidal effusions.[56] Also, extensive Valsalva episodes from severe emesis can reportedly cause bilateral choroidal detachments.[62]

In patients with severe hypertension and kidney failure, hypoproteinemia leads to a decreased oncotic pressure that facilitates the formation of choroidal detachments by disruption of the choroidal osmotic gradient.[63,64]

Intraocular inflammation is another common cause of choroidal effusion. Inflammation of the uveal tract of any type can result in choroidal effusions that are commonly associated with vitreitis, chorioretinitis, and exudative retinal detachments. A few of the different underlying causes to consider include sarcoid, syphilis,[65] Harada syndrome,[66] and sympathetic ophthalmia. A thorough history, physical, and serologic workup usually are required to make the correct diagnosis in these conditions, which will determine the appropriate treatment.

Uveal effusions accompanied by a red, painful eye may be indicative of orbital or scleral inflammation.[67,68] Secondary choroidal folds, shallow anterior chamber, and angle-closure glaucoma can also be present in cases of posterior scleritis.[68] Ultrasonography is helpful in evaluating posterior scleritis and usually reveals choroidal and scleral thickening with low reflective infiltration of the Tenon capsule.[69] A rheumatologic workup is indicated for posterior scleritis, and testing for human immunodeficiency virus (HIV) is necessary when bilateral choroidal effusions are present.[70,71] Orbital cellulitis and pseudotumor can incite a secondary scleritis that also can result in uveal effusions.

Another common setting for the development of choroidal effusions occurs after ocular trauma or surgery. Blunt ocular trauma has been associated with temporary choroidal detachments.[72] Inflammation and hypotony after a penetrating ocular injury can result in traumatic ciliochoroidal effusions. A cyclodialysis cleft must be considered when persistent hypotony and uveal effusions occur. A combination of hypotony, inflammation, and surgical trauma is responsible for choroidal effusions in the postoperative period. The effusions usually occur within a few days or weeks after surgery and dissipate with resolution of the hypotony and inflammation. Choroidal detachments related to panretinal photocoagulation, transscleral cryotherapy, or cilioablation are caused by increased permeability of the choroidal vasculature after thermal injury. Choroidal effusion from these interventions can be reduced by dividing treatment over multiple sessions,[73] and they usually self-resolve.

Choroidal effusions have been associated with idiosyncratic drug reactions secondary to sulfonamides.[74] These patients experience an acute myopic shift in conjunction with anterior chamber flattening and occasional angle closure resulting from choroidal effusions.[75] The mechanism of action is postulated to be

a hypersensitivity reaction with increased ciliochoroidal permeability and resolves within days of discontinuing the offending drug.[74]

Abnormalities of the sclera can cause increased resistance to protein diffusion through the sclera and obstruct venous outflow. These changes can precipitate formation of uveal effusions, which commonly will complicate cases with nanophthalmos where the sclera is markedly thickened.[76] For this reason, nanophthalmic eyes undergoing intraocular surgery often require prophylactic sclerectomy with vortex vein decompression.[54,77] These methods are also effective for spontaneous nanophthalmic uveal effusions. Systemic mucopolysaccharidosis with abnormal scleral deposition of mucopolysaccharide causes thickening and secondary choroidal effusions. Nonrhegmatogenous retinal detachments also are associated with these conditions.[78]

Idiopathic Uveal Effusion Syndrome

Idiopathic uveal effusion syndrome is another condition with ciliochoroidal effusions and nonrhegmatogenous retinal detachments that usually affects healthy, middle-aged men. These patients have normal-sized eyes, normal intraocular pressure, episcleral venous dilation, mild vitreitis, marked exudative retinal detachments with shifting of the subretinal fluid, and bilateral involvement.[79,80] RPE alterations are also present that resemble leopard spots. These lesions are hyperfluorescent without leakage on FA.[50] Thickened sclera is also a common finding that may be due to abnormal accumulation of proteoglycans and can result in reduced flow of proteins across the sclera.[81] The theory of scleral flow impedance is supported by the effective surgical treatment with quadrantic lamellar sclerectomies, which leads to rapid resolution of the uveal effusions and exudative detachments.[82]

Choroidal malignant melanomas, choroidal metastases, and other ocular neoplasias are rare causes of uveal effusions. Associations have been described with leukemia, lymphoma, reactive lymphoid hyperplasia, and paraneoplastic uveal melanocytic proliferation[50] (Fig. 16–2D). Ultrasonography is often necessary to distinguish the tumor from the uveal effusion, and a thorough medical history with systemic workup is required to determine the primary tumor source.

What Is the Differential Diagnosis for Choroidal Effusions?

Hemorrhagic choroidal detachments and choroidal melanomas are commonly misdiagnosed as choroidal effusions. Ultrasonography is the most useful diagnostic tool for differentiation of these entities. Effusions will reveal high-reflective choroidal thickening or serous elevation versus a solid mass with low internal reflectivity characteristic of melanomas. A suprachoroidal hemorrhage contains low to medium reflective echoes and may be associated with severe eye pain and a history of recent eye trauma or surgery. Scleral folds associated with hypotony sometimes are confused with choroidal effusions, but the folds are irregular without a serous component and easily differentiated with ultrasonography.

Suprachoroidal Hemorrhage

A suprachoroidal hemorrhage is an accumulation of blood in the suprachoroidal space between the choroid and sclera. The clinical appearance is similar to a choroidal effusion with a brownish orange, lobular elevation, and smooth convex surfaces. They have a solid appearance that does not undulate with eye movements.

Originally, the rupturing of posterior ciliary arteries compromised by hypertension and arteriosclerosis was thought to account for the development of suprachoroidal hemorrhages.[83] Animal models later implicated the vasculature of the ciliary body, where small choroidal effusions could spread to the ciliary body and lead to rupture of the ciliary body vessels, resulting in a large suprachoroidal hemorrhage.[84] These discoveries led to the hypothesis that a continuum exists between small choroidal effusions and expulsive hemorrhages.

What Causes a Suprachoroidal Hemorrhage?

Suprachoroidal hemorrhages occur after penetrating ocular trauma or intraocular surgery. A suprachoroidal hemorrhage is classified as either expulsive or nonexpulsive, depending on whether or not intraocular contents are displaced from the eye. The overall incidence of an expulsive hemorrhage during intraocular surgery is estimated at 0.19%, with the highest rate during keratoplasty followed by vitreoretinal, glaucoma, and cataract surgeries in decreasing order. Independent risk factors include glaucoma, elevated intraocular pressure, increased axial length, and intraoperative tachycardia.[85]

Nonexpulsive suprachoroidal hemorrhages are also encountered during surgery for glaucoma,[86–88] cataracts,[89] and vitreoretinal disorders.[90–91] The ability to maintain intraocular pressure and a small incision size may be important intraoperative factors that prevent a suprachoroidal hemorrhage from becoming expulsive; however, suprachoroidal hemorrhages also

occur postoperatively and are more common after glaucoma filtering procedures.[86–88,91]

What Is the Treatment for Suprachoroidal Hemorrhages?

Mild to moderate suprachoroidal hemorrhages usually self-resolve with time and require only observation.[86,91] Severe suprachoroidal hemorrhages, however, require more invasive management to prevent phthisis bulbi[86,90] or the need for enucleation.[92] The earliest surgical treatments of suprachoroidal hemorrhages were performed with a simple scleral puncture to drain the suprachoroidal space[93,94] and later included reformation of the anterior chamber.[95] Traditionally, sclerotomies are made along the equator in the quadrants involved with the hemorrhage, and the blood is massaged out. The optimal time to intervene is after the clot liquefies over a few weeks, which allows more complete drainage. With recent advances in vitrectomy, additional techniques are available that improve the patient's outcome. This is achieved after vitrectomy by synchronously elevating the intraocular pressure with infusion of air,[88,96] balanced salt solution,[97,98] or sodium hyaluronate[87,91] during formation of the sclerotomies. This maneuver maintains the intraocular pressure and provides an additional force to facilitate drainage of the blood. Additionally, perfluorocarbon placed on the retina creates a posterior tamponade that displaces the blood anteriorly and allows for drainage through anterior sclerotomies at the pars plana.[99]

What Is the Prognosis after a Suprachoroidal Hemorrhage?

The outcomes after a suprachoroidal hemorrhage are variable, depending on its severity and whether or not it was expulsive. Generally, mild nonexpulsive hemorrhages do well and will self-resolve over several weeks. Severe cases may progress to phthisis bulbi and require enucleation. Surgical intervention usually improves the prognosis,[87,91,98] but a large percentage will still have poor outcomes and not regain preoperative visual acuity.[88]

Pseudovitelliform Macular Degeneration

Pseudovitelliform macular degeneration is a disorder that resembles Best vitelliform dystrophy but that develops in adults and has a normal or mildly abnormal elecrooculogram.[100–105] It was first described by Gass as "peculiar foveomacular dystrophy"[100] and is synonymous with adult Best disease,[105] vitelliform macular degeneration,[106] and adult-onset foveomacular PED.[107] The clinical findings are usually bilateral, and an autosomal dominant transmission may exist.[100,107]

What Is the Clinical Presentation of Pseudovitelliform Disease?

The patients originally described by Gass[100] had mild bilateral visual disturbances with little or no progression of visual loss over time; however, severe visual loss from pseudovitelliform degeneration has been reported.[103] On average, the patients are around 50 years of age at presentation.[104] The typical appearance is bilateral, with an elevated, yellowish, oval macular lesion about one third disc area in size associated with perimacular drusen[100,104] (Fig. 16–3). Histopathology suggests that the lesion is the result of subretinal accumulation of lipofuscin liberated from RPE and associated with dominantly inherited drusen.[100] Therefore, the appearance of a localized neurosensory detachment overlying turbid, yellowish, subretinal fluid is common. With time, the lipofuscin often resorbs and areas of RPE atrophy may develop.[104]

What Are the Features of Pseudovitelliform Degeneration with Fluorescein Angiography?

On FA, the yellowish material will cause early blockage of the choroidal hyperfluorescence. By mid and late phases, the lesion gradually develops hyperfluorescence with intense late staining of the yellowish, subretinal material. In some cases, the lesion develops a pseudohypopyon appearance, and the upper clear portion has early hyperfluorescence, in contrast to the hypofluorescence of the lower portion with turbid fluid (Fig. 16–3). Pseudovitelliform lesions often have associated drusen, which are evident as punctate areas of early hyperfluorescence and late staining. Chronic lesions with resorption of the lipofuscin and areas of RPE atrophy develop a window defect with early hyperfluorescence and mild, late staining of the atrophic areas. Leakage of fluorescein suggestive of secondary choroidal neovascularization is not associated with pseudovitelliform degeneration.

How Do You Differentiate between Best's Disease and Pseudovitelliform Macular Degeneration?

Best's disease presents at a young age in patients with a strong family history because of the autosomal-dominant transmission. On the contrary, pseudovitelliform degeneration occurs in the middle-aged and older population, and there is usually no family history. Electrophysiologic testing is a reliable distinguishing factor. An electrooculogram is markedly abnormal in Best's vitelliform dystrophy and is usually

normal or only slightly abnormal in pseudovitelliform degeneration. The two disorders also have distinct clinical presentations. Best's disease presents with a large, vitelliform lesion, which progresses through a "scrambled-egg" stage and on to a hypertrophic scar. During this process, the patient is often asymptomatic until the vitelliform lesion disintegrates accompanied by a sharp decline in vision. In comparison, the pseudovitelliform lesion is smaller and often associated with drusen. The visual acuity is usually normal or mildly reduced in the early stage. Over time, the lesion may resolve spontaneously with maintenance of good vision, or it may progress to an atrophic scar with severe visual loss.[104]

Macular Edema

Parafoveal Telangiectasia

Telangiectasia was described by Reese as a disorder of the retinal vasculature with ectasia of capillaries that are irregularly dilated and tortuous and associated vascular incompetence.[108] These abnormalities may involve the macula and periphery; however, when involvement is limited to the capillaries surrounding the foveal avascular zone, the condition is referred to as parafoveal telangiectasia. This condition initially was divided into a developmental or congenital group related to Coats' disease or an acquired group that presented in an older population.[109] Gass and Blodi revised the original classification based mainly on the degree of capillary involvement and the progression of the disease.[110] The details of this classification will be discussed later in this chapter.

What Is the Clinical Presentation of Parafoveal Telangiectasis?

Most patients with parafoveal telangiectasia are asymptomatic or experience a mild, gradual decline in central vision. Metamorphopsia is an uncommon symptom in this disorder unless there is a secondary complication with choroidal neovascularization.

Examination of the fundus often reveals prominent telangiectatic capillaries within the macula that contain microaneurysmal and saccular dilations (Fig. 16–7). Right-angle venules are often associated with the abnormal area. The temporal region of the macula is usually involved and commonly has a whitish discoloration. Serous exudation from the telangiectasias can lead to macular edema and formation of lipid precipitates. Chronic changes are evident with areas of RPE atrophy and hyperplasia. In addition, unusual, highly refractile deposits are occasionally present in the inner retina overlying the area of telangiectasia.[111]

What Are the Various Types of Parafoveal Telangiectasia?

The classification devised by Gass and Blodi[110] divides parafoveal telangiectasia with respect to congenital or acquired development and whether or not it is unilateral or bilateral. Unilateral congenital parafoveal telangiectasia, group 1A, typically is found in middle-aged men. Obviously, this class is unilateral and involves one to two disc areas of the temporal macula. Visual loss in group 1A is usually mild and associated with macular edema. Although spontaneous resolution of the edema can occur,[109] laser

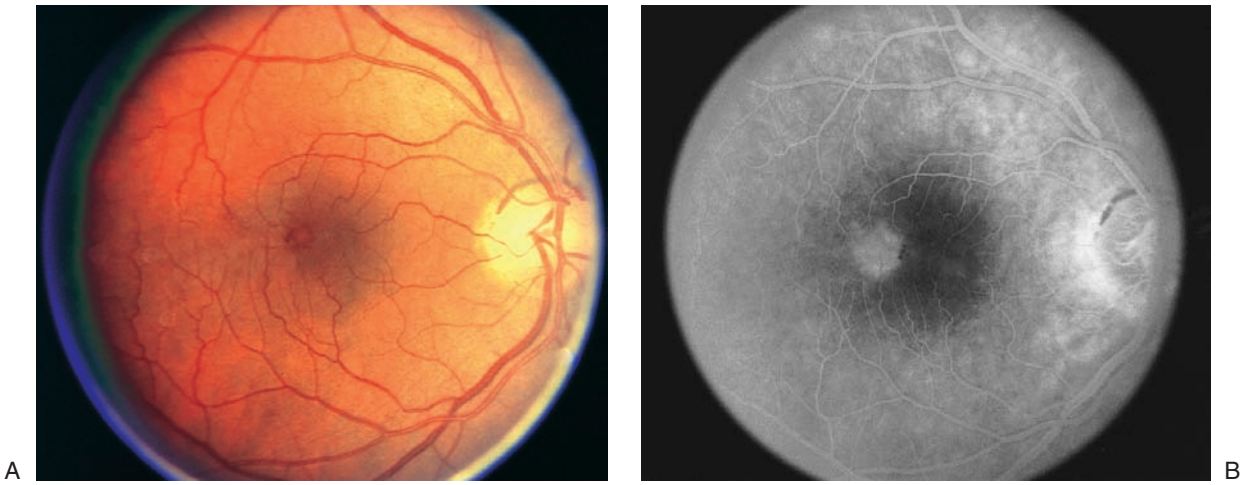


FIGURE 16–7. Fluorescein angiography of idiopathic parafoveal telangiectasia. (A). Color fundus photograph with grayish sheen and telangiectatic vessels temporal to the macula. (B). Late-phase angiogram reveals diffuse leakage temporal to the fovea from the area of telangiectasia.

photocoagulation of the telangiectatic area also can facilitate improvement.[109,112]

Unilateral idiopathic parafoveal telangiectasia, group 1B, is an acquired form, again found in middle-aged men, and has a smaller area of involvement. The capillary telangiectasia in this group is limited to one clock hour along the foveal avascular zone. Leakage and secondary macular edema or lipid exudates are unusual in group 1B patients. Therefore, visual acuity is rarely compromised, and treatment is unnecessary.

The most common form, group 2A patients, have bilateral acquired idiopathic parafoveal telangiectasias (IPT). This occurs later in life during the fifth and sixth decades, and it equally affects men and women. Bilateral involvement of an area less than one disc diameter temporal to the fovea is the usual presentation. All the perifoveal capillaries may be involved, however. This form typically has minimal serous exudation and no lipid deposits. Juvenile occult familial idiopathic juxtafoveolar retinal telangiectasia, group 2B, has been described in two brothers with subretinal neovascularization associated with juxtafoveal telangiectasia. No right-angle venules, RPE changes, or crystalline deposits were noted in these cases.[110]

Careful biomicroscopic examination allows subdivision of group 2 into five stages.[113] Stage 1 is typically discovered in asymptomatic, fellow eyes with no clinical abnormalities; however, FA will disclose mild staining of the outer parafoveal, temporal retina in the late phase without any evidence of capillary dilation. A grayish appearance develops in the temporal, parafoveolar retina with loss of transparency in stage 2, but no telangiectatic vessels are present. By stage 3, telangiectatic capillaries and dilated, right-angle venules are evident. Increased leakage from the abnormal capillaries is present on angiography. In stage 4, hyperplastic foci of RPE develop in the area of telangiectasia. Severe visual loss can occur with the development of subretinal neovascularization and retinochoroidal anastomosis in stage 5. This can lead to the accumulation of subretinal fluid, hemorrhage, and lipid. Tiny, highly refractile, golden, crystalline deposits can form within the inner parafoveolar retina in stages 2 through 5 in about 50% of patients. An unusual round, yellow intraretinal lesion approximately 100 to 300 μ in size can develop in 5% of patients.[113] This lesion is similar to pseudovitelliform macular degeneration, but it can be differentiated by the presence of telangiectasis on FA.

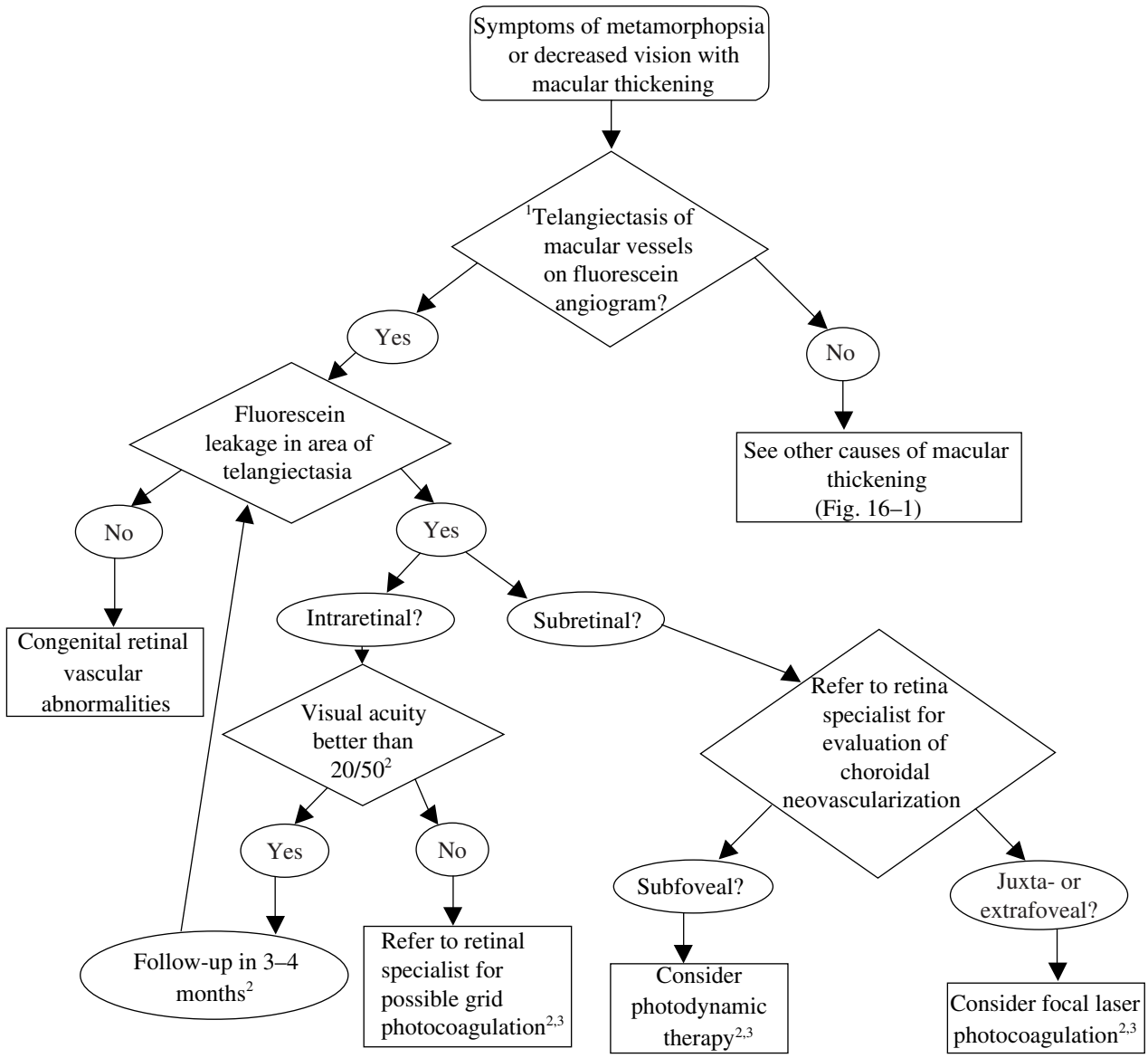
Occlusive idiopathic juxtafoveolar retinal telangiectasia, group 3, is a rare, bilateral condition with progressive obliteration of the parafoveal capillaries and enlargement of the foveal avascular zone.[113] Visual loss is usually severe and has an acute or gradual onset. Telangiectatic changes are often minimal and develop in the late stages. Some patients have an associated hereditary oculocerebral syndrome with optic atrophy and abnormal deep-tendon reflexes.

What Are the Fluorescein Angiographic Findings in Idiopathic Parafoveal Telangiectasis?

The most common and dramatic findings on fluorescein angiography in IPT are the vascular abnormalities with telangiectatic capillaries and dilated, right-angle venules that are usually temporal to the fovea (Fig. 16–7). These changes are easily appreciated during the early and middle phase of the angiogram. In the late phase, mild to moderate leakage of dye occurs in the area of telangiectasia and appears to accumulate in the outer retina (Fig. 16–7B). Before any vascular abnormalities develop, however, FA in stage 1 IPT can reveal subtle staining of the outer retina in the late phase. When hyperplasia of the RPE occurs in stage 4 IPT, these areas will block fluorescence. Finally, in stage 5, a retinochoroidal anastomosis may be present diving toward the outer retina from the inner circulation associated with subretinal neovascularization in a juxtafoveal or subfoveal location. This subretinal neovascularization usually has early hyperfluorescence with prominent late leakage, and any secondary subretinal hemorrhage will cause blockage of choroidal hyperfluorescence.

What Is the Treatment for Idiopathic Parafoveal Telangiectasia?

Most patients with IPT will be asymptomatic or complain of only mild visual disturbances. The most common reason for visual loss is related to macular edema secondary to the incompetent telangiectatic vessels. If the area of edema is relatively large (greater than one disc diameter) and the visual acuity is moderately affected (worse than 20/40), laser treatment can be considered (Fig. 16–8). Grid treatment with laser photocoagulation in the area of telangiectasia has been evaluated in some cases without benefit.[112,114] Treatment often is limited in IPT as a result of the proximity of the fovea. When IPT is complicated with choroidal neovascularization (CNV), severe visual loss can occur. If the lesion is juxtafoveal, traditional laser photocoagulation may be of benefit if the fovea can be spared. In addition, treatment of subfoveal CNV in IPT with photodynamic therapy is considered controversial. Although photodynamic therapy may spare the macular retina with treatment of the underlying CNV, there is concern that the selectivity of photody-



[1]Excludes other causes of telangiectasia: ectasia of capillaries with irregular dilation, tortuosity, and incompetence (i.e., diabetes, branch vein occlusion, or radiation retinopathy)
[2]Specific indications and guidelines for treatment and follow-up period may vary between retina specialists
[3]Deferral of treatment should be considered if patient is asymptomatic or has good visual acuity (e.g., better than 20/30)

FIGURE 16–8. Management of idiopathic parafoveal telangiectasia.

namic therapy to treat CNV may be lost because of the incompetence of the telangiectatic vessels. This could lead to a photodynamic effect of the retina and further visual loss.

What Is the Differential Diagnosis for Parafoveal Telangiectasis?

Parafoveal telangiectasia is a primary vascular abnormality and can easily be distinguished from other disorders that lead to secondary telangiectasia. Branch vein occlusions often lead to telangiectatic vessels in the macula, but the presence of sectorial intraretinal hemorrhages and venous blockage on FA will differentiate it from IPT. Radiation retinopathy also can induce telangiectasias, but there are usually multiple affected areas, cotton-wool spots, retinal neovascularization, and a history of radiation treatment that facilitate the diagnosis. Patients with diabetes can develop telangiectasias,[115] and there is an interesting

association of abnormal glucose metabolism in patients with IPT.[116] Finally, IPT with secondary CNV can be distinguished from age-related macular degeneration by the presence of drusen.

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17

Retinal Detachment

SCOTT M. STEIDL

Evaluation of a Retinal Detachment

What are the Symptoms of a Retinal Detachment?

Common symptoms include (1) visual field loss, often described as a "curtain" or "veil" coming down over a portion of the visual field; (2) abrupt loss of uniocular visual acuity, the hallmark of a detachment that involves the macula (Table 17–1); (3) floaters, objects in the visual field that originate in the vitreous; (4) photopsia, or light flashes; or (5) metamorphopsia, or image distortion. An approach to evaluating the symptoms of photopsias and floaters is outlined in Figure 17–1.

What Are the Signs of a Retinal Detachment?

All retinal detachments involve separation of the retina from the retinal pigment epithelium (RPE). On examination, it is important to define the shape of the retinal elevation as irregular, concave, or convex because these configurations both support the diagnosis of a retinal detachment and help point to its cause. Some findings associated with retinal detachments are outlined in Table 17–2.

Binocular indirect ophthalmoscopy is the best method to diagnose and characterize a retinal detachment. Scleral depression must be used to explore the peripheral retina for possible retinal breaks. In the absence of clear media, B-scan ultrasonography can indicate the presence of a retinal detachment, determine its shape, and identify shifting fluid in the case of an exudative detachment. A more detailed description of retinal detachment types can be found in Table 17–3. General shapes of retinal detachments are depicted in Figure 17–2, and photographs are shown in Figure 17–3.

TABLE 17–1. Symptoms of Retinal Detachment

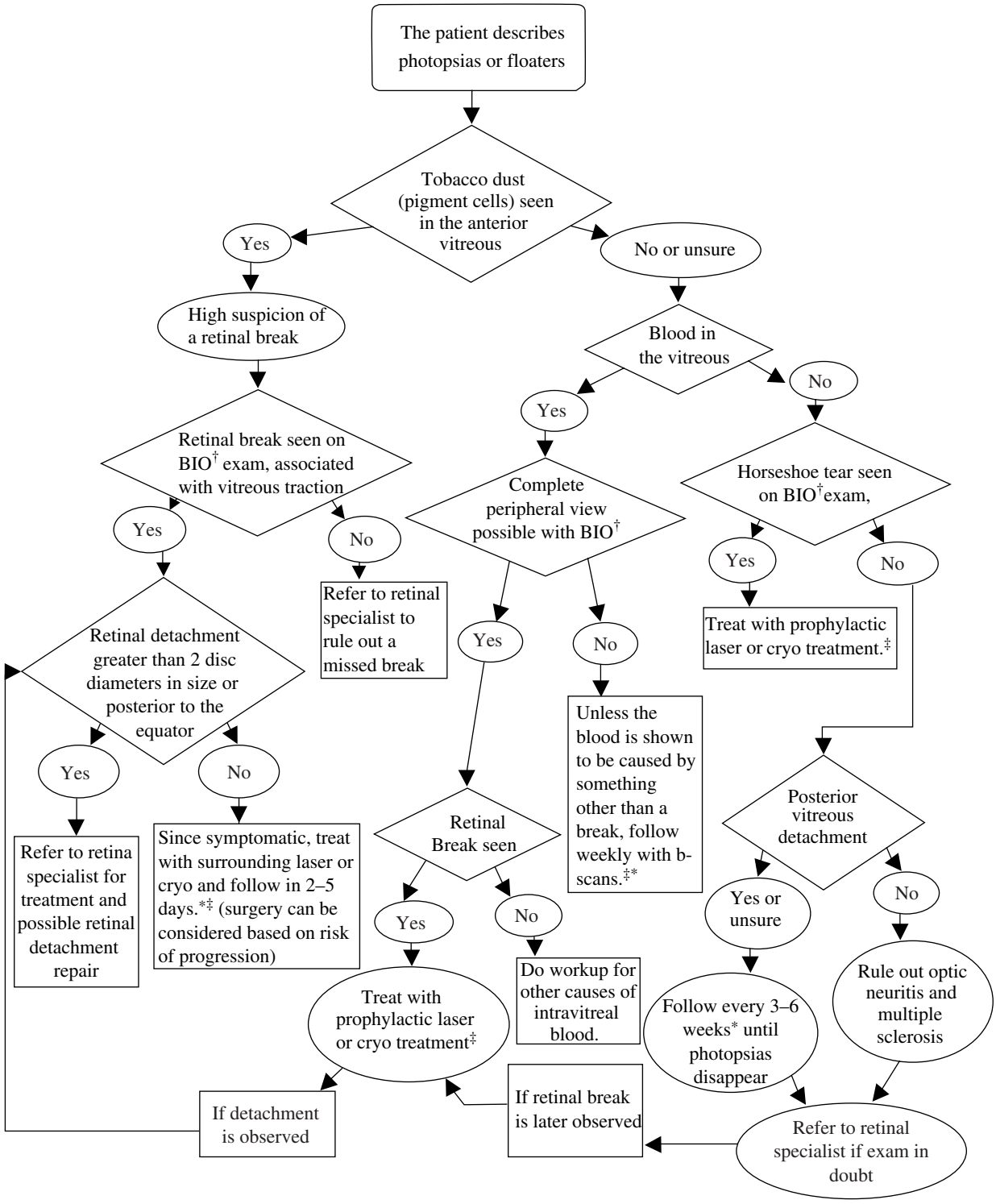
Loss of visual field
If from macular detachment, severe loss of visual acuity is described.
If due to peripheral detachment, the loss in visual field is usually described as a "veil" or "curtain" over the affected portion of the visual field.
Metamorphopsia
Image distortion
Floaters[a]
Objects that move with eye movement in the visual field, usually associated with posterior vitreous detachment, blood, cellular, or inflammatory debris
Photopsia[a]
An abnormal perception of light (typically lasting less than 1 second if due to retinal disease)

[a]These are also symptoms of retinal breaks

How Do You Categorize a Retinal Detachment?

A retinal detachment can be categorized as *rhegmatogenous*, *exudative*, or *tractional*. A *rhegmatogenous* retinal detachment is associated with a retinal break (Fig. 17–2). The detached retina has an irregular surface associated with surface wrinkling caused by intraretinal edema (Fig. 17–2). Fluid can move through the break, causing the detachment to change size or shape as the eye moves. Pigmented particles can move through the break into the anterior vitreous. These particles are called *tobacco dust*, or the *Schaeffer sign,* and are seen with slit-lamp examination.

An *exudative* retinal detachment is the result of a damaged RPE pump or increased leakage from retinal or choroidal vessels, usually the result of inflammation (Figs. 17–2 and 17–3B). Typically, the detachment margins are less well defined than with other retinal detachments. These detachments are generally smooth on the surface and convex shaped. Most patients will exhibit "shifting" of subretinal fluid with changing head position as heavier subretinal fluid moves to a new gravity dependent position.



*Schedules for follow-up intervals are not well established and may need to be altered on an individual basis. †Binocular Indirect Ophthalmoscopy. §Dialysis, or symptomatic nonhorseshoe tears in patients with a history of retinal detachment in the fellow eye, traction associated with the break, or large subclinical detachments may be considered for treatment. ‡We favor referral to a retinal specialist for management.

FIGURE 17–1. Management of the patient with flashes or floaters.

TABLE 17–2. Findings Associated with Retinal Detachment

Findings	*Type of Detachment Typically Associated with the Findings*
Retinal elevation	Rhegmatogenous, traction, exudative
Tobacco dust (anterior vitreous pigment cells)	Rhegmatogenous
Vitreous hemorrhage	Rhegmatogenous, traction, exudative (less commonly)
Inflammation	Rhegmatogenous, exudative
Ocular hypopnea (acute)	Rhegmatogenous, exudative
Ocular hypertension (chronic)	Rhegmatogenous

Traction retinal detachments are typically the result of cicatricial (scarring) processes caused by systemic disease states, such as diabetes (Fig. 17–3C) or nonsystemic disease, states such as proliferative vitreoretinopathy (Fig. 17–2). A pure traction detachment does not shift with head movement, and its surface typically is altered to a flat or a concave appearance.

Detachments also may have mixed mechanisms that combine characteristics of more than one type, such as a traction detachment with a retinal tear or an exudative detachment with a tractional component. The characteristics associated with the individual types of retinal detachment as well as the predisposing conditions are outlined in Tables 17–3 and 17–4. A method for determining the type of retinal detachment and its basic management is outlined in Figure 17–4.

TABLE 17–3. Types of Retinal Detachment

Rhegmatogenous retinal detachment
- These detachments are the result of a retinal break, usually a horseshoe tear (Fig. 17–5A)
- Typically, folds or "rugae" are observed on the surface (Fig. 17–2)
- The retinal surface moves with eye movement or scleral depression (it does not "shift")

Exudative retinal detachment
- Subretinal fluid clearance mechanisms are overwhelmed by excessive vascular exudation
- Inflammation is usually the cause
- No breaks are present
- A convex "dome" configuration to the retina is characteristic, often with shifting subretinal fluid (Fig. 17–2)

Traction Retinal Detachments
- The underlying disease processes create fibrous or fibrovascular membranes that pull the retina away from the retinal pigment epithelium
- These detachments typically assume a flat, concave (Fig. 17–3C), or "funnel"-shaped retinal contour (Fig. 17–2)

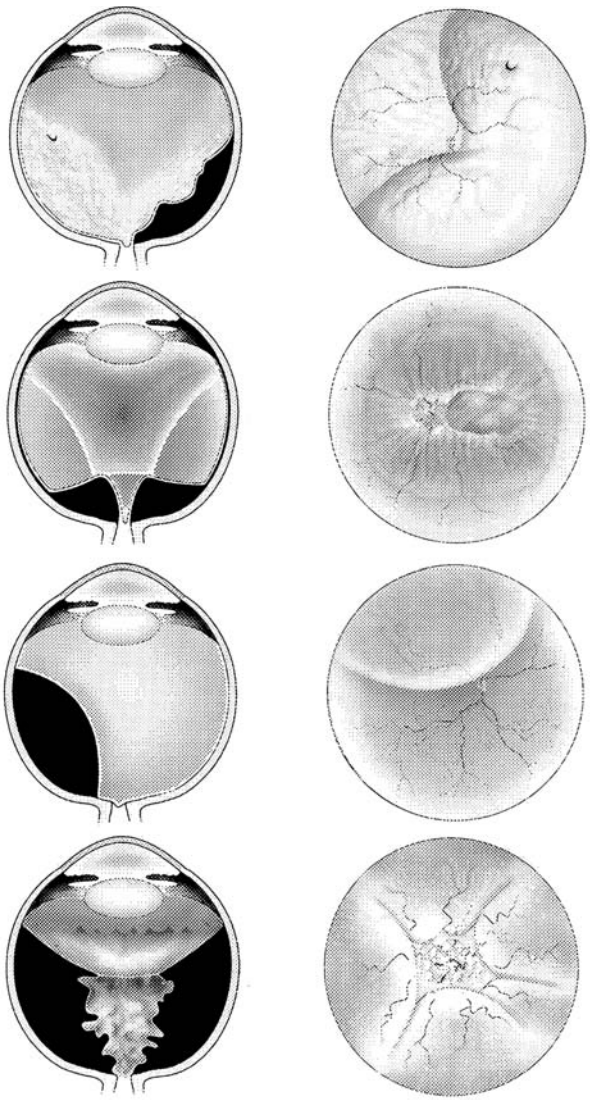


FIGURE 17–2. Various configurations of retinal detachments, with the side view on the left and front view on the right. *(Top row)* Rhegmatogenous retinal detachment with horseshoe tear and wrinkled retinal surface due to intraretinal edema. *(Second row)* Diabetic traction retinal detachment with elevation of the retina at the major vessels caused by vitreous traction. *(Third row)* Exudative retinal detachment with dome shaped contour that shifts with head movement. *(Bottom row)* Traction detachment associated with proliferative vitreoretinopthy, in a funnel configuration.

Rhegmatogenous Retinal Detachment

What Clinical Features Are Suggestive of Retinal Detachment with Retinal Breaks?

A rhegmatogenous retinal detachment is a retinal detachment with an associated break in the retina. It takes on a whitened appearance and develops a characteristic wrinkled pattern of folding. This wrinkling

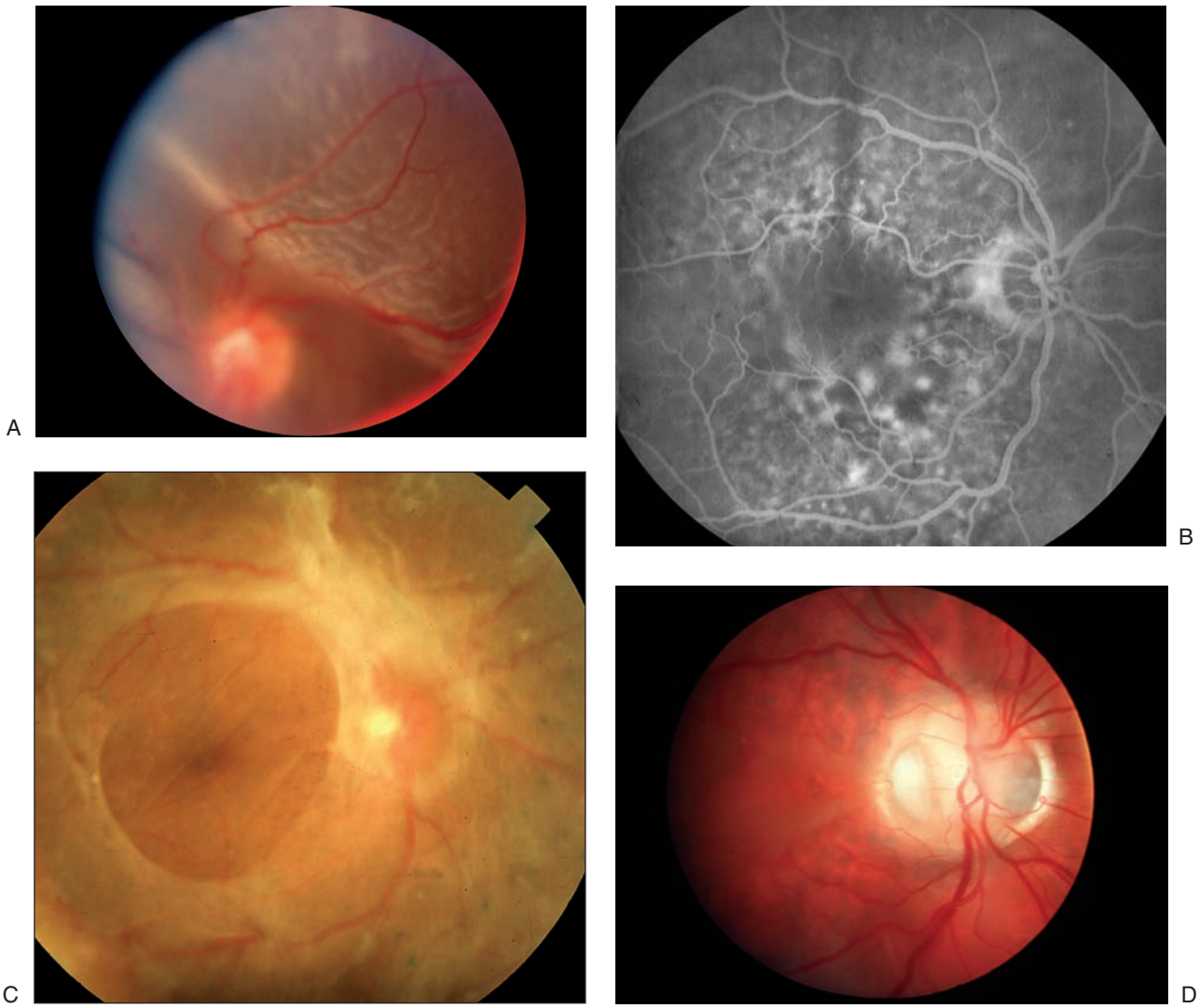


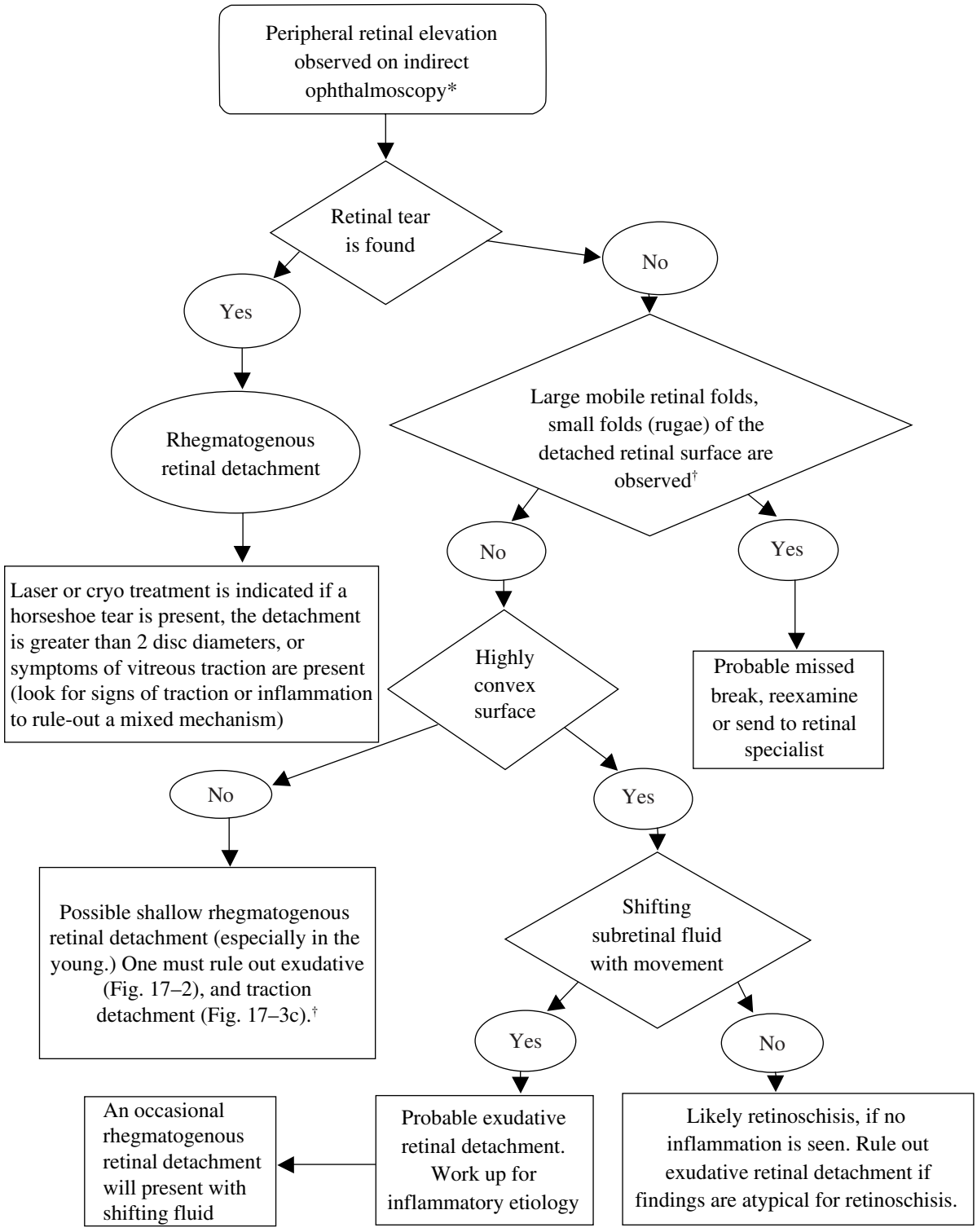
FIGURE 17–3. Types of retinal detachment. (A). Rhegmatogenous retinal detachment. As retinal edema increases, small white folds within the detachment may develop. (B). Fluorescein angiogram of a patient with a shallow exudative retinal detachment caused by steroid use after heart transplant surgery. Note the multiple areas of leakage at the level of the retinal pigment epithelium. (C). Traction retinal detachment resulting from proliferative diabetic retinopathy. (D). A shallow central macular detachment resulting from an optic pit.

is the result of intraretinal edema, not membrane formation. For a break to lead to a retinal detachment, there usually must be accompanying changes in the vitreous gel, such as an increase in vitreous liquefaction, vitreous contraction, or sudden shifting of the vitreous from eye movement. Vitreous liquefaction, also referred to as syneresis, often occurs before development of a posterior vitreous detachment (PVD).

TABLE 17–4. Factors Predisposing to Retinal Detachment

Myopia
Lattice degeneration
New cataract surgery or yttrium–aluminum–garnet (YAG) laser capsulotomy
Trauma
Positive family history
Posterior vitreous detachment
Previous retinal detachment in the fellow eye

A *Weiss ring* is the portion of the cortical vitreous attached to the optic nerve that dislocates after a PVD. It is later seen as a floating ring in the central vitreous cavity. As the posterior vitreous starts to detach, traction at sites of abnormally strong vitreoretinal adhesion develop and are a common cause of development of a horseshoe tear. Tractional forces acting on the retina may create photopsias often described as "flashes." Horseshoe tears are commonly associated with single or clumped pigment cells in the anterior vitreous called tobacco dust. This finding



*Isolated macular retinal elevation is rarely due to retinal breaks in the absence of high myopia.
† We suggest a referral to a retinal specialist if questions exist, or treatment is required.

FIGURE 17–4. Signs of retinal detachment: Management of the patient with retinal elevation and retinal break (rhegmatogenous retinal detachment).

is seen only with careful examination of the anterior vitreous using a slit lamp. If a patient describes the new onset of flashes or floaters, it is prudent to note that tobacco dust was not observed if breaks are not found.

Other conditions occasionally are confused with rhegmatogenous retinal detachment. *Retinoschisis* is a splitting of the retina usually seen in the periphery, which elevates the inner retinal surface in a smooth, rigid, dome-shaped structure. Retinoschisis causes an "absolute" scotoma as a result of the loss of middle retinal synaptic connections between the outer photoreceptor layer and the inner ganglion cell layer. Either outer or inner layer breaks in the split retina can form. If both occur, a retinal detachment can develop.

Choroidal melanomas often cause a "collar-button" formation observed on B-scan ultrasonography. This mushroom-shaped extension of the melanoma under the retina is caused by constriction at the point of its entrance through the Bruch membrane, resulting in a detached retina, which becomes elevated and draped over the surface of the melanoma. Choroidal detachments may be caused by many conditions but are most commonly caused by ocular surgery, such as glaucoma filtering surgery, cataract surgery, and scleral buckling procedures. They are typically smooth and solid appearing with a brown–red color. They do not move with eye movement and commonly are associated with exudative detachments. Choroidal detachments may be hemorrhagic or serous in origin and, unlike retinal detachments, they do not respect the anterior boundary of the ora serrata, often elevating the pars plana.

What Features Help to Differentiate between Types of Retinal Breaks?

The retinal tear most commonly associated with retinal detachment is the horseshoe tear (Figs. 17–2 and 17–5A). The tear is caused by vitreous traction on the anterior retinal surface producing a torn flap of elevated retina that is drawn into the vitreous cavity. Horseshoe tears often are seen in conjunction with lattice degeneration (Fig. 17–5B). Traction at the edge of lattice lesions is thought to predispose to break formation; however, tears can form anywhere in the fundus of patients with lattice degeneration. The operculated retinal tear (Fig. 17–5C) is a piece of retina that previ-

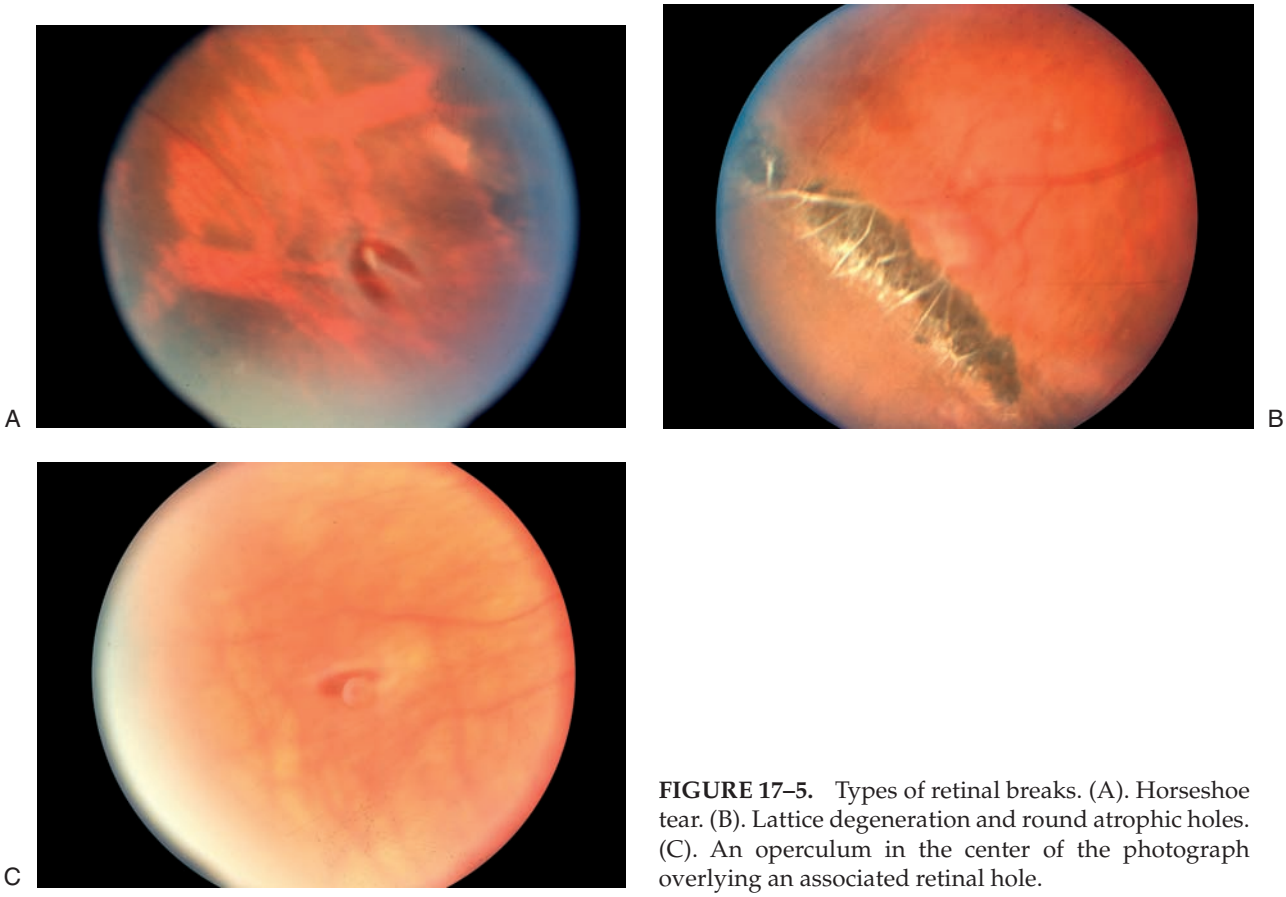


FIGURE 17–5. Types of retinal breaks. (A). Horseshoe tear. (B). Lattice degeneration and round atrophic holes. (C). An operculum in the center of the photograph overlying an associated retinal hole.

ously tore away from the retina as a result of abnormal vitreoretinal attachment and traction. The portion attached to the vitreous gel is left floating freely above the retinal surface, and the retinal defect takes the form of a round hole. Atrophic retinal holes pose little threat of causing a symptomatic retinal detachment, even if retinal elevation or PVD develops.[1] These holes are the result of degenerative disease and usually are not associated with abnormal vitreous attachment.

A retinal dialysis (Fig. 17–3A) is a peripheral break, usually at the ora serrata. The vitreous base spans the defect and is adherent to the anterior and posterior edge of the break. It may be many clock hours in size. It carries a better prognosis than the giant tear, which forms posterior to the vitreous base. Because a giant tear does not have vitreous base attachment to the posterior tear edge, the edge is prone to fold and gape. This makes the giant tear likely to cause retinal detachment.

Does Myopia Predispose to Retinal Detachment?

More than half of nontraumatic retinal detachments occur in myopic eyes. In one study, the risk of detachment for myopia ranging from −1 to −3 diopters was four times that of emmetropic controls.[2] The risk was 10 times greater for eyes with myopia of more than 3 diopters. Myopia is also a significant risk factor for retinal detachment following cataract extraction. For this reason, some ophthalmic surgeons do not recommend removal of the clear lens as a means of correcting myopia.

What Is the Role of Lattice Degeneration in Retinal Detachment Development?

Lattice degeneration is found in 6 to 8% of the general population and in 30% of eyes with retinal detachments.[3] Given these statistics, it may seem dangerous to leave these lesions untreated; however, the literature has not reported clear benefit to their prophylactic treatment. For example, Byer found lattice lesions to be responsible for retinal detachments in only 3 of 423 eyes over an 11-year period.[4] If a patient with bilateral lattice degeneration has had a retinal detachment in one eye, and if the eyes are highly myopic, the chances of subsequent retinal detachment in the fellow eye are compounded by these multiple factors.[5] Prophylactic therapy of non-horseshoe breaks appears warranted only in cases where multiple risk factors exist, such as (1) pseudophakia with high myopia, (2) a history of a fellow eye retinal detachment; (3) tears with expanding retinal elevation; or (4) extensive vitreous traction.[6]

What Is the Association of Cataract Surgery to Retinal Detachment?

Cataract surgery by any method increases the risk of retinal detachment six to seven times more than nonsurgically treated patients.[7–9] Additional studies suggested that retinal detachment after cataract surgery is more common in young myopic patients and more common after laser posterior capsulotomy.[10,11] Posterior capsule tears at the time of cataract surgery add to the risk of retinal detachment.

What Is the Role of Trauma in the Development of Retinal Detachments?

Patients who undergo blunt or penetrating injury to the eye have increased risk for rhegmatogenous retinal detachment.[12] The presence of blood increases the risk of retinal detachment to 73% after penetrating injury. Most surgeons delay vitrectomy following penetrating trauma for at least 72 hours to allow for healing, further diagnostic evaluation, decreased uveal congestion, and spontaneous separation of the posterior hyaloid. Typically, a scleral buckle is placed at the time of vitrectomy surgery.[13]

What Does a Retinal Detachment Mean for the Fellow Eye?

Patients with a history of retinal detachment are at increased risk of developing a retinal detachment in the fellow eye.[14] The incidence of retinal detachment in the fellow eye, despite treatment, ranges from 1.8 to 6.8%.[15] The risk is heightened after cataract extraction.[16] In one study, the frequency of retinal detachment was four times higher with aphakic patients compared with phakic patients in one study.[17]

How Does a Positive Family History Impact on Retinal Detachment Development?

Hereditary vitreoretinal disease may predispose to retinal detachment. Stickler syndrome is the most common inherited cause of retinal detachment, and in type 2 Stickler syndrome, a specific gene mutation has been linked to the COL2A1 locus.[18] Hereditary diseases that predispose to retinal detachment often include risk factors such as myopia, lattice degeneration, and vitreous syneresis. A partial list of ocular systemic conditions associated with retinal detachment is outlined in Table 17–5.

Posterior Vitreous Detachments and Retinal Detachment

A degree of PVD is seen with most rhegmatogenous retinal detachments. If posterior vitreous separation

TABLE 17–5. Conditions Associated with Rhegmatogenous Retinal Detachment

Hereditary disorders
Wagner–Jansen–Stickler syndrome
Marfan syndrome
Familial retinal dialysis
Ehlers–Danlos
X-Linked juvenile retinoschisis
Goldman–Favre
Retinal conditions
Lattice degeneration
Axial myopia
Retinoschisis

occurs without forming a tear, the risk of retinal detachment decreases significantly.[17] The prevalence of retinal detachment increases with age,[19] but it also may occur in younger patients with myopia, inflammation, or previous intraocular surgery.[20] A retinal tear will be found in about 15% of patients with new flashes or floaters caused by a PVD.[21–23] If vitreous hemorrhage or pigment cells are observed in the vitreous, the risk of a retinal tear increases substantially.[22]

What Is the Significance of a Symptomatic Retinal Tear?

About half of the symptomatic horseshoe tears (flap tears) will cause a retinal detachment unless treated adequately.[24–26] Treating the lesion with adequate laser or cryotreatment nearly eliminates the chance of retinal detachment.

How Are Suspected Retinal Breaks Evaluated?

Retinal evaluation for suspected breaks or retinal detachment requires indirect ophthalmoscopy combined with scleral depression. Often peripheral retina can be seen despite the presence of vitreous hemorrhage. In certain cases, bed rest with the head elevated and bilateral eye patching has been advocated by specialists to hasten settling of the blood and improve the retinal view.[27] For situations where the peripheral retina cannot be evaluated adequately, consultation with a specialist in vitreoretinal disorders is recommended. Patients at high risk should be educated about the warning symptoms of PVD and retinal detachment and the value of prompt evaluations.[28]

If a retinal tear develops into a rhegmatogenous retinal detachment, vision will be lost unless the detachment is repaired. Visual acuity usually improves and stabilizes after successful retinal reattachment. In patients who develop detachment of the macula, reading vision may not be achieved even with successful attachment of the retina. An approach to evaluation of patients with suspected retinal breaks is outlined in Table 17–6. In general, any patient about whom there is a concern of a retinal tear or retinal detachment should undergo prompt evaluation by a retinal specialist or ophthalmologist skilled in indirect ophthalmoscopy and scleral depression.

How Should the Patient with Retinal Breaks Be Managed?

Laser photocoagulation and cryotherapy are the standard treatments used in prophylactic management of retinal breaks. If symptomatic horseshoe breaks are found, treating them with these modalities is usually recommended. Nevertheless, not all reports suggest a high likelihood of horseshoe breaks developing into retinal detachments if they are chronic and asymptomatic. A study by Hyams and colleagues suggested that chronic horseshoe breaks generally do not benefit from prophylactic treatment.[29] The use of judgment in choosing the correct management often requires experience and developed observational skills.

Treatment applied to a horseshoe tear should adequately surround the lesion, particularly around the horns (anterior extensions) of the tear. This will lead to development of a scar between the retina and adjacent tissues, stopping the movement of fluid through the hole. An inadequate treatment applied to horseshoe tears is the most frequent cause of subsequent retinal detachment.[30–32] A cryoprobe offers the advantage of providing scleral depression and easily delivered treatment to the visualized lesion. It carries the disadvantage of requiring locally injected anesthesia. A horseshoe tear or a retinal dialysis should be treated by surrounding it with either cryotreatment or laser treatment. Laser is usually done at a slit lamp with a contact lens; however, laser applied by indirect ophthalmoscopic delivery also permits anterior treatment and makes the use of scleral depression possible. A method for determining the treatment of retinal breaks is outlined in Table 17–7.

What Is Done at the Follow-up Examination after a Posterior Vitreous Detachment Has Been Observed?

Patients who have an acute PVD should have the subsequent history and examination elements covered during follow-up examination. A change in visual symptoms or a new history of intraocular surgery should be documented. The visual acuity and the results of an evaluation of the status of the vitreous, macula, and peripheral fundus should be documented. If the patient has a vitreous hemorrhage or vitreoretinal traction, a reexamination should be scheduled within 3 to 6 weeks and generally requires the experience of a vitreoretinal specialist.[33,34] A tear

TABLE 17–6. Evaluation of Patients with Retinal Breaks

Topics and Elements to Include	*Reason*
In the patient history:	
Family history	It may reveal inherited vitreoretinal disease
Prior eye trauma or surgery	Increased risk of retinal break formation
Myopia	Increased risk of retinal break formation
Lens status	Increased risk of retinal breaks with aphakia (no lens) and pseudophakia (lens implant)
Symptomatic posterior vitreous detachment	Increased risk of retinal break formation
In the examination:	
Slit-lamp biomicroscopy	
Status of the vitreous	To look for signs of a retinal break (hemorrhage/pigment cells/vitreous)
Biomicroscopic macular examination	For visual prognosis: prognosis is poor if the evaluation macula is detached For plan formulation: to expedite retina consultation with a "macula on" retina detachment. Look for a Weiss ring (signifying a posterior vitreous detachment and increased risk of breaks)
Confrontation visual fields	Detect a large retina detachment
Peripheral indirect ophthalmoscopy	Look for breaks, or retinal detachment
Measurement of refractive error	Evaluate for myopia (increased risk of retinal breaks)
B-scan ultrasonography if the media is opaque	Define location and type of detachment, if present

should be suspected in a patient who has a vitreous hemorrhage that obscures retinal details in the absence of conditions predisposing to hemorrhage, such as diabetes mellitus. A B-scan evaluation should be done and repeated at close intervals. No consensus of opinion exists regarding the optimal interval between visits in this situation. Frequent visits, for example, every 2 to 10 days, while the hemorrhage is settling or clearing help to determine whether the patient should be followed up or have treatment. This avoids missing a retinal detachment in a patient who has difficulty determining changes in vision. If any question regarding patient management develops, the skills of a vitreoretinal specialist should be sought.

What Should Be Done at the Follow-up Examination after a Retinal Break Has Been Treated?

If a patient is treated for a horseshoe retinal break, he or she should be asked to report back to the treating ophthalmologist if new visual field loss or floaters are observed. Although optimal intervals for follow-up evaluation have not been established, we suggest that patients be seen within 2 days to a week of treatment because chorioretinal scarring may take more than 5 days to develop. Based on the size of the break, if tractional forces or other general risk factors for retinal detachment are observed, the patient should be seen again within 6 weeks to look for subretinal fluid accumulation beyond the edge of the treatment. If tractional forces are minimal or a low risk of detachment exists, the interval can be extended. At follow-up visits, it also is important to examine the retina for possible new breaks.

TABLE 17–7. An Approach to Management of Retinal Tears and Holes in Patients Photopsias or New Floaters

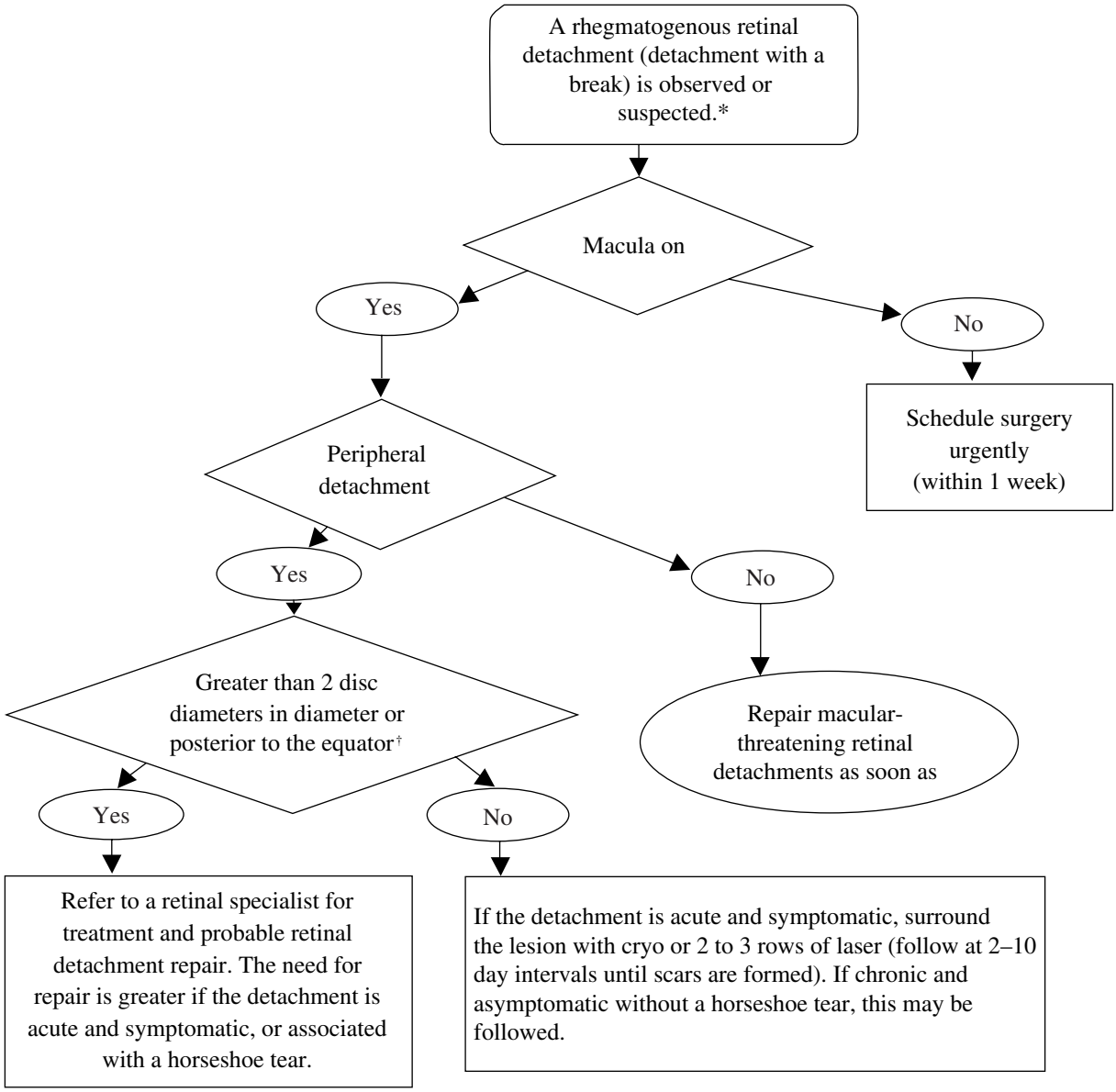
Lesion	*Suggested Treatment*
Horseshoe tear	Always treat
Dialysis	Always treat
Operculated tear	Treat rarely[a]
Atrophic hole	Treat rarely[a]
Lattice degeneration	Treat rarely[a]

[a]The threshold for treatment should be lowered if retina elevation is seen or direct vitreous traction can be visualized in the setting of an acute PVD.

Adapted from the American Academy of Ophthalmology Preferred Practice patterns.

How Should a Rhegmatogenous Retinal Detachment Be Managed?

For the management of a rhegmatogenous retinal detachment, determining the timing of management requires knowing whether the event is chronic or acute and whether the macula is involved (Fig. 17–6). Chronic detachments produce slow changes in visual fields that the patient initially might not notice. In general, the patient with a large or posterior retinal detachment should be urgently sent to a vitreoretinal specialist for surgical evaluation. Timing of surgery may be important for improving final visual results. Some retinal detachments, such as shallow pediatric detachments, may be difficult to diagnose. If any question exists, especially in the face of decreased vision, one should err on the side of caution and refer the patient to a retinal specialist, even if the patient is inconvenienced by the time, travel, or distance involved in the referral examination.



*We favor referral to a retinal specialist for management of rhegmatogenous retinal detachments.

†The size and character of limited retinal detachments, which are likely to progress to involve the macula, are not well established and remain a point of controversy.

FIGURE 17–6. Management options for rhegmatogenous retinal detachment.

Demarcation lines are changes in pigmentation at the border of a chronic detachment. They take weeks to develop. If the macula is attached in the presence of an advancing acute detachment, surgical intervention should be performed promptly to avoid macular detachment. If surgery must be delayed, bed rest and bilateral patching may decrease vitreous movement and temporarily halt progression of a detachment.[28] The exact timing of surgery for "macula-on" and "macula-off" detachments is a point of debate; however, it is generally thought that macula-threatening detachments should be managed emergently, whereas macula-off detachments can be scheduled within 7 days or more.[35]

What Is Proliferative Vitreoretinopathy?

Proliferative vitreoretinopathy (PVR) is the primary cause of failures of retinal detachment repair. It is an abnormal proliferation of membranes of cellular origin on the retinal surface (Fig. 17–2 and Table 17–8). PVR occurs after about 5% of rhegmatogenous retinal

TABLE 17–8. Types of Proliferative Vitreoretinopathy (PVR) and Understanding the Terminology

Types of PVR	*Location on the retina*	*Features*
Focal	Posterior or anterior	Star-fold
Diffuse	Posterior or anterior	Confluent star-folds (localized preretinal membranes)
Subretinal	Posterior or anterior	Strands near or around disk, or linear subretinal membranes in any combination of orientations
Circumferential	Usually anterior	Contraction and anterior displacement of the retina and posterior hyaloid face (if severe, a central funnel-like displacement of the retina with radial retinal folds develops)
Anterior displacement	Anterior at the vitreous base	Vitreous base contraction, that drags the retina anteriorly with development of a peripheral retinal trough

detachment repairs. It occurs more frequently after vitreous hemorrhage, large retinal tears, severe inflammation, and complicated surgery.[36]

How Do You Diagnose Proliferative Vitreoretinopathy?

If PVR has caused extensive tractional force to be placed on the retina, the complaint is usually that the vision is becoming dim or dark. Because PVR usually is a contraction of the inner surface of the retina, it manifests primarily as localized areas of wrinkling. In the early stages, small localized "star folds" or "multiple star folds" of PVR develop. Subretinal PVR also can form. It typically presents as linear or lacy fibers, which can cause retina to drape over the membranes like fabric over a clothesline. Subretinal PVR may elevate the posterior retina over the optic nerve by constricting and encircling it from the subretinal space, like a napkin ring around a napkin. These subretinal membranes may lie flat or cause varying amounts of retinal detachment. The effect of PVR on the retina varies but ultimately may lead to extensive complex detachments.

What Causes Proliferative Vitreoretinopathy?

It is not known what causes PVR, but it is thought that PVR develops from membranes on the retinal surface derived from cells of glial and retinal pigment epithelial origin. Glial cells may migrate from the retina through defects in the internal limiting membrane. Retinal pigment epithelial cells have been shown to migrate through retinal breaks and preferentially collect in gravity-dependent areas, especially after cryotherapy.[37] In the setting of retinal breaks, PVR develops into a retinal detachment combining traction and rhegmatogenous processes. The damage caused by PVR may be limited, but it is often extensive, leading to large retinal detachments that are difficult to treat. This requires surgical "membrane peeling" or release of tractional forces through scleral buckling. Rarely, in long-standing cases, retinotomy formation is required to release tractional forces and allow retinal relaxation. Traditional retinal detachment surgery for PVR involves closing all retinal breaks and using internal tamponade of gas or silicone oil. Despite these efforts, PVR is often uncontrollable. The optimal future management of proliferative membranes in PVR may involve pharmacologic, not surgical management.[38]

Exudative Retinal Detachment

What Symptoms Suggest an Exudative Retinal Detachment?

In the presence of an exudative retinal detachment, patients may complain of decreased visual acuity and visual field loss as well as metamorphopsia or floaters. As with rhegmatogenous retinal detachments, photopsias may be described; however, a retinal break must be ruled out in this circumstance. Anything from mild to extensive loss of vision may be described. Disease categories associated with exudative retinal detachment are listed in Table 17–9. Conditions associated with exudative retinal detachments are listed in Table 17–10.

What Signs Are Associated with Exudative Retinal Detachment?

The hallmark feature of an exudative retinal detachment is a smooth, dome-shaped elevation of the retinal surface, which shifts with head position. The detachment is devoid of the retinal folds typically seen with rhegmatogenous detachments. The spectrum of exudative disease may span the extremes of a very limited posterior pole macular elevation, such as with central serous chorioretinopathy, to extensive exudative retinal detachment nearly filling the vitreous cavity, as seen in advanced Coats' disease or exophytic retinoblastoma. Exudative retinal detachments may coexist with detachments of the choroid. An approach to evaluating a suspected exudative retinal detachment is shown in Figure 17–7.

Exudative retinal detachments include macular detachments with 20/20 vision and yet also may include large, chronic serous retinal detachments with finger-counting vision or worse. Intraocular pressure may

TABLE 17–9. Exudative Retinal Detachments

Thickened sclera: causes outflow resistance in emissary channels
Neoplasia: can cause blood–retinal barrier breakdown or blockage of vessels by space-occupying lesions and immunoglobulin deposition
Inflammatory disease (nonvascular) and infections: are generally due to blood–retinal barrier breakdown
Inflammatory disease (with vasculitis): vessel wall infiltration and lumen blockage

(Data from Rajiv A, Tasman WS, McNamara JA. Nonrhegmatogenous retinal detachment. In: Ryan SJ et al (eds.). *Retina*, vol 3. St. Louis; Mosby; 1989: 584–585, with permission.)

decrease if ciliary body inflammation is present. Fluorescein angiography may demonstrate focal exudation with conditions such as central serous chorioretinopathy, whereas lacy hyperfluorescence is observed with subretinal neovascularization, and retinal vascular abnormalities are seen with conditions such as Coats' disease.

What Are the Proposed Causative Mechanisms in Exudative Retinal Detachments?

For an exudative retinal detachment to occur, the normal hydrostatic pressure gradients, or transport mechanisms that maintain RPE–retinal adhesion must be abnormal. Excessive extracellular fluid in the subretinal space causes the detachment. Damage to the transport mechanisms of the RPE typically decreases fluid movement from the subretinal space into the choroid. Defects in choroidal vasculature or retinal vasculature may cause fluid to collect in the subretinal space. Osmotic pressure from extracellular protein, and changes in metabolic fluid transport through the RPE also may play a role.[39] It has been argued that widespread RPE dysfunction is necessary to maintain a large exudative retinal detachment.[40,41]

What Are Some Idiopathic Causes of Exudative Retinal Detachment

Idiopathic causes of exudative retinal detachment include central serous chorioretinopathy, Coats' disease, and uveal effusion syndrome. Central serous chorioretinopathy (CSC) is a condition of unknown cause that results in self-limited macular retinal detachment. Typically, one or more points of leakage through the RPE into the subretinal space can be identified on fluorescein angiography. Vision usually returns to normal, although chronic recurrent disease can occur associated with vision loss in a small subset of patients. Patients with acute episodes may develop severe vision loss if associated with systemic administration of steroids or uncontrolled hypertension. Coats' disease may cause small or large exudative retinal detachments, typically in young male patients. Fluid as well as hard exudate may collect locally or in distant parts of the fundus (commonly in the macular region). Telangiectasia may develop as a result of abnormal endothelium. If large retinal detachments develop in the young, it may be difficult to distinguish this presentation from exophytic retinoblastoma.[42]

TABLE 17–10. Some Conditions Associated with Exudative Retinal Detachment

Idiopathic
Central serous chorioretinopathy
Coats' disease
Uveal effusion syndrome
Congenital anomalies
Nanophthalmos
Optic pits
Morning-glory syndrome
Hereditary
Familial exudative vitreoretinopathy
Surgical
Intraocular surgery
Scleral buckle surgery
Retinal photocoagulation
Infection
Syphilis
Herpes zoster
Toxoplasmosis
Autoimmune
Vogt–Koyanagi–Harada syndrome
Sympathetic ophthalmia
Intermediate uveitis
Vasculitis
Polyarteritis nodosa
Wegener granulomatosis
Rheumatoid arthritis
Vascular-hemodynamic
Toxemia of pregnancy
Age-related macular degeneration
Hypertensive retinopathy
Diabetic retinopathy
Chronic renal failure
Hematologic
Thrombotic thrombocytopenic purpura
Sickle cell disease
Disseminated intravascular coagulation
Neoplastic
Choroidal melanoma
Choroidal nevus
Choroidal metastasis
Choroidal hemangioma
Benign reactive lymphoid hyperplasia
Multiple myeloma
Leukemia

MANAGEMENT

Laser photocoagulation to the points of exudation may be helpful for CSC and Coats' disease. Fluorescein angiography is used to determine areas of leakage.

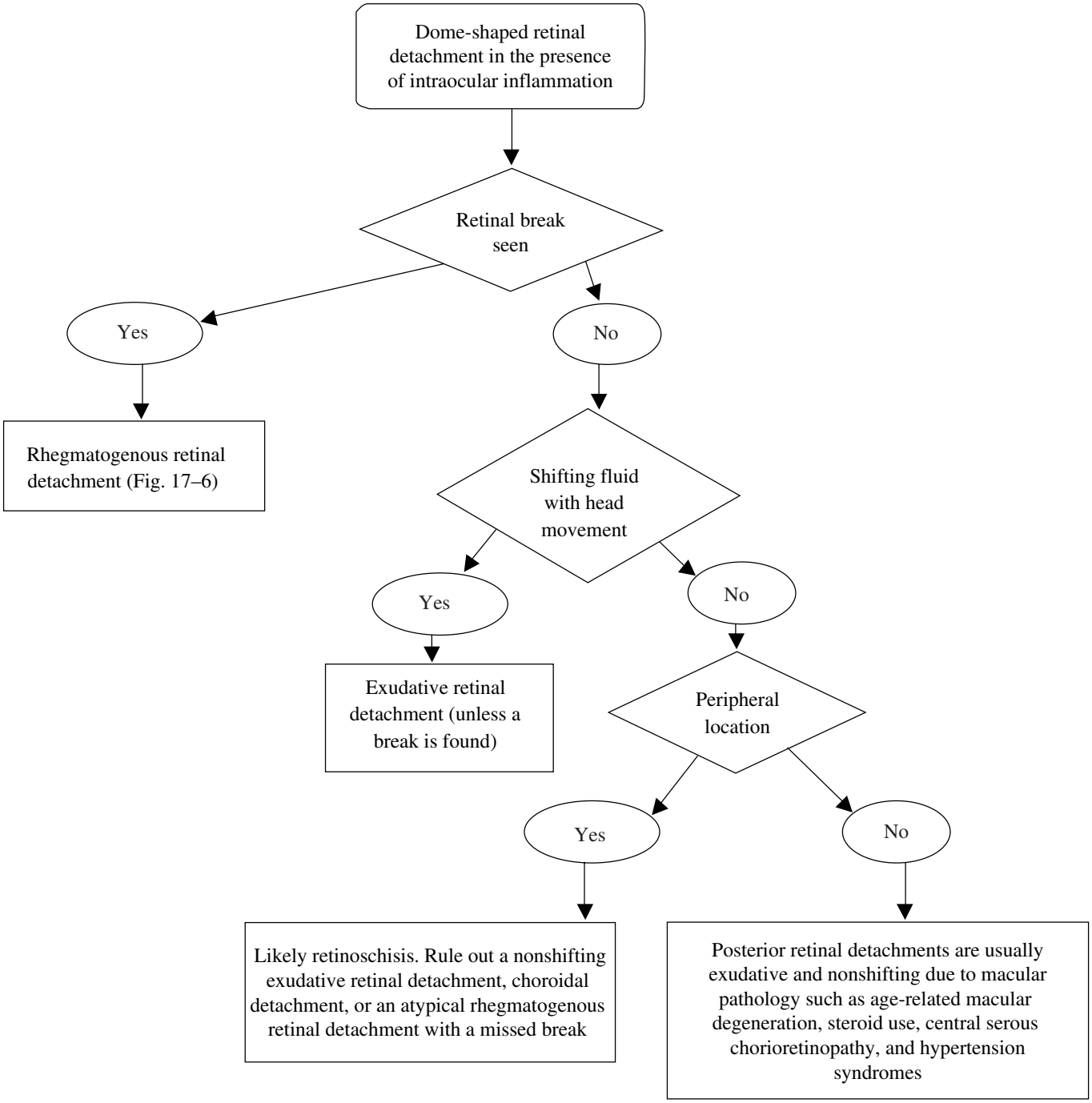


FIGURE 17–7. Evaluation of suspected exudative retinal detachment.

Retinal detachments associated with peripheral idiopathic choroidal detachments define the uveal effusion syndrome. Patients with this condition tend to be middle-aged men, typically complaining of loss of superior visual field. Bullous retinal detachments or macular detachments may occur. Other findings include dilated episcleral veins, blood in the Schlemm canal, normal intraocular pressure, and widespread retinal pigment epithelial multifocal hyperplasia ("leopard spots"). Examination of the fundus shows shifting fluid associated with the retinal and choroidal detachments. On B-scan ultrasonography, choroidal thickening, and, in some patients, short axial length are encountered.

Because this syndrome is not associated with inflammation, steroid use is inappropriate. Reports suggest that decompressing the area around the vortex vein with scleral resections leads to an effective treatment.[43]

What Congenital Anomalies and Inherited Diseases May Lead to Exudative Retinal Detachment?

Congenital anomalies that can lead to exudative retinal detachment include nanophthalmos, optic pits, and morning glory syndrome (Table 17–10). Unlike uveal effusion syndrome, which can occur in a normal-appearing eye, nanophthalmos is a disorder characterized by a small eye with an associated small cornea, thickened sclera, and shallow anterior chamber. Most pedigrees suggest autosomal-recessive inheritance.[44] Angle-closure glaucoma can develop as a result of lens size. Surgical intervention has been met with complications, including retinal and choroidal detachments. In addition, the scleral thickness has been postulated to cause secondary compression of vortex veins and diminished outflow of blood.[45] Surgically created scleral windows can diminish complications from subsequent operations, such as cataract surgery.[46]

An optic pit is a defect in the optic nerve leading to retinal detachment (Fig. 17–3D). This condition has been considered a congenital condition associated with aberrant closure of the superior end of the embryonic fissure.[47] Whether or not this is true remains unknown. Detachment of the retina in the presence of an optic pit occurs generally between the ages of 20 and 40 years. The causes of optic pit-related detachment fall into two primary theories. One school of thought is that liquid originating in the vitreous cavity enters the subretinal space.[48] The other proposed source of macular fluid with optic pits is from the subarachnoid space.[49]

Treatment of optic pits has included photocoagulation along the temporal edge of the optic nerve as well as vitrectomy and long-lasting gas injection.[50,51] The most common method of detachment repair associated with optic pits appears to be retinal detachment surgery with vitrectomy, gas tamponade, and laser photocoagulation. In morning-glory syndrome and optic-nerve coloboma formation, macular retinal detachments also appear to develop either as a result of communication with the subretinal space in the vitreous cavity[52] or with the subarachnoid space.[53] Vitreous surgery has appeared to be effective in managing this disorder for detachments presumed to be of vitreous origin, and successful management through the use of optic-nerve sheath decompression has been described for documented cases with subarachnoid-macular communication.[53]

What Hereditary Condition Leads to Exudative Retinal Detachment?

Familial exudative vitreoretinopathy (FEVR) is an autosomal-dominant disease, which usually affects both eyes asymmetrically. It has a wide range of findings and can lead to exudative retinal detachment. Children may have pendular nystagmus or strabismus. FEVR also may present with ischemia and retinal tractional membranes resembling advanced stages of retinopathy of prematurity. Affected children lack a history of prematurity or oxygen treatment. Long-term prognosis is generally poor, worse if onset is before the age of 3 years.[54]

Management

Children with strabismus need to be identified and referred appropriately. Treatment with laser treatment or cryotreatment to avascular areas may control the neovascularization. Detachments can be managed by scleral buckling[55] or vitreous surgery.[56]

What Are Surgical Causes of Exudative Retinal Detachments?

Detachments resulting from secondary inflammation can be caused by laser photocoagulation and cryotreatment. Detachments of the retina are probably the result of a breakdown of the blood–retinal barrier.

Management

Oral administration of 60 to 80 mg of prednisone per day may be helpful. It is important to distinguish this condition from CSC because steroid treatment for CSC could cause severe vision loss.

Scleral buckle surgery may lead to damage to the vortex veins from compression by the buckle, excessive cryotreatment, or surgical damage to the veins.[57] Prednisone, 60 to 100 mg per day, has been used with success for exudative detachments after buckle surgery.[58] Surgical adjustment of the buckle may be required. Ocular hypotony and serous or hemorrhagic choroidal detachment, often associated with retinal detachment, can form spontaneously after glaucoma filtration surgery.

Management of this disorder is complex and involves treating the source of the hypotony, commonly excessive filtration, or bleb leaks. Extensive choroidal detachments may be drained, but indications for treatment are controversial, and they typically resolve spontaneously. For late-onset hypotony after filtration surgery, topical steroids and cycloplegic drops have

been advocated.[59] Often team management combining retina and glaucoma specialists provides the best patient care.

What Infections Can Cause Exudative Retinal Detachments?

It has been recognized that secondary syphilis may be a cause of not only exudative retinal detachment but also uveal effusion associated with choroidal thickening.[60] Under rare circumstances, pleuritis and secondarily exudative retinal detachment can develop from herpes zoster,[61] toxoplasmosis,[62] or multiple types of bacterial infection. It is assumed the blood–retinal barrier breakdown is the cause of subretinal fluid collection.

Management

Management of all infectious causes of retinal detachment starts with treating the underlying infection. Vitreous surgery or scleral buckling techniques can be used if holes develop or tractional membranes form. Antiinflammatory medications can be used, depending on the extent of inflammation and the control of the infection with antibiotic treatment.

What Autoimmune Diseases Can Cause Exudative Retinal Detachment?

Vogt–Koyanagi–Harada syndrome (VKH) syndrome is a multiorgan disorder often found more frequently in patients with increased pigmentation, particularly of Japanese, Hispanic, African-American, or American Indian ancestry. The classic ocular findings include poliosis (whitening of the lashes), alopecia (loss of hair), perilimbal and cutaneous vitiligo (whitening), headache, decreased hearing, vertigo, and tinnitus. Fluorescein angiography typically reveals multiple pinpoint leaks through the RPE in both eyes. Similar findings may be seen with leukemia or metastatic disease. Preferential thickening of the choroid is characteristic of VKH, unlike posterior scleritis, where scleral thickening is more typically observed. This is usually visible by magnetic resonance imaging (MRI) scanning and, to a lesser extent, with B-scan ultrasound examination,[63] where VKH syndrome typically displays low internal choroidal reflectivity.[64]

If steroid therapy is initiated early, good vision can be maintained in most cases.[65] Paradoxically, it is possible to develop a retinal detachment from use of steroids in rare cases. These detachments may be associated with multiple focal RPE defects observed on fluorescein angiography.

After penetrating trauma or surgical trauma, sympathetic ophthalmia infrequently occurs in the fellow eye (the sympathetic eye) but may leave the patient bilaterally blind without aggressive therapy. The anterior form of the disease is dominated by a granulomatous anterior uveitis. The posterior form is dominated by optic-nerve inflammation as well as inflammation of the choroid and ciliary body. Up to 58% of cases have been reported to have exudative retinal detachments.[66] Like VKH syndrome, it may be associated with the finding of meningoencephalitis.[67] Other similarities between these two diseases include association with human lymphocyte antigen types and an in vitro T-cell response to uveal or retinal antigens.[68]

Both evisceration and enucleation seem safe and effective methods to decrease the risk of sympathetic ophthalmia.[69] Steroids are usually required for control of inflammation and serous retinal detachment. Cytotoxic immunosuppressive or cyclosporine therapy may be required in difficult cases.

Intermediate uveitis (peripheral uveitis or pars planitis) is an insidious chronic disease of unknown cause. Typically affecting young adults, it causes floaters, decreased vision, and macular edema. Variable degrees of periphlebitis and peripheral whitish exudate ("snow-bank" formation) can develop. Choroidal detachments and bullous retinal detachments can form.[70] Subtenon steroid injections or oral steroids are the treatments of choice. In extreme cases, peripheral cryotreatment has been considered to be of benefit.

What Finding in Vasculitis Is Typically Associated with Exudative Retinal Detachment?

Scleritis is generally the cause of exudative detachment in vasculitic disease. It is bilateral in 50% of patients, and vision ranges from 20/30 to 20/200. Retinal detachments form primarily in the posterior form of the disease: *posterior scleritis*. Conditions that have been commonly associated with posterior scleritis include polyarteritis nodosa, Wegener granulomatosis, and rheumatoid arthritis. Variable amounts of pain may be associated with scleritis, but often pain is minimal or absent.[71] Serous retinal detachment and choroidal thickening can be associated with scleritis. The choroidal thickening associated with this disorder may simulate an intraocular mass. Scleral thickening, combined with choroidal thickening observed on B-scan ultrasonography in combination with an overlying retinal detachment, is highly suggestive of this scleritis. B-scan ultrasonography often reveals an area of echolucency associated with the fluid generated by this process in the subtenon space, often referred to as a "T" sign. The fluorescein angiography usually shows pinpoint defects at the level of the RPE. Steroid

treatment, either systemic or as a retrobulbar injection, may be effective.[72] Indomethacin also has been reported to be effective.

What Are Some Vascular-Hemodynamic Causes of Exudative Retinal Detachments?

The disc scarring caused by choroidal neovascularization associated with age-related macular degeneration is well known to cause both hemorrhagic and serous retinal detachments. Extensive choroidal neovascularization caused by multiple membranes can cause massive subretinal exudation with areas of hemorrhage.[73] Detachments of the RPE also may occur. This may appear as a dark mass and must be differentiated from choroidal melanoma.

Small choroidal neovascular membranes may benefit from laser treatment as outlined by the macular photocoagulation study.[74] Small membranes in patients with poor visual acuity have the best response to treatment if the membranes are subfoveal. Macular translocation surgery and photodynamic laser therapy may be beneficial for certain membranes.[75,76]

Idiopathic polypoidal choroidal vasculopathy is a condition characterized by orange–red sacular vascular structures seen near the optic disc at the level of the choriocapillaris or slightly deeper in the choroidal tissue. Recurrent pigment epithelial detachments or subretinal hemorrhages may be observed. It is unclear whether these lesions represent a variant of macular degeneration or a separate disease process. With indocyanine green angiography, the sacular structures are outlined in the early phase of the angiogram and lose their hyperfluorescence in the late phase.

Many of these lesions will involute with light laser treatment. The long-term benefit of laser treatment is unknown.

Hypertension resulting from renal failure may lead to vascular occlusive damage to the choroid and subsequent fluid exudation and detachment.[77] Retinal detachment also may occur with renal failure in the absence of systemic hypertension. In this scenario, associated whitish subretinal exudate and RPE abnormalities may be present.[78] In the absence of hypertensive disease, the mechanism of serous retinal detachment development is unclear. Changes in osmotic properties and electrolyte balance may be a cause. It is also recognized that exudative retinal detachment can happen in renal failure as a result of systemic corticosteroid therapy.[79]

Management of systemic hypertension typically leads to the resolution of associated retinal detachment. In normotensive renal patients with retinal detachment, decreasing steroid dosage, if possible, often allows resolution of the detachment.

In the presence of severe systemic hypertension (malignant hypertension), multiple systemic complications can occur. These include neurologic, cardiac, renal, and gastrointestinal secondary complications. Many causes of systemic hypertension can lead to retinal detachment, including pregnancy-induced hypertension syndrome.[80] Detachments associated with malignant hypertension often are associated with pronounced disc edema and intraretinal and preretinal hemorrhages. The mechanism of serous exudation appears associated with choroidal ischemia and resulting breakdown of the blood–retinal barrier.[81] Fluorescein angiography in this setting typically reveals not only leakage from the retinal and choroidal vasculature but also areas of nonperfusion. Control of systemic blood pressure is the primary method of treatment.

Which Hematologic Disorders Can Lead to Exudative Retinal Detachments?

Systemic disease associated with widespread coagulopathy, such as disseminated intravascular coagulation (DIC), or damage that results in focal vascular occlusion from embolic phenomena may lead to exudative retinal detachments. Occlusion and necrosis of the arterioles and capillaries are the common findings. In DIC, widespread thrombotic events result in depletion of clotting factors and platelets. It is typically the result of sepsis, collagen vascular disease, or abruptio placentae. The results are damage to multiple organ systems, including the choroidal vasculature.[82] Management involves treatment of the underlying disorders.

Sickle cell disease has been reported to result in exudative retinal detachment, possibly from subretinal leakage caused by peripheral neovascular "sea fans." Laser treatment of the surrounding avascular retina may lead to resolution of neovascularization. Treatment of the feeder vessels also has been reported to cause resolution of retinal detachment.[83]

Do Neoplastic Diseases Lead to Exudative Retinal Detachment?

Many neoplastic diseases can cause subretinal exudation. This generally appears to be caused by blood–retinal barrier breakdown. Diagnosis is aided by the techniques of fluorescein angiography, B-scan ultrasonography, computed tomography scanning, and MRI scanning. Choroidal hemangioma is a reddish orange hamartoma that causes diffuse thickening of the choroid in Sturge–Weber syndrome. Localized solitary choroidal hemangiomas also occur and are often asymptomatic unless located in the macula. Occasionally, these tumors cause a serous retinal detachment.

RPE atrophy may be seen in cases of chronic detachment.

Photocoagulation to the surface of the hemangioma will flatten the retina in most cases.[84] Radiation also has been shown to successfully treat choroidal hemangiomas.

Bilateral diffuse melanocytic proliferation is a syndrome of diffuse uveal thickening associated with carcinoma elsewhere in the body. Loss of vision occurs from toxic damage to the retina or RPE or from bilateral exudative retinal detachment. Multiple slightly pigmented choroidal "tumors" develop throughout the fundus. Pinpoint and patchy staining on fluorescein angiography is due to RPE depigmentation from melanocytic infiltration.[85]

Benign reactive lymphoid hyperplasia (BRLH) is a disorder that primarily affects older adults. Most cases are unilateral with mononuclear cellular inflammation.[86] A number of these patients exhibit serous retinal detachment associated with decreased visual acuity. The choroid may have yellow infiltrates. Distinguishing BRLH from posterior scleritis may be extremely difficult. There may be a greater tendency to formation of a choroidal mass in scleritis than with BRLH. There is also a greater association with eye pain. Although scleral thickening may be present in BRLH, one does not see the diffuse thickening observed in uveal effusion syndrome. Yellowish lesions are unlikely to present as discrete single or multiple elevated lesions like those seen in metastatic disease. Large cell lymphoma typically presents with scattered yellowish choroidal lesions and vitreous cells. When differentiating BRLH from large cell lymphoma, monoclonal lymphocytes do not help in the diagnosis.

Biopsy of extrascleral nodules adjacent to the optic nerve may help in differentiating large cell lymphoma from BRLH. A definitive diagnosis of large cell lymphoma is notoriously difficult, however, and requires a highly skilled pathologist. It may require multiple vitrectomy specimens to obtain diagnostic confirmation. If steroid treatment is initiated in patients with BRLH, these nodules will typically disappear.[87]

Both choroidal melanoma and choroidal nevus may cause visually significant serous retinal detachment, metamorphopsia, and vision loss. Unlike a nevus, a melanoma typically exhibits leakage on fluorescein angiography. The A-scan ultrasonography (echography) reveals rapidly decaying internal echo spikes and low internal reflectivity. Choroidal melanomas may be confused with hemorrhagic choroidal detachments but usually can be distinguished by low reflectivity on A-scan ultrasonography.

Laser photocoagulation lightly applied to the surface of the nevus will promote subretinal fluid reabsorption. Laser treatment of a choroidal melanoma may promote fluid reabsorption, but heavy treatment associated with tumor therapy initially may result in increased serous retinal detachment, typically resolving over time. Some treatments for melanoma include proton-beam treatment, plaque radiation, transpupillary thermotherapy, or enucleation.

A macular detachment resembling CSC may be seen in cases of leukemia with uveal infiltration. Fluorescein angiography of leukemic infiltration typically reveals pinpoint areas of leakage much like Harada disease. Infiltration may form a tumor-like mass. RPE clumping also may be seen in response to the infiltration of the choroid.[88]

Tractional Retinal Detachment

What Are the Symptoms of Tractional Retinal Detachments?

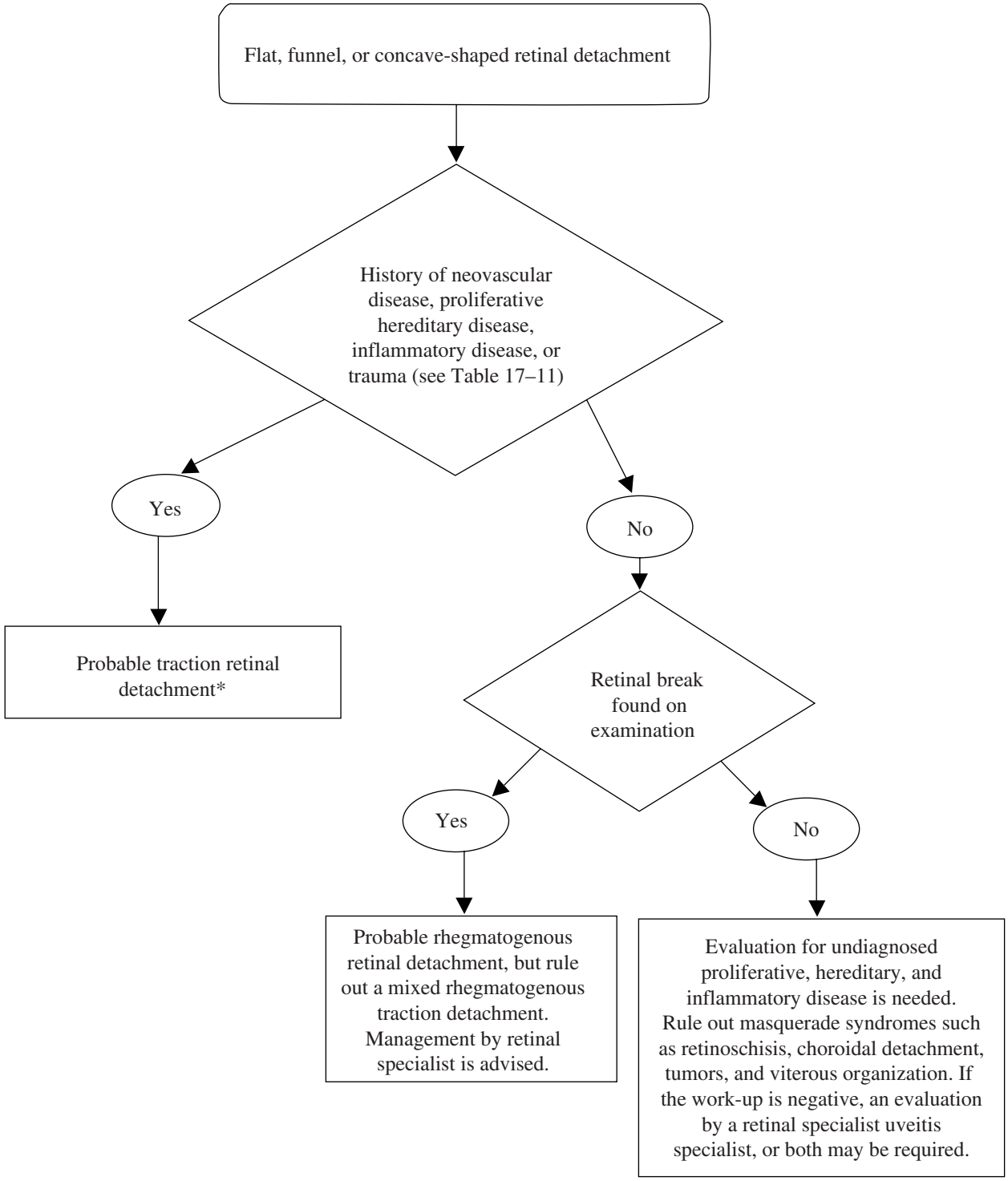
It is common for patients who develop tractional retinal detachments to have associated decreased visual acuity and visual field loss. If the tractional detachment develops in an adult, such as seen with diabetic disease, these patients may describe floaters, metamorphopsia, and photopsias, and they may suffer severe vision loss.

What Are the Signs of Traction Retinal Detachments?

It is not uncommon for the retina to take on the appearance of a concave posterior detachment in diabetic proliferative disease. Other forms of tractional retinal detachments in adults may occur in the posterior pole or in the periphery. Common causes would be penetrating ocular injury and postsurgical PVR. These can display either posterior fundus or anterior fundus tractional disease leading to detachment. Sickle cell retinopathy and venous occlusive disease also may cause tractional elevation of the retina in adults.

These detachments rarely extend anteriorly beyond the ora serrata. Exceptions to this would be in diseases associated with primary anterior findings, including persistent fetal vasculature (persistent hyperplastic primary vitreous), retinopathy of prematurity, or anterior proliferative vitreoretinopathy.

Traction detachments are typically stationary on kinetic ultrasound testing. The whitish tractional membranes are often easily seen with indirect ophthalmoscopy and are distinctive in appearance from exudative and primary rhegmatogenous retinal detachments (Fig. 17–2). A method for evaluating tractional retinal detachments is outlined in Figure 17–8.



*A surgeon experienced in binocular indirect ophthalmoscopy must rule out a rhegmatogenous retinal detachment

FIGURE 17–8. Evaluation of suspected traction retinal detachment.

How Do Tractional Retinal Detachments Form?

The basic common pathogenic mechanism in traction detachments involves development of tractional membranes. These exert circumferential forces (like a tightening belt), anterior–posterior forces (pulling the posterior retina toward the anterior segment), tangential retinal forces (traction parallel to the retinal surface), and subretinal forces (causing tenting of the retina or a "napkin-ring" tightening around the retina from underneath). Most of these detachments can be managed with vitreous surgery with the peeling of preretinal membranes or the cutting of tractional bands that elevate the retina. Placement of a scleral buckle on an eye may both relieve traction and also decrease the risk of subsequent redetachment. The scleral buckle is commonly used in the setting of PVR or trauma to decrease the chance of widespread retinal detachment forming from a combined rhegmatogenous and tractional detachment.

How Do Specific Diseases Cause Tractional Retinal Detachment?

When a patient develops proliferative diabetic retinopathy and associated retinal detachment, vitreous traction on the retina typically develops along the major arcade blood vessels at sites of recent or regressing neovascularization (Fig. 17–2). Elevation of these blood vessels into the vitreous is a common finding that leads to a taut posterior vitreous face overlying the macula associated with elevation of the retina along the vascular arcades and possible elevation of the macula. The posterior vitreous face may be detached in a taut membranous-like structure, which extends from the arcade vessels to the vitreous base. There are many variations in the presentation of diabetic traction detachments, based on the location of the pathology and the location of previous laser photocoagulation. A large group of diseases may cause traction retinal detachment, and some of these are listed in Table 17–11.

Detachments resulting from nondiabetic neovascular disease, such as sickle cell disease, sarcoidosis, Eales disease, and vein occlusions may have variable presentations. They are commonly associated with tractional forces that develop initially in the peripheral fundus because of the development of peripheral neovascularization. Retinopathy of prematurity (ROP) less frequently develops into total retinal detachments in developed countries because of early intervention with laser photocoagulation or cryotherapy. When detachments occur in these conditions, they may be partial or total detachments, often with initial traction occurring in the midperiphery, oriented in an anterior posterior direction. The peripheral retina is commonly thrown into anterior loops as the detachment progresses especially with ROP. Any of a variety of funnel-type configurations may ensue in extreme cases. It is also possible to develop subretinal traction in the forms of bands or plaques in ROP.

TABLE 17–11. What Conditions Can Cause Tractional Retinal Detachment?

Neovascular disease
Proliferative diabetic retinopathy
Retinopathy of prematurity
Sarcoidosis
Sickle cell retinopathy
Vein occlusion
Familial exudative vitreoretinopathy
Eales disease
Hereditary disease
Norrie disease
Incontinentia pigmenti
Familial exudative vitreoretinopathy
Von Hipple–Lindau disease
Inflammatory disease
Toxocariasis
Intermediate uveitis
Proliferative vitreoretinopathy
Pars planitis
Persistent fetal vasculature (persistent hyperplastic primary vitreous)
Cytomegalovirus retinitis
Trauma
Proliferative vitreoretinopathy
Penetrating ocular injury
Previous surgery

Hereditary Disease Associated with Traction Retinal Detachment

Both Norrie disease and incontinentia pigmenti patients may develop traction detachments secondary to peripheral neovascularization, similar to those seen with retinopathy of prematurity. Von Hipple syndrome may lead to exudation associated with localized tractional components that may detach the retina in that area.

Persistent Fetal Vasculature (Persistent Hyperplastic Primary Vitreous)

This disorder may lead to large retinal detachments or retinal folds. It is a result of persistence of the hyaloid vascular system and may lead to microophthalmia and cataracts. The vasculature may grow into the lens.

Inflammatory Conditions

Toxocara canis is an organism associated with toxocariasis that can cause marked inflammation on the death

of the organism. A large retinal fold emanating from the optic disc to the point of a peripheral granuloma is a common finding. Tractional bands associated with this disease may subsequently pull the retina off in a traction detachment. Retinal folds may be seen with intermediate uveitis and may lead to tractional detachment.

Trauma

Penetrating injury may lead to a tractional detachment. This is particularly likely in the context of penetrating injury and vitreous hemorrhage. If injury is blunt and nonpenetrating, the ensuing vitreous organization and tractional membrane formation are usually the mechanisms of retinal detachment.

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SECTION IV

The Inflamed Eye and Retinal Disease

18

Infectious Uveitis

ALI DJALILIAN AND ERIC SUHLER

Toxoplasmosis

What Is the Life Cycle of *Toxoplasma gondii*?

Toxoplasma gondii is an obligate intracellular protozoan. The parasite is found all over the world. Members of the cat family are the definite host. The oocysts are found uniquely in the intestinal mucosa of cats.[1] The oocysts are excreted and released into the environment. Humans become infected directly by ingesting oocysts or indirectly by ingesting tissue cysts present in undercooked meat from infected animals (pork, lamb, or chicken and rarely beef). The cysts release tachyzoites, which are the active infectious form that can travel to the muscle and neural tissue, including the retina. The tachyzoites also may pass through the placenta to the fetus. The latent form of *T. gondii* is the tissue cyst (bradyzoite), which contains hundreds of thousands of organisms. The organism can remain dormant in the tissue cysts for many years, and its release is responsible for the recurrent nature of the ocular disease.[1]

What Is the Epidemiology of Toxoplasmosis?

Toxoplasmosis is very common. At least 50% of the adult population has been exposed to *Toxoplasma* as evident by a positive antibody titer.[2] The incidence of a positive titer increases with age. In the United States, about 2 to 6 per 1000 women acquire the infection during pregnancy, with about 40% risk of transmitting the infection to the fetus. Previously, most cases of ocular toxoplasmosis were felt to be due to congenital infection; however, there is evidence, particularly in Brazil, that acquired toxoplasmosis accounts for most of the cases of ocular toxoplasmosis.[3] Overall, ocular toxoplasmosis accounts for nearly one third of all cases of posterior uveitis.

What Are the Manifestations of Acquired Toxoplasmosis?

Acquired toxoplasmosis in the non-immune-compromised adult is frequently asymptomatic. The most common manifestation is lymphadenopathy (90%) followed by fever, malaise, and sore throat. More severe disease can occur, affecting muscle, skin, brain, heart, and kidney. In the immunocompromised host, in particular acquired immunodeficiency syndrome (AIDS) patients, the disease can be a fulminant central nervous system disease that rapidly leads to death.

What Are the Manifestations of Congenital Toxoplasmosis?

About 1 per 1000 newborns becomes infected.[2] The earlier the disease is acquired in pregnancy, the greater the risk to the fetus. In neonates, the disease occurs in a clinical spectrum ranging from no signs or symptoms to bilateral retinochoroiditis, seizures, and intracranial calcifications. The presence of immunoglobulin M (IgM) antibodies against toxoplasmosis confirms the diagnosis. In many of the asymptomatic cases, ocular lesions are not present at birth and develop later.

What Are the Typical Signs and Symptoms of Ocular Toxoplasmosis?

Ocular toxoplasmosis is a unilateral disease in most cases. Most symptomatic cases are due to reactivation of the disease due to release of tachyzoites from dormant tissue cysts in the retina. The characteristic finding is a cream-colored retinal lesion (satellite lesion) adjacent to an old atrophic chorioretinal scar (Fig. 18–1). Cells are found in the vitreous, particularly overlying the active lesion. Adjacent to the active retinitis one may see hemorrhage and sheathing of the

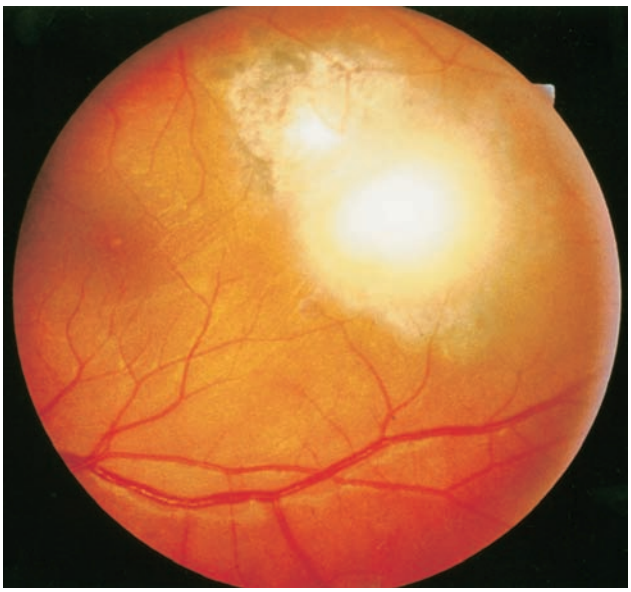

FIGURE 18–1. An old pigmented scar with an adjacent more active lesion in a patient with ocular toxoplasmosis.

retinal blood vessels. Anterior chamber cells can be seen and may appear as granulomatous or, less commonly, as nongranulomatous uveitis. The intraocular pressure may become elevated during active inflammation.

In cases where the vitreous haze and cellular reaction are profound, patients become symptomatic. The most common symptoms are blurriness and floaters. Rarely, if the lesions involve the macula, optic nerve, or the vascular arcades, the patient can experience profound loss of vision.

How Is Ocular Toxoplasmosis Diagnosed?

The diagnosis of ocular toxoplasmosis is primarily clinical and is based on the typical ocular features. Serologic evidence of *Toxoplasma* infection is important to document exposure to the organism. The presence of IgG antibody at any titer even in undiluted serum (1:1) is considered positive. IgM antibodies suggest recent infection. A negative titer is evidence against the diagnosis and should alert the physician to other diagnoses. The type of serologic testing that is most reliable is still debatable, although the enzyme-linked immunosorbent assay (ELISA) is recommended by many. The Sabin-Feldman dye test requires live organisms and is used less frequently. It is important to realize that a positive antibody titer, which may be seen in nearly half of all adults, only indicates previous exposure and should be interpreted based on other clinical findings. Serologic examination of the aqueous or detection of the *Toxoplasma* DNA by polymerase chain reaction (PCR) also has been used to determine specifically ocular infection in patients with positive serum antibodies.

What Is the Differential Diagnosis of Ocular Toxoplasmosis?

The differential diagnosis includes other causes of infectious retinitis, such as tuberculosis, toxocara, syphilis, cytomegalovirus, *Candida* organisms, and herpes simplex. Other causes of uveitis, such as sarcoidosis, also may manifest in a similar fashion. All patients with suspected ocular toxoplasmosis should also have their human immunodeficiency virus (HIV) status determined. If the patient is HIV positive, an evaluation of the central nervous system is mandatory.

When Should Ocular Toxoplasmosis Be Treated?

In immune-competent patients, the disease is self-limited. The natural history of a reactivated ocular lesion is resolution by 6 weeks to 6 months. Peripheral lesions without significant inflammation are generally observed and not treated. Treatment is recommended in all the following situations (Fig. 18–2): (1) there is a lesion within the temporal arcade, (2) a lesion is abutting the optic nerve or threatening a large retinal vessel, (3) a lesion has induced a large degree of hemorrhage, or (4) a lesion has induced enough vitreal inflammation to reduce the vision to below 20/40 (or a two-line drop from baseline).

How Is Ocular Toxoplasmosis Treated?

Several regimens can be used to treat ocular toxoplasmosis. The most common drug combination is sulfadiazine (1 g orally four times daily), pyrimethamine (50-mg load, then 25 mg orally once or twice a day) given concomitantly with folinic acid (leucovorin) 5 mg orally three times a week. A baseline blood count and platelet count should be obtained and repeated on a weekly basis while the patient receives pyrimethamine. Prednisone is judiciously added at a dose of 20 to 40 mg per day, beginning 12 to 24 hours after initiating specific antimicrobial therapy. Corticosteroids never are prescribed alone and never are administered by periocular injection. Topical corticosteroids and cycloplegics are used adjunctively in patients with anterior chamber reaction.

Alternative regimens include clindamycin (150 to 300 mg orally three to four times daily) combined with sulfasalazine. Psuedomembranous colitis is a concern with clindamycin use. Trimethoprim-sulfamethoxazole (one double-strength twice daily) also has been used with success. Likewise, azithromycin (250 mg daily) has been used successfully. Most recently, atovaquone (Mepron) has been used at a dose

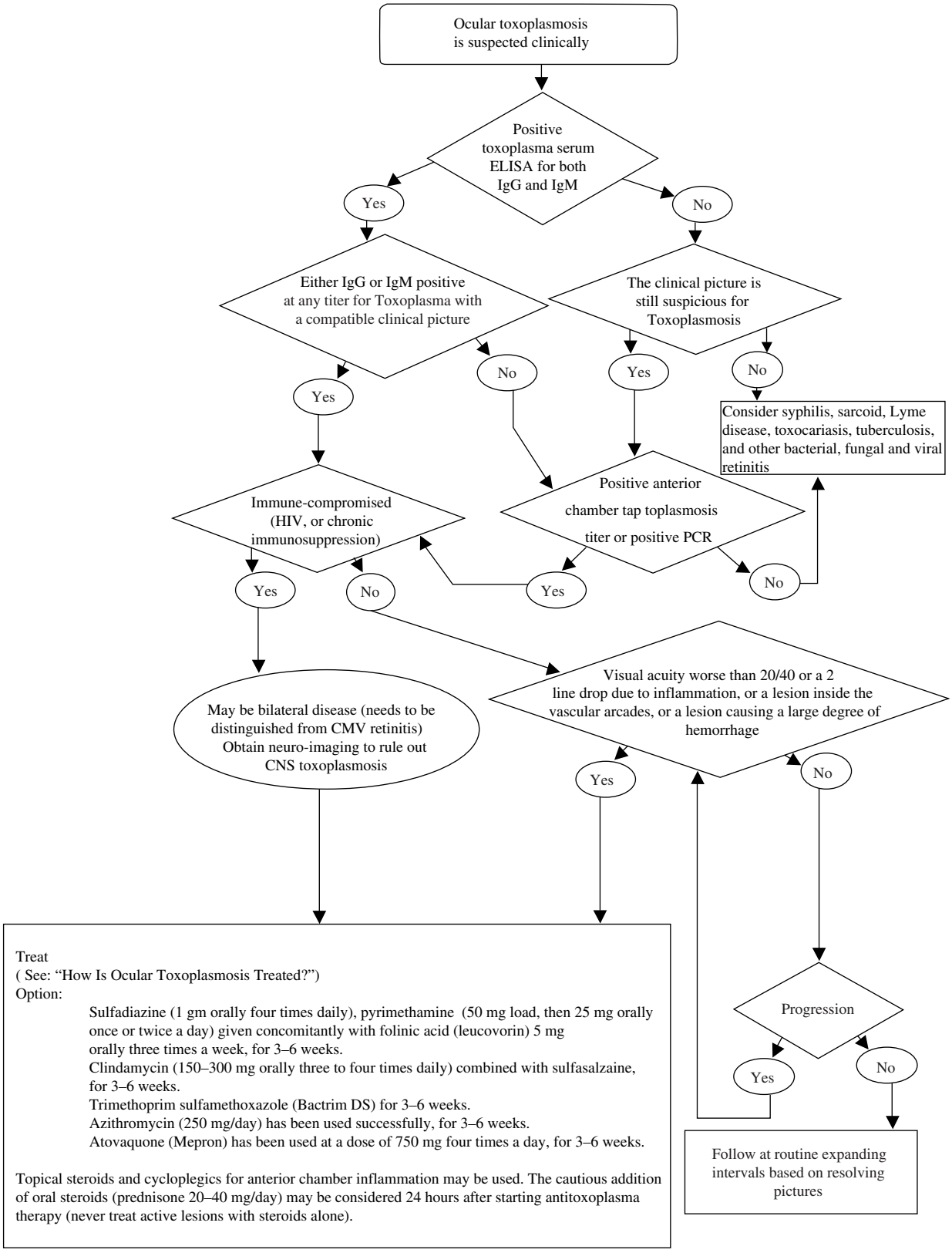

FIGURE 18–2. Evaluation and management of suspected toxoplasmosis. ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; IgM, immunoglobulin M; PCR, polymerase chain reaction; CMV, cytomegalovirus; CNS, central nervous system.

of 750 mg four times a day. In all regimens, systemic treatment typically is given for 3 to 6 weeks.

Why Does Toxoplasmosis Recur?

It is important to realize that all these regimens are targeting the tachyzoites (the active infectious form) and generally do not affect the tissue cyst. Although atovaquone has proven to be cysticidal in vitro, it remains to be seen clinically whether it can eradicate the organism. Therefore, toxoplasmosis can recur even after treatment because the tissue cysts generally survive. In patients with multiple recurrences, long-term prophylactic therapy with the preceding agents may reduce the likelihood of reactivation.

Endophthalmitis

What Are the Various Types of Infectious Endophthalmitis?

Infectious endophthalmitis can be divided into *exogenous* and *endogenous* types. In exogenous infections, the organism enters the eye from the external environment. The subtypes of exogenous endophthalmitis include postoperative, traumatic, and bleb-associated. In endogenous endophthalmitis, the organism reaches the eye through the vascular system.

What Are the Features of Acute Postoperative Endophthalmitis?

Acute postoperative endophthalmitis is primarily a bacterial disease. The sources of bacteria are usually the eyelids and conjunctiva. The incidence is 0.1 to 0.4%.[4,5] Wound problems appear to be an important contributing factor. Most cases occur within 3 to 7 days after surgery but may occur up to two weeks. Pain, decreased vision, conjunctival hyperemia, anterior uveitis with fibrin, hypopyon, and vitreitis are the characteristic features of acute bacterial endophthalmitis. The most common organisms isolated are *Staphylococcus epidermidis,* followed by *S. aureus*, *Streptococcus* species, and gram-negative organisms, such as *Serratia marcescens*, and *Pseudomonas* species.

How Is Acute Postoperative Endophthalmitis Treated?

The treatment of acute postoperative endophthalmitis was the subject of the Endophthalmitis Vitrectomy Study (see Chapter 22's Fig. 22–2).[6] This study found that cases in which the visual acuity at presentation is better than light perception could be managed with vitreous tap and injection of intravitreal antibiotics. On the other hand, in cases where the visual acuity is light perception only, the visual outcome was better if immediate pars plana vitrectomy and injection of antibiotics were performed. The combination of vancomycin and ceftazidime is the most common choice of antibiotics for intravitreal injection. Whereas systemic corticosteroids may be useful for reducing intraocular inflammation, systemic antibiotics were not shown to be beneficial. The role of intravitreal corticosteroid injection remains controversial.

What Are the Features of Chronic Postoperative Endophthalmitis?

Chronic postoperative endophthalmitis begins more than 2 weeks after surgery. It typically presents as a chronic uveitis that can be partially suppressed with topical corticosteroids. The visual acuity is usually good. One of the most common organisms responsible for chronic postoperative endophthalmitis is *Propionibacterium acnes*.[7] The typical patient with *P. acnes* presents with chronic low-grade anterior segment inflammation that starts from 2 months to 2 years after surgery. White plaques composed of bacteria are often seen between the intraocular lens and the posterior capsule. *S. epidermidis*, which typically presents 6 weeks after surgery, can also cause a chronic postoperative endophthalmitis. Likewise, fungal endophthalmitis, most commonly due to *Candida* species, may present at 3 months after surgery.

How Is Chronic Postoperative Endophthalmitis Diagnosed?

Besides the clinical features, the diagnosis is primarily based on culture data. In case *of P. acnes*, it is important to inform the microbiology laboratory not to discard the cultures after the usual 3 to 4 days. Because the organism is slow growing, cultures should be maintained for 14 days.

How Is Chronic Postoperative Endophthalmitis Treated?

Chronic postoperative endophthalmitis caused by *S. epidermidis* can be treated successfully with intravitreal injection of vancomycin. Therapy for *P. acnes* endophthalmitis usually involves a combination of vitrectomy, posterior capsulectomy, and intravitreal vancomycin. Although the intraocular lens does not need to be removed at the time of initial therapy, recurrent cases are managed with repeat intravitreal antibiotics and removal of residual posterior capsule and intraocular lens. The treatment for fungal endophthalmitis is discussed later herein.

What Are the Characteristics of Fungal Infections?

Fungal infections can be exogenous (postsurgical or posttraumatic) or endogenous. Fungal endophthalmi-

TABLE 18–1. Characteristics of Fungal Infections (Postsurgical and Endogenous)

Organism	*Risk Factor*	*Ocular Features*
Candida sp.	IV drug use, chronic IV therapy, surgery	Yellow–white chorioretinal lesions, vitreous fluff balls
Aspergillus sp.	IV drug use, immunosuppression, surgery	Yellow–white chorioretinal lesions, vitreous fluff balls
Cryptococcus neoformans	Immunocompromised, lymphoma	Yellow–white chorioretinal lesions, often with meningitis
Blastomyces dermatitidis	Systemic blastomycosis	Panuveitis
Coccidioides immitis	Southwest United States	Punched out choroidal lesions, yellow chorioretinal lesions

IV, intravenous.

Modified from Nussenblatt RB, Whitcup SM, Palestine AG. *Uveitis: Fundamentals and Clinical Practice*, 2nd ed. St. Louis: Mosby–Year Book; 1996, with permission.

tis usually presents as a chronic pan-uveitis. Fluffy deep yellow–white retinal or choroidal lesions are frequently present, and the vitreous often contains "fluff balls." The patient may not be symptomatic for days or even months until he or she develops blurred vision or floaters. Later in the course, redness, pain, hypopyon and dense vitreitis may occur. *Candida* species are the most common organisms responsible for endogenous (as well as exogenous) fungal endophthalmitis. *Candida* endophthalmitis usually occurs in chronically ill patients with an indwelling catheter. It is also a frequent complication of intravenous drug use. *Aspergillus* species are the second most common cause of endogenous fungal endophthalmitis. Table 18–1 summarizes the features of the more common organisms that can lead to fungal endophthalmitis.

How Is Fungal Endophthalmitis Treated?

For exogenous infections that are limited to the eye, vitrectomy combined with intravitreal amphotericin B is the mainstay of therapy. Oral fluconazole or ketoconazole also may be beneficial. Endogenous endophthalmitis requires systemic amphotericin B along with intravitreal amphotericin B.

What Are the Organisms Associated with Posttraumatic Endophthalmitis?

Posttraumatic endophthalmitis can develop after penetrating injuries. The most common organisms are *S. epidermidis*, *Bacillus cereus*, *S. aureus*, and fungi. Endophthalmitis due to *B. cereus* characteristically has a very fulminant course with rapid progression.

What Are the Characteristics of Bleb-Associated Endophthalmitis?

Infection after filtering surgery is one of the morbidities associated with this procedure. The use of antifibrotic agents, the presence of bleb leaks, and the inferior location of the bleb are among the main risk factors for developing endophthalmitis. Typically, these infections occur late and are preceded by conjunctival injection and discharge. The most common organisms are *Streptococcus* species (including pneumococcus) and *Haemophilus influenza*. Treatment includes vitreous cultures, intravitreal antibiotics, and vitrectomy for the more severe cases.

Cytomegalovirus Retinitis

What Is the Epidemiology of Cytomegalovirus Retinitis?

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes class that causes an asymptomatic or mononucleosis-like syndrome in healthy adults. More than half of all adults have evidence of previous CMV infection. CMV infection of the retina occurs as an opportunistic infection only in immunosuppressed persons or in infants with congenital infection. In the past, chemotherapy and organ transplantation, particularly of the kidneys, were the most common causes of CMV retinitis. In the current era, however, AIDS has led to a significant rise in the number of cases of CMV retinitis. Most recently, the number of new cases of CMV retinitis has declined significantly with the introduction of highly active antiretroviral therapy (HAART).

How Common Is Cytomegalovirus Retinitis in the AIDS Population?

In AIDS patients, CMV retinitis is the most common ocular complication. It probably occurs clinically in 15 to 20% of these patients at some time.[8] It typically occurs when the CD4 count reaches below 50 cells per microliter, and it is rarely seen if the CD4 is greater than 100 cells per microliter. The introduction of potent antiretrovirals has led to a dramatic decline in the incidence of CMV retinitis; nonetheless, new cases of CMV are still emerging in patients for whom HAART fails.

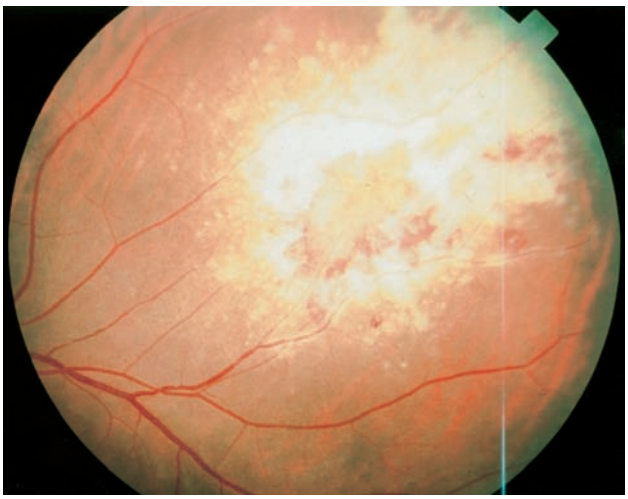

FIGURE 18–3. Perivascular retinal infiltrates with scattered hemorrhages in a typical case of cytomegalovirus retinitis.

What Is HAART?

A combination of several antiretroviral agents, HAART has been highly effective in reducing the number of HIV particles in the bloodstream (as measured by the viral load) and more importantly in increasing the CD4-positive T-lymphocyte count. The typical regimen involves one protease inhibitor and two nucleoside reverse transcriptase inhibitors.

What Is the Typical Presentation of CMV Retinitis?

Cytomegalovirus retinitis begins as small white retinal infiltrates that if seen early may resemble a cotton-wool spot. Two types of clinical appearance may be seen.[1] The typical presentation is a perivascular fluffy white lesion with many scattered hemorrhages. The other presentation is a granular-appearing lesion that has few associated hemorrhages and often has a central area of clearing with atrophic retina and stippled retinal pigment epithelium (Fig. 18–3). The latter presentation is seen more typically in the peripheral retina. Occasionally, it may present with periphlebitis (frosted-branch angiitis). There is usually a low-grade vitreitis associated with CMV retinitis, and there may be fine anterior-chamber keratic precipitates. Vision is normal unless the optic nerve or fovea is involved. CMV retinitis typically presents in one eye first, with the other eye becoming involved several months later.

How Does Cytomegalovirus Retinitis Progress?

Cytomegalovirus retinitis progresses in two ways. New lesions may form that are not physically near an old lesion, probably by hematogenous spread. Second, and most common, an old lesion spreads at its borders to involve a new, previously uninfected retina. The rate of progression is approximately 250 μ per week. In assessing the progression of CMV retinitis, it is important to pay attention to the border of the lesion and look for advancement or new lesions. Clearing at the center of the lesion should not be interpreted as improvement because the whiteness will gradually decrease as the retina becomes atrophic.

Visual loss from CMV retinitis may occur in several ways. Most commonly, the infected retina develops an absolute scotoma due to retinal necrosis. As the macula is involved, the central vision is lost. In some patients, paramacular CMV will produce macular edema, which is a reversible cause of visual loss if it can be treated before the active virus progresses through the fovea. The optic disc can also be involved with severe loss of vision. Last, the retina can develop a rhegmatogenous retinal detachment because there is vitreous traction on the thin, atrophic retina.

How Often Do Patients with Cytomegalovirus Retinitis Develop a Retinal Detachment, and How Is It Treated?

Retinal detachment develops in about 20% of patients with retinitis; 50% of these patients develop detachment in the second eye if there is retinitis. The greater the degree of peripheral retinal involvement, the greater the risk of retinal detachment. The mechanism of detachment in CMV retinitis is vitreous traction on the thinned, atrophic retina. Multiple retinal breaks are usually present, and large relatively posterior breaks can be seen.

The surgical treatment can be challenging. Scleral buckling is appropriate when the breaks are located near the vitreous base. In CMV retinitis, however, these breaks tend to be more posterior. A more effective approach is vitrectomy, endolaser, and the use of a long-lasting retinal tamponade, namely, silicone oil. Silicone oil significantly reduces the risk of redetachment. The silicone oil typically is left in place as long as the patient is at risk for CMV.

Laser also has been used to demarcate areas of retinitis and thereby prevent detachment. This approach is not uniformly successful, and the retinitis can progress through the laser burns.

What Are the Drug Treatments Available for Treating Cytomegalovirus Retinitis?

The most important and effective treatment for the long-term control of CMV retinitis is appropriate antiretroviral therapy, which can increase the number of circulating CD4 cells and allow the patient's own immune system to contain CMV. For the acute treatment of CMV retinitis, however, numerous of medications are available.

Ganciclovir

Ganciclovir was the first drug approved for the treatment of CMV. Induction therapy involves 5 mg per kilogram of body weight given intravenously twice a day for 14 days. This typically halts the progression and results in the development of a less active lesion in more than 90% of patients. Because the drug is virostatic, recurrences are common unless the underlying immunosuppression can be altered. Maintenance therapy is given at a dose of 5 mg per kilogram of body weight per day, 7 days per week, to reduce the chance of relapse. The main toxicity of ganciclovir therapy is neutropenia. Neutrophil counts typically decrease during the second week of therapy or during maintenance therapy. Neutropenia was a major contraindication to continued ganciclovir therapy until the development of granulocyte colony-stimulating factor (GCSF; Neupogen). Injection of Neupogen one to three times per week helps to increase the neutrophil count and function.

Oral ganciclovir, which has a low bioavailability, can be used for maintenance therapy as an alternative to intravenous ganciclovir. The typical dose is 3 to 6 g per day. The main advantage of oral administration is that it eliminates the need for long-term intravenous catheter and related complications.

Alternatively, ganciclovir may be injected directly into the vitreous at a dose of 2 mg in 0.1 mL. Therapeutic levels are maintained for 62 hours; thus, two injections per week must be given. This will result in long-term remission. This approach is useful when systemic therapy is not possible because of neutropenia. With repeated injections, the risk of vitreal hemorrhage, infection, and retinal detachment increases. In addition, intravitreal therapy does not treat possible systemic infections with CMV, such as CMV colitis. A novel approach to intravitreal therapy is the use of the ganciclovir implant (VITRASERT) (Fig. 18–4). This is a slow-release device that lasts about 8 months. It is surgically implanted through the pars plana. It provides the most effective therapy for the control of local disease; however, it does not prevent CMV retinitis in the fellow eye or prevent extraocular CMV infections. Martin and colleagues reported that patients treated with an implant alone are also at a significantly greater risk for developing Kaposi sarcoma compared with those who additionally received oral or systemic ganciclovir at maintenance doses.[9] Therefore, patients not receiving potent antiretrovirals should simultaneously receive systemic ganciclovir (or valganciclovir) in addition to an implant.

Valganciclovir

An oral prodrug of ganciclovir, valganciclovir, was approved for use as both induction and maintenance therapy. Oral valganciclovir is rapidly absorbed and hydrolyzed to ganciclovir. The oral bioavailability of ganciclovir after oral valganciclovir administration is high. Oral valganciclovir 900 mg provides a daily exposure of ganciclovir comparable to that of intravenous ganciclovir 5 mg/kg. A single, randomized, nonblinded study indicated that oral valganciclovir (900 mg twice daily for 3 weeks, then 900 mg once daily) and intravenous ganciclovir (5 mg per kilogram of body weight twice daily for 3 weeks, then 5 mg/kg once daily) were equally effective in the treatment of newly diagnosed CMV retinitis in 160 patients with AIDS.[10] Valganciclovir appears to have a similar tolerability profile to intravenous ganciclovir during in-

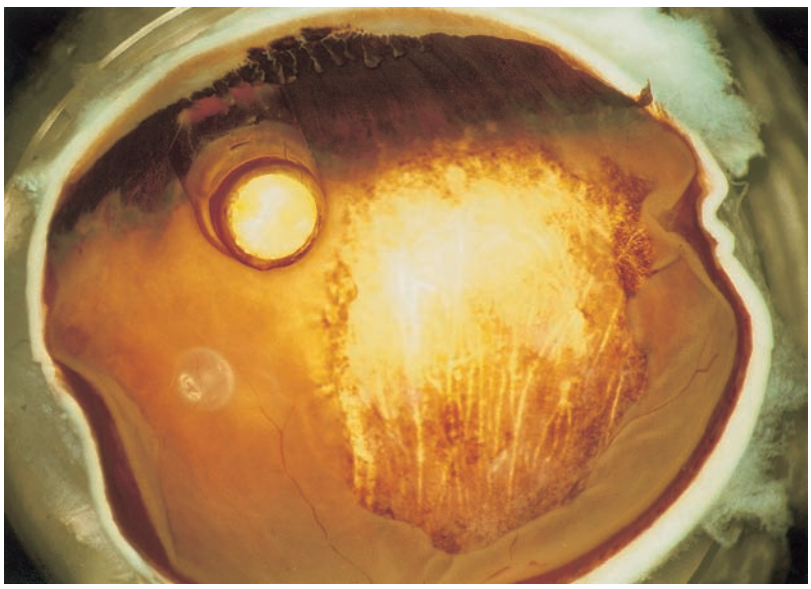

FIGURE 18–4. An autopsy eye of a patient with a history of cytomegalovirus retinitis and a ganciclovir implant in the pars plana.

duction therapy in patients with AIDS and newly diagnosed CMV retinitis.

Foscarnet

Foscarnet inhibits the replication of CMV in a slightly different manner from ganciclovir. It is administered intravenously with a 2-week induction dosage of 90 mg per kilogram of body weight twice daily, followed by 90 to 120 mg per kilogram of body weight daily. Nephrotoxicity is the main side effect. Overall, it appears to be equally effective as ganciclovir for the treatment of CMV retinitis. The median time to progression is about 8 weeks for both drugs; however, foscarnet may offer a survival advantage for patients with normal renal function. Intravitreal injection of foscarnet (2.4 mg/0.1 mL) also can be used alone or in combination with intravitreal ganciclovir for patients with recurrent or resistant cases of CMV retinitis.

Cidofovir

Cidofovir is a nucleotide analog indicated for the treatment of CMV retinitis in patients with AIDS. The recommended induction dose is 5 mg per kilogram of body weight once a week for 2 consecutive weeks, followed by 5 mg per kilogram every 2 weeks as maintenance therapy. The main side effect is nephrotoxicity; thus, all patients require regular monitoring of the serum creatinine and urine protein levels. Systemic administration of cidofovir can lead to hypotony and uveitis; thus, periodic eye examination is recommended. Intravitreal injection of cidofovir is also effective, but it is generally not recommended given the risk of uveitis and severe hypotony.

Fomivirsen

Fomivirsen is an antisense drug that is given by intravitreal injection. Although it has been approved by the U.S. Food and Drug Administration (FDA), it is used infrequently because of the adverse effects that include uveitis and elevated intraocular pressure.

When Can Anti-cytomegalovirus Therapy Be Discontinued?

Previously, all AIDS patients with CMV retinitis required long-term and frequently indefinite therapy to prevent relapses. With the introduction of potent antiretroviral therapy, however, many patients will have enough immune recovery to prevent future recurrence of CMV retinitis. Therefore, it is now recommended that anti-CMV therapy be safely discontinued in patients with sustained elevation in CD4+ T-cell count (greater than 100 to 150 cells/μL for 2 to 3 months) with an undetectable HIV viral load in response to HAART.

What Is Immune-Recovery Uveitis, and How Is It Treated?

Immune-recovery uveitis is an intraocular inflammatory reaction that occurs in HIV patients with previous CMV retinitis whose immune function has improved on HAART. It is marked by prominent inflammation in the anterior chamber and the vitreous frequently in association with macular edema. Clinically, there is no active retinitis, and the previous CMV lesions remain inactive (Fig. 18–5). Immune-recovery uveitis is thought to be due to an inflammatory response to the CMV antigens still present in the eye.[11] Treatment is indicated when the vision is reduced secondary to macular edema. Periocular steroid injections have been used with variable success to treat the macular edema.

Acute Retinal Necrosis

What Are the Clinical Features of Acute Retinal Necrosis?

The typical patient with acute retinal necrosis (ARN) is immunocompetent who presents with floaters and decreased vision. The earliest retinal lesions are small patchy, white-yellow areas in the midperiphery that tend to enlarge, increase in number, and coalesce over time. The American Uveitis Society has published a set of diagnostic criteria that must be met for the diagnosis of ARN syndrome[12]: (1) one or more foci of retinal necrosis with discrete borders in peripheral retina (Fig. 18–6), (2) rapid progression of disease if antiviral therapy has not been given, (3) circumferential spread of disease, (4) evidence of occlusive vasculopathy with arteriolar involvement, and (5) a prominent inflammatory reaction in the vitreous and anterior chamber. Optic neuropathy, scleritis, and pain support the diagnosis but are not required. Most cases begin with unilateral disease; the second eye becomes involved in almost one third of the cases, usually within 1 to 6 weeks. The natural course of the disease is for the acute inflammation to subside within 2 to 3 months, following which the retina begins to develop large tears in thinned and atrophic areas. Retinal detachments (which develop in up to 86% of the patients) are one of the main causes of severe visual loss in this disease. A differential diagnosis for ARN can be seen in Table 18–2.

What Is the Etiology of Acute Retinal Necrosis?

Whereas most cases of ARN are thought to be caused by the herpes zoster virus, herpes simplex types 1 and 2 also have been implicated as a cause of the disease.[13] Holland and colleagues[14] demonstrated certain human leukocyte antigen (HLA) associations, suggest-

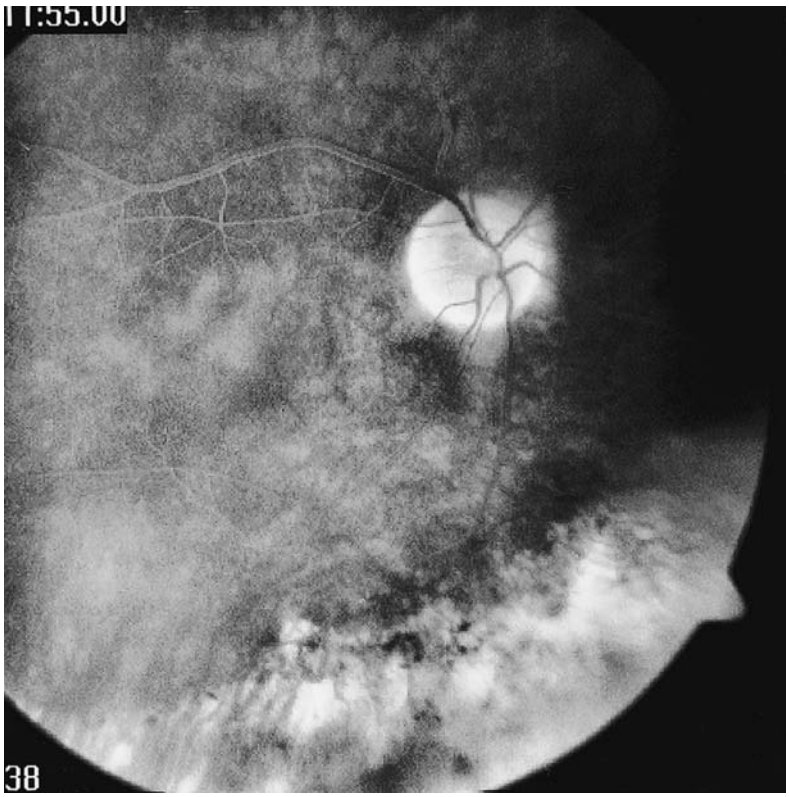

FIGURE 18–5. A fluorescein angiogram demonstrating macular edema characteristic of immune recovery uveitis in a patient with a history of cytomegalovirus retinitis (inferior scar).

ing that some people may have a genetic predisposition to developing the ARN syndrome on infection with herpes viruses.

How Is Acute Retinal NecrosisTreated?

MEDICAL

Although there are no randomized prospective studies, most patients appear to benefit from treatment with acyclovir. A typical regimen for patients with ARN involves a 10- to 14-day course of intravenously administered acyclovir, 500 mg/m^2 every 8 hours, followed by oral acyclovir 800 mg five times a day for an additional 6 weeks. The goal of therapy is to hasten resolution and prevent contralateral spread. Retrospective studies have found acyclovir to be effective in reducing the risk of contralateral disease; however, it does not appear to affect the vitreitis or the subsequent development of retinal detachment. Systemic corticosteroids can be added once the patient has received 24 to 48 hours of acyclovir. Some researchers suggest the use of aspirin to prevent retinal vascular occlusions.

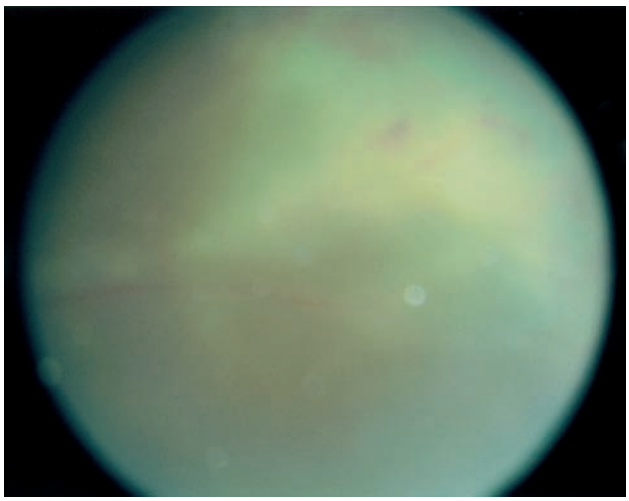

FIGURE 18–6. Peripheral retinitis with prominent vitreous inflammation in a patient with acute retinal necrosis.

TABLE 18–2. Differential Diagnosis of Acute Retinal Necrosis Syndrome

Bacterial or fungal endophthalmitis
Behçet disease
Cytomegalovirus retinitis
Progressive outer retinal necrosis syndrome
Sarcoidosis
Syphilis
Toxoplasmosis
Pars planitis
Intraocular lymphoma

Modified from Nussenblatt RB, Whitcup SM, Palestine AG. *Uveitis: fundamentals and clinical practice.*

Surgical

Prophylactic laser photocoagulation has been used to demarcate a zone between involved and uninvolved retina potentially to prevent retinal detachment. Retinal detachments in patients with ARN are typically difficult to repair. Vitrectomy, fluid-gas change, and endolaser have been suggested for cases of complicated detachments. Likewise, silicone oil has been used with success in some patients.

Progressive Outer Retinal Necrosis

What Are the Clinical Features of Progressive Outer Retinal Necrosis?

Progressive outer retinal necrosis (PORN) is a rapidly progressive retinitis that is seen in immunocompromised patients, most commonly in AIDS patients. The typical lesions are multifocal deep retinal opacification that later become confluent. Initially, these lesions may be mistaken as CMV retinitis; however, the extremely rapid progression distinguishes PORN. Unlike ARN, there is minimal intraocular inflammation and no vascular involvement.[1]

What Is the Etiology?

Most commonly, PORN is associated with the herpes zoster virus. Many patients will have a previous or concurrent episode of zoster dermatitis.

What Are the Treatment and the Prognosis?

Various combinations of induction doses of intravenous ganciclovir, foscarnet, and acyclovir as well as intravitreal ganciclovir and foscarnet have been tried with only limited success. Unfortunately, the visual prognosis for patients with PORN is poor. Retinal detachments occur in 70% of eyes despite prophylactic laser retinopexy. Nearly two thirds of the cases result in no light-perception vision.

Pneumocystis carinii

Which Patients Are Most Susceptible to *Pneumocystis carinii* Choroiditis

Immunocompromised patients, particularly those with HIV, are the most susceptible group to *P. carinii* infections. It mainly presents with pulmonary involvement as an interstitial pneumonia. *P carinii* choroiditis is an extrapulmonary form usually seen in patients not on prophylactic therapy or in those receiving inhaled pentamidine that only prevents the pulmonary infection. Currently, oral trimethoprim/sulfamethoxazole is the standard prophylactic therapy for *P. carinii* infections.

What Are the Typical Features of *Pneumocystis carinii* Choroiditis?

P. carinii choroiditis is characterized by multifocal white plaques in the choroids with little evidence of intraocular inflammation. The lesions rarely cause visual loss because they are located beneath the retinal pigment epithelium and have no associated inflammatory response.[1]

What Is the Treatment for *Pneumocystis carinii* Choroiditis?

All patients with *P. carinii* choroiditis are presumed to have systemic dissemination and require hospitalization for a thorough evaluation, most importantly of the pulmonary system. The treatment usually involves a 3-week course of intravenous trimethoprim and sulfamethoxazole or intravenous pentamidine. Long-term prophylaxis is essential to prevent the high recurrence rate.

Diffuse Unilateral Subacute Neuroretinitis

What Is the Etiology of Diffuse Unilateral Subacute Neuroretinitis?

Diffuse unilateral subacute neuroretinitis (DUSN) is caused by a nematode. It is typically acquired by oral ingestion; the larva reaches the eye and migrates in the subretinal space, causing destruction of the retina outer segments. Worms of two different sizes have been described.[15] A smaller worm, between 400 and 1200 μ, is seen most commonly in the southeastern United States. The smaller worm may actually be *Toxocara canis*. The larger worm (1500 to 2000 μ) has been seen in patients in northern and midwestern states. *Baylisascaris procyonis*, an intestinal roundworm of raccoons and skunks, has been proposed for the larger worm.

What Are the Ocular Features ?

As the name applies, DUSN is a unilateral disease, and only rarely occurs bilaterally. It begins as recurrent gray-white retinal lesions in scattered areas. There is often moderate vitreous inflammation at the time of activity; however, in some cases, there may be no inflammation. Optic-disc swelling may be present. As the disease progresses, there is increasing optic atrophy, narrowing of the retinal vessel, pigment epithelial stippling, and further loss of visual field. In some patients, subretinal tracks that correspond to previous movement of the worm may be seen. Careful examination with a contact lens may reveal a motile worm in the subretinal space. The central visual acuity depends on the degree of macular involvement. At least half of the cases will have a visual acuity less

than 20/200. The electroretinogram is significantly decreased. Patients are usually in good health and have no systemic signs or symptoms of parasitic disease.[1]

How Is Diffuse Unilateral Subacute Neuroretinitis Treated?

Medical therapy with corticosteroids has not been effective. Antihelminthic agents have been used successfully in some cases, but they are not consistently effective. DUSN can be treated by laser photocoagulation of the worm. This will halt the progression of the disease but will not improve the visual acuity. Death of the worm after laser treatment is not associated with an increase in inflammatory response.

Tuberculosis

What Is the Causative Organism of Tuberculosis, and How Is It Detected?

Tuberculosis is caused by *Mycobacterium tuberculosis*, a bacterium that may be identified by its acid-fast staining pattern in infected secretions, bodily fluids, or tissues; however, the organism may be very difficult to detect and is fastidious in culture. PCR technology is being applied to diagnosis in some laboratories but is experimental and not widely available.

Evidence of infection with *M. tuberculosis* is detected clinically by administration of the purified protein derivative (PPD) skin test, also known as the *Mantoux test*. The purified protein alluded to in this test is an extract of the tuberculous bacillus. A positive test leads to induration at the inoculation site due to a type IV hypersensitivity response. The PPD skin test is read 48 to 72 hours after inoculation. Infected patients become sensitized to the PPD skin test, or "convert" to a positive skin test, from 2 to 10 weeks after initial infection. An intermediate strength PPD is appropriate for most patients; in patients with a history of tuberculosis or a positive PPD in the past, however, the intermediate strength test may cause a severe dermatologic reaction. In such patients a lower-strength PPD may be used. Patients with a history of bacillus Calmette-Guerin (bCG) immunization will have increased evidence of delayed hypersensitivity to the PPD skin test; however, this hypersensitivity is variable in duration and is rarely as large as the response engendered by natural infection. Hence, large, positive PPD reactions that persist for many years after immunization should be considered positive, and treatment should be recommended. Intradermal administration of control antigens such as trichophyton, tetanus, mumps, or *Candida* organisms also should be used to ensure that tested patients are not anergic, which could indicate numerous other conditions, including systemic immune suppression, sarcoidosis, or even military tuberculosis.[16]

A relatively small percentage of patients with tuberculosis develop ocular disease; hence, a positive PPD is not diagnostic of tuberculous eye disease in patients with ocular inflammation. Discovery of tuberculous organisms in the affected ocular tissues or ocular fluids is either by histologic methods or culture is confirmatory, but such evidence may be extraordinarily difficult to find. Evidence of typical systemic or ocular disease, typical chest roentgenographic findings of pulmonary tuberculosis, or positive response to empiric treatment often is required to confirm a diagnosis of tuberculous ocular inflammatory disease.

What Is the Natural History of Tuberculosis?

M. tuberculosis is most commonly spread in aerosol droplets. These may be present in the coughs, sneezes, or vocalizations of infected patients. The organisms are not highly infective, and prolonged exposure is often required, although certain patients may be more highly infectious than others. Once the organisms have been inhaled, a self-limited, asymptomatic pneumonia occurs with subsequent granuloma formation. The characteristic caseating granulomatous lesions initially calcify and may remain inactive for many years or indefinitely. Tuberculous organisms are engulfed from the pulmonary granulomas and transported to regional lymph nodes, where they are either contained or allowed to spread to extrapulmonary sites. Reactivations occur secondary to alterations in the immune status of the host brought about by age, illness, or systemic immunosuppression. Most affected patients in the United States are immunosuppressed, elderly, or impoverished, and prevalence is increased in minority groups. Untreated tuberculosis leads to a chronic wasting disease, which is eventually fatal.[16]

What Are the Ocular Manifestations of Tuberculosis?

Ocular manifestations of tuberculosis occur in only 1 to 2% of affected patients. The classic ophthalmic manifestation of tuberculosis is a granulomatous anterior uveitis, with mutton-fat keratic precipitates, iris granulomas, and posterior synechiae. Tuberculosis may cause anterior, posterior, intermediate, or panuveitis, however, and should be considered in the differential diagnosis of patients not only with granulomatous uveitis but severe nongranulomatous disease as well as other atypical presentations such as smoldering or relapsing disease. Choroidal granulomas are the most common ophthalmic finding in patients with pulmonary or disseminated tuberculosis and

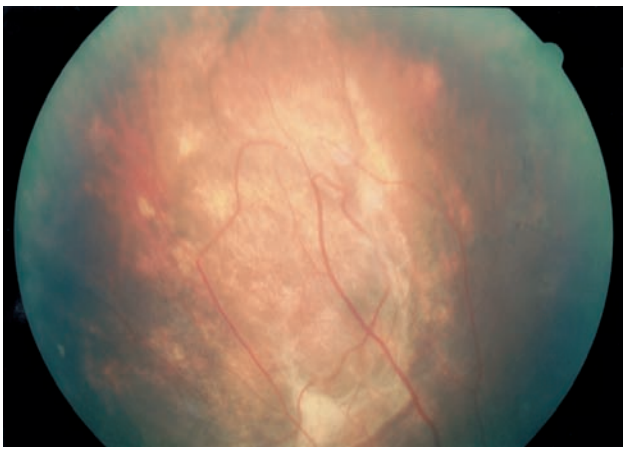

FIGURE 18–7. A large choroidal granuloma in a patient with a history of systemic tuberculosis. The lesion regressed with anti-tuberculous therapy.

may present as a unifocal or multifocal choroiditis, with the possible subsequent development of choroidal neovascularization (Fig. 18–7). Choroidal granulomas tend to occur near the posterior pole and may be associated with exudative retinal detachments. Tuberculosis has been associated with Eales disease, manifest by retinal vasculitis, ischemia, neovascularization, and vitreous hemorrhage. Interstitial keratitis and phlyctenular keratitis are not caused by tuberculous infection per se but are frequent immunologic sequelae to tuberculous infection. Tuberculosis is an uncommon but classic cause of scleritis, usually necrotizing and anterior. Other anterior segment findings may include conjunctivitis, tubercles of the eyelids, or primary infection of the nasolacrimal mucosa. Orbital or optic nerve findings may include tubercles impinging on the optic nerve or disc, optic neuropathy, or tuberculous neuroretinitis. Endogenous endophthalmitis has been reported after intravesicular bCG injection and confirmed by vitreous cultures.[1,17]

How Is Tuberculosis Treated? What Special Considerations Are Made for Treatment of Immunosuppressed Patients?

Antibiotic regimens are under constant change, and infectious disease consultation should be considered to assist in management of tuberculosis patients. Agents used to treat tuberculosis include isoniazid (INH), rifampin (RIF), pyrazinamide, ethambutol, and streptomycin. Single-drug therapy may be used for PPD "converters" without evidence of systemic disease. All regimens for treatment of pulmonary or extrapulmonary tuberculosis include at least two drugs to guard against the development of drug resistance, with up to five used simultaneously in multidrug-resistant tuberculosis. The most commonly used regimens in the United States use INH and RIF for at least 9 months, with additional drugs used for the first 2 to 3 months.

In patients with ocular inflammatory disease, which is questionably related to TB, some researchers advocate an INH therapeutic test, with a positive test result considered if the patient improves over 1 to 2 weeks of treatment. The results of such a test may be confounded by the concomitant use of topical or systemic corticosteroids and by the waxing and waning natural history of tuberculous ocular inflammation. Accordingly, once a decision to treat is made, treatment should be given for at least 3 to 6 months with two or more drugs before any decision about efficacy is rendered. Infectivity of infected patients drops dramatically within 2 weeks of institution of appropriate antimicrobial therapy.

Treatment regimens are the same for immunosuppressed and immunocompetent individuals; however, immunosuppressed patients may present with more disseminated disease, have increased toxicity or side effects from medications, and have increased likelihood of relapse.

What Follow-up Is Required after Treatment of Tuberculosis?

Relapses after appropriate treatment with good compliance occur in less than 1% of cases. Recurrences typically present symptomatically; hence, routine testing is not recommended for asymptomatic patients who have completed appropriate therapy.

What Is the Differential Diagnosis of Tuberculosis?

Tuberculosis, as noted already, may have a polymorphic appearance in the eye; therefore, this diagnosis should be entertained in any patient with uveitis, scleritis, or keratitis, or any of the other manifestations noted previously. Other granulomatous uveitides that may occur and present similarly to tuberculous uveitis include syphilis, sarcoidosis, Lyme disease, Vogt–Koyanagi–Harada disease, sympathetic ophthalmia, or multiple sclerosis. Immunosuppressed patients have an increased risk of tuberculosis as well as other infectious uveitides, such as toxoplasmosis (which may also demonstrate a granulomatous anterior uveitis), CMV retinitis, *P. carinii* choroiditis, herpesvirus retinitis, or atypical mycobacterial infection. Posterior manifestations of tuberculosis may imitate any of the retinal or choroidal "white-dot syndromes." Intraocu-

lar lymphoma must always be considered in long-standing or atypical disease.

Syphilis

What Is the Causative Organism of Syphilis, and How Is It Detected?

Syphilis is caused by *Treponema pallidum*, a motile bacteria that belongs to the spirochete family. These spirochetes can be detected by dark-field microscopy in infected bodily fluids. Multiple serologic tests exist for the diagnosis of *T. pallidum* infection in bodily fluids. These can be subdivided into two different types of assays, nontreponemal (or reagin) and treponemal tests.

Nontreponemal assays that are commonly used include the rapid plasma reagin (RPR) and Venereal Disease Research Laboratories slide test (VDRL). These tests are equally sensitive and frequently are used for the initial screening for syphilis. Both tests assay for the presence of nonspecific (reaginic) antibodies against cardiolipin by microscopic (VDRL) or macroscopic (RPR) flocculation of an antigen suspension. Cardiolipin is a lipoidal antigen that results from the interaction of *T. pallidum* against host tissues and questionably a lipoidal antigen of *T. pallidum* itself. The RPR and VDRL are about 59 to 87% sensitive for primary syphilis and increase to nearly 100% during secondary syphilis but generally disappear or are markedly decreased after treatment. Sensitivity drops during untreated late syphilis, with estimates ranging from 37 to 94%.[16]

Treponemal tests include the fluorescent treponemal antibody absorption test, or FTA-ABS, or the microhemaglutination assay for antibodies to *T. pallidum* (MHA-TP). The treponemal tests are more sensitive than the non-treponemal tests in all stages, but they are more expensive and difficult to perform. They are frequently used to confirm positive results of a nontreponemal tests. The FTA-ABS is performed first absorbing the patient's serum against nonpathogenic treponemes (sorbent) to remove nonspecific antibodies that might cross-react with *T. pallidum*. The remaining serum is then reacted against slide-fixed *T. pallidum*. After the addition of fluorescein-labeled anti-human gamma globulin, fluorescent microscopy is used to detect and quantify specific antibodies against *T. pallidum*. FTA-ABS is 85 to 100% sensitive in primary syphilis, nearly 100% in secondary syphilis, and remains above 96% for treated or untreated late syphilis. The MHA-TP is less sensitive than the FTA-ABS for primary syphilis (64 to 87%) but is comparable to the FTA in later stages of the disease. In a positive MHA-TP, microhemagglutination of *T. pallidum*–covered sheep or turkey erythrocytes is observed when these erythrocytes are exposed to sorbent-absorbed patient serum. Both tests are 98 to 99% specific and, when combined with a positive nontreponemal test, yield a high positive predictive value for syphilis.[16]

Congenital syphilis is acquired via transplacental transmission. Patients will have positive VDRL and FTA-ABS because of passive transplacental transfer of IgG. Therefore, congenital syphilis must be diagnosed with IgM FTA-ABS, indicating actual infection in the infant. A method for evaluating suspected syphilis can be seen in Figure 18–8.

What Is the Natural History of Syphilis?[1,16]

The natural history of syphilitic infection may be divided into three primary stages of active infection and a latent phase. Primary syphilis begins about 4 weeks after infection. It is defined by the appearance of chancres, which begin as erythematous papules at the site of inoculation and progress to form eroded, painless ulcers. Chancres usually occur in the genital region but may uncommonly manifest in nongenital skin and mucosa, including the eyelids and conjunctiva. The chancre usually resolves within 1 to 2 months of appearance. Multiple chancres may appear in immunosuppressed patients.

Secondary syphilis, which begins 4 to 10 weeks after the onset of symptoms, is typically marked by the appearance of a generalized maculopapular or pustular rash, which preferentially involves the palms and soles and uncommonly results in scarring. Other constitutional symptoms may involve virtually every organ system in the body.

Latent syphilis begins in the first year after infection. Infectious mucocutaneous lesions may recur during this time, known as early *latent syphilis*. During the subsequent time period, known as *late latent syphilis*, infectious relapses are rare.

About two thirds of patients remain in this latent phase; however, one third or about 33%, go on to develop tertiary syphilis, subdivided into *cardiovascular syphilis*, *benign tertiary syphilis*, and *neurosyphilis*. Cardiovascular syphilis is caused by endarteritis of the vaso vasorum of the large vessels in the chest, leading to aneurysm formation, aortitis, aortic regurgitation, or coronary ostial stenosis. Benign tertiary syphilis is characterized by the appearance of gumma, which are areas of granulomatous inflammation that often involve the bones, skin, respiratory tract, larynx, liver, and stomach, although any organ may be involved. Neurosyphilis includes meningeal and brain parenchymal disease, neurotrophic Charcot joints, and tabes dorsalis, which is manifest as optic atrophy,

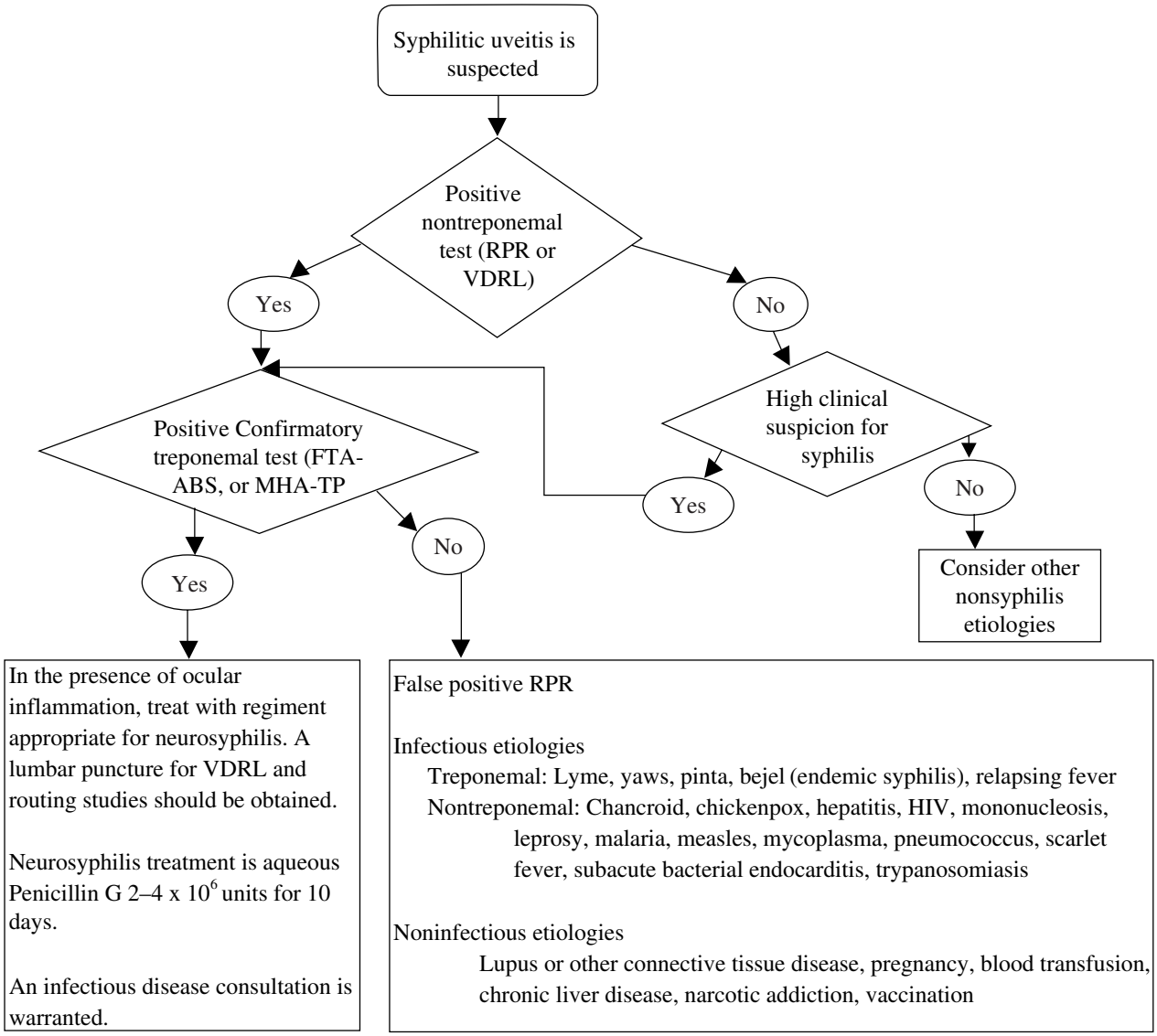

FIGURE 18–8. Evaluation of suspected syphilitic uveitis. RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratories; FTA-ABS, fluorescent treponemal antibody absorption test; MHA-TP, microhemaglutination assay for antibodies to *Treponema pallidum*.

Argyll–Robinson pupils, and signs and symptoms of demyelinating disease.

What Are the Ocular Manifestations of Syphilis?[1,18]

Each stage of syphilitic infection has typical ophthalmic manifestations. Ocular manifestations in primary syphilis are uncommon; chancres of the eyelid or conjunctiva may occur.

In early secondary syphilis, and perhaps in all syphilis, anterior uveitis is the most common manifestation. Chorioretinitis and vitreitis are the typical findings of the late secondary stage but may be seen in early secondary stage as well. Eyelid and anterior segment findings in secondary syphilis may include blepharitis, madarosis, conjunctivitis, keratitis, scleritis, episcleritis, and iris nodules. Other posterior segment findings may include disc edema, exudative retinal detachment, retinal vasculitis, subretinal fibrosis, neuroretinitis, and a retinitis pigmentosa–like secondary pigmentary retinopathy.

The gummatous lesions of tertiary syphilis may involve the eyelid skin or orbital periosteum. The most common corneal finding is unilateral interstitial keratitis. Punctate stromal keratitis with iritis also may occur. As in secondary syphilis, blepharitis, madarosis, conjunctivitis, scleritis, and episcleritis may occur. Lens dislocations have been reported. Posterior segment manifestations are similar to those seen in secondary syphilis. Neuroophthalmic manifestations in-

clude Argyll–Robertson pupils, disc edema, optic neuritis, optic atrophy, and oculomotor palsies.

Typical ocular manifestations of congenital syphilis include pigmentary retinopathy and bilateral interstitial keratitis. Glaucoma also may develop because of congenital syphilitic keratouveitis.

How Is Syphilis Treated?[1,16]

Antibiotic regimens are under constant change, and infectious disease consultation should be considered to assist in management of syphilis patients. Primary and early secondary syphilis stages may be treated with oral antibiotics. Currently accepted regimens include procaine penicillin, 2.4 million units with concomitant probenecid, 1 g taken daily for 10 days. Penicillin-allergic patients can be treated with erythromycin, 500 mg every 6 hours, or doxycycline, 200 milligrams daily, for 15 days.

In its later stages, including late secondary, latent, and tertiary syphilis, intravenous antibiotics are required. The standard regimen is 10 days to 2 weeks of intravenous aqueous crystalline penicillin G, 2.0 to 4.0 million units every 4 hours. Although ocular inflammatory disease may occur in early secondary syphilis, syphilitic posterior uveitis connotes a high probability of neurosyphilis and accordingly should be treated with intravenous antibiotics.

Congenital syphilis is treated with intravenous or intramuscular penicillin and should be treated in conjunction with a pediatrician or perinatologist. Treated patients may develop rebound inflammation because of hypersensitivity response to treponemal antigens liberated by bacteriolysis. This response, called a *Jarisch–Herxheimer response*, may lead to exacerbations of uveitis or interstitial keratitis and may require treatment with steroids.

What Follow-up Is Required after Treatment of Syphilis?

Patients with syphilis should have their VDRL tested at 3, 6, and 12 months after therapy. The VDRL should become nonreactive within a year of successful therapy. Indications for retreatment include clinical evidence of syphilis, failure of an initially high VDRL titer to decrease at least fourfold, or if a previously VDRL nonreactive becomes reactive.

What Is the Differential Diagnosis of Syphilis?

Syphilis is often referred to as the "great imitator" because of its diversity in ocular and systemic presentation. Lyme disease, which is caused by the spirochete *Borrelia burgdorferi*, has a similar, triphasic life cycle and may have very similar ophthalmic manifestations. Any patient with history of tick bites, residence in endemic or heavily wooded areas, or other typical manifestations of Lyme disease, such as erythema chronicum migrans, should be tested for this disease. Serologic tests for Lyme disease are falsely positive in about 10% of cases, however, mitigating against indiscreet testing in uveitic patients without typical ocular, systemic, or demographic features. Any positive Lyme serology should be followed up with confirmatory Western blot testing, with multiple positive bands required to confirm the diagnosis. Bejel (endemic syphilis), yaws, and pinta are all treponemal diseases that can lead to positive VDRL and FTA but are clinically differentiated from venereal syphilis; they must be considered in endemic areas. Other forms of infectious uveitis must also be considered, especially in immunosuppressed patients. The differential diagnosis of granulomatous uveitis includes tuberculosis and sarcoidosis, which, like syphilis, may have a polymorphic ocular appearance, along with multiple sclerosis, Vogt–Koyanagi–Harada syndrome, and sympathetic ophthalmia. Other spirochetal infections, such as leptospirosis and relapsing fever, also should be considered.

What Special Considerations Are Made for Treatment of Syphilitic Eye Disease in Immunosuppressed Patients?

Immunosuppressed patients, including patients with AIDS, are at high risk for other opportunistic infections. In addition, many HIV-positive patients are at high risk for having contracted other infectious diseases and should be appropriately assessed. Serologic evidence of syphilis may not appear until the later stages in immunosuppressed patients, and the CSF VDRL may be negative in immunosuppressed patients. The time course and aggressiveness of the disease in immunosuppressed patients are often accelerated, and treatment failures occur more commonly. Immunosuppressed patients are more likely to progress to neurosyphilis and always should be treated with an antimicrobial regimen adequate for neurosyphilis. Additionally, advanced or severe sequelae of disease, including ARN, syphilitic retinitis, panuveitis, and retinal detachment are more common in the immunosuppressed population.

Lyme Disease

What Is the Causative Organism of Lyme disease and How Is It Detected?

Lyme disease is caused by *B. burgdorferi*, a motile bacteria that belongs to the spirochete family. The organism was discovered in 1982, seven years after the first described outbreak of an inflammatory arthropathy with characteristic skin rash and associated neurologic

and cardiologic disease in a group of children in Lyme, Connecticut. *B. burgdorferi* is transmitted by ticks of the Ixodes family from a multitude of natural hosts, including deer, mice, and domestic pets. It is most common in three portions of the United States: the northeast from Massachusetts to Maryland; the Midwest, including Minnesota and Wisconsin; and on the West Coast in California and Oregon. These areas have in common proximity to heavily wooded areas with plentiful natural hosts for the Ixodid ticks that carry the disease. Because of modern-day travel and migration, however, Lyme disease has been reported in most of the United States and Europe, Asia, and Australia.[16]

Serologic diagnosis of Lyme disease may be obtained either by immunofluorescent assay (IFA) or by ELISA, with the latter test more sensitive in all stages of the disease. The ELISA assay for Lyme disease is about 90% sensitive and specific within a few weeks of infection. Therefore, this test carries a 10% false-negative and false-positive rate. Any positive tests should be confirmed with a Western blot; multiple positive bands are required for a confirmatory result. A fourfold rise in IgM titers against *B. burgdorferi* in patients with a clinical history consistent with Lyme is the most reliable indicator of disease; however, this increase is not often documented. A peculiar feature of this disease is the persistence of IgM titers throughout infection, perhaps due to spirochetal inhibition of the helper-T-cell-dependent mechanism allowing B-cell immunoglobulin class switching.

Because of the relatively high rate of false positives, Lyme titers should not be ordered indiscriminately for patients with uveitis; the use of this test should be limited to patients with a clinical history or physical findings suggestive of Lyme disease. The positive predictive value in patients with an atypical history for Lyme disease has been estimated to be less than 20%. False-positive results may be seen in other spirochetal disease, including syphilis and Rocky Mountain spotted fever, as well as infectious mononucleosis, some neurologic disorders, and autoimmune disease.

What Is the Natural History of Lyme Disease?[1,16]

Similarly to its spirochetal cousin *T. pallidum*, *B. burgdorferi* causes a triphasic disease response in humans. Early infection is divided into local (stage 1) and disseminated (stage 2) disease. Late or persistent disease is characterized as stage 3.

Three to 32 days after being bitten by an infected tick, 60 to 80% of patients manifest the typical cutaneous lesion of stage 1 disease, erythema chronicum migrans. This skin rash is characterized by an oval or annular, erythematous lesion with spreading borders, often with a "bull's-eye" or target morphology. It typically fades after 3 to 4 weeks but may recur in untreated patients. Patients recall a tick bite in approximately half of cases. Other symptoms of stage 1 disease include regional lymphadenopathy and flulike illness.

Stage 2 (disseminated) disease may begin within days to weeks after infection. During this time, the organism may spread hematogenously to many organs. Neurologic manifestations are common and include severe headaches, stiff neck, peripheral neuropathies, and unilateral or bilateral Bell palsy. Radicular pain and cerebrospinal pleocytosis (Bannwarth syndrome) may occur. Cardiac involvement develops in 4 to 8% of patients; this involvement ranges from first-degree to complete atrioventricular block and acute myocarditis. Rheumatologic manifestations include oligoarticular arthritis, intermittent arthralgias, and musculoskeletal pain.

Stage 3 infection is characterized by prolonged episodes of arthritis, chronic fatigue, and chronic neurologic manifestations, including ataxia, chronic encephalomyelitis, spastic paraparesis, and dementia. Erythema chronicum migrans may recur. Transplacental transmission has been reported in two patients whose mothers contracted Lyme disease in the first trimester of pregnancy.

What Are the Ocular Manifestations of Lyme disease?[1,19]

Each stage of Lyme disease has typical ophthalmic manifestations. The most common eye finding in stage 1 (local) disease is conjunctivitis, which occurs in 11% of patients in this stage of disease. In stage 2, or disseminated, disease, the most common ocular manifestations are conjunctivitis and uveitis. The most common inflammatory manifestations of Lyme disease are episcleritis, iridocyclitis, and intermediate uveitis with or without cystoid macular edema. Less common manifestations include panuveitis, retinal vasculitis, diffuse choroiditis, or exudative retinal detachments simulating Vogt–Koyanagi–Harada syndrome. Neuroophthalmic manifestations of Lyme disease may occur in early disease and may include cranial nerve palsies, of which the most commonly occurring are Bell's palsies. Other neuroophthalmic manifestations that have been reported include diplopia secondary to oculomotor neuropathies, cortical blindness, bilateral paralytic mydriasis, optic neuritis, neuroretinitis, or orbital myositis. The characteristic ocular manifestation of stage 3 (persistent) Lyme is bilateral interstitial keratitis. Episcleritis also may occur.

How Is Lyme Disease Treated?

Current recommendations for the treatment of Lyme disease are as follows. Early infection may be treated with oral antibiotics. Suggested regimens include tetracycline, 250 mg four times daily, doxycycline 100 mg twice daily, or amoxicillin 500 four times daily for 10 to 30 days. In children, the recommended oral agents are amoxicillin or penicillin V, dosed by weight, or erythromycin in penicillin-allergic patients. Patients with mild ocular disease may respond to this treatment. Late, neurologic, or severe ocular disease typically is treated with intravenous antibiotics. The current agent of choice is ceftriaxone, which is administered 2 g daily for 14 days, or penicillin G, 20 to 24 million units daily for the same duration. Some evidence suggests that treatment with corticosteroids may predispose to antibiotic failure; hence, patients with known or suspected Lyme disease should only be given topical steroids concomitantly with antibiotic treatment. Empiric antibiotic treatment for patients with high suspicion for Lyme disease may be appropriate. Antibiotic regimens are under constant change, and infectious disease consultation should be considered to assist in management of patients with Lyme disease.

What Is the Differential Diagnosis of Lyme Disease?

Syphilis, which is caused by the spirochete *T. pallidum*, has a similar life cycle to *B. burgdorferi* and may have very similar ophthalmic manifestations. Other items in the differential diagnosis include tuberculosis and sarcoidosis, which like Lyme disease may have a polymorphic ocular appearance, and other spirochetal infections, such as leptospirosis or relapsing fever. Lyme disease may manifest as anterior, intermediate, posterior, or panuveitis; an exhaustive discussion of the differential diagnosis of each of these is beyond the scope of this text. Other diseases to be considered in the differential of intermediate uveitis include multiple sclerosis, inflammatory bowel disease, and idiopathic uveitis of the pars planitis subtype; other posterior uveitides in the differential for Lyme would include many of the "white-dot" syndromes as well as masquerade syndromes.

Cat-scratch Disease

What Is the Etiologic Agent of Cat-scratch Disease, and How Is It Detected?[16]

The etiologic agent of cat-scratch disease (CSD) is *Bartonella henselae*, a fastidious, pleiomorphic, gram-negative bacterium. In the early 1980s, *Rochalimaea henselae* was discovered by independent investigators in biopsy specimens of patients with CSD. It was classified in the Rochalimaea family because of its molecular and morphologic similarity to *Rochalimaea quintana*, the etiologic agent of trench fever. *R. henselae* and *quintana*, along with other *Rochalimaea* species, was reclassified into genus *Bartonella* in the 1990s, leading to the current taxonomic classification.

Until the last ten years or so, CSD was diagnosed by skin testing, histology, or culture of infected bodily fluids. The Hanger-Rose skin test used purified extracts from body fluids of patients with known CSD and has been abandoned because of concern over infectious disease transmission. Histologic evidence of CSD is gained by biopsy of involved tissue, most often an inflamed and enlarged lymph node. Warthin–Starry (modified silver) staining reveals pleomorphic bacilli clustered around blood vessels, germinal centers, or microabscesses. The organism is fastidious and extraordinarily difficult to grow in culture.

In the last 10 years, serologic testing using immunofluorescence has revolutionized and standardized the detection of *B. henselae* infection and has led to the recent explosion in knowledge regarding this pathogen and its ocular and systemic effects. The commercially available immunofluorescent assay has a described sensitivity of 84%, specificity of 96%, and positive predictive value of 91%. Significant positive titers are seen in 3% of normal, asymptomatic controls.

What Is the Natural History of Cat-scratch Disease? How Often Is the Eye Involved?[16,20]

In most (89%) "typical" cases, infection with *Bartonella* manifests as a self-limited regional adenopathy in the lymph nodes draining the area of inoculation. Incubation period is 1 to 7 weeks after exposure. Inoculation most often is related to a scratch, bite, or lick from a bacteremic kitten (usually less than 1 year of age). Fleas are the vector of infection between cats, and there is anecdotal evidence of direct spread from fleas to humans. One of the most common "atypical" manifestations of CSD is Parinaud oculoglandular syndrome, or POGS, which is present in 6% of patients with the disease. Neurologic complications occur in 1 to 2% of cases and include neuroretinitis as well as aseptic meningitis, encephalitis, seizures, transverse myelitis, cerebral vasculitis or abscess, peripheral neuropathy, polyneuritis or radiculitis, and Bell's palsy.

Other less common systemic complications of *B. henselae* infection include osteomyelitis, bacillary peliosis hepatitis or splenitis, culture-negative endocarditis, hemolytic anemia, hilar adenopathy, pleural effusions, and bacteremia.

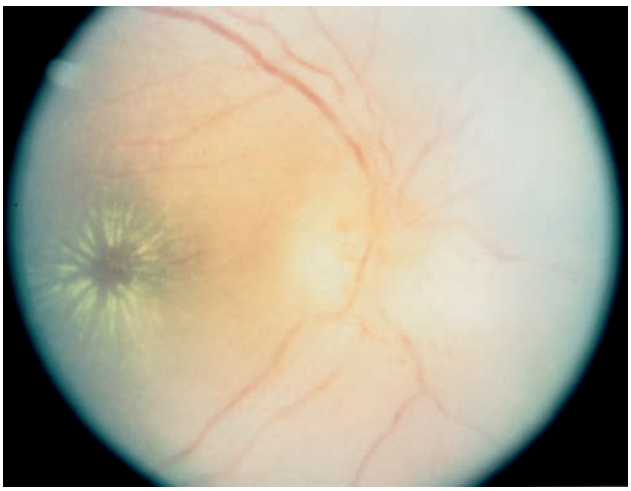

FIGURE 18–9. A patient with neuroretinitis (optic-nerve swelling and macular star) from cat-scratch disease.

What Are the Ocular Manifestations of Cat-scratch Disease?[20,22]

The two most common ocular manifestations of cat-scratch disease (CSD) are POGS and neuroretinitis. POGS is generally thought to be the most frequent ocular association of CSD, occurring in approximately 6% of cases. POGS is characterized by a unilateral granulomatous conjunctivitis accompanied by preauricular, mandibular, or cervical adenopathy.

Bacillary angiomatosis (BA) is a less common anterior segment manifestation. BA is a vascular neoplasm often found in immunosuppressed patients with CSD. It may appear on the conjunctiva and may be clinically indistinguishable from Kaposi sarcoma.

Neuroretinitis is characterized by the clinical syndrome of optic-nerve edema with concomitant or subsequent exudative maculopathy, typically manifesting as "macular star" lipid exudates (Fig. 18–9). It is typically grouped with the neurologic manifestations of CSD, which occur in 1 to 2% of patients; however, one series described neuroretinitis in 26% of patients in an infectious diseases clinic with confirmed *B. henselae* infection. The development of the "macular star" exudate may be preceded by a serous macular detachment. The typical clinical history of neuroretinitis associated with CSD is abrupt, profound unilateral vision loss, with usual recovery of vision over weeks to months. In most series, more than 90% of patients recover vision of 20/40 or better. In the acute stages, vitreous or anterior chamber cell may be seen, and an afferent pupillary defect may be present. Other posterior segment manifestations may include retinovascular occlusions, multifocal retinal, subretinal, or choroidal infiltrates, optic neuritis, and vascular or inflammatory masses of the optic-nerve head.

How Is Ocular Cat-scratch Disease Treated?

As noted, the natural history of CSD neuroretinitis is quite good, with most patients recovering visual acuity greater than 20/40 without treatment. Most providers opt to treat, given the low morbidity of doing so. Additionally, the infectious disease literature supports treating neurologic manifestations of CSD, such as neuroretinitis, with oral antibiotics. The standard of treatment for POGS is oral antibiotics. In a review of 268 patients, the following antibiotics were found to be effective in treatment of *B. henselae*: rifampin (effective in 87% of patients reviewed), ciprofloxacin (84%), gentamicin (73%), and trimethoprim-sulfamethoxazole (58%). Doxycycline has been used with and without rifampin with reported success in some case series.[21]

There is no consensus as to the length of treatment for neuroretinitis; regimens from 4 to 8 weeks have been reported. Systemic steroids have been used in some series and have not been shown to be beneficial or harmful. Recommended course of therapy is 4 to 6 weeks with POGS or until the patient is afebrile for 1 week with decreasing adenopathy and no constitutional symptoms for 5 to 10 days.

What Is the Differential Diagnosis for the Ocular Manifestations of Cat-scratch Disease?

In one series, two thirds of tested neuroretinitis patients had serologic evidence *of B. henselae*, compared with a prevalence of 3% in the general population. Based on this finding, CSD appears to be the predominant causative factor for neuroretinitis. Other etiologic differential diagnostic considerations include syphilis, toxoplasmosis, tuberculosis, Lyme disease, leptospirosis, toxocariasis, tularemia, sarcoidosis, and Herpesviridae infections. In addition, malignant hypertension, diabetic papillopathy, and pseudotumor cerebri may cause disc edema with macular star exudates, which is usually bilateral. Neuroretinitis as a presenting manifestation of multiple sclerosis has *not* been described. Differential diagnosis of unilateral granulomatous conjunctivitis includes chlamydia, tularemia, tuberculosis, sporotrichosis, and syphilis.

Bacillary angiomatosis in immunosuppressed patients with CSD must be differentiated from Kaposi sarcoma. Histologic analysis of biopsy specimens is required for this distinction.

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19

Noninfectious Inflammation

RONALD BUGGAGE

Categorizing Uveitis

How Is Uveitis Defined?

Strictly speaking, *uveitis* is defined as inflammation of the uvea that is composed of the iris, ciliary body, and choroid. Clinically, the term *uveitis* is used more broadly to define any condition that causes intraocular inflammation. This is because inflammatory processes within the uveal tract frequently spill over into the adjacent anterior chamber, vitreous, and retina. Similarly, inflammatory disorders primarily affecting the retina and sclera may involve the uveal tissues.

What Are the Causes of Uveitis?

There are many causes of uveitis, including infections such as syphilis, toxoplasmosis, herpes simplex, and tuberculosis or malignancies like primary central nervous system (CNS) lymphoma and leukemia. Most causes of uveitis are the result of either primary ocular or systemic immune-mediated or autoimmune diseases in which cell-mediated immunity is believed to a play major role.

How Common Is Uveitis?

Uveitis ranks as the fourth most common cause of blindness in developing countries, behind macular degeneration, diabetic retinopathy, and glaucoma. The prevalence of uveitis from all causes is estimated at 40 per 100,000, with an annual incidence of about 15 per 100,000.[1] Uveitis affecting the posterior segment is responsible for 10% of all cases of blindness in developed countries.[2] Although uveitis affects persons of all age groups, it is diagnosed more frequently in patients aged 20 to 40 years. In this age group, uveitis has been reported to equal diabetic retinopathy as the leading cause of blindness in developed countries. Children constitute 5 to 10% of patients with uveitis.[3]

How Is Uveitis Classified?

Many different approaches have been developed in an attempt to organize the various causes of uveitis and to help the practitioner to reach the correct diagnosis when faced with a patient with intraocular inflammation (Table 19–1). Although none of the classification schemes alone is perfectly complete, each has individual merit. When used collectively, they require that the examiner carefully consider the patient's demographics, history, and clinical findings to generate a differential diagnosis that will direct the diagnostic testing needed to determine the most probable cause of the uveitis. The simplest classification scheme divides the causes of uveitis into *infectious* and *noninfectious*. From a practical point of view, this distinction is the most important because it will dictate the approach to treatment with either specific antibiotics or immunosuppressive therapy. A second classification scheme attempts to categorize the various causes of uveitis as *acute* or *chronic* on the basis of their clinical course. In another scheme, uveitis is classified as granulomatous if findings consistent with granulomas are present on ophthalmic examination and nongranulomatous when no evidence of ocular granulomas is found. The most widely accepted and used classification scheme for uveitis is the *anatomic* classification, which divides uveitis into four categories (anterior, intermediate, posterior, and panuveitis), depending on the primary site of inflammation in the eye.

How Do You Distinguish between Acute and Chronic Uveitis?

Acute uveitis has an abrupt, symptomatic onset of the ocular inflammation in one or both eyes. Although recurrent, each new episode of ocular inflammation or flare spontaneously resolves, and the eye becomes quiet within 6 weeks even in the absence of treatment.

TABLE 19–1. Classification Schemes for Uveitis

Infectious (diseases caused by parasites, viruses, fungi, bacteria, or mycobacteria) or
NonInfectious (diseases of immune-mediated or unknown etiology)
Acute (duration of ocular inflammation less than 6 wk) or
Chronic (duration of ocular inflammation greater than 6 wk)
Granulomatous (granulomatous lesions associated with ocular inflammation) or
Nongranulomatous (ocular inflammation not associated with granulomatous lesions)
Anatomic
Anterior (ocular inflammation primarily affecting the iris, ciliary body pars plicata, anterior chamber, and corneal endothelium)
Intermediate (ocular inflammation primarily affecting the vitreous, ciliary body pars plana, and peripheral retina)
Posterior (ocular inflammation primarily affecting the retina and choroid)
Panuveitis (ocular inflammation involving the entire uvea and adjacent layers without a predominant focus)

Most causes of acute uveitis are either idiopathic or associated with the class I human leukocyte antigen, HLA-B27. Examples of such diseases include HLA-B27-associated anterior uveitis, ankylosing spondylitis, and Reiter syndrome. Behçet syndrome and many of the white-dot syndromes are examples of acute posterior segment uveitis.

Uveitis is considered chronic if the intraocular inflammation persists for 6 weeks or longer with or without treatment. Most noninfectious causes of uveitis are chronic. Sarcoidosis is the most common cause of chronic posterior segment uveitis. Other types of chronic uveitis that affect the posterior segment are birdshot retinochoroidopathy, serpiginous choroidopathy, multifocal choroiditis, pars planitis, and primary intraocular lymphoma.

How Do You Differentiate between Granulomatous and Nongranulomatous Uveitis?

Uveitic diseases can be classified as nongranulomatous or granulomatous by the absence or presence of specific clinical findings on ocular examination suggestive of the presence of granulomas in the eye. Granulomas are discrete collections of macrophages, epithelioid cells, and giant cells surrounded by chronic inflammatory cells and fibroblasts. In the eye, granulomatous inflammation manifests by the presence either of greasy-appearing or "mutton-fat" keratic precipitates, nodular lesions in the iris stroma (Busacca nodules) or pupillary margin (Koeppe nodules), and lesions subjacent to the retinal pigment epithelium (RPE), known as Dalen-Fuch nodules. Only a limited number of uveitic diseases, such as sarcoidosis, sympathetic ophthalmia, multiple sclerosis (MS), lens-induced uveitis, syphilis, tuberculosis, and the Vogt–Koyanagi–Harada (VKH) syndrome, are known to cause granulomatous inflammation in the eye. Some diseases, such as sarcoidosis, MS, and toxoplasmosis, can present with either a granulomatous or nongranulomatous appearance.

How Do You Define Uveitis Anatomically?

The International Uveitis Study Group has proposed an anatomic classification for uveitis divided into four categories: anterior, intermediate, posterior, and panuveitis.[4] According to this classification scheme, the type of uveitis is defined by the location of the primary site of inflammation in the eye. Anterior uveitis is diagnosed when the intraocular inflammation is predominantly limited to the anterior segment or structures, including and anterior to the lens–iris diaphragm. In severe cases of anterior uveitis, inflammatory cells from the anterior chamber may spill over into the retrolental space, producing an anterior vitreitis. Other terms used for anterior uveitis are iritis, iridocyclitis, and anterior cyclitis.[5] Some causes of anterior uveitis include the HLA-B27-associated diseases, juvenile rheumatoid arthritis, sarcoidosis, Behçet disease, Fuch heterochromic iridocyclitis, and masquerade syndromes (Table 19–2).

Intermediate uveitis is characterized by inflammation that primarily affects the pars plana, vitreous, and vessels of the peripheral retina. Inflammatory cells originating in the middle segment of the eye typically diffuse throughout the vitreous cavity and may escape into the anterior chamber, producing a concomitant anterior uveitis. Diseases commonly associated with intermediate uveitis are sarcoidosis, inflammatory bowel disease (IBD), MS, and pars planitis (Table 19–3). Other names in the literature that describe patients with intermediate uveitis include vitreitis, peripheral exudative retinitis, cyclochorioretinitis, chronic posterior cyclitis, and peripheral uveoretinitis.[6]

TABLE 19–2. Causes of Anterior Uveitis

Idiopathic
HLA-B27 associated anterior uveitis
Ankylosing spondylitis
Reiter syndrome
Psoriatic arthritis
Inflammatory bowel disease
Juvenile rheumatoid arthritis
Fuch heterochromic iridocyclitis
Sarcoidosis
Syphilis
Masquerade syndromes

HLA, human leukocyte antigen.

TABLE 19–3. Causes of Intermediate Uveitis

Noninfectious
Idiopathic
Intermediate uveitis of the pars planitis subtype (pars planitis)
Sarcoidosis
Inflammatory bowel disease
Multiple sclerosis
Primary intraocular lymphoma
Masquerade syndrome
Infectious
Lyme disease
Syphilis
Tuberculosis

The term *posterior uveitis* defines ocular inflammatory conditions that primarily affect the retina and choroid. Although the vitreous is not the primary focus of the inflammation in posterior uveitis, vitreitis is typically present as a result of the spillover of inflammatory cells from the retina or choroid into the vitreous cavity. Similarly, in cases of moderate or severe posterior uveitis, inflammatory cells can reach the anterior chamber. Posterior uveitis can be further classified as retinitis if the retina alone is affected, choroiditis if the choroid alone is affected or as retinochoroiditis or chorioretinitis to denote inflammatory conditions affecting both layers simultaneously. Posterior uveitis also can be described as focal or multifocal. Toxoplasmosis and toxocariasis are causes of posterior uveitis typically characterized by a focal lesion, whereas fungal and viral pathogens, sarcoidosis, sympathetic ophthalmic, the VKH syndrome, serpiginous choroidopathy and birdshot retinochoroidopathy characteristically cause multifocal lesions. Retinal vasculitis refers to those causes of posterior uveitis in which the primary focus of inflammatory disease seems to be the retinal vasculature. Many causes of retinal vasculitis are associated with systemic diseases such as Behçet syndrome, systemic lupus erythematosus (SLE), Wegner granulomatosis, and sarcoidosis (Table 19–4). Finally, the term *panuveitis* is used to describe diseases characterized by intraocular inflammation simultaneously affecting all intraocular structures without a predominant focus in any segment. The most frequently diagnosed causes of panuveitis are syphilis, sarcoidosis, the VKH syndrome, infectious endophthalmitis, Behçet syndrome, and sympathetic ophthalmia (Table 19–5). In this chapter, the term *posterior segment* refers to ocular structures posterior to the lens–iris diaphragm and the term *posterior segment uveitis* will include conditions classified anatomically as intermediate, posterior, and panuveitis.

TABLE 19–4. Noninfectious Causes of Posterior Uveitis

Noninfectious causes of multifocal posterior uveitis
Sarcoidosis
Masquerade syndromes
Vogt–Koyanagi–Harada syndrome
Serpiginous choroidopathy
Birdshot chorioretinopathy
Sympathetic ophthalmia
Multifocal choroiditis
White-dot syndromes
Multiple evanescent white dot syndrome (MEWDS)
Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
Acute retinal pigment epitheliitis
Acute zonal occult outer retinopathy (AZOOR)
Punctate inner choroidopathy (PIC)
Primary intraocular lymphoma
Masquerade syndromes
Noninfectious systemic diseases that cause retinal vasculitis
Behçet disease
Sarcoidosis
Multiple sclerosis
Crohn disease
Wegener granulomatosis
Systemic lupus erythematosus
Polyarteritis nodosa
Polymyositis/dermatomyositis
Postvaccination syndrome
Buerger disease
Takayasu disease
Cogan syndrome
Sjögren syndrome
Allergic granulomatosis
Noninfectious primary ocular diseases that cause retinal vasculitis
Idiopathic
Eales disease
Intermediate uveitis of the pars planitis subtype
Birdshot retinochoroidopathy
Masquerade syndromes

Signs and Symptoms of Uveitis

Symptoms of Uveitis

The most common symptoms of uveitis affecting the posterior segment are blurred vision, floaters, and visual loss. In some cases, the patient may be asymptomatic. The blurred vision may be the result of protein and inflammatory cells in the anterior chamber or vit-

TABLE 19–5. Causes of Noninfectious Panuveitis

Syphilis infection
Endophthalmitis
Sarcoidosis
Vogt–Koyanagi–Harada syndrome
Behçet disease
Sympathetic ophthalmia

reous, cataract, or the sequelae of intraocular inflammation, such as macular edema or hypotony. Floaters can be attributed to aggregates of vitreal inflammatory cells, vitreous syneresis, and detachment of the posterior vitreous, which can produce mobile opacities that cast shadows upon the retina. The major cause of visual loss in patients with posterior segment uveitis is cystoid macular edema. Visual loss also may result from secondary glaucoma, retinal neovascularization with vitreous hemorrhage, retinal detachment, epiretinal membranes, subretinal neovascularization, subretinal fibrosis, and atrophy of the optic nerve, RPE, or choroid. Ocular pain in patients with uveitis can be attributed to inflammation in the iris and ciliary body. Patients with posterior uveitis, however, are often asymptomatic or complain only of mild ocular discomfort. Severe pain is unusual and may be the result of increased intraocular pressure resulting from angle closure, pupillary block, or the development of scleral inflammation (sclerouveitis). Other symptoms, such as photopsias, metamorphopsia, micropsia, macropsia, scotomas, dyschromatopsia, and nyctalopia, may be reported in patients with posterior segment uveitis and in many cases correlate with the presence of lesions in the fundus.

What Are the Signs of Uveitis in the Anterior Segment?

Signs of uveitis in the anterior segment of the eye include ocular injection, band keratopathy, keratic precipitates, aqueous cell and flare, hypopyon, anterior and posterior synechiae, and cataract. Conjunctival injection associated with uveitis can be differentiated from conjunctivitis by the lack of involvement of the fornix and palpebral conjunctiva. Conjunctival injection is a typical sign of acute anterior uveitis but is less common in posterior segment uveitis. Ciliary flush or circumlimbal injection is considered to be an external marker of ciliary body inflammation and a more specific marker of uveitis. Band keratopathy, the subepithelial deposition of calcium salts in the middle third of the cornea, is frequently found in children with chronic uveitis but is infrequently seen in adults. Keratic precipitates, aggregates of inflammatory cells that usually deposit on the lower half of the corneal endothelium, are the most common corneal finding in uveitis. Nongranulomatous keratic precipitates are composed of neutrophils and lymphocytes and appear clinically as punctate, fleck-like, linear, or stellate endothelial opacities. Granulomatous keratic precipitates, composed of macrophages and giant cells, are larger, rounder, and often appear pigmented and greasy, hence the term *mutton fat*. The presence of keratic precipitates does not define the activity of the intraocular inflammation because they can occur later in the active disease course and may persist after the uveitis has resolved. Anterior chamber cells or inflammatory cells circulating within the aqueous humor are required for the diagnosis of anterior uveitis and panuveitis. Although usually found in most cases of intermediate uveitis, anterior chamber cells may not be found in milder cases of posterior uveitis. *Flare*, the ability to visualize a beam of light in the anterior chamber, is a manifestation of increased vascular permeability in the anterior segment. Although typically accompanying cells in the anterior chamber, flare alone is not a sign of active inflammation because damaged anterior segment blood vessels may continue to leak proteins into the anterior chamber long after the active inflammation has resolved. A hypopyon, the acute accumulation of inflammatory cells that layer in the inferior angle, is an uncommon finding in uveitis that always should raise the differential of an infectious endophthalmitis, Behçet disease, and HLA-B27- associated uveitis. *Synechiae* are adhesions between the iris and the anterior chamber angle or cornea (peripheral anterior synechiae) or the pupillary iris and lens (posterior synechiae). Although they can develop within days after the onset of severe intraocular inflammation, synechiae are more typical of chronic or recurrent types of uveitis. Posterior subcapsular cataracts are the most common lens opacity associated with uveitis. Uveitis can be associated with elevated intraocular pressure or hypotony. Increased intraocular pressure can result from trabeculitis, clogging of the trabecular meshwork by inflammatory debris, angle closure, or pupillary blockage caused by peripheral anterior and posterior synechiae, respectively. Hypotony may result from ciliary body detachment caused by a cyclitic membrane or dysfunction due to inflammation.

What Are the Posterior Segment Signs of Uveitis?

The salient clinical signs of the uveitis in the posterior segment are vitreitis, retinal vasculitis, cystoid macular edema, swelling of the optic disc, and the presence of focal or multifocal retinal or choroidal infiltrates. Vitreitis characterized clinically as vitreous cells and haze (a reduction in vitreous clarity) is caused by the infiltration of cells and protein derived from inflammatory foci in the ciliary body, retina, or choroid into the vitreous cavity. The cellular exudate in the vitreous may be localized to the retrolental space (*anterior vitreitis*) or concentrated above a chorioretinal lesion, but it is more likely to be diffuse within the cortical vitreous. Aggregates of inflammatory cells appearing as grayish white opacities in the vitreous, called *snowballs*, provide an obvious explanation for the patient's

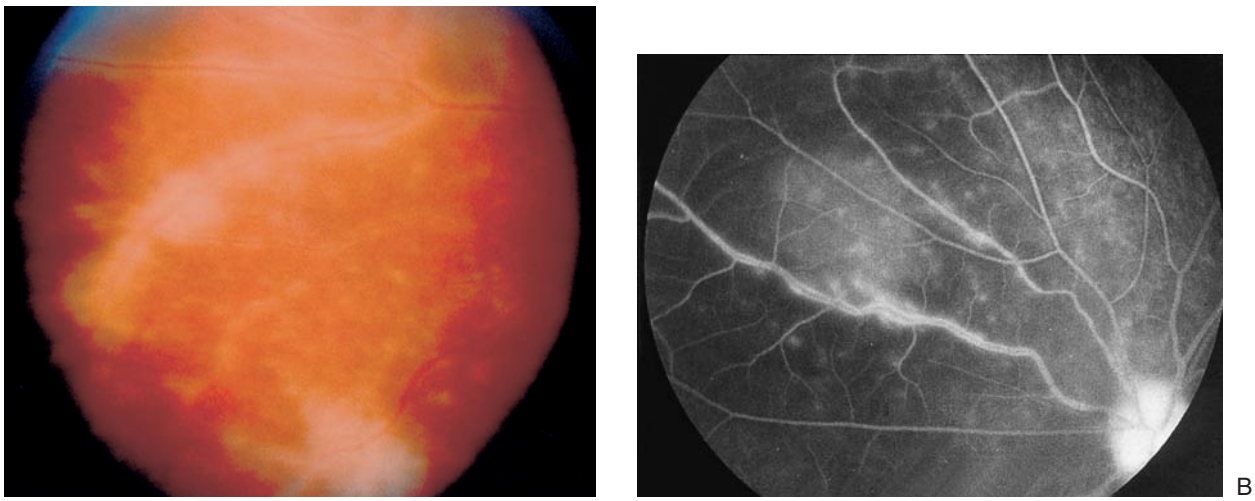


FIGURE 19–1. Retinal vasculitis. (A). Prominent sheathing, the accumulation of inflammatory exudates around retinal vessels, can be seen in this case of severe retinal vasculitis. (B). The fluorescein angiogram shows staining and leakage along the retinal venules characteristic of retinal vasculitis.

complaints of floaters. Other common vitreal findings in posterior segment uveitis are vitreous syneresis, posterior vitreous detachments, and vitreous veils (aggregates of inflammatory material adherent to synergetic vitreous strands). On resolution of the uveitis, the vitreous haze rapidly clears, but the cells, snowballs, and veils tend to persist, with many of the remaining cells taking on a pigmented appearance.

Retinal vasculitis is clinically denoted by perivascular sheathing (exudation of inflammatory cells along vascular walls) on ophthalmoscopy and by vascular leakage and staining of the vessel walls on fluorescein angiography (Figs. 19–1 and 19–2). Retinal vasculitis limited to the peripheral or anterior retinal vessels with sparing of the vessels in the posterior pole is characteristic of an intermediate uveitis and may result in perivascular hemorrhages and peripheral retinal ischemia as a result of capillary dropout leading to peripheral retinal neovascularization. Retinal vasculitis in the posterior pole, in contrast, is more likely to induce venous dilatation, splinter hemorrhages, cotton-wool spots, and vascular occlusion that can result in macular ischemia or cystoid macular edema. Generally, retinal vasculitis in the posterior pole can be distinguished from noninflammatory causes of retinal vascular occlusion, like central or branch retinal vascular occlusion by the absence of vascular sheathing and other evidence of intraocular inflammation. Inactive vasculitis is characterized by perivascular sheathing without angiographic leakage and attenuated retinal vessels that may appear sclerotic. Cystoid macular edema, retinal edema, and edema of the optic nerve, intraretinal infiltrates, and exudative retinal detachments all are manifestations of vascular permeability in patients with uveitis.

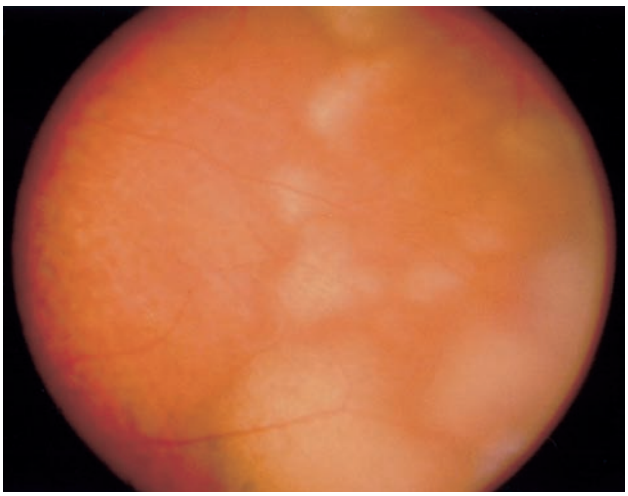


FIGURE 19–2. Primary intraocular lymphoma. Note the creamy appearance and indistinct margins of subretinal tumor masses in the peripheral retina. The lack of clarity of the photograph is due to the grade 1+ vitreous haze.

The presence of retinochoroidal or chorioretinal lesions distinguishes intermediate uveitis from cases of posterior and panuveitis. The chorioretinal or retinochoroidal lesions that define posterior and panuveitis may have a wide variety of appearances. In some cases of posterior uveitis, the recognition of a particular appearance or pattern of distribution by the lesions or their association with certain demographic, systemic, or other ocular findings may allow a specific diagnosis to be made, but there is considerable overlap. Important clinical features to note about the fundus lesions in patients with posterior uveitis are their size, distribution, location, and degree of activity. In general, ac-

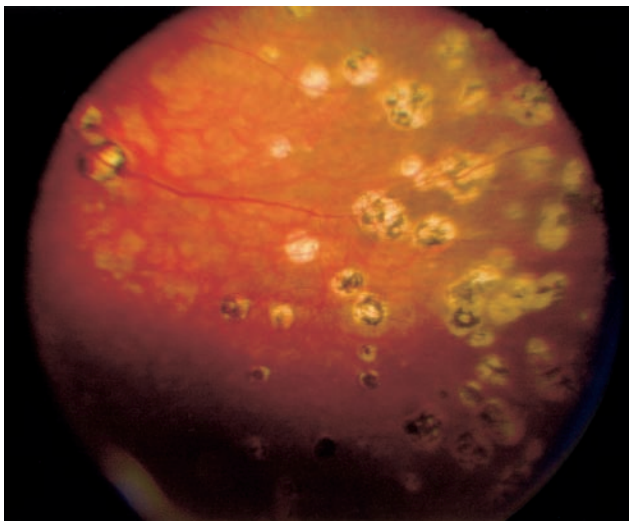


FIGURE 19–3. Multifocal choroiditis. Depicted here are multiple, inactive, variably pigmented "punched-out" chorioretinal lesions that can be seen in a variety of other conditions causing posterior uveitis, including sarcoidosis, the Vogt-Koyanagi-Harada (VKH) syndrome, and sympathetic ophthalmia.

tive lesions have ill-defined margins, appear as creamy with a yellowish coloration, may be associated with retinal edema or opacification, and have no associated RPE hyperpigmentation (Fig. 19–2). In contrast, inactive lesions more often have distinct edges; appear more white or whitish gray because of fibrosis; might be associated with atrophy of the adjacent retina, RPE, and choroidal tissues; and are frequently pigmented as a result of RPE proliferation (Fig. 19–3).

Posterior Segment Uveitis

How Is the Severity of Posterior Segment Uveitis Determined?

The severity of uveitis may be determined not only by the findings on the clinical examination but also by an assessment of the way the ocular disease has responded to previous therapy and the affect of the ocular disease on the patient's quality of life and daily activities. An objective quantification of the intraocular inflammation during the ophthalmic examination is the most important tool used to determine the severity of the uveitis. In the anterior chamber, cells and flare are recorded, whereas in the vitreous cavity, vitreous cells and haze are recorded. Anterior chamber cells and flare are best seen by directing a 1 mm × 1 mm slit lamp beam into the anterior chamber using the highest illumination obliquely across the eye and focusing posterior to the cornea. According to the grading scheme utilized at the National Eye Institute (NEI) for anterior chamber cells a grade of 0 to 4+ is given by counting the number of cells within the light beam[7] (Table 19–6). It is important to differentiate white blood cells that signify active inflammation from pigmented cells, such as red blood cells and iris pigment epithelial cells, which also can be seen in the anterior chamber but do not indicate an active uveitis. Flare is proportional to the concentration of protein in the aqueous humor. Clinically, flare is graded on a scale from 0 to 4+ (Table 19–6), the latter representing anterior segment protein leakage so extensive that a fibrin clot is present.[7] Fluorophotometry and the laser flare meter are ophthalmic instruments that also can be used to objectively assess the degree of aqueous flare. The quantification of vitreous cells and haze can be more difficult in patients with active anterior uveitis, cataract, or posterior synechiae. Furthermore, the vitreous cells may be localized to only a part of the vitreous cavity. Using the NEI approach (Table 19–7),

TABLE 19–6. Grading of Anterior Chamber Cells and Flare

Number of cells	*Cell Grade*
0	0
1–5	Trace
6–15	1+
16–25	2+
26–50	3+
>50 or hypopyon	4+
Slit beam	Flare grade
Slit beam is optically undetectable	0
Slight (any appreciable light in slit beam)	1+
Mild (iris and lens details clear through slit beam)	2+
Moderate (iris and lens hazy through slit beam)	3+
Severe (plasmoid aqueous or fibrin present in anterior chamber)	4+

Modified from Nussenblatt RB, Whitcup SM, Palestine AG. Examination of the patient with uveitis. In: Nussenblatt RB, Whitcup SM, Palestine AG, eds. *Uveitis: Fundamentals and Clinical Practice*. St. Louis: Mosby; 1996:58–68, with permission.

TABLE 19–7. Grading of Vitreous Cells and Haze

No. of Cells[a]	*Description*	*Grade*
0–1	Clear	0
2–20	Few opacities	Trace
21–50	Scattered opacities	1+
51–100	Moderate opacities	2+
101–250	Many opacities	3+
>250	Dense opacities	4+

[a]Cells are counted using a Hruby, 90- or 78-diopter lens.

Modified from Nussenblatt RB, Whitcup SM, Palestine AG. Examination of the Patient with Uveitis. In: Nussenblatt RB, Whitcup SM, Palestine AG, eds. *Uveitis: Fundamentals and Clinical Practice*. St Louis: Mosby; 1996:58–68, with permission.

vitreous cells are graded from 0 to 4+ using a Hruby, 90- or 78-diopter lens at the slit-lamp biomicroscope to view the vitreous cells in retroillumination.[7] In the vitreous, haze is believed to be a better indicator of active inflammation than vitreous cells because the degree of haze combines the optical effect of the cellular infiltrate and protein leakage in the vitreous cavity. Our grading scale from 0–4+ for vitreous haze (Table 19–7) includes a trace grade and is based on the view of the optic disc and posterior retina using an indirect ophthalmoscope and 20 diopter lens.[8] In assessing the degree of vitreous cells using this method, it is important to correct mentally for corneal and lens opacities and anterior segment inflammation. The use of photographic standards makes this system more reproducible than other subjective grading schemes.[8]

The use of ancillary ophthalmic tests also can be helpful in determining the severity of uveitis in the posterior segment and may aid in the discrimination of the various uveitic diseases. Fluorescein angiography is valuable for the detection of retinal and choroidal infiltrates, vascular staining and leakage, retinal, optic disc and cystoid macular edema, retinal nonperfusion and neovascularization, and subretinal neovascular membranes. Indocyanine green (ICG) angiography is useful for revealing the extent of choroidal inflammatory lesions. B-scan ultrasonography and ultrasound biomicroscopy (UBM) can demonstrate choroidal thickening, retinal and vitreous detachments, vitreous inflammatory debris, pars plana exudates, particularly when the posterior pole cannot be viewed because of posterior synechiae and media opacities. Additionally, ultrasonography is beneficial for the interpretation of intraocular masses. Electrophysiologic studies, such as the visual evoked potential (VEP), can help to differentiate optic nerve disease from retinal damage resulting from chronic intraocular inflammation; electroretinography (ERG) and electrooculography (EOG) generally show nonspecific reduction in cases of uveitis corresponding to the extent of chorioretinal disease.

The patient's subjective view of his or her ocular condition should be elicited when the history is taken. Previous medications given to treat the uveitis, the affect of the medications on the intraocular inflammation, and the course of the disease once treatment is tapered or withdrawn should be carefully recorded. It is also important to know how the patient tolerated the recommended therapy, specifically whether corticosteroids were prescribed. This information, together with an accurate assessment of the objective clinical findings, determines the severity of the uveitis in a given patient and forms the basis for recommending an appropriate tailored therapeutic regimen.

How Is a Differential Diagnosis for Posterior Segment Uveitis Generated?

A differential diagnosis should be developed for each patient with uveitis after completion of a thorough history and ophthalmic examination and before any diagnostic tests are ordered or therapy instituted.[9] The exercise of generating the differential diagnosis should be performed even if the diagnosis seems certain clinically. The differential diagnosis is a useful guide for determining which laboratory and ancillary studies should be requested and provides ready diagnostic alternatives if the patient does not respond appropriately to therapy or later develops new ophthalmic or systemic symptoms or signs. A differential diagnosis can be easily developed by considering the answers to the following questions: Is the disease acute or chronic? Is the inflammation granulomatous or nongranulomatous? Where is the inflammation located in the eye? How did the disease respond to previous therapy? Is the disease unilateral or bilateral? What are the demographics of the patient? What associated systemic symptoms and physical signs does the patient have? The significance of the responses to the first four of these questions have been addressed previously in this chapter; therefore, only the last question is considered here.

Although one eye may be affected first, most causes of posterior segment uveitis involve both eyes within the first several months. Causes of uveitis that frequently involve a single eye even after months or years include sarcoidosis, Behçet disease, and infectious causes of uveitis, such as toxoplasmosis, acute retinal necrosis, and postoperative endophthalmitis. Demographic considerations, such as the patient's age, sex, race, ethnic heritage, geographic residence, dietary habits, animal exposure, travel history, social behaviors, and sexual habits, can lead the ophthalmologist to suspect certain types of uveitis. Age is particularly important because certain causes of uveitis are more common among patients of specific age group. For example, in children younger than 5 years, the most likely cause of posterior segment uveitis is infectious or neoplastic. Children aged 5 years to adolescence with posterior segment uveitis are more likely to have juvenile rheumatoid arthritis with spillover from the anterior segment or intermediate uveitis. Sarcoidosis and primary intraocular lymphoma should be strongly considered in any patient over the age of 50 years with new-onset posterior segment uveitis. The white-dot syndromes tend to affect women more commonly than men. Sarcoidosis is the most frequent cause of uveitis in African Americans in the United States. Patients from ethnic groups characterized by darker skin pigmentation are more

susceptible to the VKH syndrome, whereas patients of northern European descent, where the incidence of the HLA-A29 is more common, are more likely to develop birdshot retinochoroidopathy. Lyme disease is most probable in persons living in the northeastern United States, where the vector is commonly found. Patients with acquired toxoplasmosis frequently report a history of exposure to cats or ingestion of undercooked meats. Finally, it must be remembered that patients with high-risk behaviors for human immunodeficiency virus (HIV) transmission are susceptible to the numerous ocular manifestations of acquired immunodeficiency syndrome (AIDS).

Specific systemic complaints and findings on physical examination that may suggest the presence of an underlying systemic disease known to cause uveitis should be sought during the history, with a comprehensive review of systems and, if necessary, consultation with other medical specialists. Symptomatic arthritis and systemic vasculitis in a patient with posterior segment uveitis are not infrequent and may result from numerous systemic diseases, including Behçet disease, sarcoidosis, Lyme disease, IBD, SLE, and other connective tissue diseases that are common to rheumatologist. Neurologic symptoms raise the possibility of MS or Behçet disease, sarcoidosis, the VKH syndrome, and SLE. Headaches and hearing difficulties temporally related to the uveitis suggest the diagnosis of the VKH syndrome and sarcoidosis. Because patients with neurologic symptoms may require neuroimaging and a lumbar puncture, they should be further evaluated in consultation with a neurologist or neuroophthalmologist. Cerebrospinal fluid pleocytosis is a frequent finding in patients with VKH, sarcoidosis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and Behçet. Lesions in the brain or optic nerves may be found in patients with sarcoidosis, primary intraocular lymphoma, MS, and Behçet disease. Behçet disease, sarcoidosis, herpes simplex and zoster, syphilis, and Lyme disease are all associated with cutaneous lesions that can be easily differentiated with the help of a dermatologist. The cutaneous lesion erythema nodosum is frequently seen in patients with Behçet disease and sarcoidosis; vitiligo, poliosis, and alopecia are characteristic of the VKH syndrome. Patients should be questioned about the occurrence of oral and genital ulcers, which will raise the possibility of Behçet disease. Diarrhea and abdominal discomfort are common manifestations of IBD. Similarly, cough and shortness of breath are frequent presentations of sarcoidosis. To rule out the possibility of Wegner granulomatosis, sinus complaints should be investigated by an otolaryngologist.

What Are Masquerade Syndromes?

Masquerade syndromes comprise a group of malignant and nonmalignant systemic or primary ocular diseases that clinically present in the eye as an intraocular inflammatory disease or uveitis. In a clinical study, uveitis masquerade syndromes were diagnosed in 5% of patients with uveitis at a tertiary center.[10] In patients with the masquerade syndromes, the ocular findings that are presumed to be a result of an immune mediated process in reality are the result of a noninflammatory disease. No specific features can be relied on to distinguish masquerade diseases that can mimic any form of uveitis. In the eye, malignant cells, pigment, pigmented epithelial cells, and melanocytic cells are easily confused with the white blood cells that define a true inflammatory uveitis. Generally, masquerade syndrome should be considered if the patient is younger than 5 or older than 50 years of age at onset of ocular disease, if the clinical features of the ocular disease and course are atypical for the presumed uveitis diagnosis, or if there is no response to adequate immunosuppressive therapy. In some cases, the diagnosis of an ocular masquerade syndrome may be the first manifestation of a potentially life-threatening disease. The most common malignant diseases that masquerade as uveitis are primary CNS or primary intraocular lymphoma in adults and acute leukemias in children. Other malignancies known to masquerade as uveitis include retinoblastoma, choroidal melanomas, metastatic systemic lymphoma, and carcinomas, of which breast and lung are now the most common. Systemic malignancies that metastasize to the eye generally do so late in the disease course and most commonly involve the choroid. Nonmalignant conditions that masquerade as uveitis include hypertension, pigment dispersion, retinal detachment, degenerative retinal diseases, systemic vascular diseases, intraocular foreign bodies, ocular trauma, and hereditary ocular diseases (Table 19–8). Fluorescein angiography is useful in the diagnosis of nonmalignant masquerade syndromes.[10] Once the diagnosis of a uveitis masquerade syndrome is entertained, the patient should undergo a thorough medical evaluation including review of systems and imaging, if needed. Diagnostic procedures, including an aqueous paracentesis, vitrectomy, or ocular tissue biopsy, should be performed without delay after the withdrawal of any immunosuppressive therapy, particularly steroids to increase the diagnostic yield. Before the diagnostic procedure, handling of the ocular specimen for routine pathologic studies, such as histology, cytology, immunohistochemistry or electron microscopy, microbiologic culture, serologic assays, or molecular analysis, should be discussed with an ocular pathologist.

TABLE 19–8. Commonly Recognized Uveitis Masquerade Syndromes

Malignant disorders
In adults
Primary central nervous system or primary intraocular lymphoma
Systemic non-Hodgkin's lymphoma metastatic to the eye
Metastatic carcinoma to the eye
Breast
Lung
Renal
Uveal melanoma
In children
Leukemia
Retinoblastoma
Medulloepithelioma
Juvenile xanthogranuloma
Nonmalignant disorders
Intraocular foreign body
Retinal detachment
Pigment dispersion syndrome
Hereditary retinal degenerations
Myopic degeneration
Hypertension
Occult ocular trauma
Ocular ischemic syndrome

What Are the Clinical Features of Primary Intraocular Lymphoma?

Primary CNS lymphoma (PCNSL) is typically a B-cell extranodal non-Hodgkin lymphoma that can originate in the brain, spinal cord, leptomeninges, and eyes. It represents 4 to 6% of all primary brain tumors and 1 to 2% of all extranodal lymphomas.[11] Primary intraocular lymphoma (PIOL) defines a subset of PCNSL in which lymphoma cells are initially present only in the eyes. PCNSL and PIOL are to be distinguished from a systemic lymphoma that has metastasized to the brain and eye, respectively. Although the incidences of both PCNSL and PIOL have increased within the last few decades, both are considered rare malignancies. Studies demonstrating the presence of DNA from the Epstein-Barr virus, human herpesvirus-6 and -8, and, most recently, *Toxoplasma gondii*, suggest a role for infectious pathogens in the development of PCNSL and PIOL.[12] The median age of onset for PCNSL and PIOL is the fifth to sixth decades of life. Because PIOL can masquerade for years as an intermediate uveitis or idiopathic vitreitis, it should be considered high in the differential diagnosis of any patient over 50 years of age with new-onset or persistent uveitis, particularly if there are any neurologic complaints. Of the 60 to 80% of patients with PIOL that eventually develop CNS disease, most do so within 1 to 2 years after the ocular disease is diagnosed.[13,14]

Floaters and blurred vision are the most common ocular complaints from patients with PIOL. The disease is bilateral in 80% of cases. Anterior segment inflammation in patients with PIOL is typically minimal, although in rare cases a neoplastic hypopyon can occur. The vitreitis in patients with PIOL appears as clumps or sheets of cells that may obscure the retina, which may or may not show yellow punctate lesions, subtle RPE elevations, pigment mottling, or large subretinal lesions that pathologically are lymphoma cells infiltrating between the RPE and Bruch membrane (Fig. 19–2). Atypical findings include iris infiltrates, vascular sheathing, hemorrhagic retinal exudates mimicking a viral retinitis, and the presence of large elevated subretinal mass lesions.[15,16] Fluorescein angiography commonly shows punctate hyperfluorescent and hypofluorescent lesions, predominantly within the posterior pole. An important clinical "pearl" is that although the disease initially may respond to immunosuppression, it ultimately becomes resistant to therapy. Another important clinical pearl is that patients with PIOL tend to have a visual acuity much better than would be expected for their degree of vitreitis. This may be because cystoid macular edema, in our experience, is extremely uncommon in eyes with PIOL unless there has been previous ocular surgery.

Evaluation of a patient suspected to have PIOL includes thorough medical and neurologic examinations to rule out evidence of a systemic malignancy, neuroimaging to detect the presence of CNS lesions, and repeated lumbar punctures with cytologic examination of the cerebrospinal fluid to rule out the presence of malignant lymphoid cells. If these examinations are not diagnostic, a vitrectomy should be performed on the eye with the worst vision or most severe vitreitis with immediate cytologic examination of the vitreous specimen to increase the diagnostic yield. If corticosteroids were given as treatment for uveitis, they should be discontinued for at least 1 month before a diagnostic procedure is done. In some cases, a chorioretinal biopsy or fine-needle aspiration biopsy of an elevated subretinal lesion may be required to obtain diagnostic tissue. PIOL is a high grade, large B-cell lymphoma. T-cell phenotypes have been reported but are extremely rare.[17] It has been demonstrated that molecular analysis of atypical lymphoid cells for rearrangements of the immunoglobulin heavy-chain gene and measurement of interleukin 10 (IL-10) and IL-6 levels in the cerebrospinal and vitreous specimens are useful adjunctive tools for the diagnosis of PCNSL and PIOL, respectively.[18,19] In these specimens, an elevated IL-10 level with an IL-10:IL-6 ratio greater than 1.0 suggests the presence of malignant lymphoid cells.[20,21]

Present treatment strategies for PCNSL include radiation alone, combined radiation and chemotherapy, and chemotherapy-only regimens.[22] The best method

of treatment for patients with PIOL or recurrent PCNSL in the eyes only has not been determined. Although ocular radiation is the most commonly reported treatment for PIOL, fewer patients are receiving radiotherapy because of the high incidence of ocular recurrence and the risks for delayed complications, such as radiation retinopathy, optic neuropathy, cataracts, glaucoma, keratoconjunctivitis sicca, persistent corneal epithelial defects, and limbal stem cell loss. Most patients with PIOL are currently being treated with chemotherapy regimens using high-dose methotrexate. The successful use of intravitreal methotrexate for the treatment of PIOL has been described.[23,24] The major complication of this therapy is ocular surface disease, which may be treated or prevented with topical folinic acid drops. Despite treatment for PIOL, recurrence is common. Because treatment involves the use of chemotherapy and the high probability of subsequent disease within the brain, patients with PIOL should be managed in consultation with a neurologist or neurooncologist skilled in the treatment of this disease.

What Are the Causes of Posterior Uveitis?

Posterior uveitis defines ocular inflammatory conditions that primarily affect the retina and choroid. As a result of direct damage to these tissues, posterior uveitis and panuveitis are a greater cause of visual morbidity than anterior and intermediate uveitis. Posterior uveitis may be a manifestation of an infectious or non-infectious disease. Common infectious causes of posterior uveitis are parasitic diseases, such as toxoplasmosis and toxocariasis; viral diseases, such as cytomegalovirus (CMV) retinitis, herpes simplex, and varicella zoster viruses, which cause acute retinal necrosis and progressive outer retinal necrosis; fungal diseases, like histoplasmosis, candidiasis, *Nocardia asteroides*, cryptococcosis; and bacterial diseases, including syphilis, Lyme disease, and tuberculosis. This chapter focuses on the noninfectious causes of posterior uveitis (Table 19–4). Noninfectious causes of posterior uveitis producing focal lesions are uncommon; therefore, solitary retinal or choroidal lesions associated with ocular inflammation should raise the possibility of an infectious disease or an intraocular malignancy. Causes of posterior uveitis characterized by multifocal lesions include multifocal choroiditis, birdshot retinochoroidopathy, serpiginous choroidopathy, sarcoidosis, and the VKH syndrome. The white-dot syndromes are a group of diseases that cause localized, well-circumscribed inflammatory lesions in the fundus. Posterior uveitides falling under this heading, including the multiple evanescent white-dot syndrome (MEWDS), acute posterior multifocal placoid pigment epitheliopathy (APMPPE), acute zonal occult outer retinopathy (AZOOR), and birdshot retinochoroidopathy, are discussed elsewhere in this text.

What Are the Clinical Features of Multifocal Choroiditis?

Multifocal choroiditis is a primary ocular disease. Clinically, patients with multifocal choroiditis have bilateral ocular findings similar to those of the presumed ocular histoplasmosis syndrome (POHS), including multiple "punched-out" chorioretinal scars ranging 50 to 200 μ at the level of the RPE and choroid and peripapillary pigment changes. Compared with ocular histoplasmosis, the chorioretinal scars in multifocal choroiditis show greater peripheral pigmentation and are more commonly found posterior to the equator (Fig. 19–3). Unlike patients with the ocular histoplasmosis syndrome, who characteristically have a clear ocular media, the posterior segment in patients with multifocal choroiditis typically shows a significant vitreitis that may spill over into the anterior chamber. Optic-disc edema is another frequent finding. Because of the anterior segment inflammation, some researchers have described the disease as multifocal choroiditis with panuveitis.

The diagnosis of multifocal choroiditis is based on the clinical findings and has been made most often in myopic women.[31] Visual loss may result from cystoid macular edema, optic neuropathy, and, as in patients with POHS, from subretinal neovascular membrane formation in the macula. Despite its similarities to POHS, a relatively low percentage of tested patients respond to the histoplasmin skin test. The cause of the disease is unknown. Treatment involves the use of corticosteroids and other immunosuppressive agents. Laser photocoagulation may be considered for subretinal neovascularization unresponsive to medical therapy. Because multifocal chorioretinal lesions are a feature of many forms of both infectious and noninfectious posterior or panuveitis, multifocal choroiditis must be differentiated from entities in the white-dot syndrome, sarcoidosis, birdshot retinochoroidopathy, PIOL, VKH syndrome, and POHS. The diagnosis probably should be excluded if there is evidence of any systemic disease known to be associated with uveitis.

What Are the Clinical Features of Serpiginous Choroidopathy?

Serpiginous choroidopathy is a rare condition that accounts for 1 to 2% of all posterior intraocular inflammatory disorders.[32] It is a clinically defined primary ocular disease characterized by progressive destruction of the RPE and choriocapillaris with secondary involvement of the outer retina. Serpiginous

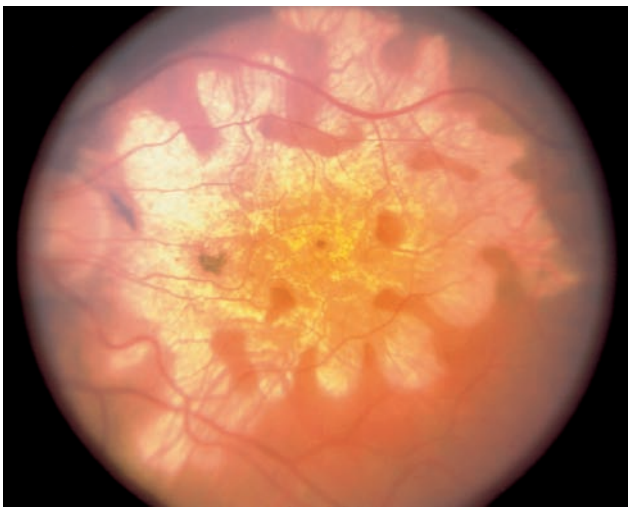


FIGURE 19–4. Serpiginous choroidopathy. This inactive lesion appears to radiate temporally from the optic disc through the macula in a pseudopodial pattern. Notice that the inner retina is intact and the larger choroidal vessels can be visualized through the atrophic outer retina and choriocapillaris.

choroidopathy has been described in the literature under a variety of names, including helicoid peripapillary chorioretinal degeneration, geographic choroidopathy, macular geographic helicoid choroidopathy and, most recently, relentless placoid chorioretinitis.[33] Serpiginous choroidopathy is typically diagnosed in the fourth to sixth decades of life, with most patients complaining of blurred vision, metamorphopsia, photopsia, and central or paracentral scotomas. It is typically a bilateral disease, although the presentation and course may be asymmetric. Examination of the anterior segment rarely shows evidence of inflammation. The vitreous is also typically quiet but may show a mild vitreitis (grade 1+ or less) in 25 to 50% of affected patients.[34] Diagnosis is made by the characteristic clinical picture of yellow–white serpiginous or pseudopodial chorioretinal lesions spreading centrifugally from the optic disc temporally more so than nasally (Fig. 19–4). Active, regressing, and inactive components of the disease are often present concurrently in different areas of the expanding lesions. Active areas, most frequently seen along the edges of the lesion, are recognized by the appearance of grayish white elevations at the level of the RPE. The inactive areas are characterized by atrophy of the choriocapillaris and overlying outer retina and marked degrees of RPE hyperpigmentation. Infrequently, cystoid macular edema, vascular sheathing, RPE detachments, disc neovascularization, and subretinal neovascularization may occur, with the last causing severe visual loss.

Serpiginous choroidopathy has a characteristic appearance on fluorescein angiography that is helpful in confirming the diagnosis. Active areas of the lesions show early hypofluorescence or blockage of the choroidal flush with late peripheral hyperfluorescence or staining. In contrast, inactive components of the lesions may show either early hypofluorescence due to atrophy of the choriocapillaris or hyperfluorescence due to RPE loss. As the angiogram progresses the inactive areas tend to show increasing hyperfluorescence resulting from progressive staining. If the centrifugal movement of the lesions from the disc to periphery bypasses the macula, the visual acuity can remain good. A decline in vision resulting from macular involvement typically occurs late in the course of the disease but may improve gradually over many months. In one variant of serpiginous choroidopathy reported as macular serpiginous choroidopathy, however, patients develop a placoid macular lesion without prior peripapillary activity early in the course of the disease and experience profound visual loss.[35] Another factor attributing to the greater visual loss in patients with macular serpiginous is the development of subretinal choroidal neovascularization, which has been reported to occur in 75% of these patients. Serpiginous choroidopathy is insidious with a prolonged course characterized by multiple often asymptomatic recurrences and a variable progression rate. Although the visual acuity will fall below 20/200 in approximately one third of the patients during the course of their disease, fewer than 5% will have less than 20/200 vision in both eyes.[34]

Serpiginous choroidopathy must be distinguished from other causes of posterior uveitis causing multifocal chorioretinal lesions, including the white-dot syndrome entities, POHS, sarcoidosis, PIOL, VKH, and multifocal choroiditis. At presentation, serpiginous choroidopathy is most commonly confused with APMPPE because of their similar appearance clinically and on fluorescein angiography. Unlike serpiginous, however, the acute lesions of APMPPE typically resolve within 2 weeks, and recurrence is uncommon. Additionally, choroidal atrophy and choroidal neovascularization are atypical for APMPPE but are common in the serpiginous form. Although good results have been obtained with combination immunosuppressive therapy including azathioprine, prednisone, and cyclosporine, the true therapeutic efficacy of any treatment is difficult to assess because spontaneous remissions and sporadic recurrences characterize the normal clinical course.

What Are the Ocular Complications of Uveitis in the Posterior Segment?

If the intraocular inflammation affecting the posterior segment is not well controlled, severe visual loss can ensue as a result of chronic cystoid macular edema,

cataract, glaucoma, hypotony, vitreous hemorrhage, subretinal neovascularization, retinal detachment, epiretinal membrane formation, subretinal fibrosis, and optic nerve atrophy. Cystoid macular edema, the most common cause of visual loss, can be diagnosed clinically, with ophthalmoscopy or fluorescein angiography showing the typical petalloid hyperfluorescence. Glaucoma and cataract formation may be the results of the intraocular inflammation itself or corticosteroids used to treat the disease. Glaucoma uncontrolled with medical therapy may require surgical intervention. Hypotony may result from a ciliary body cleft, detachment, or, more commonly, ciliary body shutdown because of chronic inflammation. Elective surgical procedures such as cataract extraction in patients with uveitis should only be considered if the ocular disease has been quiet for at least 3 consecutive months before the operative date. Preoperatively, the patient should receive increased doses of immunosuppressive medications in an attempt to prevent a postoperative flare, which frequently occurs during the first postoperative week. Neovascularization may occur in response to retinal ischemia from vasculitis or vasoocclusion. Vitreous hemorrhage is an infrequent complication of the neovascularization that may require surgical intervention. Subretinal fibrosis and subretinal neovascularization are most frequently associated with diseases characterized by subretinal or choroidal infiltrates. Phthisis bulbi is the ultimate complication of uveitis.

Intermediate Uveitis

What Are the Causes of Intermediate Uveitis?

Intermediate uveitis is characterized by inflammation predominantly involving the vitreous and peripheral retina. As a diagnostic entity, intermediate uveitis represents between 10 and 39% of all uveitis cases.[25] Intermediate uveitis may exist as an isolated idiopathic disorder (referred to as *idiopathic intermediate uveitis* or *idiopathic vitreitis*), or it may be associated with a number of underlying diseases. Intermediate uveitis of the pars planitis subtype is a specific form of idiopathic intermediate uveitis that is distinguished by the deposition of exudative material in the region of the pars plana and peripheral retina. Noninfectious causes of intermediate uveitis include sarcoidosis, MS, IBD, and uveitis masquerade syndromes, most commonly PIOL (Table 19–3). Infectious causes of intermediate uveitis that are discussed elsewhere in this text include syphilis, Lyme disease, and toxocariasis. More recently, infection with the human T-cell lymphotrophic virus type 1 (HTLV-1), which is endemic in Japan and the Caribbean, has been associated with an intermediate uveitis, HTLV-1-associated uveitis.[26] This chapter focuses on the noninfectious causes of intermediate uveitis. Sarcoidosis will be described further with the causes of panuveitis.

In most cases, the causes of intermediate uveitis can be diagnosed or strongly suggested by careful attention to the patient's clinical history with a thorough review of systems, findings on ocular and physical examination, and the appropriate use laboratory investigations and ancillary tests (Fig. 19–5). Each of the infectious causes of uveitis can be diagnosed with standard serologic tests, which should be performed when clinically indicated. On completion of the appropriate diagnostic evaluations, the causes of intermediate uveitis that are not associated with evidence of a systemic disease known to cause uveitis and for which no other plausible explanation exists can be considered idiopathic.

What Are the Clinical Features of Intermediate Uveitis of the Pars Plana Subtype (Pars Planitis)?

Intermediate uveitis of the pars plana subtype is a primary ocular disease distinguished clinically from other causes of intermediate uveitis by the accumulation of inflammatory material in the region of the pars plana, vitreous base, and peripheral retina. Pars planitis typically occurs in children and young adults in their teens to early forties. In 80% of cases, the disease is bilateral, although up to 40% of patients will have asymmetric involvement. Floaters and blurred vision are the most common ocular symptoms. Many patients maybe entirely asymptomatic, and complaints of ocular pain and redness are uncommon. Ophthalmic examination typically shows a white conjunctiva without ciliary injection, despite the presence of a mild to moderate grade anterior uveitis with nongranulomatous keratic precipitates. The cornea may show band keratopathy in children and rarely peripheral corneal edema with linear keratic precipitates (similar to a Khodadaust line). Posterior subcapsular cataracts are frequently seen, but synechiae are uncommon. Typically, a mild to moderate vitreitis is present in the posterior segment accompanied by a posterior vitreous detachment and vitreous syneresis. Clumps of inflammatory cells suspended in the inferior vitreous cavity, called *snowballs*, are considered a characteristic feature of pars planitis and sarcoidosis. Diffuse peripheral perivascular sheathing is a common finding. Cystoid macular edema and optic disc edema occur in about 50% of patients with active disease.[7] The sine qua non of pars planitis are the pars plana exudates, also called *snow banks* (Fig. 19–6). The pars plana exudates are most commonly located inferiorly due to gravity and are best visualized by scleral depression. In severe cases, the snow banks may extend beyond the horizontal level and encircle the

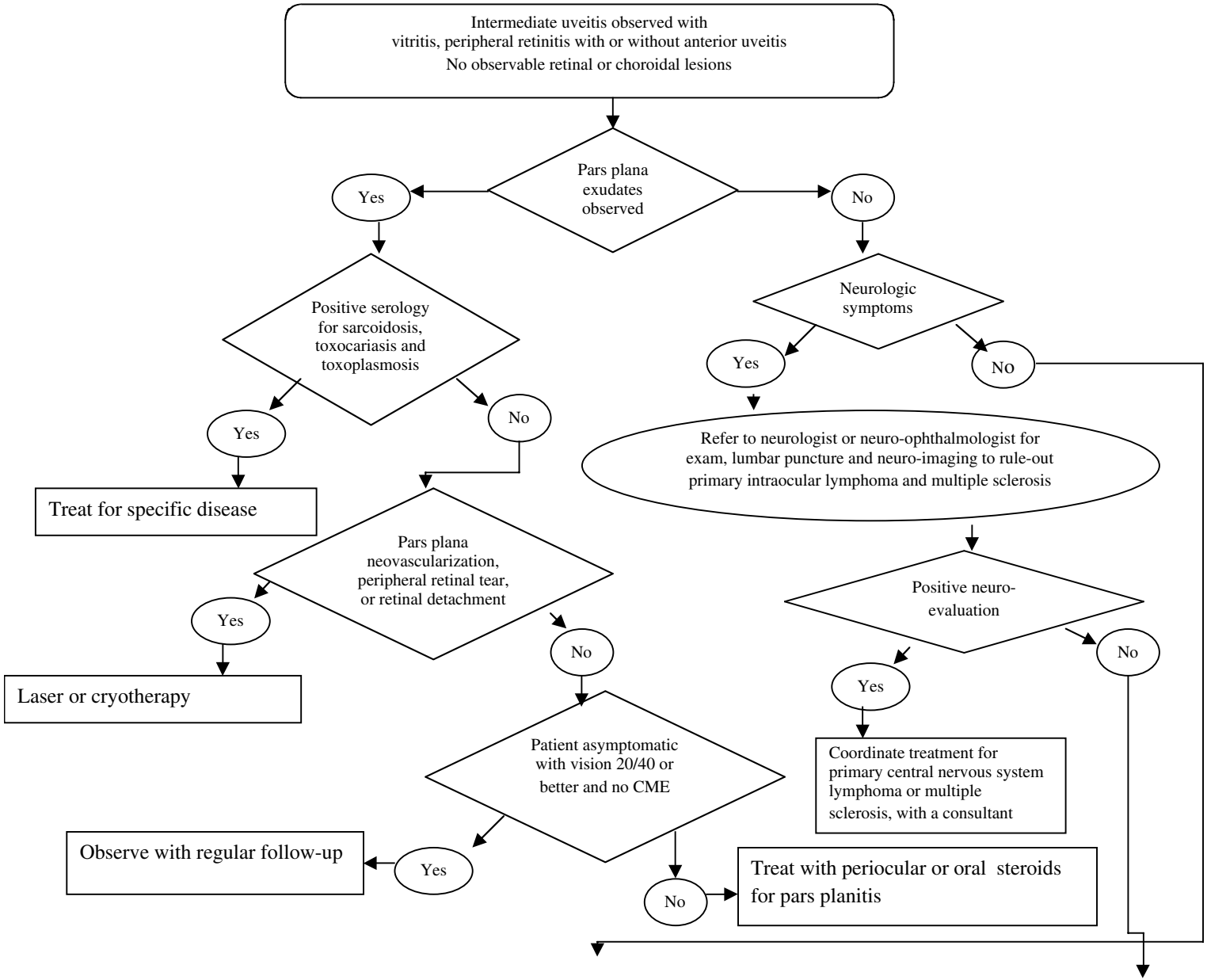


FIGURE 19–5. Intermediate uveitis. CME, cystoid macular edema.

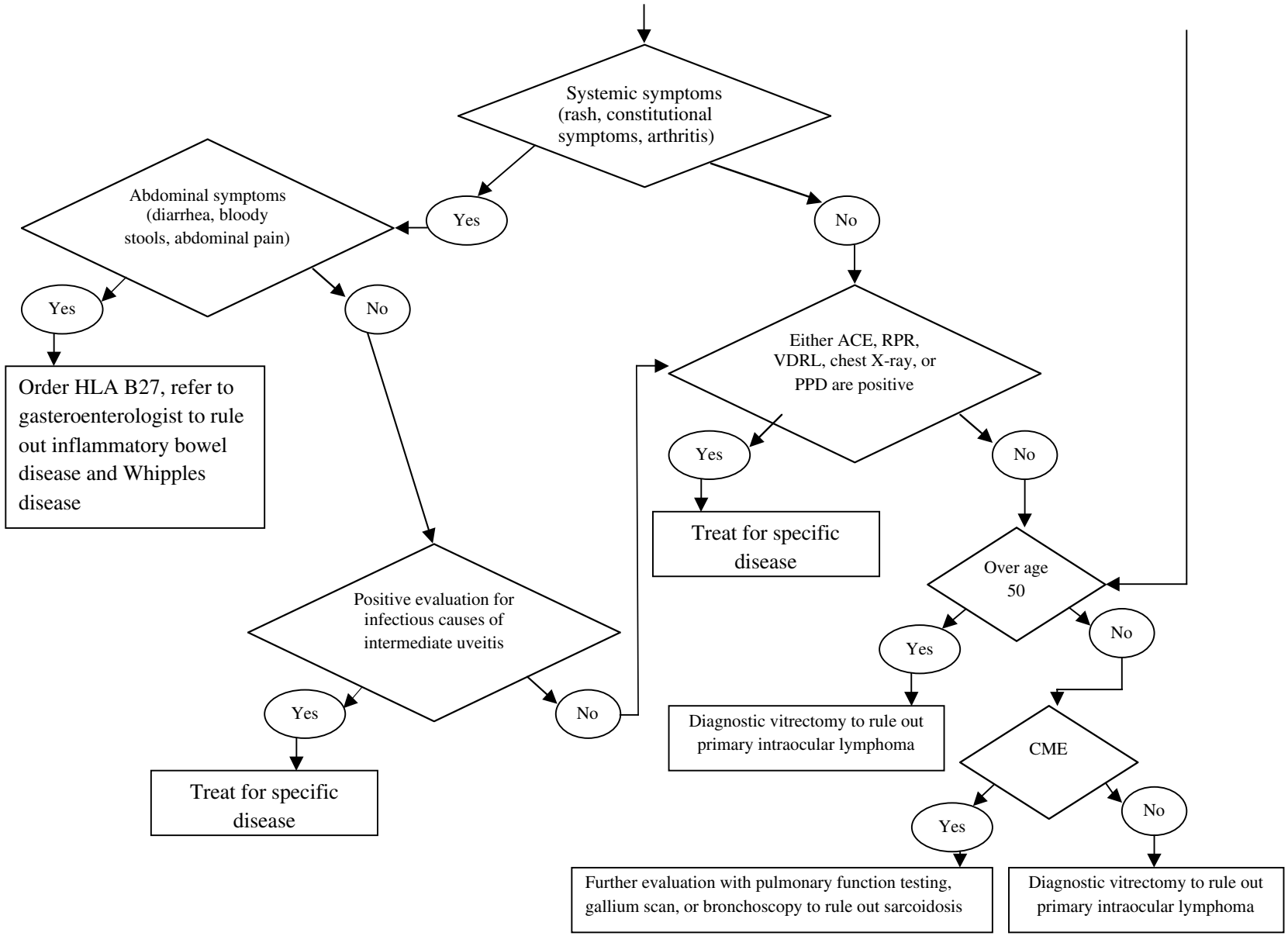


FIGURE 19–5. *Continued.* ACE, angiotensin converting enzyme.

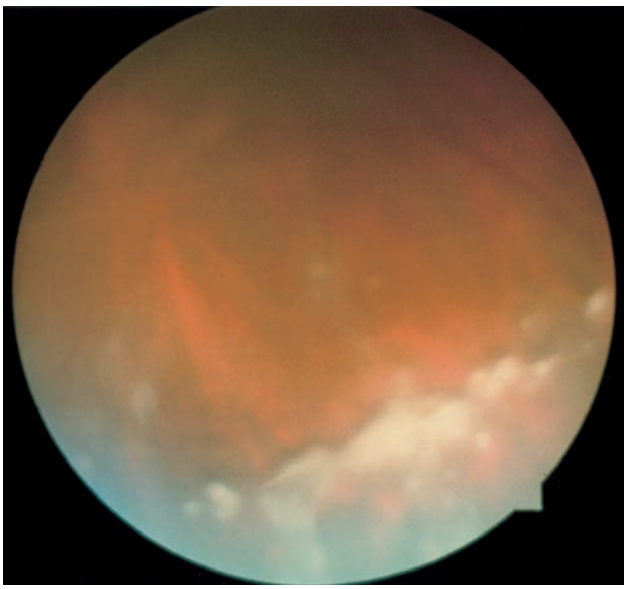


FIGURE 19–6. Intermediate uveitis of the pars plana subtype (pars planitis). The accumulation of white fibrinoinflammatory material as shown here in the region of the pars plana and peripheral retina, referred to as pars plana exudates or snow banks, distinguishes pars planitis from other causes of intermediate uveitis.

entire pars plana. Pathologically, the pars plana exudates or snow banks are composed of an amalgamation of fibrous and glial tissue, blood vessels, condensed vitreous, and inflammatory cells, including lymphocytes and macrophages. The snow banks must be examined carefully for the presence of neovascularization and any associated rhegmatogenous, tractional, or exudative retinal detachments. Neovascularization arising within a snow bank, on the disc, or in the peripheral retina may be a source of vitreous hemorrhage in patients with pars planitis. Cystoid macular edema is the primary cause of visual loss in affected patients.

Although pars plana exudates are considered virtually pathognomonic for pars planitis, the diagnosis can be made only after other conditions that can cause vitreitis, snowballs, and peripheral inflammatory lesions having the clinical appearance of snow banks are ruled out. Such conditions include sarcoidosis, syphilis, Lyme disease, MS, primary intraocular lymphoma, IBD, and, particularly in children, toxocariasis. Fluorescein angiography is useful to confirm the presence of macular edema and vasculitis not apparent by ophthalmoscopy. Ultrasonography may be used to demonstrate the presence of pars plana exudates when a view of the peripheral retina cannot be obtained. In addition to medical therapy with corticosteroids, patients with pars planitis may benefit from surgical intervention. Laser photocoagulation and cryotherapy have been used to treat neovascularization within the pars plana exudates or peripheral retina and to prevent the progression of a tractional or rhegmatogenous retinal detachment. In selected cases, patients may benefit from the surgical removal of vitreous opacities by a pars plana vitrectomy.

What Are the Clinical Features of Intermediate Uveitis Associated with Multiple Sclerosis?

The prevalence of MS in the United States ranges from six to eight per 100,000, with the disease occurring in women almost twice as often as men.[27] Although the exact cause is unknown, MS is presumed to be an autoimmune disease against the myelin protein, which forms a sheath around neuronal axons in the brain, spinal cord, and optic nerves. Pathologically, MS is characterized by inflammatory demyelinating lesions in the CNS. Studies suggest that both genetic and environmental factors play a role in the development of MS, and there is a strong association with the HLA-DR2 antigen.[28] The diagnosis of MS is made by identifying neurologic symptoms that occur over time and affect different areas of the CNS. Often the symptoms of MS are so transient and mild that the patient may not remember them. Significant symptomatic episodes, however, last for weeks to months. Neurologic symptoms suggestive of the MS include dysarthria, ataxia, vertigo, patchy paresthesias, bladder or bowel dysfunction, and facial or extremity weakness. The ocular symptoms most frequently reported in patients with MS are due to optic neuritis and include acute visual loss, retrobulbar pain, pain on eye movement, abnormal color vision, scotomas and Uhthoff phenomena. Diplopia and nystagmus are reported less commonly.

The clinical course of MS is variable, with most patients experiencing multiple relapses and spontaneous remissions, particularly in the early stages of the disease. MS must be considered in any female patient with the clinical findings of intermediate uveitis and any neurologic symptoms, particularly, if there is evidence of concurrent or previous optic-nerve disease. Uveitis has been reported in 2.5% of patients with MS, an incidence about 10 times greater than that of the general population. [29] Uveitis may precede or follow the onset of clinical symptoms suggestive of MS. The anterior segment inflammation in patients with intermediate uveitis associated with MS may be granulomatous or nongranulomatous and is more likely to be severe than other causes of intermediate uveitis. A prominent feature in the posterior segment is perivenous sheathing and vascular leakage, which can result in visual loss as a result of cystoid macular edema.

A diagnostic evaluation for multiple sclerosis should include neuroimaging and a lumbar puncture. Magnetic resonance imaging (MRI) is the study of choice. Multiple, contrast-enhancing, ovoid, demyelinating white-matter plaques in the periventricular region of the brain or in the optic nerves are consistent with the diagnosis of MS. The cerebrospinal fluid, which is abnormal in more than 90% of cases of MS, may reveal elevated immunoglobulin G (IgG) levels, an increased IgG:albumin ratio, and the presence of oligoclonal IgG bands. The diagnostic evaluation for multiple sclerosis and the therapy of intermediate uveitis associated with multiple sclerosis are best managed in consultation with a neurologist or neuroophthalmologist. In addition to immunosuppressive agents used to treat other forms of intermediate uveitis, treatment strategies may include the use of newer agents specifically for MS, such as interferons and glatirameracetate (copolymer-1).

What Are the Clinical Features of Intermediate Uveitis Associated with Inflammatory Bowel Disease?

The term *inflammatory bowel disease* includes ulcerative colitis and Crohn disease, two distinct clinicopathologic entities. Ulcerative colitis is limited to the colon and rectum and is primarily a continuous inflammatory disease of the colonic mucosa. Crohn disease, which most commonly affects the terminal ileum, can cause patchy, transmural inflammatory lesions anywhere along the entire length of the gastrointestinal tract. Bloody stools and abdominal pain are a prominent feature of ulcerative colitis and Crohn disease. Bloody diarrhea is more common in ulcerative colitis than in Crohn's disease. In ulcerative colitis, the abdominal pain is cramping and often is relieved by a bowel movement, whereas in Crohn's disease, the abdominal pain is constant and unrelieved after a stool is passed.

Ocular disease associated with IBD occurs in fewer than 10% of patients with Crohn's disease and in an even smaller percentage of patients with ulcerative colitis.[30] The presence of ocular involvement in patients with IBD is almost always associated with at least one other extraintestinal manifestation, such as erythema nodosum, ankylosing spondylitis, sacroiliitis, sclerosing cholangitis, and chronic active hepatitis, which occur in about 25 to 40% of patients. IBD has been associated with both anterior and intermediate uveitis and retinal vasculitis. Other ocular inflammatory conditions associated with IBD include episcleritis, scleritis, conjunctivitis, peripheral corneal ulcers, idiopathic orbital inflammation, and optic neuritis. Cystoid macular edema and cataract are the most likely causes of visual loss in patients with intraocular inflammation secondary to IBD. Patients with anterior uveitis who are also HLA-B27 positive have an increased risk of sacroiliitis.

All patients with intermediate uveitis should be questioned about gastrointestinal symptoms such as abdominal pain, diarrhea, or bloody stools. Because patients with anterior uveitis who are also HLA-B27 positive have an increased risk of sacroiliitis, systemic evaluation should include HLA testing as well as tests to rule out the other causes of intermediate uveitis. Because the severity of the ocular disease tends to parallel that of the intestinal symptoms, therapy for the uveitis should be instituted in consultation with a gastroenterologist. The ocular inflammation associated with IBD typically responds to treatment with topical, periocular, or systemic steroids, but in more severe cases other immunosuppressive agents may be needed.

Retinal Vasculitis

What Are the Causes of Retinal Vasculitis?

Inflammation of the retinal vessels is a common feature of inflammatory disease in the posterior segment and may occur in cases of intermediate, posterior, and panuveitis of almost any cause. Retinal vasculitis is defined clinically by the presence of vascular sheathing and by the demonstration of vascular leakage and staining of the vessel walls on fluorescein angiography (Fig. 19–1). Although any retinal vessel may be affected, retinal venules (*periphlebitis*) tend to be affected more commonly than arterioles (*periarteritis*). Retinal vasculitis results in visual loss from macular edema due to vascular leakage and retinal ischemia caused by vascular occlusion. Retinal vasculitis may be a manifestation of many potentially life-threatening systemic vasculitides. Systemic vasculitides associated with retinal vascular lesions, but not necessarily intraocular inflammation, include Wegener's granulomatosis, SLE, polyarteritis nodosa, polymyositis, dermatomyositis, Buerger disease, Sjögren syndrome, and Takayasu's disease (Table 19–4). Although such conditions are considered causes of posterior uveitis, vitreitis is not a primary feature of these diseases unless the vasculopathy is sufficiently severe to cause ischemia or necrosis. Sarcoidosis, Behçet disease, MS, and Crohn's disease are the systemic diseases that cause retinal vasculitis typically associated with intraocular inflammation. Almost all infectious diseases causing posterior segment intraocular inflammation are causes of retinal vasculitis. Noninfectious primary ocular diseases with retinal vasculitis as a prominent feature include idiopathic retinal vasculitis, Eales disease, birdshot retinochoroidopathy, and pars planitis (Fig. 19–7).

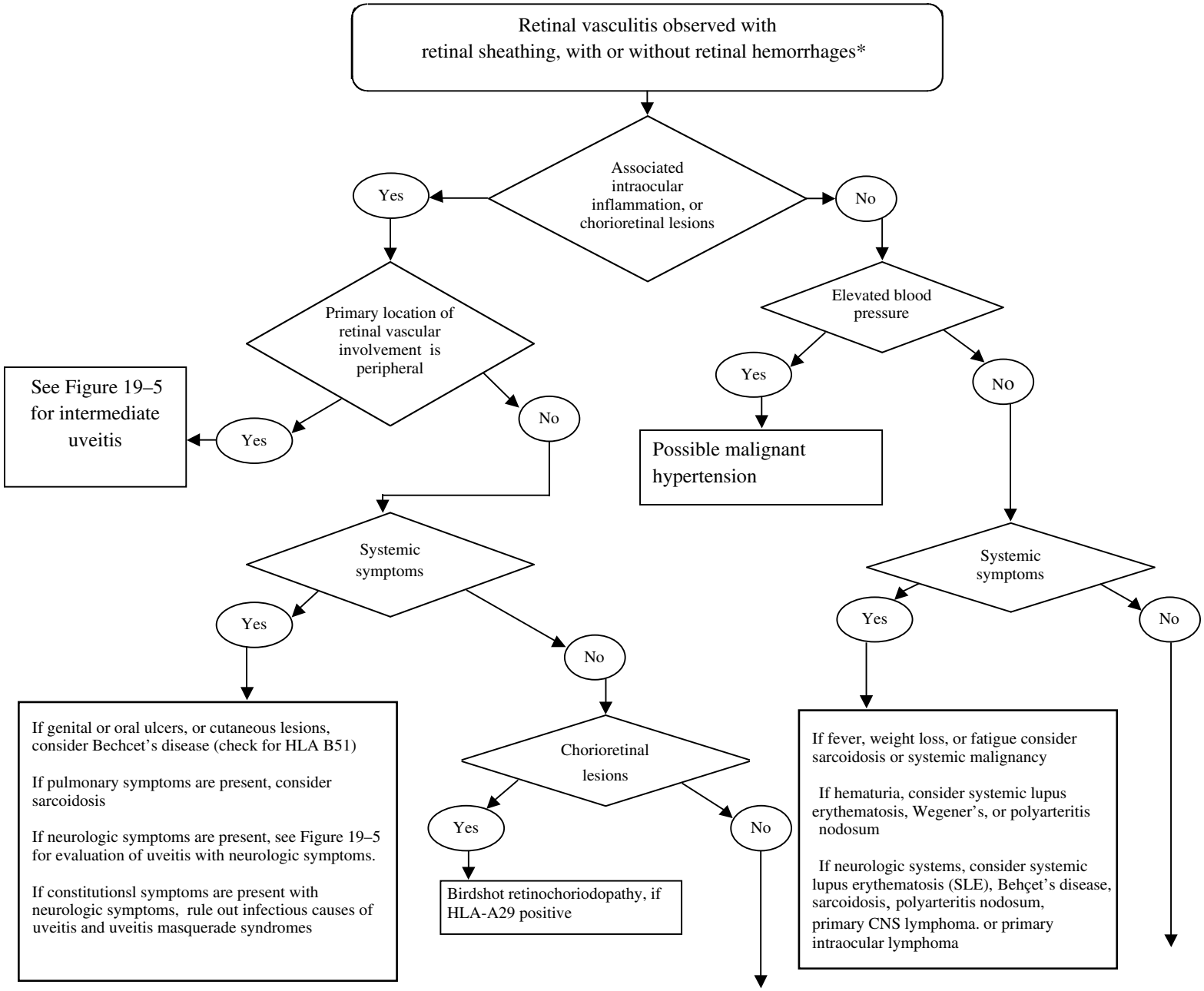
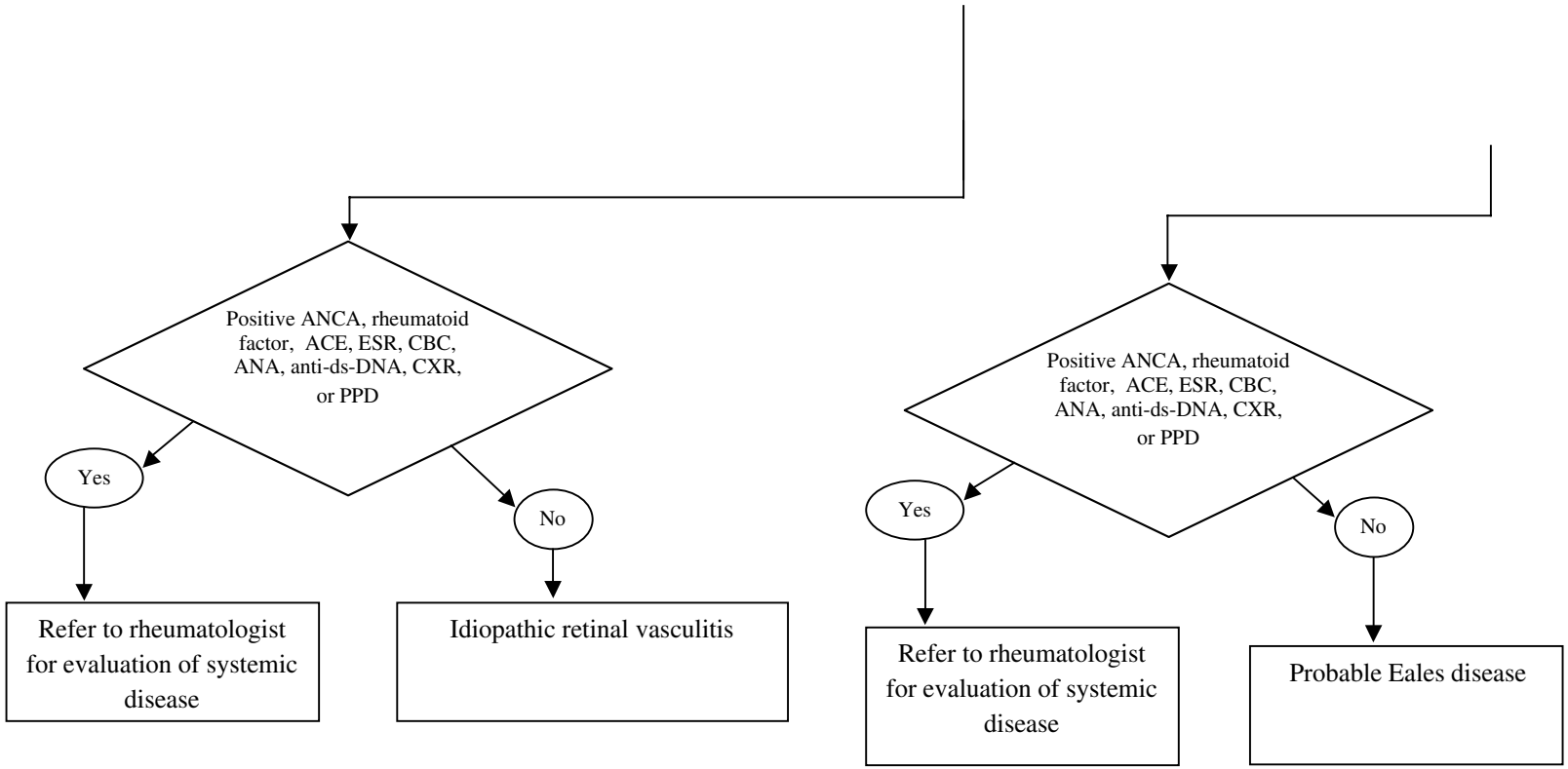


FIGURE 19–7. Retinal vasculitis observed with retinal sheathing. ANCA, antineutrophil cytoplasmic autoantibody; ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; CBC, complete blood count; ANA, antinuclear antibodies; CXR, chest X-ray; PPD, purified protein derivative.



*If the patient is symptomatic, obtain a fluorescein angiogram. If cystoid macular edema (CME) is seen, treat with periocular steroids, if no CME is seen observe with regular clinical follow-up and evaluate the condition with this clinical pathway. If the fluorescein shows capillary nonperfusion or neovascularization, treat with immunosuppression and, if no improvement is seen, consider laser photocoagulation.

FIGURE 19–7. *Continued.*

What Are the Clinical Features of Idiopathic Retinal Vasculitis?

Idiopathic retinal vasculitis is a primary inflammatory disease of the retinal vessels, occurring in the absence of systemic vasculitis or associated systemic disease. Idiopathic retinal vasculitis usually occurs in young adults often before the age of 40; distribution between males and females is equal. Unlike systemic vasculitides, which are known to be caused by type III hypersensitivity reactions with immune complex deposition in the walls of blood vessels, idiopathic retinal vasculitis is a presumed autoimmune disease mediated by T-lymphocytes.[36] Patients with retinal vasculitis frequently complain of blurred vision, loss of vision, scotomas, and floaters; however, those with peripheral disease may be asymptomatic. Dyschromatopsia, metamorphopsia, and difficulty reading may be noted in cases with macular involvement. The anterior segment in patients with retinal vasculitis is typically quiet or shows only mild evidence of inflammatory disease. The posterior segment often shows vitreitis that may obscure visualization of the fundus, vitreous snowballs inferiorly, and vitreous detachment. The salient feature of retinal vasculitis is vascular sheathing that can be described as whitening or blurring of the retinal vessel border (Fig. 19–1A). Typically, the sheathing is discontinuous, showing skip areas along the course of the vessel, and it is more commonly seen in the peripheral retina anterior to the equator. Other common posterior segment findings in patients with retinal vasculitis include cystoid macular edema and optic disc edema or pallor. In severe cases, there may be evidence of retinal vascular occlusion and ischemia with retinal hemorrhages, cotton-wool spots, and larger areas of retinal necrosis and edema that may mimic retinal infiltrates or exudative lesions. Complications of retinal vasculitis include retinal neovascularization, macular ischemia, and retinal detachment, the latter occurring least frequently. Neovascularization, a sequela of chronic retinal ischemia, occurs in about 10% of patients with retinal vasculitis. Fluorescein angiography in patients with retinal vasculitis reveals staining of the optic disc and affected vessels and leakage from the venules, capillaries, and less commonly arterial vessels (Fig. 19–1B). Vascular occlusions, areas of nonperfused retina, and neovascularization also may be identified. Macular ischemia resulting from the closure of perifoveal capillaries can be identified on fluorescein angiography by an enlarged or irregular foveal avascular zone. Pathologic studies of autopsy eyes from patients with retinal vasculitis have revealed perivascular lymphocytic cuffing with T-cells in the blood vessel walls supporting the diagnosis.

Laboratory investigations should include complete blood count (CBC), routine chemistries, angiotensin converting enzyme (ACE), rapid plasma reagent (RPR) test, Venereal Disease Research Laboratory (VDRL) test, HLA phenotype, and chest radiography. In patients with ischemic retinal vasculitis, coagulation studies, including fibrinogen, prothrombin time, thrombin time, activated partial thromboplastin time, protein S, protein C, and antithrombin III levels, and anticardiolipin and antiphospholipid antibodies should be performed. Serology to rule out an infectious disease should be considered if clinically indicated. A positive HLA A-29 may raise the possibility of birdshot retinochoroidopathy.

Although some cases of idiopathic retinal vasculitis may be insidious and ultimately burn out over time, in other cases, the disease can be rapidly progressive. The visual prognosis is related more to the severity of the disease than to duration, with about 50% of patients experiencing a poor visual outcome. Periocular or systemic corticosteroids are the first line of therapy for idiopathic retinal vasculitis. Once initiated, therapy may be required for several years. High-dose oral steroids or pulsed intravenous methylprednisolone followed by an oral taper have been recommended for severe cases.[36] Azathioprine, cyclosporine, and methotrexate all have demonstrated benefit in the treatment of this disease and are useful in lowering the daily steroid requirement. Laser photocoagulation is infrequently needed for the treatment of idiopathic retinal vasculitis if adequate immunosuppression is used. Indications for laser treatment include persistent neovascularization resulting in recurrent vitreous hemorrhage or in neovascular glaucoma. It is important to remember that the eye must be made as quiet as possible before laser therapy is given to avoid inducing cystoid macular edema. Surgery may be needed to treat the complications of the disease, such as retinal detachment, nonclearing vitreous hemorrhage, and secondary glaucoma resulting from steroid therapy.

What Are the Clinical Features of Eales Disease?

Eales disease is an idiopathic obliterative vasculopathy that affects primarily the peripheral retina without evidence of an associated vitreitis, uveal inflammation, or associated systemic disease.[37] Eales disease is named for Henry Eales, an ophthalmologist who described a syndrome of recurrent vitreous and retinal hemorrhages in young men with epistaxis and constipation. Uncommon in the United States, Eales disease is most commonly diagnosed in India, Pakistan, and Afghanistan, where it commonly affects

young men more frequently than women between the ages of 20 and 30 years. Typically, the disease is bilateral, although often asymmetric. Patients usually present with symptoms of vitreous hemorrhage, such as floaters or decreased vision. Vascular sheathing of predominantly retinal venules is the most characteristic ocular finding in Eales disease. Peripheral retinal nonperfusion ranging from small areas in the far periphery to massive areas extending into the posterior pole is a common finding in all patients with Eales disease. Cystoid macular edema may be present in eyes with extensive sheathing. White obliterated retinal vessels or ghost vessels are often seen in the areas of nonperfusion. Retinal hemorrhages, microaneurysms, arteriovenous shunts, and venous beading may be noted at the junction of perfused and nonperfused retina that is generally sharply demarcated clinically. The retinal nonperfusion leads to the eventual development of disc or retinal neovascularization, typically along the junction of perfused and nonperfused retina. Findings on fluorescein angiography include hyperfluorescence or staining of the sheathed retinal vessels, areas of nonperfusions, arteriovenous shunting and neovascularization. The neovascularization often is accompanied by a prominent fibrous tissue component that may contract and cause a vitreous hemorrhage or retinal detachment. Anterior chamber cells and flare and vitreous cells may be observed in patients with Eales, but they are considered uncommon and, if marked, should suggest alternative diagnosis.

The natural course of the disease is variable; however, because the primary site of disease is the peripheral retina, most patients maintain good vision. Vitreous hemorrhage, retinal detachment, and neovascular glaucoma are the most common causes of severe visual loss.[37] Peripheral scatter laser photocoagulation to the ischemic retina is the treatment of choice. Vitrectomy may be required for patients with persistent vitreous hemorrhage. Immunosuppressive therapy is not generally effective for this disorder. The differential diagnosis includes diabetes, sickle cell retinopathy, SLE, Wegener's granulomatosis, and other retinal vasculopathies associated with systemic disease. Although an association with tuberculosis hypersensitivity has been suggested, the exact cause of the disease remains unknown.

What Are the Clinical Features of Retinal Vasculitis Associated with Systemic Diseases?

Sarcoidosis, Behçet's disease, MS, and IBD are the most common systemic diseases that typically show retinal vasculitis as part of the intraocular inflammatory disease. Apart from these conditions, retinal vasculitis is also known to be associated with several systemic entities, most of which can be considered as collagen vascular diseases (Table 19–4). Ocular disease may be a presenting sign of a collagen vascular disease; however, in most cases, the underlying diagnosis is already known, or there are constitutional symptoms suggestive of a systemic disease at the onset of ocular involvement. In addition to causing retinal vasculitis, this group of disorders also may present as peripheral ulcerative keratitis, episcleritis, scleritis, uveitis, optic neuritis, and orbital inflammation. The pathogenesis of disease for each of these conditions is believed to be an immune-mediated attack against vascular antigens. The most commonly encountered collagen–vascular diseases associated with retinal vasculitis are discussed.

Systemic lupus erythematosus is a classic immune complex disorder that is diagnosed by both clinical and laboratory criteria.[38] Laboratory findings useful for the diagnosis of SLE include antinuclear antibodies (ANA), antibodies to double-stranded DNA, and anti-SM antibodies. Serum complement levels tend to correlate with disease activity. Ocular involvement is uncommon in patients with SLE but may be severe and sight threatening when it occurs. The retinal vascular disease in patients with SLE is most commonly vasoocclusive and typically is not associated with an intraocular inflammation. Sheathing of the retinal vessels is not commonly seen. CNS vasculitis frequently manifests concomitant with the retinal involvement. Retinal neovascularization is a problematic sequela of the retinal involvement that may require laser photocoagulation if there is an inadequate response to the use of aggressive immunosuppression, which may involve the use of cyclophosphamide.

Wegener granulomatosis is a systemic disease characterized by a necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, a focal necrotizing glomerulonephritis, and a small vessel vasculitis involving a number of organ systems. Ocular involvement including uveitis, scleritis, orbital inflammation, and retinal vasculopathy occurs in about 16% of patients and may be the presenting sign of the disease.[36] A serum antineutrophil cytoplasmic antibody (ANCA) test should be performed in all patients with retinal vasculitis. There are two patterns of the ANCA test, a cytoplasmic pattern (cANCA) and a peripheral pattern (pANCA). The cANCA is believed to be more specific for Wegener and is useful in diagnosing and following the clinical course of patients with this disease. It should be kept in mind that the ANCA test may be negative in Wegener granulomatosis localized to the orbit or eye but may become positive

over time. Like sarcoidosis, a definitive diagnosis of Wegener granulomatosis requires a tissue biopsy. Treatment of Wegener granulomatosis includes the use of high-dose prednisone and cyclophosphamide.

Polyarteritis nodosa (PAN) is an uncommon necrotizing systemic vasculitis involving medium-sized muscular arteries and smaller arterioles. The incidence of PAN is 5 to 10 cases per million per year; men are affected most commonly.[39] Systemic features include fever, malaise, palpable purpura, cutaneous ulcers, and multiple mononeuropathies. Renal, intestinal, and cardiac involvements are common causes of morbidity. PAN may involve the eye in up to 20% of patients and can present with bilateral iritis, vitreitis, and retinal vasculitis involving both arterioles and venules. There are no laboratories that are specific for PAN, although a positive pANCA is frequently found. Current therapy usually consists of corticosteroids and for severe cases cyclophosphamide. Cogan syndrome, a possible variant of PAN described as a nonsyphilitic interstitial keratitis associated with hearing loss, also has been associated with retinal vasculitis.[36]

Relapsing polychondritis is a systemic inflammatory disease of connective tissue that causes inflammatory destruction of the cartilage of the nose, ear lobes, and trachea that can result in fatal respiratory compromise.[36] The disease affects both sexes equally and occurs in all age groups peaking in patients between 40 and 50 years old. Ocular involvement may occur at the onset of disease or later during the disease course. Conjunctivitis, episcleritis, scleritis, and anterior uveitis are the most frequent findings. The retinal disease is most commonly vasoocclusive. Retinal vasculitis associated with retinal hemorrhages, exudates, and serous retinal detachments and optic neuropathy have been described less frequently. No laboratory studies are specific for relapsing polychondritis, which is diagnosed based on its clinical features. Treatment includes the use of systemic steroids combined with azathioprine, cyclosporine, or cyclophosphamide.

Because many of the patients with collagen–vascular disease associated with ocular involvement have or may develop a potentially fatal systemic disease, these patients should be followed up in conjunction with a rheumatologist or medical internist comfortable with management of these conditions. The best mode of treatment for ocular involvement not associated with active systemic disease has not been determined and often compounded by the presence of neovascularization. In general, immunosuppression is the first line of therapy in an attempt to turn off the supposed underlying inflammatory process. Patients with progressive neovascularization not responding to immunosuppression should be considered for laser photocoagulation. There is anecdotal evidence that panretinal photocoagulation may have a beneficial effect on the course of the retinal vascular disease, even with no evidence of neovascularization. In some cases, however, panretinal photocoagulation has induced severe intraocular inflammation.

Panuveitis

What Are the Causes of Panuveitis?

The term *panuveitis* is used to describe ocular inflammation simultaneously affecting the entire uvea and adjacent intraocular structures without a predominant focus in any location. Sarcoidosis, the VKH syndrome, Behçet's disease, and sympathetic ophthalmia are the noninfectious causes of panuveitis that are discussed in this section. Each of these conditions is a cause of chronic intraocular disease that may present or recur over time as more limited anatomic forms of uveitis during their disease course. With the exception of Behçet's disease, they all may show granulomatous features and, except for sympathetic ophthalmia, they all are associated with systemic manifestations. Sarcoidosis, the prototypical granulomatous intraocular inflammatory disease, can mimic any ocular disease and therefore must be considered in the differential diagnosis for all cases of anterior, intermediate, posterior uveitis and panuveitis. The onset of uveitis in either eye following any ocular trauma or surgical procedure should raise the possibility of sympathetic ophthalmia. The VKH syndrome is a rare systemic granulomatous disease directed at tissues containing melanocytes that may include the eyes, inner ear, meninges, hair, and skin. Behçet's disease is a generalized occlusive vasculitis that most commonly presents as a retinal vasculitis but typically is classified as a panuveitis because of its proclivity to cause an acute hypopyon uveitis, which must be distinguished from HLA-B27-associated uveitis and endophthalmitis.

What Are the Clinical Features of Sarcoidosis?

Sarcoidosis is a multisystem granulomatous disease that most commonly involves the lungs, skin, lymph nodes, and eyes, although any organ in the body can be affected. The etiology of sarcoidosis is unknown. The disease is presumed to be initiated by an infectious agent, although no organism has been isolated to date. The inflammatory response and granulomatous infiltrates characterizing the disease are thought to be the consequence of an exaggerated immune response to the putative organism. In the United States, sarcoidosis is 8 to 10 times more frequent among African Americans than whites, having an estimated prevalence of 82 per 100,000 in this population.[40] Al-

though sarcoidosis can develop at any age, the disease is typically diagnosed in adults between 20 to 50 years of age. In children and elderly adults with uveitis sarcoidosis and a masquerade syndrome should be high in the differential diagnosis. In children under 5 years of age, the ocular disease is most commonly a granulomatous anterior uveitis that is associated with a polyarticular arthritis, rash, and lymphadenopathy. Pulmonary disease is less common, occurring in about one third of these younger patients.

Most adult patients with sarcoidosis present with pulmonary involvement that may manifest as cough, shortness of breath, wheezing, or dyspnea on exertion. Another common presentation is with generalized symptoms, such as fever, fatigue, and weight loss. Many patients, however, may be asymptomatic at the time of diagnosis. Nontender, subcutaneous granulomatous nodules and cutaneous erythema nodosum frequently found on the lower extremities are a common finding. Neurologic involvement, including cranial nerve palsies, particularly Bell's palsy, aseptic meningitis, peripheral neuropathy, and myopathy, occur in 5% of patients with sarcoidosis. Other common systemic manifestations of sarcoidosis include lymphadenopathy, splenomegaly, liver abnormalities, arthritis, myositis, and pericarditis.

Between 25 and 50% of patients with systemic sarcoidosis develop uveitis. Sarcoid uveitis is diagnosed when ocular inflammation is found in a patient with extraocular findings diagnostic of sarcoidosis. Typically bilateral, the ocular disease may be unilateral or very asymmetric. In the eye, sarcoidosis may present as an anterior, intermediate, or posterior uveitis that may remain limited in its anatomic spectrum or progress to a full panuveitis. Although most frequently a cause of granulomatous uveitis, sarcoidosis also may cause a nongranulomatous uveitis. Patients commonly present with symptoms of blurred or decreased vision, dry eyes, ocular pain or discomfort, and floaters. Ophthalmic findings in the anterior segment include orbital and cutaneous granulomas, enlarged lacrimal glands, and palpebral and bulbar conjunctival nodules. The cornea most commonly shows large "mutton-fat" keratic precipitates with nummular corneal infiltrates and inferior areas of endothelial opacification being noted less frequently. Posterior and peripheral anterior synechiae, when extensive, result in elevated intraocular pressure or secondary uveitic glaucoma resulting from angle closure or iris bombe. Koeppe and Busacca type iris nodules are often seen in the more severe cases of anterior segment disease. Posterior segment involvement in sarcoidosis occurs less frequently than anterior segment disease. The vitreous typically shows varying degrees of vitreitis, with vitreous snowballs and debris located in the inferior vitreous cavity. Evidence of a peripheral retinal vasculitis with sheathing and exudates similar to the snow banks seen in pars planitis may be found on careful examination of the anterior retina. Posteriorly, the retinal vessels, primarily venules, also may show patchy sheathing with associated hemorrhages, retinal exudates, and perivascular nodular granulomatous lesions called *candle-wax drippings*, or *en taches de bougie*. Retinal or disc neovascularization may be the sequela of retinal ischemia attributable to the vasculitis. Multifocal, raised yellowish lesions at the level of the RPE, called Dalen-Fuch nodules, and in the deeper choroid are common findings during the active course of the disease. As the inflammation resolves, the lesions may evolve into punched-out hypopigmented or heavily pigmented chorioretinal scars (Fig. 19–3). Nodular granulomas reaching several disc diameters in size may cause localized mass lesions in the retina, choroid, and optic nerve. Optic disc hyperemia or swelling not associated with visual dysfunction often is a frequent posterior segment finding. Retinal neovascularization and neovascularization of the disc reported in about 15% of patients usually respond well to antiinflammatory therapy.[40] By comparison, subretinal neovascularization is less common and less amenable to medical therapy. Visual loss in sarcoidosis is most commonly due to cystoid macular edema, optic neuritis due to granulomatous infiltration of the optic nerve, and secondary glaucoma.

The diagnosis of sarcoidosis is confirmed with a tissue biopsy showing noncaseating or nonnecrotizing granulomas or granulomatous inflammation in a patient in whom all other causes of granulomatous disease, such as tuberculosis and fungal infections, have been excluded. Nodular lesions identified on the skin, conjunctiva, or lacrimal glands are easily biopsied and, if diagnostic, can spare the patient a time-consuming, invasive, and costly workup. Because the disease most commonly affects the lungs, the diagnostic evaluation initially should include a chest radiograph, which may reveal hilar or paratracheal adenopathy in up to 90% of patients with sarcoidosis.[40] If the chest radiograph is inconclusive, a more sensitive computed tomography scan of the thorax may be obtained to demonstrate evidence of pulmonary disease. Although the finding of lymphocytosis by bronchoalveolar lavage is a frequent finding in sarcoid patients, this alone is not diagnostic of the disease. Transbronchial biopsy may be diagnostic in 60% of patients with a normal chest radiograph and up to 90% of patients with pulmonary abnormalities. Pulmonary function tests may suggest the diagnosis by revealing evidence of limited diffusing capacity before the onset of radiographic abnormalities.[41] Pulmonary macrophages and vascular endothelium and epithelioid

cells in granulomas produce angiotensin converting enzyme (ACE). An elevated serum ACE level is found in 60 to 90% of patients with active systemic sarcoidosis but may be in the normal range in a patient with inactive disease or isolated disease like uveitis.[42] Because ACE levels may be high in normal children, it is a less useful diagnostic test for sarcoidosis in children. Elevated ACE levels have been reported in the aqueous humor and cerebrospinal fluids of patients with ocular and CNS sarcoid uveitis and neurosarcoidosis, respectively. Serum lysozyme levels may be elevated in patients with sarcoidosis but are less specific than serum ACE as a marker for the disease. Findings on routine laboratory studies that may be suggestive of sarcoidosis include hypercalcemia and hypercalciuria, lymphopenia, and elevated alkaline phosphatase. Abnormal macrophage function in patients with sarcoidosis is manifested by anergy to mycobacterial antigens, such as purified protein derivative (PPD), mumps virus, and *Candida* organisms. The demonstration of anergy in a patient with other clinical features of sarcoidosis supports the diagnosis. A gallium scan, which detects concentrated radioactive gallium in areas of inflammation, can be useful for showing involvement of organs such as the lungs, lacrimal glands, and parotid gland, which then can be considered for biopsy.

The clinical course of ocular sarcoidosis can be acute and self limited or chronic, recurrent, and relentless. With appropriate treatment, many patients retain functional visual acuity. The mainstay of therapy for both systemic and ocular sarcoidosis is corticosteroids. Anterior segment disease can be managed with topical or periocular corticosteroid injections. Systemic therapy typically is required for bilateral posterior segment uveitis. Patients with ocular and neurosarcoidosis typically require higher daily doses of corticosteroids than patients with pulmonary disease. Other immunosuppressive agents, such as cyclosporine and methotrexate, have demonstrated therapeutic benefit in the management of sarcoidosis and should be considered early for patients with chronic sarcoidosis requiring prolonged steroid therapy.

What Are the Clinical Features of Sympathetic Ophthalmia?

Sympathetic ophthalmia (SO) is rare primary ocular disease diagnosed by history and clinical findings. SO is diagnosed when, following a traumatic or iatrogenic injury to one eye (referred to as the exciting eye), the fellow uninjured eye (referred to as the sympathizing eye) develops granulomatous intraocular inflammation. Although evidence of ocular inflammation in the sympathizing eye may occur as early as 5 days to as late as 50 years after the injury to the exciting eye, most cases occur within 2 to 3 months and rarely more than 1 year after the inciting event. Traumatic perforations of the globe, with or without direct uveal prolapse, are the most common types of injury associated with SO. Perforating ulcers, severe contusion following blunt injury, and scleral rupture are also known causes. Surgical procedures associated with SO include cataract extraction, vitrectomy, secondary intraocular lens placement, trabeculectomy, contact and noncontact yttrium–aluminum–garnet (YAG) laser cyclodestruction, cyclocryotherapy, and proton-beam and helium ion irradiation. SO has been reported to occur after about 0.2% of penetrating ocular injuries and 0.01% of intraocular surgeries.[43]

Symptoms that herald the onset of ocular inflammation in the sympathizing eye, including photophobia, tearing, blurred vision, ocular pain, and redness, in the exciting eye may be masked because of the prior injury. Ocular examination may reveal evidence of severe panuveitis in both eyes. Frequent findings include large mutton-fat granulomatous keratic precipitates, anterior chamber cells, peripheral anterior and posterior synechiae, granulomatous iris nodules, vitreitis, and multifocal choroidal lesions both deep and at the level of the RPE (Dalen–Fuch nodules) (Fig. 19–8). Histopathologic examination of eyes with sympathetic

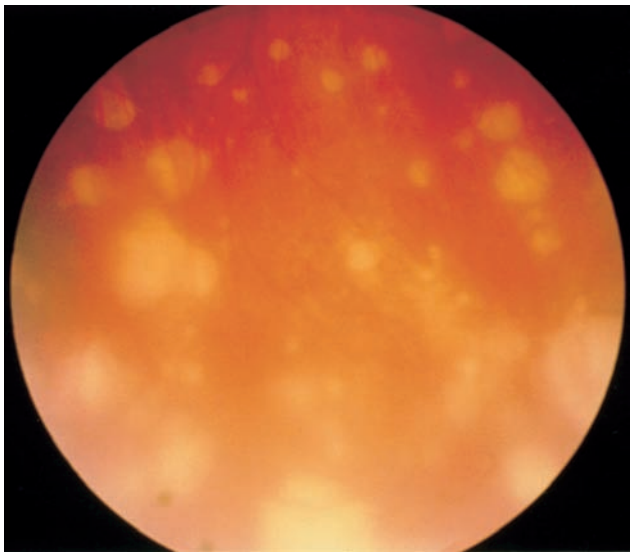


FIGURE 19–8. Sympathetic ophthalmia. The multifocal lesions seen here, called Dalen-Fuch nodules, also may be seen in other causes of granulomatous posterior uveitis, such as sarcoidosis and Vogt–Koyanagi–Harada (VKH) syndrome. Pathologically, Dalen–Fuch nodules are small granulomas located subjacent to the retinal pigment epithelium (RPE). Active Dalen-Fuch nodules (inferior) are creamy, have indistinct margins, and are slightly elevated, whereas inactive nodules (superior) appear atrophic with circumscribed margins and may become pigmented, as in Figure 19–3.

ophthalmia shows diffuse uveal thickening caused by a granulomatous inflammatory infiltrate composed of lymphocytes, macrophages, epithelioid cells, giant cells, and well-defined granulomas. Dalen–Fuch nodules, small granulomas located between the RPE and Bruch membrane, are a characteristic finding in sympathetic ophthalmia that also can be seen in other granulomatous diseases affecting the posterior pole such as sarcoidosis and VKH. A distinct pathologic feature that helps to differentiate sympathetic ophthalmic from other causes of panuveitis is the sparing of the choriocapillaris by the choroidal infiltrate.

The course of sympathetic ophthalmia is chronic with frequent exacerbations. Although the exact cause of sympathetic ophthalmia is not known, it is believed to be a cell-mediated or type IV hypersensitivity reaction against retinal or uveal antigens elaborated at the time of the inciting injury to the exciting eye. Improved wound closure, early removal of severely damaged blind eyes, and the use of enucleation rather than evisceration for the removal of ocular contents has significantly reduced the incidence of sympathetic ophthalmia. Early and aggressive treatment of SO is important for achieving good visual results. Immunosuppression with high doses of systemic prednisone with the subsequent addition of cyclosporine constitutes the front-line therapeutic approach. Removal of the inciting eye after the onset of disease is controversial particularly if the eye retains visual potential.

What Are the Clinical Features of the Vogt–Koyanagi–Harada Syndrome?

The VKH syndrome is a rare cause of bilateral granulomatous posterior or panuveitis. Although the etiology is unknown, it is a presumed autoimmune disease directed against melanocytic antigens including tyrosinase family proteins. This hypothesis may explain why tissues with more pigmentation, such as the eye, and patients with increased pigmentation are at greater risk for the disease. The disease primarily affects patients between 20 and 50 years of age; occurrences in children are considered uncommon. In the United States, VKH represents about 1% of all uveitis cases; persons of African, Asian, Hispanic, and American Indian ancestry are most commonly affected.[44] In addition to the ocular disease, patients with VKH may develop cutaneous, auditory, and CNS disease concurrent with or following the onset of the ocular disease. Symptoms of the ocular disease include decreased vision, floaters, ocular pain, redness, and photophobia. About 30% of patients develop hearing loss or tinnitus early in the course of the disease. Severe headache, stiff neck, loss of consciousness, paralysis, and seizures are manifestations of CNS involvement. Cerebrospinal fluid examination when CNS symptoms are present may show pleocytosis or an increased number of lymphocytes. Thirty percent of affected patients develop cutaneous disease including vitiligo, poliosis, madarosis, and alopecia.

Examination of the anterior segment may reveal granulomatous keratic precipitates, peripheral anterior and posterior synechiae, and iris nodules. Perilimbal vitiligo (Sugiura sign) has been reported in 85% of Asian patients.[45] Hypotony may occur in severely inflamed eyes, and secondary glaucoma may result from blockage of aqueous outflow resulting from peripheral and posterior synechiae. Posterior segment examination during the active phase of the disease may reveal a heavy vitreitis with vitreous opacities, an exudative retinal detachment (Fig. 19–9A), Dalen–Fuch's nodules, and optic disc hyperemia or swelling. Later in the disease course, because of the diffuse loss of choroidal pigmentation, the fundus may develop

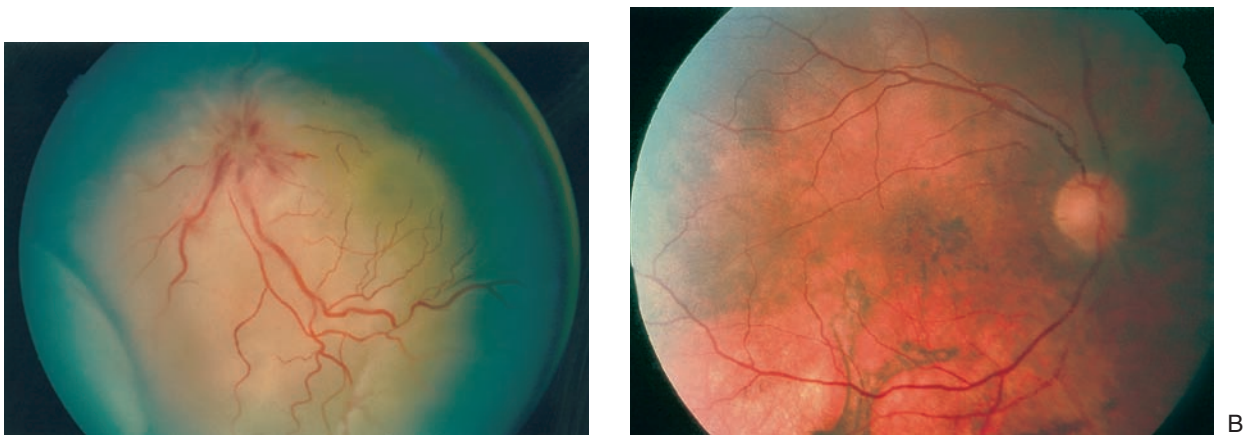


FIGURE 19–9. Vogt–Koyanagi–Harada (VKH) syndrome. (A). An exudative retinal detachment without anterior segment findings (Harada disease) is a common presentation of the VKH syndrome. (B). After the disease has become quiet, the fundus may acquire a "sunset-glow" appearance because of the loss of retinal pigment epithelium (RPE) and choroidal pigmentation.

an orange-red discoloration referred to as a *sunset-glow fundus* (Fig. 19–9B). Alternatively, the fundus may show diffuse multifocal areas of hypopigmented or hyperpigmented chorioretinal scars.

The diagnosis of VKH is based on the recognition of pathognomonic clinical features that have recently been revised.[46] Fluorescein angiography characteristically reveals multifocal areas of leakage at the level of the RPE in the early phase of the study, with subsequent subretinal pooling of dye and optic disc staining. Ultrasonography demonstrates diffuse choroidal thickening. Recently, HLA-DR4 has been shown to have a strong association with the VKH syndrome. Histopathologically, the disease is characterized by a marked loss of melanocytes and a diffuse granulomatous infiltration similar to that seen in SO but distinguished by involvement of the choriocapillaris not observed in SO.

Although there are variations, the disease typically occurs in three phases. The prodromal phase is characterized by symptoms of flu-like illness that includes headache, low-grade fever, vertigo, meningismus, tinnitus, and hearing loss that may be permanent. The ocular disease with a rapid loss of vision is salient in the acute phase, with both eyes being involved concurrently or onset of disease in the second eye within a few weeks of the first. Patients entering a convalescent phase tend to have a fair visual outcome; however, many patients continue to have a chronic, recurrent, or persistent disease with a poor visual outcome.

The differential diagnosis for VKH includes the other causes of infectious and noninfectious panuveitis. The diagnosis of VKH is excluded if there is a history of ocular trauma preceding the onset of the ocular disease. VKH presenting as an exudative retinal detachment (Harada disease) is typically differentiated from multifocal central serous retinopathy and uveal effusion syndrome by its associated inflammatory disease (Fig. 19–9A). Posterior scleritis may be excluded by the absence of pain and scleral thickening. Corticosteroids are the treatment of choice for VKH. For patients presenting with bilateral retinal detachments, high-dose steroids or intravenous methylprednisolone followed by an oral taper may be required. For patients with recurrent disease during the steroid taper, the use of additional immunosuppressive agents such as cyclosporine as a steroid sparing agent should be considered.

What Are the Clinical Features of Behçet's Disease?

Behçet's disease is a chronic, relapsing systemic vasculitis that may affect multiple organ systems with varying degrees of severity.[47] A rare cause of panuveitis in the United States, Behçet's syndrome is most commonly diagnosed in men living in or with ancestry from around the Mediterranean basin, the Middle East, and East Asia. The most common ocular symptom of Behçet's disease is a sudden, painless onset of visual blurring or loss of vision. The ocular disease in Behçet's disease occurs in 68 to 100% of cases and is most commonly a retinal vasculitis affecting both venules and arterioles. Examination of the anterior segment may reveal a nongranulomatous anterior uveitis of mild to moderate severity with fine stellate keratic precipitates or an acute hypopyon in severe episodes that may or may not be associated with conjunctival injection or a ciliary flush. Posterior segment exam may reveal a mild or marked vitreitis that may obscure the posterior pole and infrequently a vitreous hemorrhage. The retina characteristically shows areas of vascular sheathing around venules (*periphlebitis*) or arterioles (*periarteritis*) with or without associated retinal hemorrhages, cotton-wool spots, or larger areas of retinal necrosis that may appear as retinal exudates. The optic nerve may show hyperemia or disc swelling. Less commonly, there also may be evidence of choroidal vasculitis in the form of a multifocal choroiditis. Cystoid macular edema, macular ischemia, and optic disc pallor resulting from ischemic optic neuropathy are common causes of visual loss. Neovascularization of the disc, peripheral retinal neovascularization, and iris neovascularization with neovascular glaucoma are late sequelae of the ischemia induced by the recurrent bouts of retinal vasculitis. In addition to the ocular disease, patients characteristically develop mucous membrane lesions, including oral, genital, and gastrointestinal ulcerations, which initially may be confused with aphthous stomatitis, sexually transmitted disease such as herpes simplex, and IBD, respectively. Erythema nodosum, a migratory thrombophlebitis, and an acne-like folliculitis are the typical cutaneous manifestations of the disease. CNS manifestations include strokes, palsies, and loss of cognitive function. A nondestructive arthritis affecting the wrists and ankles also may occur.

The diagnosis of Behçet disease is based on the constellation of clinical symptoms and signs. At the NEI, we rely on the Japanese criteria for the diagnosis of Behçet's disease, which defines four major criteria and several minor criteria.[48] Although not a diagnostic criterion, *pathergy*, the formation of a pustule after being punctured intradermally with a sterile hypodermic needle, is also suggestive of the diagnosis. The increased incidence of HLA-B51 among patients with Behçet's disease may suggest a genetic predisposition to the disease.

The cause of Behçet's disease is unknown. It is hypothesized to be an autoimmune vasculitis in which the vascular endothelium of small vessels is the target.

Although initially the vasculitis was thought to be the result of immune complex deposition, more recent studies suggest that it is mediated by autoreactive T cells. The clinical course of Behçet's disease is characterized by acute exacerbations and spontaneous remissions, with each exacerbation having the potential to cause irreversible damage to the ocular tissues. It has been reported that up to 73% of patients with ocular Behçet's disease develop blindness.[49] Unlike other causes of uveitis, systemic steroids are not the mainstay of therapy for Behçet's disease. In Asia, colchicine has been found to be useful for the control of the extraocular manifestations but not for the ocular disease. Cyclosporine and azathioprine, when used alone or in combination with corticosteroids, appears to be an effective therapy that can be used for an extended time. Alkylating agents may be necessary in patients who are intolerant to cyclosporine, azathioprine, and prednisone or with sight-threatening disease while on these medications.

Management of Uveitis

How Do You Treat Posterior Segment Uveitis?

The most important decision to be made before the institution of therapy for patients with uveitis affecting the posterior segment is whether the cause of the intraocular inflammatory disease is infectious or noninfectious. In cases where this is decision cannot be made with certainty following a thorough medical assessment, including an evaluation by an infectious disease specialist, consideration should be given to referring the patient to a uveitis specialist. The next step is to assess the severity of the posterior segment intraocular inflammation to determine whether there is an indication to treat and to determine objective factors that can be followed to assess the patient's response to treatment. For patients with active disease who have not experienced any visual loss, the main indication for treatment is sight-threatening disease, which is defined as any inflammatory process that is likely to cause loss of central vision or visual field in the immediate future if allowed to progress. Equally important for patients who have already lost vision as a result of uveitis affecting the posterior segment, the indication for treatment should be to prevent any further visual loss.[50]

Antibiotic therapy should be instituted without delay for cases of intermediate uveitis caused by an infectious pathogen. If primary intraocular lymphoma or a uveitis masquerade syndrome is high in the differential, it should be excluded by the appropriate diagnostic evaluation before immunosuppressive medications are started. For cases of uveitis associated with a systemic disease, patients should be referred to a medical internist or specialist for evaluation and treatment of any nonophthalmic manifestations of their disease. To avoid exposure to the potential adverse effects of immunosuppressive therapy, some uveitis specialists defer treatment for some cases of noninfectious intermediate uveitis in asymptomatic patients with a visual acuity of 20/40 or better who are without evidence of macular edema or significant vasculitis in the posterior pole. The NEI recommends therapy for all patients with macular edema and posterior pole vasculitis, even if the patient remains asymptomatic and the visual acuity has not been affected.

Immunosuppression is the mainstay of therapy for patients with noninfectious posterior segment uveitis. With few exceptions, corticosteroids are the first line of therapy for patients with active disease. Topical corticosteroids and cycloplegic agents are useful for anterior segment inflammation that may accompany posterior segment disease but alone are inadequate therapy for a phakic patient with active posterior segment inflammation. The frequency of administration of the topical corticosteroids should depend on the severity of the inflammation in the anterior segment. We have found that prednisolone acetate (pred-forte) is superior to other topical corticosteroid formulations in the control of anterior segment inflammation and topical nonsteroidal antiinflammatory agents are of no appreciable benefit. The major complications of topical corticosteroid therapy are steroid induced elevations in intraocular pressure and an increased rate of cataract development, which are also known sequelae of persistent intraocular inflammation. Periocular steroid injections into subtenon space or transseptally through the lower lid can be effective for the control of both anterior and posterior segment intraocular inflammation, including cystoid macular edema. Generally, we reserve the use of periocular steroids for patients with unilateral disease. Less frequently, we administer periocular steroid injections to patients on systemic therapy with bilateral uveitis who may need additional therapy for more severe disease in one eye as well as for patients with bilateral disease requiring greater immunosuppression who are intolerant to additional systemic therapy. For periocular therapy, we typically use 1 mL of triamcinolone (40 mg/mL) per injection and give a series of three injections 2 to 4 weeks apart. Although they are useful, the main drawbacks to the use of periocular steroids is their greater potential to cause elevated intraocular pressure and cataract as well as cosmetically significant ptosis and orbital fat prolapse.

Patients with active bilateral sight-threatening posterior segment uveitis are best treated with systemic

immunosuppressive therapy (Fig. 19–10). Because systemic immunosuppression can affect several body systems, before the institution of therapy, it will be necessary to obtain an assessment of the patient's general health and the patient's suitability for specific immunosuppressive agents. This information can be obtained by full medical evaluation and laboratory studies that will serve as baseline data for follow-up.

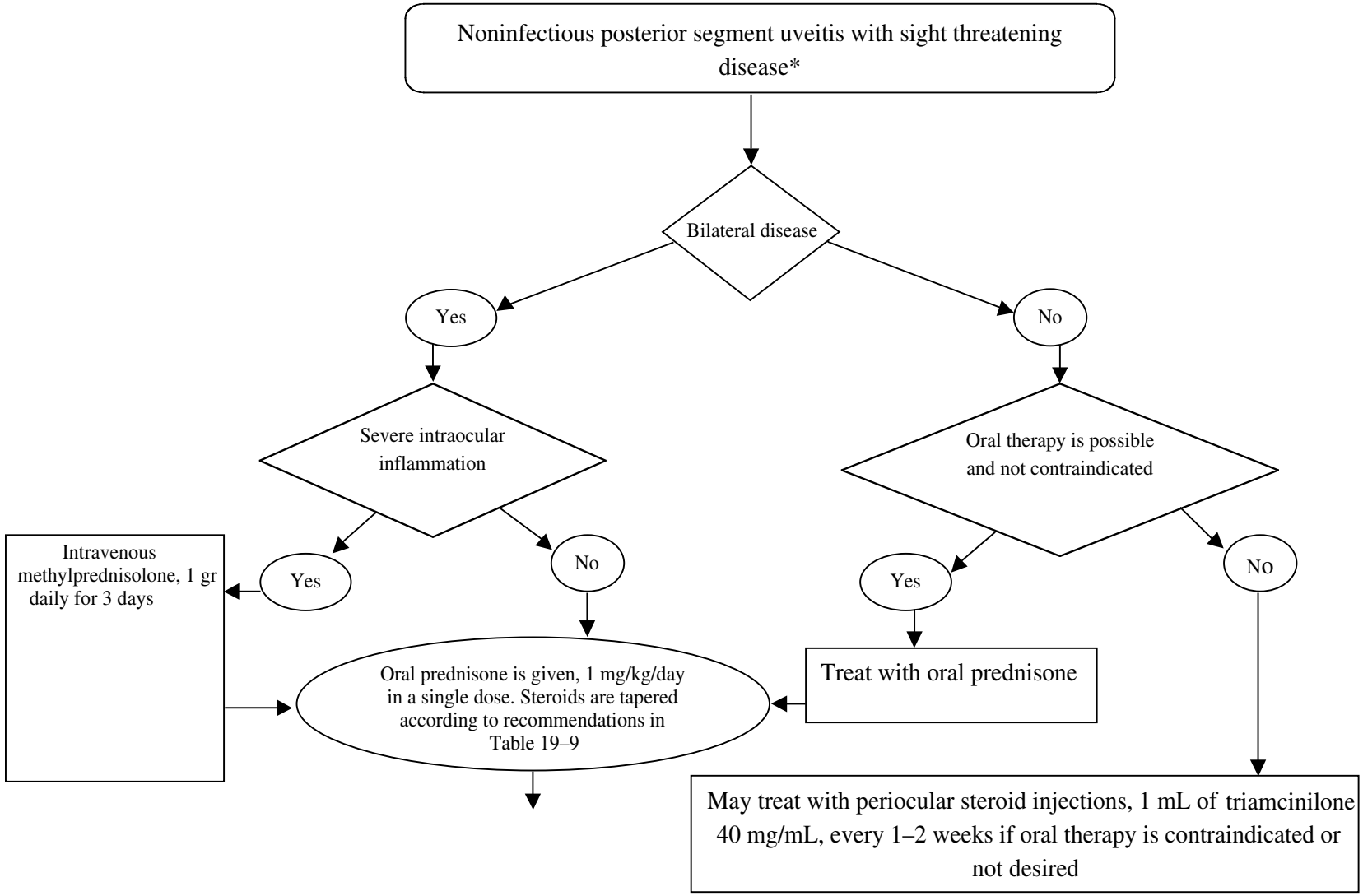
Required pretreatment studies include a CBC and differential, serum chemistries including blood urea nitrogen, creatinine, magnesium and calcium, liver function tests, urinalysis, blood pressure measurement, chest x-ray, and PPD skin test.

The detection of preexisting systemic disease or laboratory abnormalities will help guide the selection of an appropriate immunosuppressive regimen for each patient. For example, systemic steroids may be contraindicated in a poorly controlled diabetic patient; antituberculosis prophylaxis may be required for a patient with a positive PPD or abnormal chest radiograph. Cyclosporine and methotrexate should be avoided in patients with evidence of renal and hepatic impairment, respectively.

The following principles should be used as guidelines for the institution of immunosuppressive therapy for patients with bilaterally active posterior segment uveitis. The first aim of therapy is to remove the inflammatory threat to vision as soon as possible. This may be achieved by using systemic corticosteroids at a dose of 0.5 to 1.0 mg per kilogram of body weight per day given in one dose. Acetazolamide (Diamox), topical and oral nonsteroidal antiinflammatory drugs, and topical steroids alone, in our experience, have limited value in the treatment of macular edema and vasculitis attributable to an active posterior segment inflammatory disease. For patients with severe, immediately sight-threatening disease, for example, VKH panuveitis with bilateral exudative retinal detachments or severe sympathetic ophthalmia, hospital admission for intravenous methylprednisolone given 1 g daily for 3 days followed by an oral systemic steroid regimen starting at 1 mg per kilogram daily may be required. In most cases, the institution of high-dose corticosteroid therapy results in a rapid objective improvement in the degree of the intraocular inflammation measurable within the first month. The diagnosis should be reconsidered prior to the institution of additional immunosuppressive therapy for patients with uveitis unresponsive to steroids during this period. Once it is apparent that the uveitis has responded to the initial therapy, the second aim of therapy is to achieve and maintain quiescence on the lowest possible dose of immunosuppressive therapy for at least a period of 3 months prior to attempting to withdraw all therapy. *Quiescence* can be defined as trace or less in anterior chamber cells and flare and vitreous cells and haze. A reasonable goal would be to taper the steroid dose to an oral equivalent of 40 mg of prednisone or less within the first 6 weeks of therapy and to 15 mg or less within 3 months. Table 19–9 provides a suggested schedule for tapering oral prednisone.[51] Because the risk of bone loss is greatest in the first few months of steroid therapy, patients should be treated with daily supplemental vitamin D (800 IU) and calcium (1500 mg). If the patient remains quiet and is able to tolerate an oral steroid dose equivalent to 10 to 15 mg of prednisone daily or less, it may be possible to maintain the patient on corticosteroids alone. In most cases, however, sustained control of the intraocular inflammation using corticosteroids alone is not possible because of their side effects or an exacerbation of the disease activity. Consequently, a second-line immunosuppressant or a steroid-sparing medication is needed (Table 19–10). Steroid-sparing agents commonly used for the treatment of posterior segment uveitis include cyclosporine, methotrexate, azathioprine, and, most recently, mycophenolate mofetil.[51] Of these, cyclosporine is considered the most effective for most causes of uveitis and should be instituted first if not contraindicated. The remaining agents are to be considered if the patient is intolerant or poorly controlled with steroids or cyclosporine used alone or in combination. Although effective, the alkylating agents, cyclophosphamide, and chlorambucil are being used for the management of uveitis less frequently.

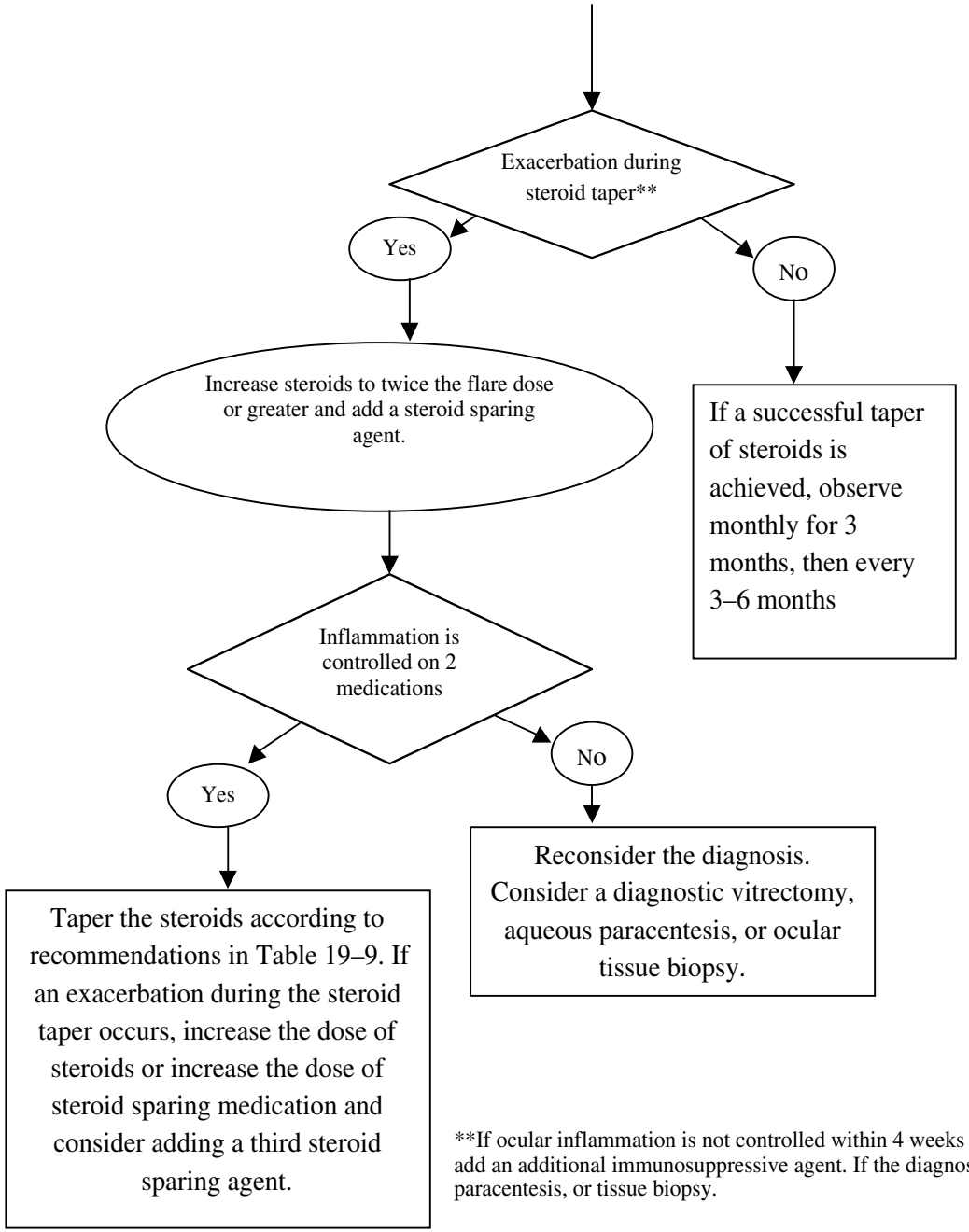
Cyclosporine inhibits the activation and recruitment of T cells. Before starting cyclosporine, the creatine clearance and serum creatinine should be documented. Cyclosporine usually is started at a dose of 3 to 5 mg per kilogram daily in a twice-daily regimen that is effective for the treatment of uveitis when used in combination with steroids or alone as monotherapy. Of the two commercially available formulations, Neoral, the microemulsion, has the greater bioavailability. The most common side effects of cyclosporine are hypertension and renal toxicity. Relative contraindications for the initiation of cyclosporine are poorly controlled hypertension, established renal disease, a decreased creatinine clearance, and age greater than 60 years because of the decreased renal reserve. Because it may take up to 6 weeks to see the effects of cyclosporine, the drug should be continued for at least 3 months before being considered ineffective.

Methotrexate, azathioprine, and mycophenolate mofetil are antimetabolites that function by inhibiting the synthesis of RNA and DNA. Methotrexate is given either orally or by subcutaneous injections. Typically, the weekly dose is initiated at 7.5 mg and increased until a therapeutic response or a maximum dose of 25 mg per week is achieved. Therapeutic responses to methotrexate may not become evident until after 6 to



*As a part of evaluation and treatment, tests to be ordered include a complete blood count with differential, serum chemistries with blood urea nitrogen and creatinine, liver function tests, serum calcium and magnesium, and urine analysis

FIGURE 19–10. Treatment of noninfectious posterior segment uveitis with sight-threatening disease.



**If ocular inflammation is not controlled within 4 weeks of starting high dose steroids but the diagnosis is certain, add an additional immunosuppressive agent. If the diagnosis is uncertain, consider a diagnostic vitrectomy, aqueous paracentesis, or tissue biopsy.

FIGURE 19–10. *Continued.*

TABLE 19–9. Corticosteroid Side Effects and Recommended Prednisone Tapering Schedule

Weight gain	
Psychosis	
Fluid retention	
Mood alteration	
Insomnia	
Irritability	
Nausea	
Cushingoid appearance	
Increased appetite	
Delayed puberty	
Pancreatitis	
Growth suppression	
Diabetes	
Adrenocortical–pituitary axis suppression	
Easy bruising	
Hirsutism	
Poor wound healing	
Cataracts	
Muscle weakness	
Glaucoma	
Osteoporosis	
Aseptic necrosis of the femoral and humeral heads	
Monitor:	Blood pressure and intraocular pressure (each visit) Blood glucose every three months Serum cholesterol and lipid profile and bone mineral density annually
Prednisone dose >40 mg/day	Decrease dose by 10 mg/day every 1 to 2 wk
Prednisone dose 20–40 mg/day	Decrease dose by 5 mg/day every 1 to 2 wk
Prednisone dose 10–20 mg/day	Decrease dose by 2.5 mg/day every 1 to 2 wk
Prednisone dose 0–10 mg/day	Decrease dose by 1–2.5 mg every 1 to 4 wk

Modified from Jabs DA, Rosenbaum JT, Foster S, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000;130:492–513, with permission.

8 weeks of therapy; therefore, the medication should be continued at least 3 months before it is considered ineffective. Liver toxicity and bone marrow suppression are reversible if detected early and the medication is decreased or stopped. Gastrointestinal symptoms, including nausea, anorexia, and stomatitis, are its most common side effects. Patients receiving this agent should abstain from alcohol use. An interstitial pneumonitis is seen less frequently. In our experience, methotrexate is less effective than the other steroid-sparing agents for the management of posterior segment uveitic diseases, with the possible exception being for the treatment of sarcoidosis. The suggested dose of azathioprine is 1 to 3 mg per kilogram of body weight per day, with the average daily dose being 50 to 150 mg daily given in a single or divided dose. Although the risk of neoplasia is the most worrisome side effect of azathioprine, the most frequent side effects are leukopenia, thrombocytopenia, and gastrointestinal disturbances. Recently, the use of mycophenolate mofetil (CellCept) supplanted the use of azathioprine in our uveitis practice at the NEI. Mycophenolate is selective, inhibiting only T- and B-lymphocytes. Studied primarily in renal and cardiac transplant patients, it has been reported to be an effective agent for the treatment of intraocular inflammatory diseases.[52,53] Mycophenolate is initiated at a dose of 1000 mg twice a day with a maximum dose of 1500 mg twice daily. Unlike the other steroid-sparing agents, the effect of mycophenolate may be noted within the first 2 weeks of initiating therapy. The most common side effects of mycophenolate are diarrhea and gastrointestinal discomfort, which usually abates after a few weeks of therapy.

The use of cyclophosphamide is generally restricted for patients with active sight-threatening disease that is intolerant to or uncontrolled by the maximum therapy with the other immunosuppressive agents described here. Cyclophosphamide is typically initiated orally at a dose of 2 mg per kilogram of body weight per day, with the usual adult dose from 50 to 200 mg daily taken on an empty stomach. Our experience in the NEI suggests that oral cyclophosphamide may be more efficacious for ocular disease than intravenous regimens. The adverse effects of cyclophosphamide include infertility, alopecia, fatigue, and gastrointestinal disturbances. There is a risk of secondary malignancy, particularly bladder cancer, in patients developing hemorrhagic cystitis. Both low- and high-dose regimens have been described for the use of chlorambucil in the treatment of uveitis.[51] The bioavailability of the drug is increased if it is taken with food. Typically, it is used with steroids, and prolonged remissions have been reported after its use. The primary adverse effects of chlorambucil are bone marrow suppression, the risk of opportunistic infections, and infertility. Because of these adverse effects, it may be reasonable to have the patient evaluated by a uveitis specialist before the administration of cyclophosphamide or chlorambucil.

After the induction of immunosuppressive therapy, the patient should be closely monitored for a response to treatment, the reactivation of disease when medications are tapered, and the onset of the side effects of therapy. The response to treatment should be measured by the patient's subjective assessment of visual function, an objective assessment of the intraocular inflammation compared with similar parameters at baseline and an assessment of the patient's overall health status, including a specific inquiry regarding medication side effects and laboratory tests. Table 19–10 describes the common side effects and the recommended follow-up for the various immunosuppressive medications. It is recommended that patients on immunosuppressive medications for posterior

TABLE 19–10. Common Adverse Effects and Recommendations for Monitoring Immunosuppressive Medications Used to Treat Posterior Segment Uveitis

Adverse Effects	*Monitor*
Cyclosporine	
Nephrotoxicity	Creatinine every 4 wk
Hypertension	CBC every 4–6 wk
Hepatotoxicity	LFTs every 3 mo
Gingival hyperplasia	Magnesium every 3 mo
Hirsutism	
Myalgias	
Tremors	
Paresthesias	
Hypomagnesemia	
Methotrexate	
Stomach upset/stomatitis	CBC every 4–8 wk
Nausea	LFTs every 4–6 wk
Anorexia	Avoid alcohol use
Hepatotoxicity (hepatitis/cirrhosis)	
Bone marrow suppression (leukopenia, thrombocytopenia)	
Interstitial pneumonitis	
Alopecia	
Rash	
Teratogen	
Azathioprine	
Nausea	CBC every 4–8 wk
Gastrointestinal upset	LFTs every 3 mo
Hepatotoxicity/hepatitis	Electrolytes every 12 wk
Increased risk of malignancy	
Bone marrow suppression (leukopenia, thrombocytopenia)	
Mycophenolate mofetil	
Abdominal pain	CBC every 4 wk
Nausea/vomiting	Electrolytes every 4 wk
Diarrhea	
Headache	
Myalgias	
Fatigue	
Leukopenia	
Opportunistic infections	
Increased risk of malignancy	
Cyclophosphamide	
Nausea/vomiting	CBC every 1–4 wk
Bone marrow suppression	UA every 1–4 wk
Alopecia	
Increased risk of infection	
Hemorrhagic cystitis	
Risk of bladder cancer	
Infertility	
Teratogen	
Chlorambucil	
Bone marrow suppression/aplasia	CBC every 1–4 wk
Opportunistic infections	
Infertility	
Teratogen	
Increased risk of malignancy	

CBC: complete blood cell count; UA, urinalysis; LFTS, alkaline phosphatase, serum glutamic oxalacetic transaminase (SGOT), or aspartate aminotransferase (AST) and serum glutamic pyruvic transaminase (SGPT) or alanine aminotransferase (ALT).

segment uveitis be followed within 2 to 4 weeks following the induction of therapy and thereafter at least every 4 to 6 weeks.

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SECTION V

Special Topics

20

Examination and Diagnosis of the Pediatric Patient

MARY ELIZABETH HARTNETT

Pediatric Retinal Examination

What Are Signs of Retinal Disease in Infants and Children?

In many retinal diseases, there is impaired central vision, visual field, night vision, or color vision. Pain is rarely present. In infants, testing for visual functions is challenging and may be difficult to interpret because the infant's visual system is not fully developed at birth. For example, visual development of grating acuity measured with Teller Acuity Cards follows a curve where adult levels of normal acuity are not attained until after the age of 4 years[1] (Fig. 20–1). Poor vision at birth may be missed because the newborn infant does not appear to respond to adult visual clues and does not describe visual symptoms. Therefore, in situations where the risk of poor vision exists, screening examinations of the retina are performed.

As a child develops, certain milestones are noted. We describe vision by observing an infant's behavior. At 6 weeks of age, a full-term infant should steadily fix on a large object, such as one's face. By 2 months of age, the child will fix and follow large objects of high contrast. With further development, the child will reach for objects and be able to see smaller objects. The child should use both eyes together and not exhibit crossing of the eyes when attentively focusing on an object. Periodic crossing may be noted if the child is focusing on something up close or if he or she is fatigued and not attentively focusing, or it may be misdiagnosed if the child has broad epicanthal folds. If the parents are concerned, however, that there is eye crossing, and none is found on a single ophthalmologic examination, it is prudent to reexamine the child at another appointment.

A young child with vitreoretinal disease may exhibit (1) failure to fix and follow an object at an appropriate age; (2) nystagmus; (3) amblyopia; (4) strabismus (Fig. 20–2); (5) conjunctival hyperemia associated with inflammation or elevated intraocular pressure; (6) difference in the size of the globes; or (7) an abnormality in pupillary reflex, such as leukocoria (Fig. 20–3). A child with vitreous floaters may describe these as familiar objects in his or her environment. For example, a child might say that he or she has a "stick" in his or her eye. In a child with a known retinal disease, parents should be suspicious of a possible problem if on more than one occasion a child describes an object in the visual space that is not present in reality.

How Is the Visual System in Infants and Children Examined?

An infant may blink in response to a penlight. When a child is able to sit up, small interesting objects can be used to get the child's attention. The examiner notes whether the child can maintain central and steady fixation with each eye. This can be done with a penlight to determine (1) whether the light reflex is in the center of the pupil, implying central fixation; (2) whether there is lack of ocular movement, implying steady fixation; and (3) whether the child maintains fixation with the eye of interest when the other eye is no longer occluded, implying maintained fixation. When the child's pupillary reflexes are centered, the eyes are orthophoric. As the examiner moves an object or penlight, he or she notes whether the child moves his or her eyes to follow the object. The examiner then covers one eye at a time to see whether the infant still follows the object with each eye. If the child prefers one eye to the other, amblyopia is suspected.

Nystagmus can be detected by determining if there is ocular movement while a child is fixating on a penlight or object. The nystagmus is described as monocular or binocular, and, if binocular, the oscillations are noted as asymmetric, conjugate, or disconjugate,

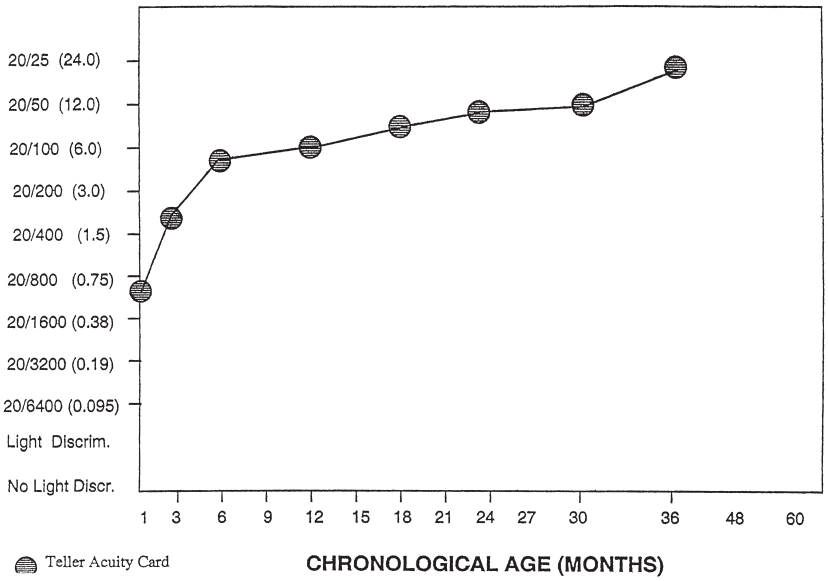

FIGURE 20–1. Visual development curve depicting visual norms obtained with Teller Acuity cards for infants aged 1 month to 4 years. (Data from Mayer DL, Beiser AS, Warner AF, Pratt EM, Raye KN, Lang JM. Monocular acuity norms for the teller acuity cards between ages one month and four years. *Invest Ophthalmol Vis Sci.* 1995;36:671–685, with permission).

meaning that the eyes will move in opposite directions. *Disconjugate movement* is described as horizontal or vertical and *conjugate nystagmus* is described as pendular or jerk.[2]

The triad of nystagmus, head bobbing, and abnormal head posture is called *spasmus nutans*. The nystagmus is often intermittent, of high frequency and small amplitude. It begins within the first year of life and lasts about a month to several years. It is often benign, but it is important to rule out other causes of monocular nystagmus or spasmus nutans, including tumors of the optic nerve, third ventricle, and thalamus, which occur in about 1% of cases.[2]

Bilateral nystagmus can be congenital, associated with spasmus nutans, or secondary to sensory deprivation. Nystagmus secondary to a sensory deprivation may not be noted at birth but develop soon after. It can be associated with reduced foveal reflexes a few months after birth when foveal maturation occurs (Fig. 20–4). Nystagmus may be associated with albinism, achromatopsia, optic-nerve hypoplasia, Leber's congenital amaurosis, coloboma, aniridia, cone dystrophies, peroxisomal disorders, and central causes. When an infant has vision loss and nystagmus, the cause should be ascertained. Consultation with a neurologist and consideration of neuroimaging are recommended. Consultation with a geneticist may be indicated. Electrophysiology may be considered to rule out congenital stationary night blindness. In an older child, a secondary sensory nystagmus may be related to a retinal condition or multiple sclerosis.

Infant and child grating visual acuity can be objectively determined by using preferential looking with Teller Acuity Cards[3,4] especially in a child too young to measure with Snellen acuity. *Preferential looking* is based on one's tendency to look at a patterned stimulus rather than a plain one. The stimuli used are equally spaced, highly contrasting stripes. By varying the width of the stripes or spatial frequency, the corresponding visual acuity can be estimated. Preferential looking does not always correspond with form visual acuity. It also may underestimate vision in infants with low vision.[5] In infants with low vision, additional methods to measure visual function are recommended. Preferential looking is useful when visual acuity level can be quantified and in longitudinal management to detect change. In older children, visual acuity testing with Allen cards, the E-chart, or with numbers if the child does not know the alphabet can be used. In addition, parents are questioned as to the infant's or child's visual behavior. Questions should include whether the child exhibits an eye preference, a difference in visual behavior in light or dark environments, and whether there is ocular pain or avoidance of light.

It may be difficult to determine visual acuity in each eye separately, particularly in the eye with poorer vision, because the infant may become uncooperative when the eye with better visual acuity is covered. In these cases, bilateral visual acuity or the vision in the better-seeing eye may be determined. The behavior of the child after having the better-seeing eye covered is noted in the record to indicate the suspicion of amblyopia.

The infant's visual system can be assessed objectively using electrophysiology. The visually evoked potential response (VER) assesses the optical pathways from the retina to the occipital cortex. The VER was reported as helpful in some diagnoses, such as albinism, where unilateral testing will show a larger-amplitude response on the contralateral side than on the ipsilateral side in 70 to 100% of cases, reflecting the

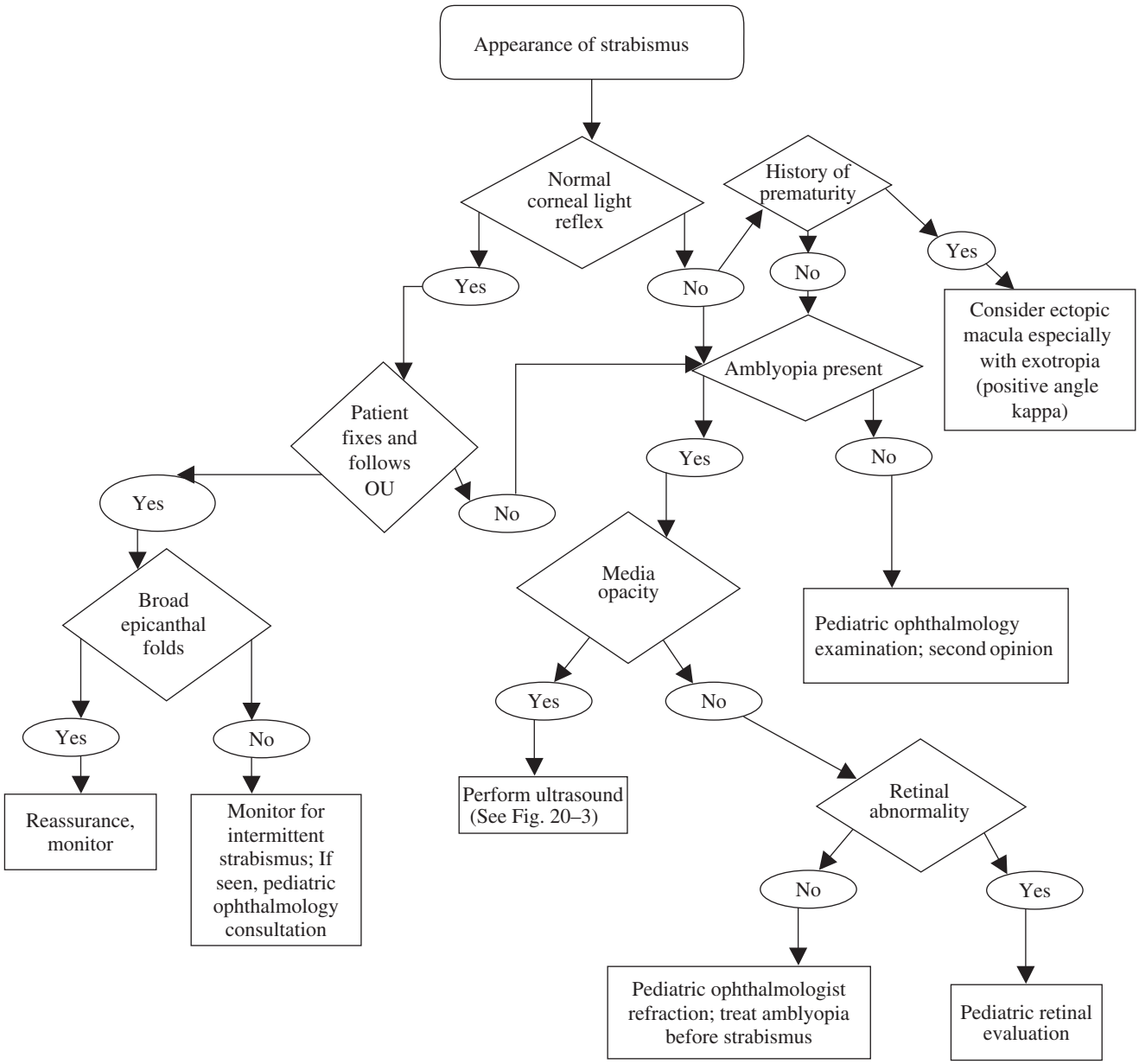

FIGURE 20–2. Clinical pathway: Appearance of strabismus. OU, oculus uterque (both eyes).

fact that the central 15 degrees of temporal retinal fibers decussate at the chiasm and travel to the contralateral lateral geniculate body instead of remaining ipsilateral.[6,7] The pattern VER also can measure macular function and is associated with the level of visual acuity.

The electroretinogram (ERG) is used to evaluate retinal function. Any child with reduced vision, sensory nystagmus, or oculodigital stimulation (pressing on the eye) may be considered for ERG. The ERG amplitude continues to increase during the first year of life.[8] In children and infants with cortical problems and delayed visual maturation, visual behavior can be reduced, even though the ERG and VER are normal. In these cases, it is possible for the vision to develop slowly.

How Is Strabismus Detected?

When a light is directed toward the eyes of a fixating child, the pupillary light reflexes should appear centered in each pupil. An eye that is turned out has *exotropia,* whereas an eye that turns in has *esotropia*. To detect which eye has a deviation, it is useful to have the child fix on an object while an occluder is brought first over one eye and then the other. As the occluder is removed from the eye, the examiner notes whether there is movement of the eye. The eye appears to

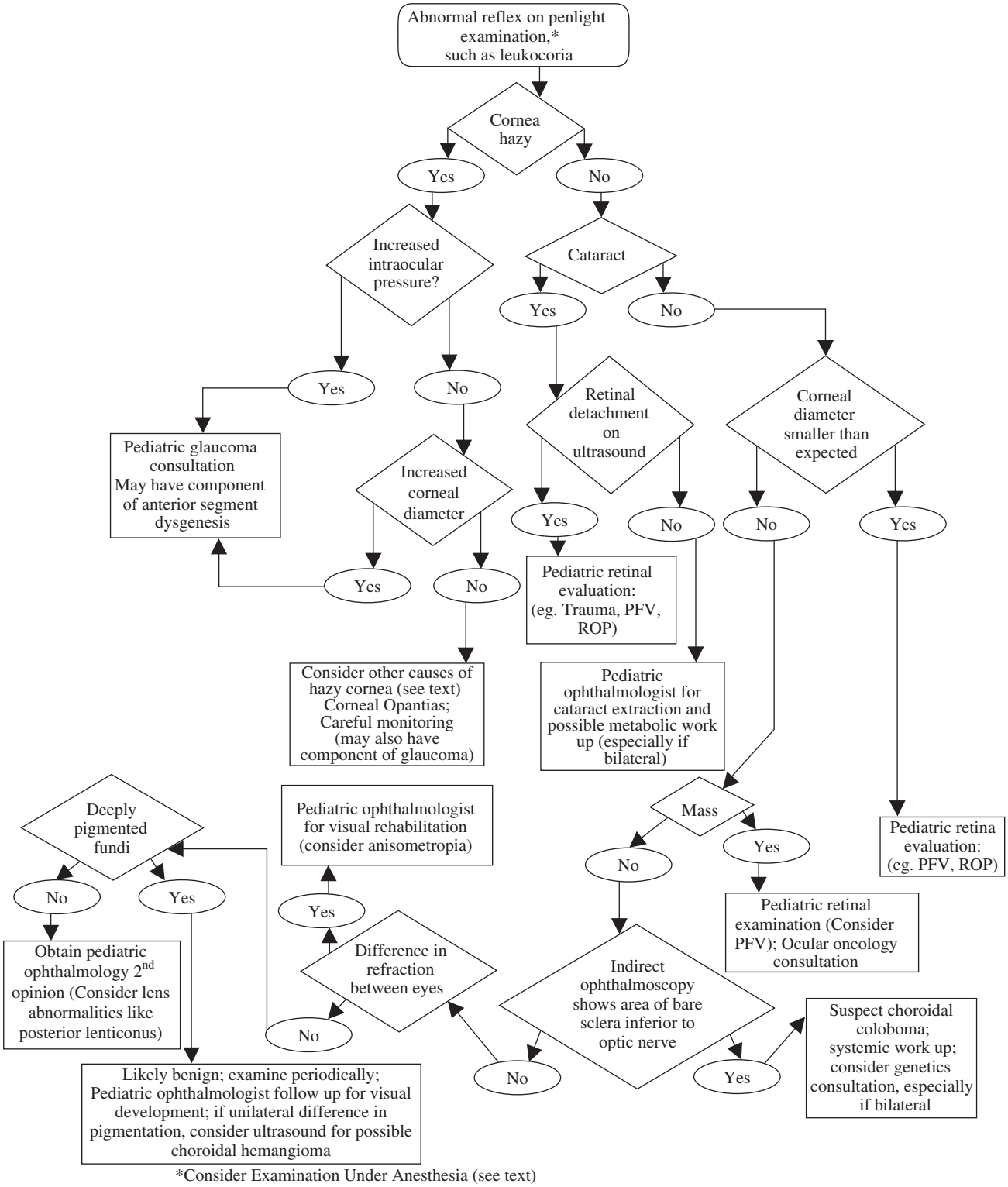

FIGURE 20–3. Clinical pathway: Abnormal reflex on penlight examination (leukocoria). PFV, persistent fetal vasculature; ROP, retinopathy of prematurity.

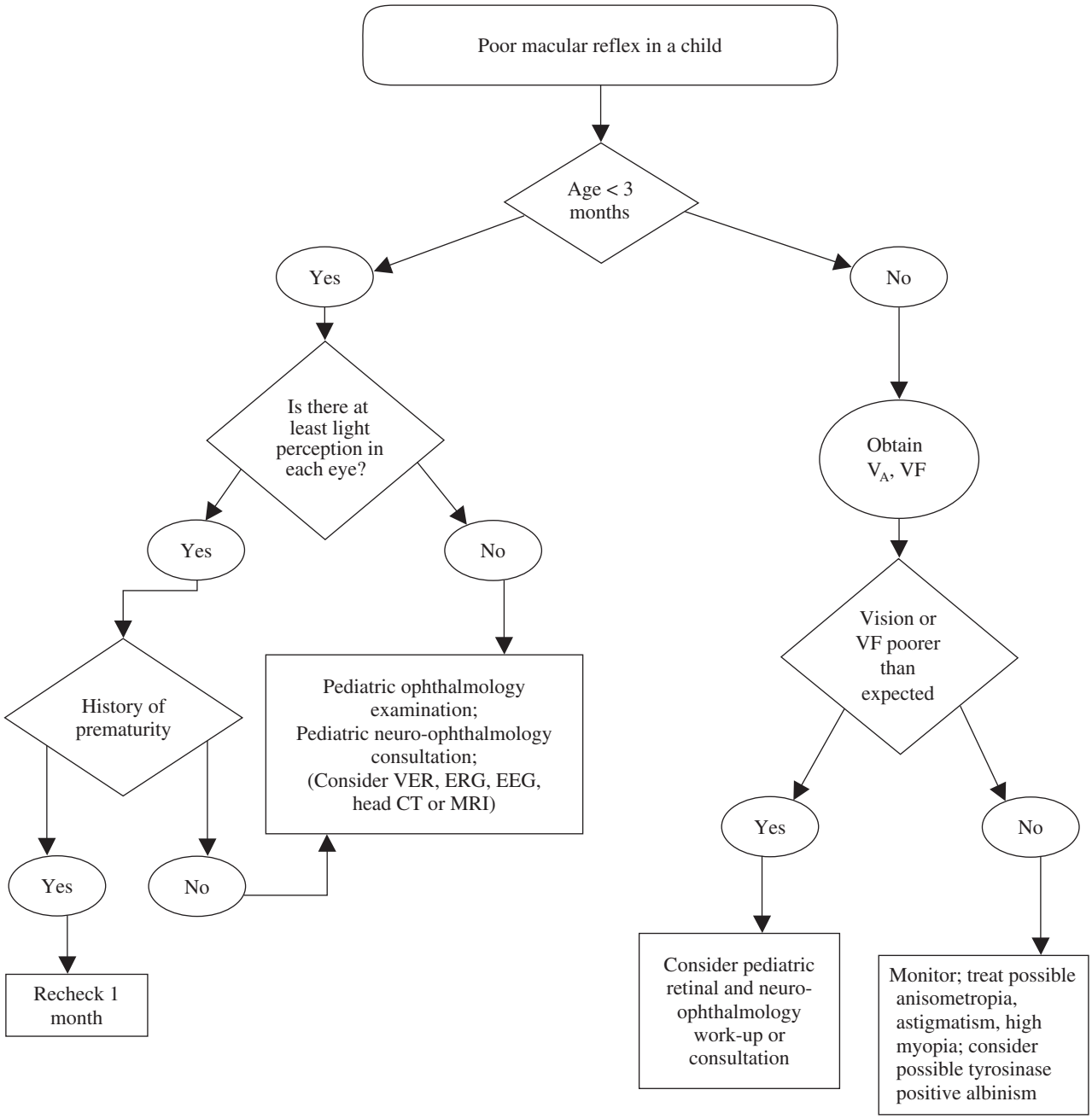

FIGURE 20–4. Clinical pathway: Poor macular reflex on indirect ophthalmoscopy in a child. VER, visually evoked potential response; CT, computed tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; ERG, electroretinogram; VF, visual field; VA, visual acuity.

move out when esotropia is present and when exotropia is present. An alternate cover examination will bring out latent strabismus. The occluder is swung from one eye to the other rapidly, and movement of the eyes is noted. The pupillary reflex can be used to estimate the amount of deviation (1 mm equals 7 degrees or approximately 15 prism diopters of deviation). Holding a prism bar in front of one eye as the alternate cover examination is performed provides a more accurate estimation. The power of the prism is adjusted during the alternate cover examination until there is no eye movement noted.

How Is the Retina in Infants and Children Examined?

In the infant and older child, it is possible to perform scleral depression without anesthesia. To perform a complete retinal examination of the posterior pole and peripheral retina with scleral depression, for example,

in screening for retinopathy of prematurity (ROP), it is necessary to restrain a small infant, for example, swaddled in a blanket and have another person gently hold the head to minimize movement. A drop of anesthetic (proparacaine 0.5%) is placed into the conjunctival cul-de-sac and a lid speculum is inserted. The retina is then examined. For ROP, the posterior pole is examined first without applying additional pressure to the globe with scleral depression, and the retinal vessels are assessed for dilatation and tortuosity (Plus disease). Scleral depression can constrict retinal vessels and, when the pressure is removed from the globe, cause them to be dilated. The optic nerve is judged as to its color and size. The macular reflex is noted. Any vascular abnormalities or pigmentary irregularities are noted. The midperipheral and peripheral retina then are examined for the maturity of retinal vessel growth. In ROP, the stage and extent of the worst stage (clock hours) are determined. Scleral depression may be useful to examine the most peripheral retina. In eyes with zone 1 and some eyes with zone 2 ROP, scleral depression may not be necessary. In lightly pigmented eyes, the visibility of the underlying choroidal vessels may mislead the examiner into thinking that the retinal vessels have fully extended to the ora serrata when they have not. One way to reduce the chance of this error is to start at the optic nerve and follow the retinal vessels to the periphery. The retinal vascular arcades are often easier to see than peripheral retinal vessels. In the deeply pigmented fundus, the contrast between retina and its vasculature may appear poor, especially when using a 28- or 30-diopter lens. Examining these eyes using a 20-diopter lens may provide a better image in these cases. It is also useful to reduce external pressure on the globe so as not to constrict the retinal vessels and render them easier to see against a deeply pigmented fundus.

An initial retinal evaluation of a child or infant should be planned to obtain the information necessary with minimal manipulation or trauma to the child. In complicated retinal evaluations, an examination under anesthesia (EUA) may still be necessary. The office examination is helpful in planning what is needed during the procedure under anesthesia. Once it is established that an EUA is necessary, a prolonged office examination of a fearful or uncomfortable child is usually unnecessary.

The examination of the retina in a child takes patience, and it is helpful not to startle the child with sudden movements. It is important to speak to the child, especially one of an older age, and to be gentle. It may be helpful to use a pacifier to calm the infant during an eye examination. Infants and children may keep their eyes open more readily if the examiner avoids touching their lids or face with hands or fingers. The examiner can steady the arm, holding the condensing lens with the other hand while the child leans up against a parent. This makes it easier to focus light onto the child's retina. It is useful to use low-light intensity of the indirect ophthalmoscope, particularly in the beginning of the examination, and it may be helpful to keep some light on in the examination room for the child who has fear of the dark. It is better to begin the retinal examination on the eye with poorer sight to get as complete an examination as possible before examining the fellow eye. If the vision in the fellow eye is normal, shining the light of the indirect ophthalmoscope into it may prevent the child from cooperating further with the examination of either eye. Sedation using chloral hydrate administered orally or rectally is used by some in children up to 3 years of age. The recommended dose of chloral hydrate is 50 mg per kilogram of body weight, up to a maximal single dose of 1000 mg.[9] In small infants born prematurely, we do not recommend chloral hydrate sedation in the office because of the risk of apnea. We also avoid its use unless a parent or competent adult can carefully observe the child for the remainder of the day.

In the older child, it is helpful to explain each step planned in the examination and not to mislead. When performing scleral depression, it is important not to press with the depressor perpendicular to the globe but rather to allow the movement of the globe to an extreme gaze to guide the depressor posteriorly and permit more tolerable depression of the far peripheral retina and ora serrata. It is also helpful to begin the examination of the peripheral retina in the superior and temporal quadrant and to end the examination at the superior and nasal quadrant. Depression in this quadrant may cause some discomfort, particularly if done before decompression of the globe has occurred from previous scleral depression.

What Is Done in the Examination under Anesthesia?

If a vitrectomy is planned, intraocular pressure is obtained with the Tono-Pen, avoiding the use of fluorescein and a handheld applanation tonometer so that visualization of the posterior segment is optimal for surgery. During an EUA, the anterior segments can be examined using the operating room microscope: The clarity of the corneas and the corneal diameters is recorded. The depth of the anterior chamber is noted. The presence of material such as fibrin or hemorrhage is noted in the anterior chamber. The iris is examined for its maturity and for abnormalities, such as transillumination defects, tumors, persistent tunica vasculosa lentis, or neovascularization. Cataracts, retrolental membranes, or subluxed lenses are noted. If the ciliary processes are pulled into the pupil, such as in

persistent fetal vasculature (PFV) or persistent hyperplastic primary vitreous, this is recorded.

The retina is examined with indirect ophthalmoscopy as described earlier in the office examination section. Increased magnification of retinal details can be achieved by using a flat contact lens placed on the cornea and the light from the operating room microscope. By increasing the magnification of the microscope, detail of the retina can be seen. The retinal field of interest can be brought into view by using a muscle hook to manipulate the globe. A 60-diopter lens also can be used to view the fundus. To focus on the retina, the microscope is moved anteriorly away from the cornea.

Photographs of the retina can be taken with a camera mounted on the microscope using either of these methods (contact lens or 60-diopter lens) to view the fundus. If a vitrectomy is planned where a very clear cornea is needed, the contact lens is avoided. Fluorescein angiography can be performed in cases where suspected vascular leakage is expected. A contact wide-angle camera is also available.[9a]

Ultrasonography can be performed to detect or characterize a retinal detachment, mass, or intraocular foreign body. This is performed in any infant or child with vitreous hemorrhage or where media opacity precludes a fundus view (Fig. 20–5), and can be done through the lid to avoid clouding the view through the cornea during surgery.

Leukocoria

What Is the Differential Diagnosis of Leukocoria?

Leukocoria is diagnosed by finding a whitish or dull rather than red reflex in the pupil when light is shined into the eye (Fig. 20–6). It may be secondary to media opacity at any level. Leukocoria or white pupil in the child should bring to mind several possible diagnoses (Fig. 20–3).

Corneal Opacities

These comprise mesodermal dysgenesis, including mutations of the PAX gene family,[10] mucopolysaccharidoses (except II and III),[11] mucolipidoses, fucosidosis, mannosidosis, Farber's disease, congenital glaucoma, syphilis, rubella, cytomegalovirus, interstitial keratitis, fetal alcohol syndrome, birth trauma, dermoid,[12] and persistent fetal vasculature, and others.

Lens Abnormalities

These include lenticonus, congenital cataract from any cause including infectious (rubella, toxocariasis, toxoplasmosis, herpes simplex, cytomegalovirus, varicella zoster), inflammatory (juvenile rheumatoid arthritis, sarcoidosis), metabolic (hypocalcemia, galactosemia, galactokinase deficiency, diabetes mellitus, mannosidosis, phosphate, Lowe aminoaciduria, homocystinuria), traumatic (amniocentesis or other trauma), developmental (persistent fetal vasculature, aniridia), Alport syndrome, and others.[13]

Vitreous Hemorrhage

This can occur with nonaccidental[14] and accidental trauma, retinoblastoma,[15] persistent hyaloid artery, persistent fetal vasculature, retinopathy of prematurity, protein C deficiency,[16] Terson syndrome,[17] disseminated intravascular coagulation disorder, or inflammation such as pars planitis or peripheral uveitis, and others.[18]

Inflammation

Inflammation can be caused by *Toxocara canis* infection,[19] toxoplasmosis,[20] peripheral uveitis,[18] cytomegalovirus retinitis,[21] endophthalmitis,[22] tumor seeding, or hemorrhage from retinoblastoma, and others.[23]

Granuloma

This can be caused by *Toxocara canis,* tuberculoma, and sarcoid granuloma, and others.

Choroidal Coloboma

Choroidal coloboma is associated with renal abnormalities and has been described as an autosomal-dominant disorder caused by mutations in one copy of the *PAX2* gene.[24]

Optic-Nerve Disorders

These disorders include peripapillary staphyloma,[25,26] optic-nerve coloboma, and morning-glory syndrome.

Vitreoretinal Disorders

Persistent fetal vasculature may be associated with cataract, vitreous hemorrhage, or retinal detachment, all of which may cause leukocoria.

Norrie disease, incontinentia pigmenti, Coats' disease, amniocentesis injury, uveitis, retinal detachment and X-linked retinoschisis may also be causes of leukocoria.

Hypopyon, posterior or anterior synechiae, and cataract can be signs of inflammation or infection, whereas in disseminated retinoblastoma, the eye may be quiet, although seeded with tumor cells if glaucoma or neovascularization is not present. If the fundus is not visible, ultrasonography (Fig. 20–5) is performed to determine whether a tumor, retinal detachment, or vitreous debris is present. To detect retinoblastoma, calcification should be sought by ultrasonography or computed tomographic scanning; however, retinoblastoma,

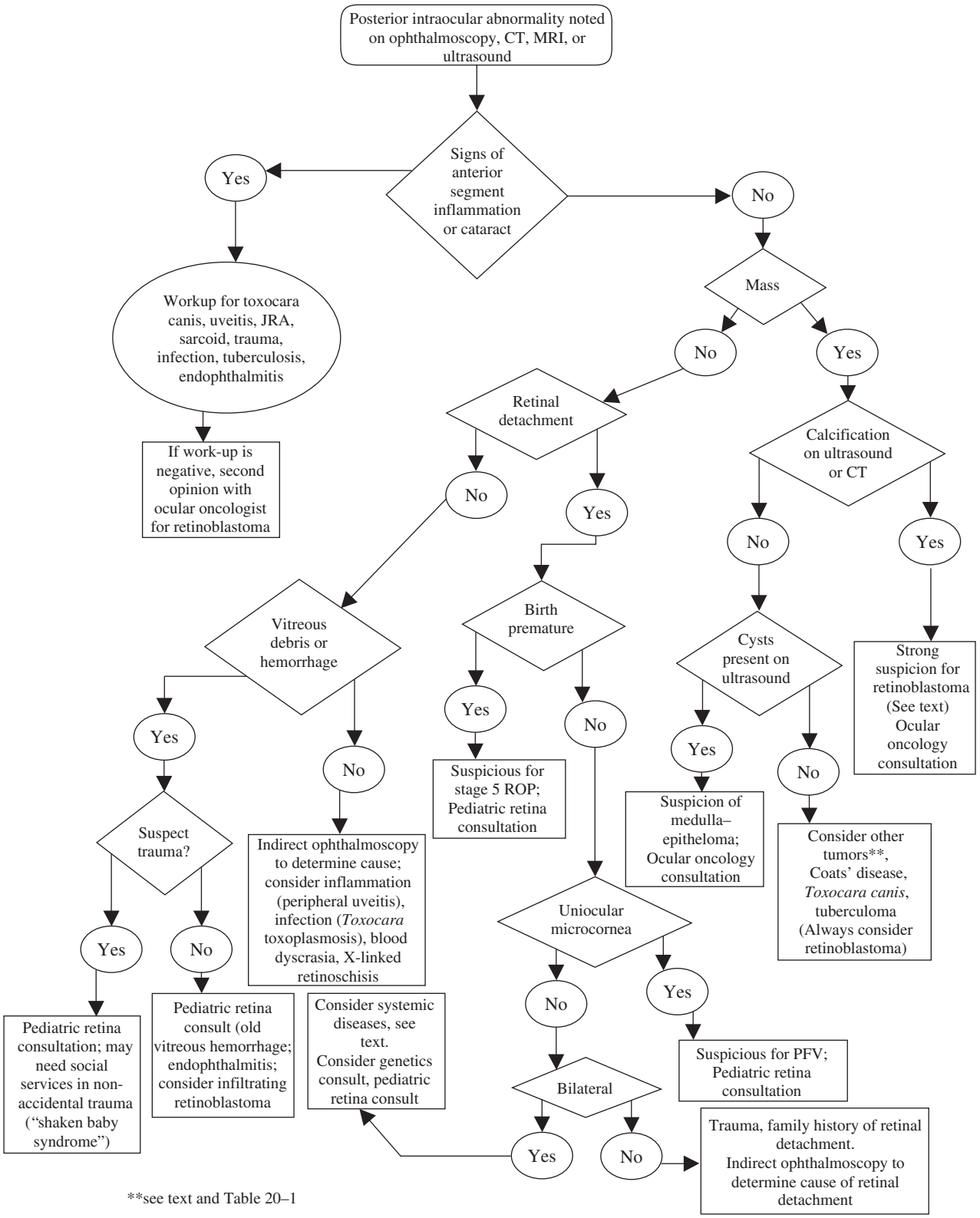

FIGURE 20–5. Clinical pathway: Posterior intraocular abnormality noted on ophthalmoscopy, computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound. JRA, juvenile rheumatoid arthritis; PFV, persistent fetal vasculature; ROP, retinopathy of prematurity.

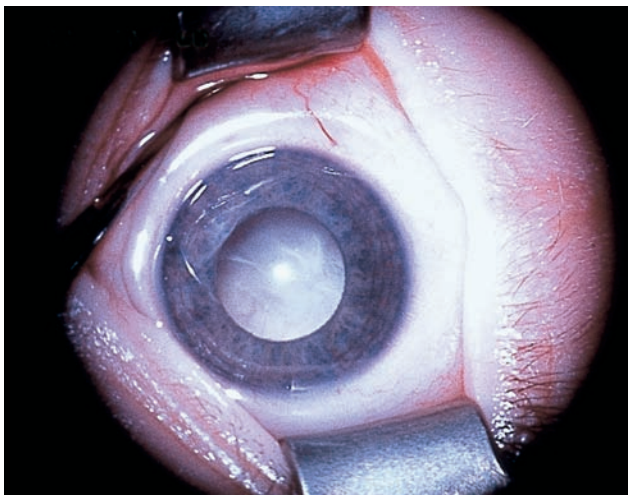

FIGURE 20–6. Leukocoria in infant eye showing retrolental membrane and underlying detached retina in stage 5 retinopathy of prematurity.

particularly those with a diffuse growth pattern, may not exhibit calcification.[23,27] The finding of bilateral microcornea with cataracts may bring to mind congenital rubella, whereas unilateral microcornea with a retrolental membrane may be associated with persistent fetal vasculature. When persistent fetal vasculature occurs bilaterally, there may be an associated systemic condition. An ERG is helpful in the diagnosis of X-linked retinoschisis, with the finding of a reduced b/a ratio, and may be helpful in some mucopolysaccharidoses associated with retinal degeneration where an increased b implicit time is noted.[11] A careful history that includes the family history is important in the workup.

What Are Some Tumors of the Posterior Segment in Children?

Tumors that occur in the pediatric age group may be malignant or benign (Table 20–1).

Retinoblastoma

Survival with retinoblastoma has increased with earlier detection and improved management. Retinoblastoma still presents challenges in diagnosis because it can present with a number of appearances, from classic leukocoria and calcified tumors to strabismus, vitreous hemorrhage, inflammation, iris neovascularization, hyphema, glaucoma, and endophthalmitis.[15,23] It is useful to have a strong suspicion of retinoblastoma in unusual presentations in children. Although vitreous hemorrhage is not common in retinoblastoma, it is more unusual to occur with other retinal tumors. Shields et al recommended that vitreous hemorrhage with or without a retinal mass in a child or teenager should prompt the suspicion of retinoblastoma.[15] Risk factors for metastasis include invasion into the orbit, choroid, or optic nerve.[28,29] Surgical trauma from fine-needle biopsy and vitrectomy also can allow access of retinoblastoma into the orbit.[15,30] It is important to obtain a second opinion, such as from an ocular oncologist, when in doubt.

Classically, retinoblastoma is diagnosed on average at 13 months of age in bilateral cases and 24 months in unilateral cases. In the rare diffuse infiltrating retinoblastoma, presentation can occur later, after 5 years of age. The types of growth include *exophytic,* where the tumor grows into the subretinal space causing an overlying nonrhegmatogenous retinal detachment; *endophytic,* where the tumor grows into the vitreous cavity; and a *diffuse infiltrating-type* tumor that can mimic inflammation. Diagnosis is facilitated through ultrasonography and computed tomography (CT) scanning[31] to detect calcification. The diffuse infiltrating form of retinoblastoma may lack calcification, however. In addition, astrocytic hamartoma, Coats disease,[32] tuberculous, endophthalmitis,[33] osseous fibroplasia associated with choroidal hemangioma, osteomas, and cyclitic membranes with bone formation may present with calcification.

TABLE 20–1. Some Ocular Tumors in Infants and Children

Malignant tumors of the retina	Retinoblastoma
	Medulloepithelioma (dictyoma)
	Adenocarcinoma (rare in children)
Malignant tumors of the uvea	Melanoma (extremely rare in children)
Benign uveal tumors	Choroidal hemangioma
	Choroidal osteoma
	Neurofibroma, neurilemmoma, leiomyoma (often in neurofibromatosis type 1)
Benign retinal tumors	Astrocytic hamartoma
	Retinal hemangioblastoma
	Congenital hypertrophy of the retinal pigment epithelium
	Combined hamartoma of the retina and retinal pigment epithelium
Optic nerve glioma	Often in neurofibromatosis type 1

Data from Damato B. *Ocular Tumors: Diagnosis and Treatment.* Oxford, England: Butterworth-Heinemann; 2000, with permission.

Retinoblastoma occurs because of a mutation in the RB gene located on the long arm of chromosome 13 at region 14. The gene normally suppresses cell division. Malignancy occurs only when both the paternal and maternal genes are malfunctioning. A somatic mutation (60%) occurs in a single cell and can lead to a solitary retinoblastoma, whereas a germline mutation (40%) produces a mutation in every cell in the body. Germinal mutations cause bilateral retinoblastomas in 75% of patients, unilateral retinoblastoma in 15%, and no tumors in 10%. Germline mutations also can cause a rare midline intracranial primitive neuroectodermal tumor (PNET). These usually occur 2 to 4 years after the diagnosis of bilateral retinoblastoma. The prognosis is poor in PNET, although chemotherapy and radiation treatment of small asymptomatic tumors have improved survival.[34] Detection remains a problem. In one series of 226 patients, neuroimaging with CT scans of the orbits and magnetic resonance imaging (MRI) of the head did not improve detection of PNET.[35]

Treatment of retinoblastoma includes chemotherapy, photocoagulation, transpupillary thermotherapy, cryotherapy, brachytherapy, external beam radiation, and enucleation.[36]

Secondary tumors are usually from osteosarcoma of the skull and long bones, cutaneous melanoma, and sarcomas. Secondary tumors may be more common after chemotherapy or radiation treatment.

Medulloepithelioma

Medulloepithelioma is a rare sporadic embryonic tumor, usually arising from the ciliary body and most often unilateral.[37,38] It is derived from embryonic nonpigmented ciliary epithelium and may be histopathologically indistinguishable from retinoblastoma. Cystic spaces filled with hyaluronic acid and undifferentiated neuroblastic cells may provide aid in the diagnosis.[39] Death occurs from intracranial invasion or rarely from metastatic disease.[37] The anterior presentation of medulloepithelioma in the eye differentiates it some from retinoblastoma. Distinguishing ultrasonographic characteristics include cystic changes, mild internal vascularity, and absence of calcification.[40] Treatment may include surgical excision or enucleation.

Choroidal Hemangioma

Choroidal hemangioma[41] in children is rare but when present is often the diffuse type that is associated with Sturge–Weber syndrome. The hemangioma tends to cause a bright red pupillary reflex. Within the fundus, the choroid appears thickened and is often red-orange in appearance (Fig. 20–7). The diagnosis may be aided by examining the fellow eye, which will appear duller in contrast. Pigment stippling and dilated tortuous retinal vessels cover the lesion. Vision is affected because the hemangioma leaks causing exudative retinal detachments. Secondary glaucoma and cataract can occur. Sturge–Weber syndrome also can lead to increased episcleral venous pressure and glaucoma. Other findings with Sturge–Weber syndrome include nevus flammeus, iris heterochromia, conjunctival and episcleral telangiectasia, ocular melanosis and leptomeningeal disease leading to seizures. Fluorescein angiography reveals early hyperfluorescence and late leakage of the hemangioma. Ultrasonography reveals high internal reflectivity without acoustic hollowness. Treatment includes observation for asymptomatic tumors and external-beam radiotherapy, brachytherapy, proton-beam radiotherapy, phototherapy, and possibly photodynamic therapy when vision is threatened or reduced.

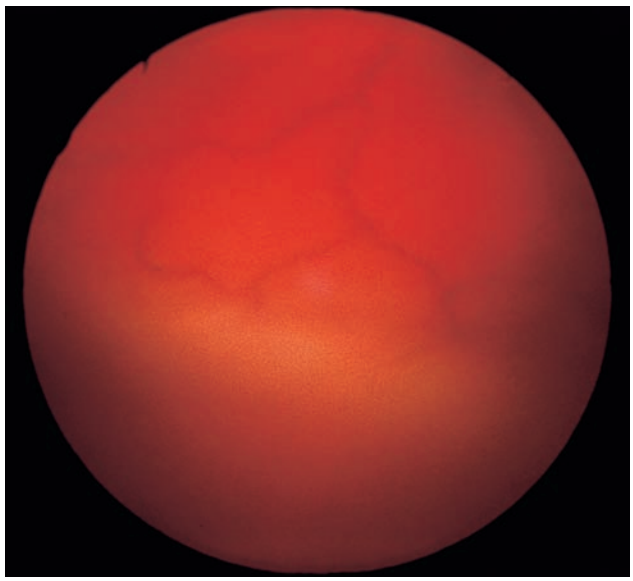

FIGURE 20–7. Diffuse choroidal hemangioma and serous retinal detachment in patient with Sturge–Weber syndrome. Note red appearance of hemangioma in the superior aspect of image and opaque retinal fold in the inferior aspect of image.

Choroidal Osteoma

Choroidal osteoma can be detected in children, although it occurs more commonly in early adulthood.[42] It may appear white, yellow, or orange and often is located adjacent to the disc or macula. Osteomas are bilateral in 25% of cases. They may be asymptomatic unless the fovea is involved by the tumor or if choroidal neovascularization occurs. Fluorescein angiography reveals diffuse irregular hyperfluores-

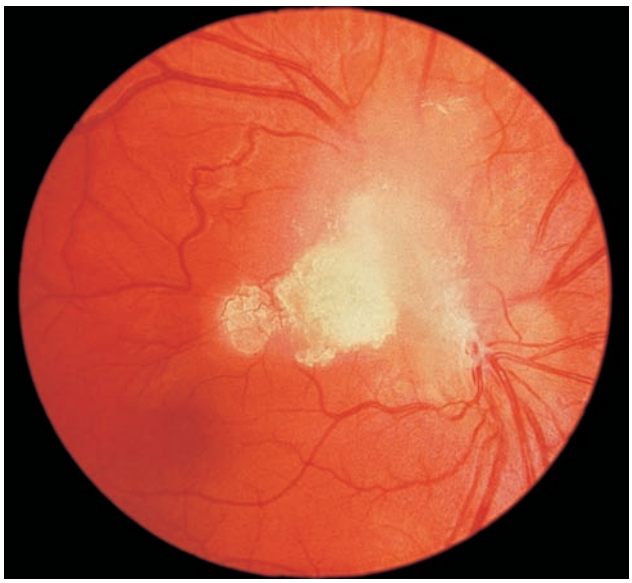

FIGURE 20–8. Solitary astrocytic hamartoma in the right eye of a young boy without tuberous sclerosis. Visual acuity was 20/25. (Photograph taken by P. Buch, CRA)

cence. Ultrasonography reveals a highly reflective anterior surface with a shadow cast into the orbit.

Astrocytic Hamartoma

These tumors can be solitary (Fig. 20–8) or multiple. Multiple lesions occur with tuberous sclerosis, an autosomal-dominant disease caused by mutations located at 9q34 and 16p13.[43,44] Ocular abnormalities occur in 50% of patients with tuberous sclerosis and include angiofibromas of the eyelid skin and conjunctiva, colobomas of iris and lens, megalocornea, and white lashes.

Astrocytic hamartomas may also occur in neurofibromatosis-1. Most astrocytic hamartomas do not require treatment. Complications from vitreous hemorrhage, neovascular glaucoma, and vitreous seeding rarely occur.[45]

Retinal Hemangioblastoma

These occur in approximately two of three patients with autosomal-dominant von Hippel–Lindau disease.[46] Symptoms usually occur in teenage years and twenties, but lesions can be detected in childhood.

The small angiomas leak and can grow, leading to exudative retinal detachment, traction retinal detachment, and blindness. These tumors are best treated when they are small, and so early detection with careful examination using a Goldmann three-mirror lens is important. Treatment of small retinal angiomas is performed with photocoagulation and cryotherapy.[47] Larger lesions may require brachytherapy or vitrectomy and endolaser. Life-long screening for associated cerebellar hemangioblastomas (25% of patients with retinal lesions), renal cell carcinoma, spinal canal hemangioblastoma, pheochromocytoma, islet cell carcinoma of the pancreas, polycythemia, and visceral cysts is important.

Congenital Hypertrophy of the Retinal Pigment Epithelium

When multiple, these asymptomatic lesions have been termed bear tracks. Solitary lesions are usually benign, but multiple bear tracks can be associated with familial adenomatous polyposis (mutation in chromosome 5), in which malignant transformation of polyps have been reported later in life.[48]

Combined Hamartoma of the Retina and Retinal Pigment Epithelium

These are usually detected in young adults but can be detected in children, sometimes causing sensory strabismus.[49] The hamartoma of glial cells, blood vessels, and retinal pigment epithelial cells invades the retina (Fig. 20–9) and may cause choroidal neovascularization, vitreous hemorrhage, epiretinal membrane, retinal contracture, wrinkling, and macular edema.

Arteriovenous Malformation

Arteriovenous (AV) malformations are nonhereditary, unilateral, and usually asymptomatic. They have been associated with macular preretinal membranes, vitreous hemorrhage, and central and peripheral venous occlusions leading to neovascular glaucoma.[50]

Coats' Disease

This unilateral sporadic disease usually affects males and has associated dilation of retinal vessels with exudation. Early on, exudates are deposited in the retina, where subretinal fluid is reabsorbed, often distant from the telangiectatic leaking vessels. The deposition may occur in the posterior pole (Fig. 20–10). When macular exudates are noted, the peripheral retina should be examined for vascular anomalies. Treatment of the leaky vessels with photocoagulation or cryotherapy can reduce leakage of telangiectatic vessels, and over time, fluid and exudates are reabsorbed.[47] Treatment may need to be repeated, especially when closing leaking arterioles. Visual acuity often remains poor once macular exudation occurs. Early treatment before the development of macular exudates is recommended, but detection may be difficult. There is no familial tendency, and the first sign in infants and young children may be sensory strabismus.

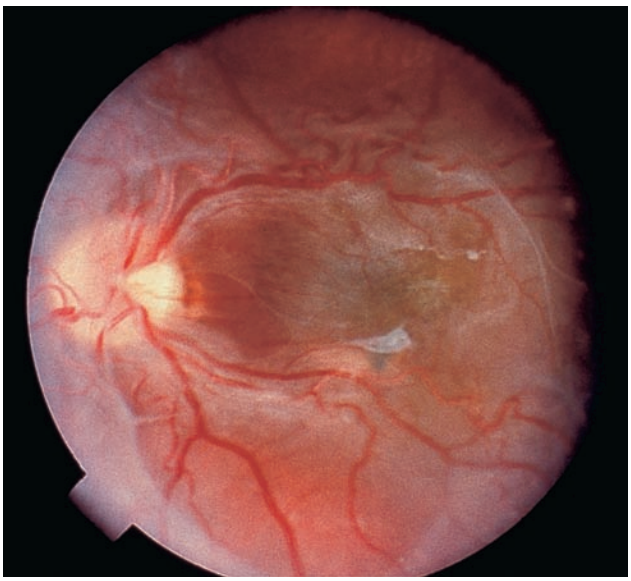

FIGURE 20–9. Combined hamartoma of the retina and retinal pigment epithelium.

Late Coats' disease can be associated with exudative retinal detachments, preretinal membranes, and subretinal organization. Coats' disease can be mistaken for exophytic retinoblastoma in that both can be associated with a retinal detachment, subretinal mass, and abnormal retinal vessels. The average age at diagnosis of Coats' disease is 3 years, whereas for unilateral retinoblastoma it is 18 to 24 months. Even at age 1 year, however, exudative Coats' disease has been diagnosed, and older children have presented with retinoblastoma.[32] In addition, calcification, a hallmark in retinoblastoma, can occur in Coats' disease and is often absent in diffuse infiltrating retinoblastoma.

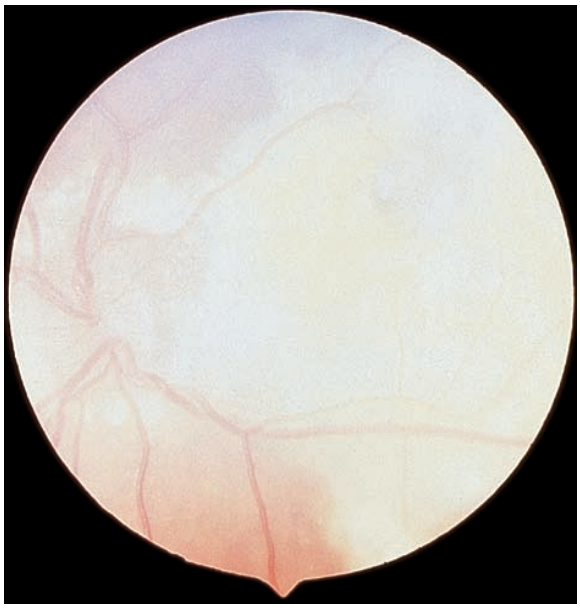

FIGURE 20–10. Coats disease in a male child. (Photograph taken with Kowa camera by M. Maio, CRA)

Patients with Coats' disease should receive timely treatment and should be followed up periodically and treated for new areas of leakage.

What Are Some Causes of Differences in Ocular Size in Infants and Children?

An enlarged cornea may be associated with congenital glaucoma in a child under 3 years of age. Glaucoma may be secondary as well, such as that associated with retinoblastoma and uveitis. Mesodermal dysgenesis also may be associated with an enlarged cornea, staphyloma, and glaucoma. Buphthalmos[51] and congenital megalophthalmos syndrome have been associated with retinal detachment and giant retinal tears.

A small corneal diameter is associated microphthalmos, with persistent fetal vasculature, retinopathy of prematurity, coloboma, and other genetic syndromes.

What Are Some Causes of Retinal Detachment in Infants and Children?

Genetic Causes

Norrie's Disease

Norrie disease causes bilateral blindness and has an X-linked recessive transmission.[52,53] Therefore, it affects males only, the mother being the obligatory carrier. Blindness is due to retinal detachment, which usually occurs within a few months after birth. Mental retardation may occur in 25% or more of patients and about a third develop progressive sensorineural deafness.[54] Patients often present with bilateral retinal detachment, exudative or traction, and blindness.

In early disease, there is often a persistent hyaloid artery and an absence or minimal development of retinal vessels. Evidence from retinal histopathology in genetically altered mice supports the line of thinking that Norrie's gene may be necessary for the regulation of retinal vascular development.[55,56]

Incontinentia Pigmenti

Incontinentia pigmenti is a rare disease that is transmitted through the mother's mitochondria. It appears X-linked dominant. Only females with one gene survive. Early, the retinal vasculature is not fully developed in the peripheral retina, leading to large avascular peripheral zones, similar to that seen in retinopathy of prematurity. Later, extraretinal neovas-

cularization at the interface of the avascular and vascularized retina proliferates and leads to traction retinal detachments.[57] Incontinentia pigmenti is often bilateral, but it may be asymmetric. It is important to be aware of the early stages of incontinentia pigmenti because laser to the peripheral avascular retina, when extraretinal neovascularization is present, may prevent further progression of the disease. Dermatologists should notify the ophthalmologist of an infant with skin lesions because these precede the retinal detachment. The skin findings appear soon after birth and appear as a linear eruption of bullae that predominantly affects the extremities. The bullae gradually resolve to leave a linear pattern of pigmentation.

Familial Exudative Vitreoretinopathy

Familial exudative vitreoretinopathy was first described by Criswick and Schepens.[47,58] The condition is often bilateral, autosomal dominant, and is thought to involve the inner retina, particularly its maturation to the ora serrata. The condition is similar in appearance to ROP, but patients are not premature or of low birth weight. Clinically, there is a temporal avascular zone, often with leakage of the vessels between the vascularized and avascular retina. Later, serous retinal detachments with exudation can occur. Traction retinal detachment can also occur. Vitreous surgery for retinal detachment may be beneficial.[59]

Stickler Syndrome (Wagner–Stickler Syndrome)

Stickler syndrome is a dominantly inherited disorder of collagen connective tissue with ophthalmic, orofacial, auditory, and articular manifestations. Orofacial characteristics include a flat midface with a depressed nasal bridge, reduced nasal protrusion, anteverted nares, and micrognathia. About 25% of patients may have some midline clefting. Deafness may be sensorineural or conductive from serous otitis media. Joint hypermobility and later degenerative arthropathy occurs.

Stickler syndrome is the most common inherited cause of rhegmatogenous retinal detachment in childhood. Most eyes, but not all, have early onset of high myopia. Congenital cataracts, vitreous abnormalities and veils, and perivascular pigmented lattice degeneration are associated. Anomalies in the anterior chamber angles can predispose to glaucoma. Several gene defects in type II collagen[60] and type XI collagen[61] have been reported in Stickler phenotypes.

The retinal detachments in Stickler syndrome are often associated with giant retinal tears and large tears along areas of lattice degeneration.[62] The lattice degeneration in Stickler syndrome can be perivascular and, therefore, extend radially from equatorial to posterior retinal locations. Retinal reattachment with scleral buckling may be difficult because of this, and vitrectomy is often necessary.

Marfan Syndrome

This autosomal-dominant syndrome is associated with abnormalities in elastin and collagen with cardiovascular abnormalities, such as dilation of the aortic root with dissecting aortic aneurysm, heart valve abnormalities, aortic regurgitation and mitral valve prolapse. Patients tend to have long, slender arms and legs, long fingers, and hypermobility of the joints, a longer lower torso than normal, and pectus excavatum. Ocular findings include enlargement of the globe,[63] ectopia lentis, filtration angle abnormalities and glaucoma, thin sclera, poorly dilating pupils, and pigmentary changes in the retinal periphery. Early vitreous syneresis and retinal breaks and detachment occur. Bilateral retinal breaks and detachments are reported in more than 50% of cases.[64] Removal of subluxed lenses via vitrectomy and lensectomy is successful, and retinal detachment is reduced in cases with intraoperative prophylactic laser treatment of lattice degeneration.[65]

Ehlers–Danlos Syndrome

Ehlers–Danlos syndrome consists of a group of hereditary connective tissue disorders caused by defective collagen synthesis, the main features being hyperelasticity and vulnerability of the skin, recurrent bleeding from fragile blood vessels, and secondary deformities of the joints. Ocular involvement is a rare occurrence,[63] for example, corneal and scleral rupture from minor blunt injury, lens displacement, and rhegmatogenous retinal detachment. Treatments with conventional scleral buckling surgery have been reported, in some instances using buckle loops glued onto thin sclera with cyanoacrylate.[66] Vitrectomy was reported with the complications of pronounced choroidal detachment and bleeding, difficulty closing the sclerotomies as a result of scleral thinning, and later anterior proliferative vitreoretinopathy with reduced vision. Surgical procedures other than primary vitrectomy should be considered.[67]

Aniridia

Aniridia may present sporadically or as an autosomal-dominant condition. Typical ocular findings are lens subluxation, cataract, hypoplasia of the fovea and optic nerve, and glaucoma. Also reported is an association with retinal detachment and giant retinal tears in eyes that become buphthalmic.[68]

Developmental Causes

Choroidal Coloboma

During the fifth to seventh week of normal development, the fetal or choroidal fissure closes by fusion of each side of the optic cup.[69] This process begins at the equator and proceeds toward the anterior aspect of the eye and toward the optic nerve. Failure of the closure of the fetal fissure can produce a variety of colobomatous lesions affecting the optic nerve, retina, choroid, lens, and iris. The location of the fetal fissure is inferior and nasal to the optic nerve. Thus, the location of developmental colobomas tends to be inferior and nasal.

A choroidal coloboma may produce a white pupillary reflex. Dilated funduscopy is performed to rule out a retinal detachment. Retinal detachment can occur secondary to a break outside of and unrelated to the coloboma[70] or from vitreoretinal traction and retinal breaks within the coloboma (Fig. 20–11). In the first case, standard scleral buckling leads to repair of the retinal detachment. In the second case, more complicated vitreoretinal surgery is required.[71,72]

A combination of four of the following features has been termed CHARGE syndrome[73]: coloboma of the eye, heart defects, atresia choanae, retardation of growth or development, genital anomalies, and ear anomalies with or without deafness. The presentation of the features may vary in severity.

Lens Coloboma

In infants and children, retinal detachment may be associated with a lens coloboma, often inferior and nasal in location, and associated with absence of zonular fibers in the area of the coloboma. Tissue may connect the posterior lens capsule with the nasal retinal periphery of the retina, causing persistence of an embryonic fold of redundant retina in the extreme fundus periphery. Such an adhesion may cause a giant retinal tear that starts nasally and may extend. When the peripheral retina is adherent to the lens 360 degrees, nonattachment of the retina results. Lens coloboma is generally bilateral.[71,74]

Peripapillary Staphyloma

Peripapillary staphyloma[25] is nonhereditary, usually unilateral, and usually associated with markedly reduced visual acuity. Cases exist with good visual acuity if the macula has not been distorted. A retinal detachment may occur within the staphyloma. Detection of the retinal detachment may require ultrasonogra-

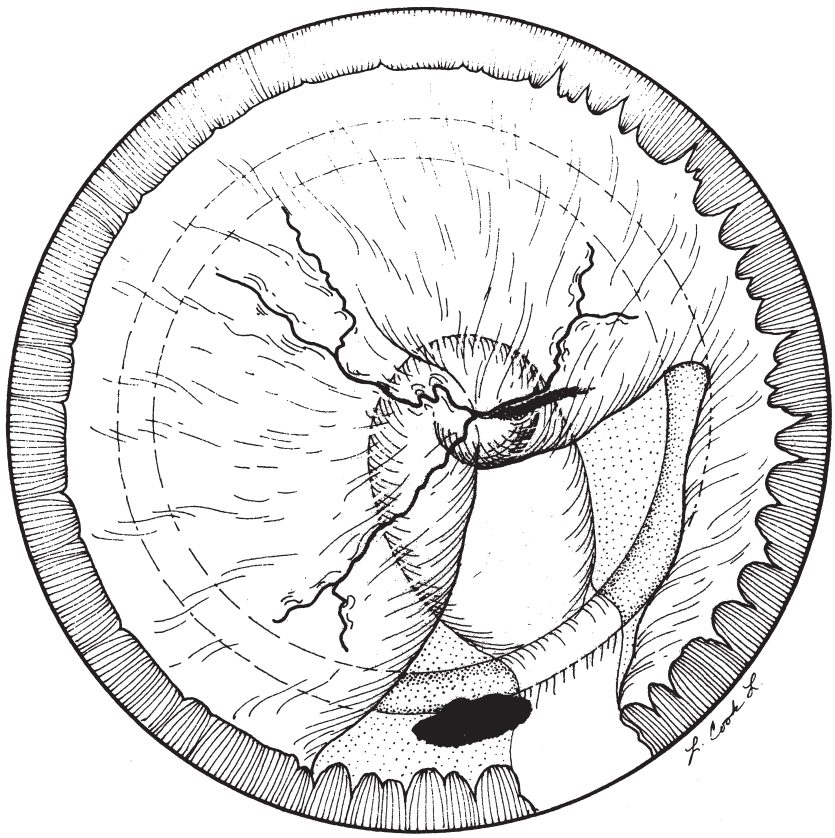

FIGURE 20–11. Retinal detachment associated with preretinal membrane overlying a retinal break within a choroidal coloboma. Vitreous hemorrhage is noted in inferior retina. (Artist L. Lhowe; reprinted with permission from Hartnett ME, Hirose T. Cyanoacrylate glue in the repair of retinal detachment associated with posterior retinal breaks in infants and children. *Retina.* 1998;18:125–129.)

phy.[26] The macular reflex is often noted to be closer to the optic nerve than usual, or it may be hidden within the staphyloma.

Persistent Fetal Vasculature

Persistent fetal vasculature, also known as persistent hyperplastic primary vitreous (PHPV), results from a failure of normal regression of the fetal vasculature. In the first trimester, the vasculature of the primary vitreous is fully developed into an anastomosing system. Regression of this vasculature begins in the second trimester, first posteriorly with the hyaloid artery system and vasa hyaloidea propria. The Bergmeister papilla and pupillary membrane are prominent at this stage. At the end of the second trimester, the pupillary membrane begins to atrophy. In the third trimester, the hyaloid artery undergoes occlusion. Bergmeister papilla and the pupillary membrane undergo variable regression.

Usually, PFV[75] occurs unilaterally. When bilateral, it is more likely to be associated with other systemic conditions,[76,77] such as trisomy 13 (also with intraocular cartilage), trisomy 15, trisomy 18, Norrie's disease, incontinentia pigmenti, Reese–Blodi–Straatsma syndrome, Walker–Warburg (agyria and hydrocephalus, retinal dysplasia, congenital nonattachment of the retina), or cocaine exposure.[78] A spectrum of findings occurs in PFV: microcornea, filtration-angle anomalies, posterior cortical lens opacities, lens coloboma, and dense vitreous condensation attached to the disc and to a retinal fold, which often extends to the nasal fundus periphery. When the vitreous and retina are involved, a traction retinal detachment is nearly always present. Vitreous hemorrhage may occur and is associated with a poor prognosis.

In some infants, there may be a persistent hyaloid artery without other features of PFV. If the hemorrhage is dense enough to cause amblyopia and does not reabsorb, then removal of it by lens-sparing vitrectomy is considered.

Other Causes

After Congenital Cataract Extraction

After congenital cataract extraction, retinal detachment may occur. The incidence is difficult to determine because the duration between cataract surgery and retinal detachment can be long. One study reported an average 20- to 30-year interval between cataract extraction and retinal detachment.[79] Because lensectomy in childhood is associated with posterior capsular opacification frequently, the posterior capsule is opened either at the time of lensectomy or by a subsequent yttrium–aluminum–garnet (YAG) laser capsulotomy.

Giant Retinal Tear

A *giant tear* is defined as a break along the posterior aspect of the vitreous base encompassing 90 degrees or more of arc. It is thought to occur secondary to vitreous liquefaction and syneresis followed by contraction of the vitreous in the anterior vitreous base region.[80] The retinal detachment associated with the giant tear is difficult to treat because of the high risk of proliferative vitreoretinopathy, risk of posterior slippage of the tear, and in children because of the firm adhesion between the posterior cortical vitreous and retina.

The treatment of giant tears has been facilitated with the use of perfluorocarbon liquids (heavy liquids) that are used as intraoperative tools to unroll the tear and reappose it to the retinal pigment epithelium (RPE).[81] Silicone oil also has been helpful in maintaining a tamponade while chorioretinal adhesion develops after laser treatment.

Giant tears in children are associated with high myopia (often 10 to 11 diopters),[82] avulsion of the vitreous base from blunt, penetrating, or surgical trauma,[83–85] and lenticular colobomas.[74] They are also more common in Wagner–Stickler syndrome, where the tears have been reported to occur along the anterior margin of the vitreous base.[86] They have been reported in atopic dermatitis.[71] The risk of a retinal break in the fellow eye of patients with giant retinal tears is about 59%.[87]

Dialysis

Retinal dialyses occur most frequently in patients under age 30 years and often have an inferotemporal location adjacent to the ora serrata. They differ from giant tears, which occur along the posterior vitreous base and from traumatic dialyses, which tend to occur in the upper nasal quadrant.[88] A retinal dialysis usually leads to a progressive retinal detachment unless treated with a scleral buckling procedure.

Lattice Degeneration

Lattice degeneration is more common among myopes. It may be seen in the teenaged years but occurs more often in older adults. It is thought to occur in approximately 6 to 10% of eyes and is associated with retinal holes in 20%.[89] Not all retinal holes lead to retinal detachment, but retinal breaks along the edges of the lattice degeneration are associated with a high risk of retinal detachment. Treatment with laser around the lattice degeneration and breaks is recommended. Some also recommend treatment around lattice degeneration when symptoms of vitreous traction are present (light flashes and floaters); in the fellow eyes of patients who had retinal detachments; in patients

with a family history of retinal detachment; or before cataract surgery, neodymium: yttrium–aluminum–garnet (Nd:YAG) capsulotomy, or laser in situ keratomileusis (LASIK).[90,91] Periodic examination with scleral depression and careful recording of lattice degeneration and retinal abnormalities is recommended.

Atopic Dermatitis

Atopic dermatitis is common in the young Japanese population. The cause is unknown, but it results in eczema that may occur on the entire body including the face. Atopic dermatitis is associated with cataracts and retinal detachment. It is thought that the associated allergic conjunctivitis stimulates patients to rub their eyes vigorously and that the trauma from this creates retinal breaks in the far peripheral retina. Cases can be managed with a scleral buckle initially; however, vitrectomy with lensectomy may be necessary[71] to close the causative retinal break at the ora serrata or anterior to it and reattach the retina. Endophthalmitis from methicillin-resistant *Staphylococcus aureus* infections was reported in the early postoperative period in a series of patients with atopic dermatitis who underwent surgery for retinal detachment.[92] It was thought that colonization of the eczematous skin and nares was the source for the infection.

Congenital Retinoschisis or X-linked Retinoschisis

Congenital retinoschisis is most often X-linked affecting males but has been reported as autosomal dominant or recessive. Presentation is with decreased visual acuity, nystagmus, or strabismus. The retina splits at the nerve-fiber layer, most often in the inferior temporal peripheral retina and in the fovea. Peripheral retinoschisis occurs in about 50% of eyes (Fig. 20–12), whereas macular changes are seen in almost 100%. The appearance of the fovea may be cystoid, not unlike that seen with cystoid macular edema (CME). The early cystic macula is not associated with hyperfluorescence on fluorescein angiography until years later when pigmentary changes and window defects occur. ERG reveals a diminished B wave or B:A ratio, indicating a dysfunction in the inner retina. Peripheral schisis involves splitting of the nerve-fiber layer.[93] Extension of schisis cavities into the macula can occur, resulting in loss of central vision.[94] Schisis cavitis can occur in multiple layers of the retina and are thought to arise as a result of a dysfunctional adhesive protein, the product of a gene mutation at Xp.22.2.[94a]

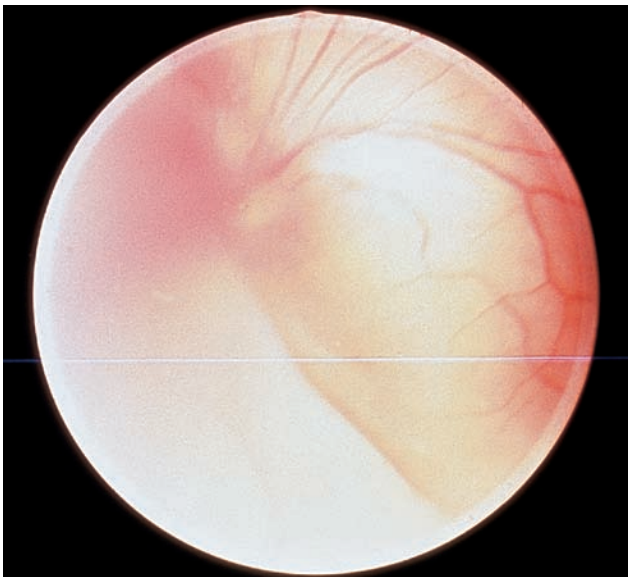

FIGURE 20–12. Schisis cavity (left in image) overhanging disc in congenital X-linked retinoschisis.

Laser treatment to collapse the schisis cavities has been reported to lead to retinal detachment. In some cases where no inner retinal holes are present, external drainage of fluid with injection of air into the vitreous has been recommended. Schisis cavities may also spontaneously flatten.[93] Vision is also threatened from dense hemorrhage into large schisis cavities, obscuration of the macula by the overhanging inner wall of the large schisis, and combined schisis/retinal detachment either from retinal breaks or traction. Retinal detachment can occur in 10 to 22% of patients. The more severe presentations of disease occur in patients younger than 10 years of age. Surgery to remove the inner wall, treatment of outer holes with photocoagulation, and tamponade with long-acting gas or silicone oil has been reported as effective in aggressive cases. Neovascularization from the retina into the vitreous can occur.[94] Photocoagulation to focal close neovascularization is often difficult but may be attempted to prevent recurrent vitreous hemorrhage.

What Are Some Causes of Vitreous Opacities in Infants and Children?

Vitreous Hemorrhage

Massive hemorrhage may occur in trauma, the child with protein C deficiency, ROP, Terson syndrome, persistent hyaloid artery, leukemia, disseminated intravascular coagulation disorder, proliferative sickle cell retinopathy, nonaccidental trauma, congenital retinoschisis, and von Willebrand disease. When an infant or child has a vitreous hemorrhage, an ultrasonographic examination is performed to exclude a retinal detachment (Fig. 20–5). If a retinal detachment

is present, surgery is considered urgently. If no retinal detachment is present, a period of observation may be considered, but concerns of occlusion amblyopia[95] and anisometropia[16] exist, even with 6 weeks of media opacity by vitreous hemorrhage in the infant. Lens-sparing vitrectomy, which reduces postoperative amblyopia, is considered to clear the visual axis.[96,97] Infants with retinopathy of prematurity and vitreous hemorrhage tend to have poorer outcomes after vitrectomy than do infants with a vitreous hemorrhage from other causes.[16]

Proliferative sickle cell retinopathy is more common in sickle cell hemoglobin C disease than in homozygous sickle cell disease. Neovascularization growing from the retinal surface onto the posterior cortical vitreous at the interface of vascularized and avascular retina is called a *sea fan* because of its appearance. It is located in the peripheral retina. Vitreous traction on the elevated sea fan is believed to lead to vitreous hemorrhage and complications associated with fibrovascular proliferation, specifically traction on the retina and retinal detachment. This complication is a rare reported occurrence in children.[98]

Trauma

See later section.

Inflammatory or Infectious

Peripheral Uveitis

Peripheral uveitis (also called *intermediate uveitis* or *pars planitis*) is associated with inflammation in the anterior and posterior segment with "snow banking" in the pars plana region. Neovascularization also may be present. Peripheral uveitis can be associated with systemic conditions, reported in 31% in a retrospective review of 83 patients.[99] Some conditions include sarcoidosis, multiple sclerosis, acquired toxoplasmosis, and juvenile rheumatoid arthritis. Recurrent, idiopathic inflammatory reactions are treated with steroids. Retinal detachment can occur secondary to tension on the retina from tractional inflammatory membranes and from subretinal membranes. Vitreous hemorrhage also has been reported. Vitrectomy may be necessary to remove vitreous opacities and reattach detached retina.[18,100]

Toxocara Canis

When accidentally ingested, the parasite of the roundworm of puppies can infect a human and cause a variety of ocular manifestations, such as uveitis, endophthalmitis, and posterior or peripheral granuloma. The diagnosis is made by clinical examination and a positive toxocara by enzyme-linked immunosorbent assay (ELISA). Treatment with steroids, anti-helminthics (such as thiabendazole and diethylcarbamazine), and, in some cases, vitreous surgery to remove preretinal membranes or the parasite is recommended.[19,101,102] Although its presentation can mimic retinoblastoma, it usually presents at an older age than does retinoblastoma. Cataracts may also occur with *Toxocara* infections and are not common with retinoblastoma.

Sarcoidosis

Sarcoidosis presents as a multisystemic granulomatous disease and is rare in children. It can occur in children in two forms. Before the age of 4 years, sarcoidosis can present with a rash, arthritis, and uveitis. Older children may manifest in a similar manner as adults, with hilar lymphadenopathy and pulmonary infiltration. Treatment is with antiinflammatory agents. Topical steroids may be sufficient for anterior uveitis, whereas for posterior uveitis, a subtenon injection or oral steroids may be needed. In some recurrent or chronic cases, methotrexate is used.[103] Management with the child's pediatrician is recommended, especially when considering systemic medication.

Juvenile Rheumatoid Arthritis

Juvenile rheumatoid arthritis (JRA) is the most common cause of pediatric anterior uveitis.[104] Treatment may be considered with steroids and methotrexate. A phase 3 clinical trial confirmed the efficacy of etanercept, a soluble tumor necrosis factor alpha p 75 fusion protein, in treating JRA.[105,106] JRA may be associated with posterior uveitis and hypotony, presumably from inflammatory membranes affecting the ciliary body.[107,108]

Endophthalmitis

Endophthalmitis after pediatric strabismus surgery is uncommon.[22] The diagnosis may be delayed because symptoms differ from those of the adult patient. In a series of six children, lethargy, anorexia, headache, and fever were the common symptoms. Signs included eye redness, increased eyelid swelling, and vitreous inflammation. Hypopyon occurred in three of six children. The diagnosis of endophthalmitis was made 5 to 8 days after strabismus surgery, 3 to 8 days after symptoms began. All eyes lost light perception. Infection was secondary to *Streptococcus pneumoniae, S. aureus,* and *Haemophilus influenzae,* organisms that can be found in the local flora in 98% of healthy infants. In these cases, globe perforation from intrascleral sutures had not always occurred. The use of 5% povidone-iodine in strabismus cases to provide prophylaxis against infection was discussed.

Masquerade Syndromes

With any uveitis, the clinician should be aware of a possible intraocular foreign body. Children may not wish to disclose information about trauma to avoid punishment or perceived betrayal of a friend. Radiographs of the orbits may be helpful to reveal a radiolucent foreign body. Ultrasound is also useful to reveal an irregularity of the sclera or globe, vitreous hemorrhage, shadowing, or a reverberation pattern associated with a foreign body.

Retinoblastoma may masquerade as vitreous hemorrhage, toxocariasis, toxoplasmosis, and endophthalmitis.[15] Leukemia can lead to intraretinal and vitreous hemorrhages, cotton-wool spots, white-centered hemorrhages, and optic-nerve swelling.[109] Acute optic-nerve involvement may require radiation treatment to reduce the risk of subsequent vision loss.[110,111] Lymphomas also may cause masquerade syndromes.[112]

Importance of Screening for Retinal Disease in Infants and Children

Retinopathy of Prematurity

Based on the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study, ROP was found to appear on average about 32 weeks' after gestation.[113] *Threshold disease* (defined as the level of severity where the risk of an untoward structural outcome like retinal detachment is 50%) peaked on average about 37 weeks' after gestation.[114] Treatment of the avascular zones with laser or cryotherapy reduced the risk of untoward structural outcome and poor vision from threshold ROP. Therefore, the current standard of care is to screen at-risk infants with dilated retinal examinations until full maturation of the retina or threshold disease occurs, whereupon treatment with laser, preferably, or cryotherapy is recommended within 72 hours.

The American Academy of Ophthalmology advocates that screening be performed in all infants born at or under 1500 g or at 28 weeks' gestational age or younger and in infants with a birth weight of more than 1500 g with an unstable clinical course[115] (Fig. 20–13). The first examination should be done before hospital discharge or at 4 to 6 weeks after birth. The infants examined in the CRYO-ROP study were all under 1251 g.[116] We screen infants before hospital discharge if there is concern that an outpatient appointment will be missed. A suitable protocol should be decided on by the screening ophthalmologists and the neonatologists at each neonatal intensive care unit as to which infants should be screened, what agents should be used for dilation of the pupils, guidelines regarding washing hands between patients, the use of gloves or gowns, and cleansing and sterilization of eyelid specula. Infants are examined every 2 weeks until their retinas are fully vascularized. Infants who develop ROP are seen weekly. If the disease is progressing rapidly or if prethreshold ROP is diagnosed, more frequent examinations are recommended.

The stage of retinopathy depends on the retinal appearance (Table 20–2). The extent of ROP reflects the number of clock hours of the worst stage. The zone is defined as the area of maturely vascularized retina. *Zone 1* is the least mature, comprising a circle, the center of which is the optic disc, and the radius twice the distance from the optic disc to the macula. *Zone 2* is outside zone 1 and still within a circle centered around the optic disc, the radius of which extends from the optic disc to the nasal ora serrata. *Zone 3* is the temporal crescent between the perimeter of zone 2 and the temporal ora serrata. Rarely is vision-threatening disease associated with zone 3 maturity.[117]

Treatment with laser, preferably, or cryotherapy to the avascular zone in threshold eyes (Table 20–3) is recommended based on the CRYO-ROP or Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) studies.[116,118] For eyes that fail treatment and develop Stages 4 or 5 ROP, the timing of vitrectomy is determined by careful repeated examinations (Fig. 20–14).[119] Treatment with lens-sparing vitrectomy[96,97] permits safer treatment for stage 4B ROP with less risk of aphakia and cataract.[96] Late dragging of the macula (Fig. 20–15) and retinal folds can reduce visual potential.

Accidental Trauma

Screening for retinal injury is performed in children who have had ocular trauma. Most ocular trauma is associated with symptoms such as pain and decreased vision. Retinal tears and detachment from blunt ocular trauma may not occur immediately after injury but, rather, days to several months after the original injury[120] and may be missed. Blunt trauma from any size object (racquetball, baseball, soccer ball, or basketball) may lead to retinal damage. Ocular injury from sports was associated with retinal detachment or intraocular foreign body in 14.4%.[121] Vitreoretinal lesions were reported as significantly more common in eyes with hyphema from blunt trauma ($p < 0.05$).[122]

When examining a child, an examination may be performed without anesthesia if the child is cooperative. In the uncooperative child or infant, if injury to the globe, particularly a rupture, is suspected based on the history, then an examination under anesthesia is indicated. If the child is cooperative and rupture of the globe is not suspected, the child may be gently restrained and carefully examined with the aid of Desmarres retractors.

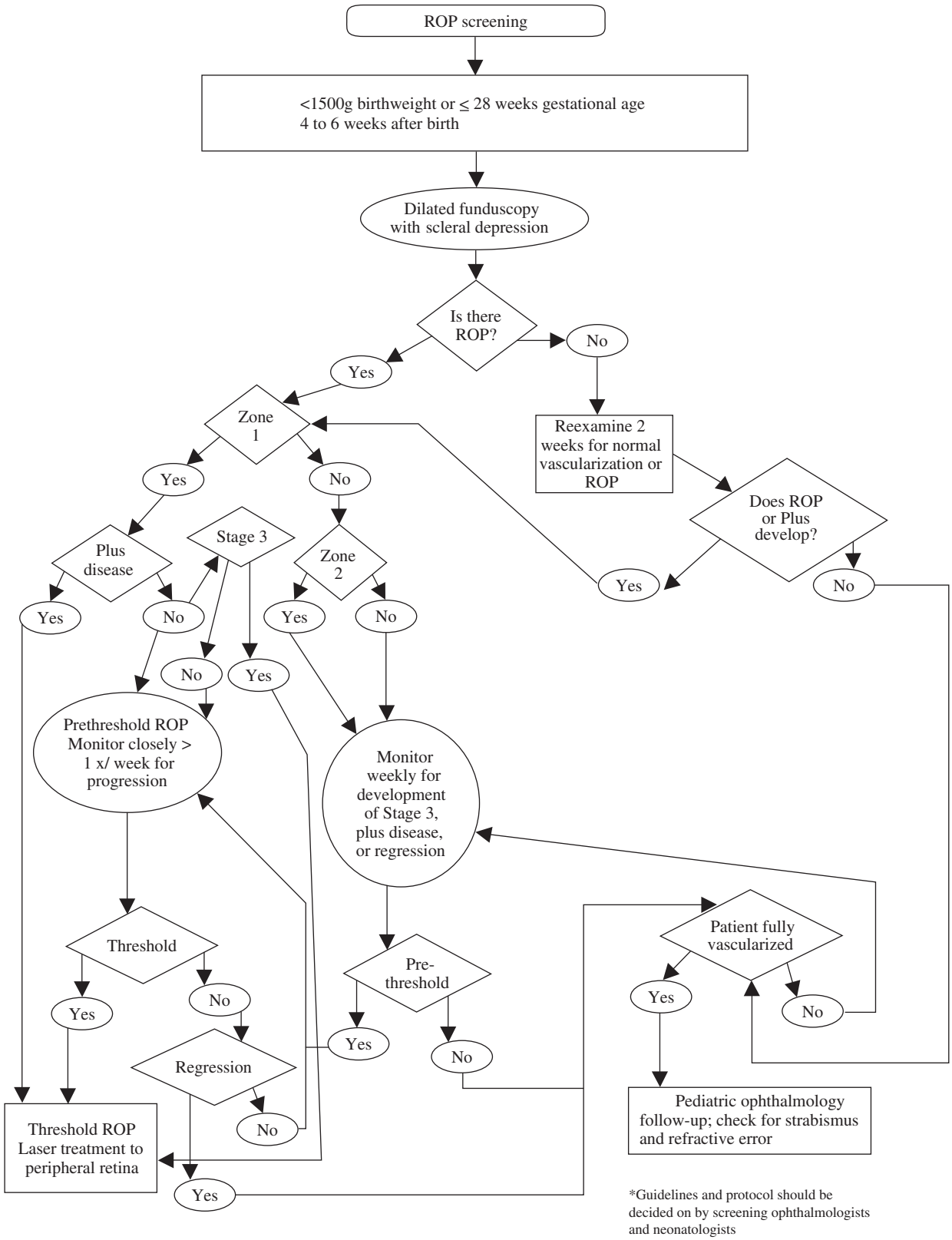

FIGURE 20–13. Clinical pathway: Retinopathy of prematurity (ROP) screening.

TABLE 20–2. Stages of Retinopathy of Prematurity

Stage	*Retinal Feature*
None	Incompletely vascularized retina
1	A line dividing vascularized from avascular retina
2	A ridge between the vascularized and avascular retina
3	Extraretinal neovascularization extending from the ridge, not including vascular remodeling posterior to the ridge
4A	Partial retinal detachment avoiding the macula
4B	Partial retinal detachment involving the macula
5	Total retinal detachment

In children and adults who exhibit self-mutilative behavior, blunt trauma may be missed, especially if the child is nonverbal. These children require close attention and are considered for periodic ocular examinations.

Nonaccidental Trauma

Ocular injury in non-accidental trauma, child abuse, may be missed, especially in the infant. In cases of suspected non-accidental trauma, the dilated funduscopic examination for intraocular hemorrhages is important. Often numerous blot hemorrhages are found throughout the fundi. (Fig. 20–16) Hemorrhages may occur at any level of the retina, choroid, and vitreous.[123] Blood-filled retinoschisis cavities are often indicative of nonaccidental trauma, but may also occur in other conditions, such as X-linked retinoschisis and von Willebrand's syndrome.[124]

In nonaccidental trauma, nonreactive pupils and a midline shift of brain structures were reported in association with increased mortality.[14] Cerebral injury and extensive preretinal macular hemorrhages were associated with profound vision loss in shaken infants. In a child with nonaccidental trauma, if the pupils are nonreactive, the recommendations are to start ventilatory support and obtain a neurosurgery consultation. If the pupils are reactive, a head CT and ophthalmology consult for a fundus examination are recommended.[14]

The presence of vitreous hemorrhage in children is associated with intracranial injury in up to 70% of cases and is associated with a poor prognosis for visual recovery despite early intervention with lens-sparing vitrectomy. In patients with Terson's syndrome, vitreous hemorrhage associated with subarachnoid hemorrhage more frequently had coma than did patients who did not have vitreous or intraocular hemorrhage.[17]

Infections

Toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis, and lymphocytic choriomeningitis virus[125] should be tested in patients with chorioretinitis noted at birth. Syphilis, although causing a pigmentary retinopathy, also often has associated interstitial keratitis. The ERG is only mildly reduced in most postin-

TABLE 20–3. Different Definitions of Prethreshold and Threshold Retinopathy of Prematurity CRYO-ROP and STOP-ROP Studies

Stage	*Zone*	*Extent*	*Plus Disease*
Based on CRYO-ROP Study[116]‡			
Prethreshold			
Any*	1	—	—
2	2	—	+
3	2	++	+++
Threshold			
3	1 or 2	5 contiguous or 8 total clock hours	+
Based on STOP-ROP Study[118]††			
Prethreshold			
Any*	1	—	—
2	2	—	+
3	2	++	+++
Threshold			
Any	1	—	+
3	1	—	—
3	2	5 contiguous or 8 total clock hours	+

+, present; —, absent; *any retinopathy less than threshold; ++extent less than threshold; +++, may be present if stage 3 extent is less than threshold; †, plus disease defined as four quadrants of dilated arteries and veins; ‡‡, plus disease defined as two quadrants of dilated arteries and veins; CRYO-ROP, Cryotherapy for Retinopathy of Prematurity; STOP-ROP, Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity.

The definition of threshold ROP was changed in the STOP-ROP study based on the poor outcome of zone 1 eyes in the CRYO-ROP study and the risk seen with plus disease. In STOP-ROP, threshold included zone 1 eyes with any ROP and 2 quadrants of plus disease, zone 1 eyes with any extent of Stage 3 ROP, and zone 2 eyes with Stage 3 ROP, and zone 2 eyes with Stage 3 of extent 5 contiguous or 8 total clock hours and two quadrants of plus disease.

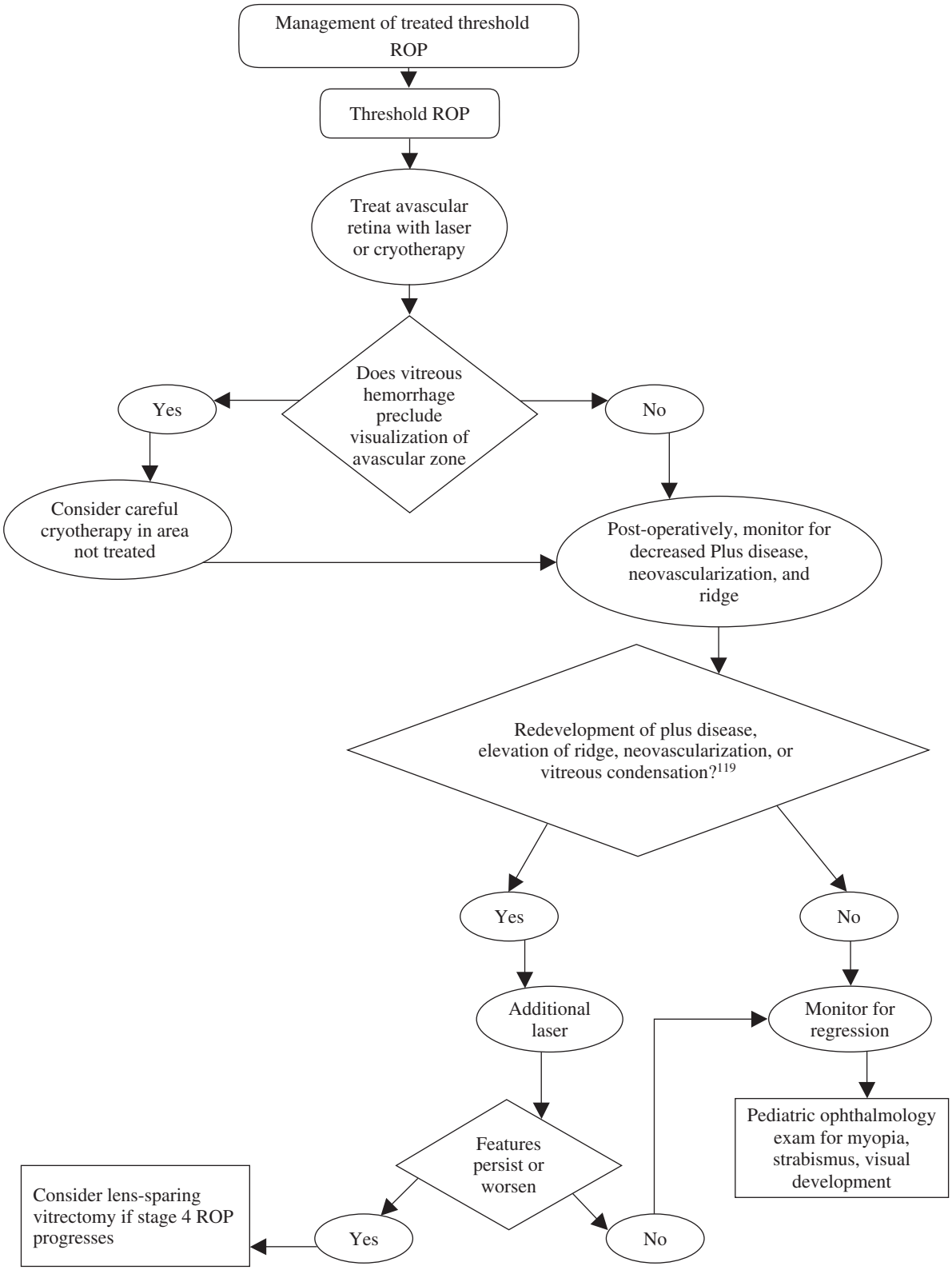

FIGURE 20–14. Clinical pathway: Management of treated threshold retinopathy of prematurity (ROP).

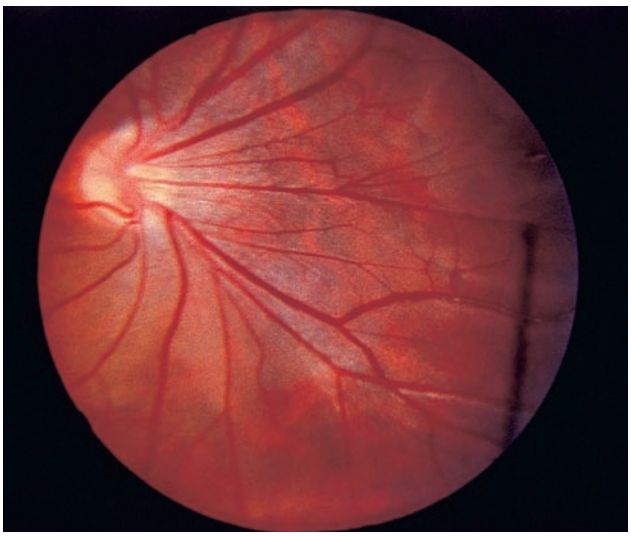

FIGURE 20–15. Dragged macula (right eye) in regressed retinopathy of prematurity.

fectious retinopathies unless extensive retinal damage has occurred.

Rubella

The rubella syndrome of microphthalmia, glaucoma, and retinopathy occurs from maternal infection with rubella before 16 weeks' gestation. Retinopathy is the most common ocular manifestation of congenital rubella. It may be subtle and localized to the macula or more widespread. Typically, the ERG is only mildly abnormal, whereas in Usher's disease, also associated with congenital deafness and pigmentary retinopathy, the ERG is extinguished. Sensorineural hearing deficits, psychomotor retardation, cardiac abnormalities,

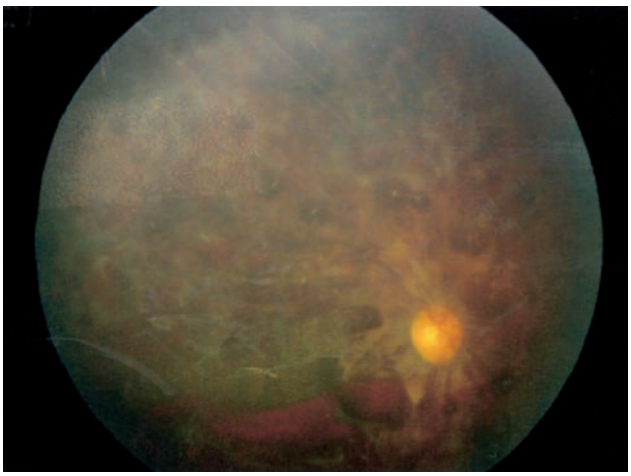

FIGURE 20–16. Nonaccidental trauma showing numerous intraretinal hemorrhages.

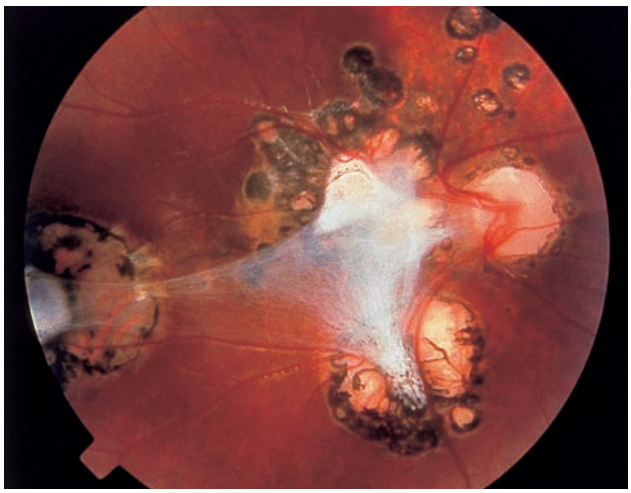

FIGURE 20–17. Photograph of fundus with macular scar from congenital toxoplasmosis. (Photograph taken by K. Barnes, BS)

and mental retardation also may occur. Cataracts, microphthalmia, and glaucoma occur, often bilaterally.[126]

Toxoplasmosis

Toxoplasmosis can occur secondary to congenital infection or after birth as an acquired infection. In congenital toxoplasmosis, patients may present with sensory strabismus, usually related to retinochoroiditis, the primary ocular pathology of congenital toxoplasmosis. Macular colobomatous lesions (Fig. 20–17) may cause reduced central vision. Recurrent inflammation and vitreous traction can lead to retinal detachment.[20] Persons with more severe ocular involvement tend to have the most extensive central nervous system deficits. Maternal exposure to toxoplasmosis in severe cases occurs during the earliest weeks of gestation.[127] The disease is transmitted maternally to the fetus. Untreated congenital toxoplasmosis may cause ocular disease in 85%.[128] With treatment, this percentage has been reduced dramatically; for this reason, some states screen for toxoplasmosis in neonates.[129]

Acquired toxoplasmosis occurs from ingestion of the cysts, trophozoites, and possibly eggs of the *T. gondii* parasite present in cats, in uncooked meats (e.g., beef, venison), on contaminated cooking surfaces, or on unwashed fruits. Postnatally acquired toxoplasmosis is less frequent than congenital but may be more prevalent than previously believed.[130] It occurs more frequently in persons under the age of 17 years. Ocular lesions can develop after the initial infection in patients with acquired disease. Toxoplasmosis can be primary, with isolated retinal lesions not associated with scars, or recurrent, with active retinal lesions associated with old inactive scars. Primary ocular toxo-

TABLE 20–4. Diagnostic Markers in Ocular Toxoplasmosis[130]

Type of Infection	*Ocular Fluids DNA (Polymerase Chain Reaction)*	*IgG*	*Serology*
Congenital	—	— IgA	
Acquired			
Acute	38%	45%	50% have a positive IgG, IgM, or IgA; 4-fold increase in IgG over time
Chronic	36%	36%	IgA not usually present
Recurrent	4%	84%	<1:512 IgG (62%)

Data from Ongkosuwito JV, Bosch-Driessen EH, Kijlstra A, Rothova A. Serologic evaluation of patients with primary and recurrent ocular toxoplasmosis for evidence of recent infection. *Am J Ophthalmol*. 1999;128:407–412, with permission.

plasmosis may occur as part of the acute phase of the systemic disease or manifest in the chronic phase.

The distinction between acute-phase and chronic toxoplasmosis is difficult because the immunoglobulin M (IgM), historically considered the hallmark of acute disease, can persist for up to 2 years after infection. There is good reason to differentiate between acute and chronic disease because corticosteroid administration in the acute phase without concomitant antiparasitic treatment is thought to lead to extensive tissue damage and possibly to more frequent recurrences.[131] Acute disease is diagnosed by the seroconversion or fourfold rise in serum IgG, the presence of IgA, or the presence of IgM[130] (Table 20–4). To improve the sensitivity of detecting acute disease, multiple serologic tests taken at different time points are recommended to follow the rise and fall of antibody levels. The presence of a serum IgA, IgM, and IgG helps support the diagnosis of acute disease.[130] When using the three serologic markers, acute phase toxoplasmosis was found in 50% of patients with primary ocular toxoplasmosis, in contrast to 2% in those with recurrent disease.[130,132] Patients with ocular disease and recently acquired infections tended to be older and had *T. gondii* DNA in ocular aqueous or vitreous more frequently than did patients with chronic disease. Patients with recurrent disease were more likely to have elevated toxoplasma IgG in their intraocular fluids. Recurrent disease was diagnosed with elevated IgG of any level and was reported to be less than 1:512 in 62% of patients.[130]

Typical toxoplasmosis lesions are defined as being at least one-half disc diameter in size with well-demarcated pigmented borders and visible sclera centrally. Because lesions have been shown to develop later in acquired cases, it is reasonable to consider treatment with antiparasitic agents in acquired disease, even when no ocular lesions are noted. Acquired toxoplasmosis may present as outer retinal lesions and as vasculitis. Acquired disease generally causes a transient illness with lymphadenopathy in immunocompetent patients. Treatment based on a survey of the American Uveitis Society[133] indicated that the following characteristics were most often considered for treatment: decreased visual acuity, lesions within 3000 μ of the fovea or 1500 μ from the optic nerve (zone 1), active retinal lesions (acquired disease), lesion of greater than one disc diameter, and moderate to severe vitreitis. The most commonly used treatment was sulfadiazine with leucovorin (folinic acid), continued for 4 to 6 weeks. Weekly laboratory testing for leukopenia or thrombocytopenia was recommended. Other choices of treatment included the addition of clindamycin with the aforementioned regimen, the use of the combination of sulfamethoxazole and trimethoprim (Bactrim DS) instead of sulfadiazine, the use of azithronyrin, and the use of corticosteroids. For neonates, some use pyrimethamine and sulfadiazine for 6 weeks followed by spiramycin therapy for 8 weeks. The cycle is repeated three times with 2-month intervals of no therapy between cycles. In children older than 2 months, the treatment regimen for sulfadiazine, pyrimethamine, leucovorin and, clindamycin should be discussed with the pediatrician. One recommendation is a 3- to 4-week course of sulfadiazine 120 to 200 mg per kilogram of body weight daily in four divided doses, pyrimethamine 2 mg per kilogram daily divided in two doses for 3 days followed by 1 mg per kilogram each day, and leucovorin 2.5 mg twice weekly after pyrimethamine is stopped. Platelets are checked weekly after a baseline. Clindamycin dose for children is 10 to 30 mg per kilogram of body weight daily every 6 hours, not to exceed adult dosage.

Toxoplasmosis can lead to retinal detachment, presumably from breaks associated with chorioretinal scars. Retinal detachment was reported to occur after an episode of ocular inflammation.[20] In a cross-sectional review of 150 patients with ocular toxoplasmosis, retinal detachment occurred in 6% and retinal breaks in another 5%. Retinal detachment or breaks were more likely to occur in ocular toxoplasmosis

when myopia was present. All retinal breaks were asymptomatic. Strong consideration of prophylactic treatment of retinal breaks in ocular toxoplasmosis was recommended.

Cytomegalovirus

Cytomegalovirus (CMV) has been reported in 3.4 to 6% of children with acquired immune deficiency syndrome (AIDS)[134,135] and in other immune-related illnesses such as severe combined immunodeficiency syndrome, congenital infection, renal transplantation, and acute lymphocytic leukemia.[21] It causes a necrotizing retinitis similar to that in adults. Children often have systemic infection concomitantly and positive nasopharyngeal cultures. CMV is associated with a reduced age-adjusted CD4 count. Screening has been recommended for CD4 counts below 20. Treatment is with antiviral agents (ganciclovir or foscarnet) and with ganciclovir implants in older children.

Other Infections

Screening for snowball-like lesions in the retina and vitreous is recommended for children with candidemia. Treatment with systemic antifungal medications may prevent endophthalmitis.[136,137] Once endophthalmitis occurs, vitrectomy and intravitreal antifungal medications, such as amphotericin B, may be necessary.

When Is Genetic Testing Performed in Retinal Disease?

Genetic testing is performed to aid in diagnosis of a disease. It can be useful for genetic counseling regarding the risk to later offspring. Genetic testing is also done to determine genotypes of certain retinal diseases, which may be helpful in the development of targeted treatment strategies. Some pediatric retinal diseases with known gene defects are described in the following. This list is ever changing because new gene associations are determined regularly.

Ancillary Tests Useful in the Diagnosis of Retinal Disease in Infants and Children

Fluorescein Angiography

Sodium fluorescein is a hydrocarbon that, when excited with blue light (465 to 490 nm), emits green-yellow light, which can be captured on sequential film frames or digital images as the dye moves through the retinal and choroidal circulations. Most fluorescein is bound to blood proteins (80%). The unbound portion is what fluoresces under blue light. The dosage of sodium fluorescein for pediatric use is 35 mg per 10 pounds of body weight.[138]

Fluorescein angiography can be performed in the office (Table 20–5) or during an EUA. The best images are produced with injection of fluorescein dye because the contrast is better than with orally delivered dye. With children, however injection may be difficult. If oral fluorescein is given, it is given in orange juice to the awake child to mask its taste.

When Is Electrophysiology Used in Pediatric Retina?

Electroretinogram

The ERG is useful in differentiating cone dystrophy from other diseases, such as Stargardt's disease. In cone dystrophy, vision is reduced and can be seen in the teenage years or any age up to 60 years. Eventually, vision drops to 20/200 to 20/400. Photopic ERG and flicker are markedly abnormal, even in the presence of a normal fundus and scotopic ERG (Table 20–6). Color vision testing is abnormal. Inheritance can be autosomal recessive, autosomal dominant, or X-linked recessive.[139] A bulls-eye maculopathy picture

TABLE 20–5. Conditions in Which Fluorescein Angiography May Be Helpful in Children

Condition	*Finding by Fluorescein Angiography*
Familial exudative vitreoretinopathy	Leakage of retinal vessels in peripheral retina
Diabetic retinopathy (may be helpful in teens or older children)	Leakage from neovascularization; optic nerve staining and leakage from retinal capillaries
Antiphospholipid antibody yndromes	Capillary nonperfusion; leakage from neovascularization
Sickle cell retinopathy and other hemoglobinopathies	Leakage from peripheral sea-fans
Toxoplasmosis	Vessel wall staining; leakage from active lesions; choroidal neovascularization associated with old scars
Peripheral uveitis	Cystoid macular edema
Stargardt's disease; cone dystrophy	Window defect in fovea (bull's-eye maculopathy)
Fundus flavimaculatus	Dark choroid in 85%
Cystoid macular edema	Intraretinal dye leakage in a petalloid pattern in macula
X-linked retinoschisis	Stellate macula or cystic appearance without fluorescein leakage

TABLE 20–6. Electroretinogram (ERG) Findings in Some Retinal Conditions

Condition	*Scotopic*	*Photopic*
Normal	Blue light No a-wave	Red light a, b-waves Oscillatory potentials
Retinitis pigmentosa	Reduced	Reduced
Cone dystrophy	Normal	Reduced
Congenital stationary night blindness	Reduced b-wave, square wave	Normal

may develop with annular loss of pigment (Fig. 20–18). Photophobia may develop. In Stargardt's disease, also with a bull's-eye maculopathy, the ERG is mildly abnormal or may not have significant abnormalities.

Retinitis pigmentosa will be associated with severely abnormal ERGs, whereas pigmentary changes secondary to infectious etiologies, such as congenital syphilis, may have normal or mildly abnormal ERGs.[140] In a patient with pigmentary retinopathy, certain ancillary tests and historical information are important to establish the diagnosis and provide possible treatment (Table 20–7). This finding is useful in the diagnosis of Usher syndrome, in which hearing deficit and retinitis pigmentosa coexist. The retina in the young patient with Usher syndrome may appear normal, although the ERG will be extinguished or markedly reduced. This contrasts with other conditions associated with hearing and visual impairment, such as congenital rubella. X-linked retinoschisis may present as an abnormal macular reflex in association with reduced visual acuity. The ERG may have a reduced b:a ratio.

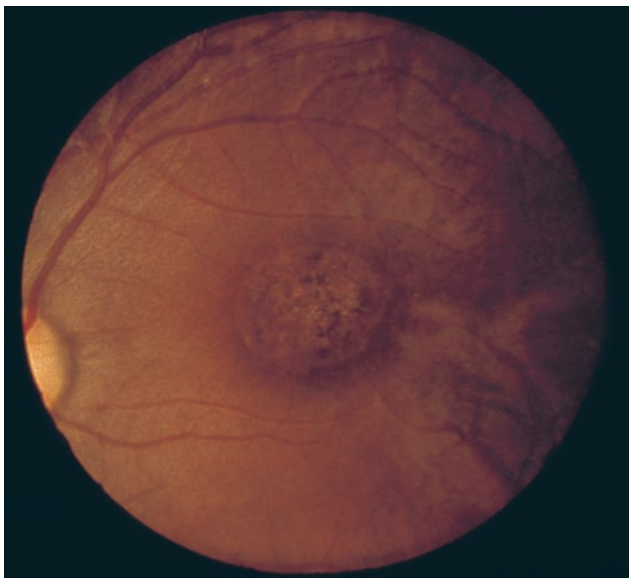

FIGURE 20–18. Photograph of bull's-eye appearance in a patient with cone-rod dystrophy.

Congenital stationary night blindness (CSNB) can be differentiated from other causes of nystagmus in infancy, such as peroxisomal disorders, Leber's congenital amaurosis, and retinitis pigmentosa, where the ERG is markedly abnormal. In CSNB, there are two different ERG responses, but the scotopic B-wave implicit time is normal.[141]

The ERG can be performed in infants under 1 year of age, often without sedation. Up to 3 years of age, chloral hydrate has been suggested to sedate the child. In children older than 3 years, it is recommended that ERG be conducted while the child is awake.[142] The ERG can be used to test retinal function in opaque media by increasing the stimulus.

Electrooculogram

This examination requires patient cooperation in order to acquire an accurate response. The electrooculogram (EOG) is a measure of the corneofundal potential between the epithelial cells mainly of the cornea and RPE. Because the RPE is metabolically more active in the dark than light, a difference in the potential between these states can be determined. The EOG reflects the function of the entire retina. When 20 to 25% of the retina is functionally normal, the EOG is normal. When the EOG is abnormal and the ERG is normal, only a few conditions are associated with this finding. In children, Best's disease is considered.[142]

Visually Evoked Potential Response

The VER records the electrical pathways from the eye to the visual cortex. It is dominated by the central 20 degrees of retina. It can be abnormal, with abnormalities of the retina, optic nerve, optic tracts, optic radiations, and visual cortex. The VER is variable among individuals but rarely differs more than 10% between the eyes of the same normal person. The VER can be used to test retinal function in opaque media by increasing the stimulus.[142]

Pattern Visual Evoked Response

The pattern visual-evoked response (PVER) is less variable among individuals than the VER. It requires the individual to see the flickering checkerboard pattern presented on a screen. By changing the size of the checkerboard, an objective estimate of visual acuity can be obtained. The response is a robust positive wave (P100) that has a normal delay of approximately 100 msec. It is important when performing the test that the child has refractive correction and that the checkerboard size causes the shortest delay to the

TABLE 20–7. Management of Some Pigmentary Retinopathies

Disorder	*Test*	*Treatment*	*Outcome*
Syphilis	Serum FTA-abs and RPR	Penicillin (neurosyphilis)	Does not restore but prevents further loss
Abetalipoproteinemia (Bassen-Kornzweig)	Serum lipoprotein electrophoresis	Treat malabsorption	Prevent further vision loss
Refsum disease	Serum phytanic acid	Adult-restrict phytanic acid in diet	Limit disease progression in adult; Childhood Refsum disease untreatable
Usher disease	Congenital sensorineural hearing loss; night blindness 5 to 15 yr	Vision and hearing support and rehabilitation	Progressive vision loss
Gyrate atrophy (peripheral retina atrophy like scalloping)	Plasma ornithine or carnitine	Restrict dietary arginine; substitute pyridoxine-responsive form	Unknown
Unilateral pigmentary retinopathy	Consider trauma, spontaneous reattachment of detached retina, siderosis and retained foreign body	For retained foreign bodies, removal may be considered; protective eyewear in trauma	Stabilizes situation
Medications (toxicity)	Quinine; hydroxychloroquine; chloroquine; chlorpromazine, thioridazine, indomethacin, gentamicin	Test ERG, EOG	Stop medication, consult with medical doctor

ERG, electroretinogram; EOG, electrooculogram.

P100 response.[142] Delayed responses to P100 occur with optic neuritis as well as vascular and compressive lesions. The PVER cannot be used to test retinal function in opaque media. It is therefore helpful to perform a VER when an abnormal PVER is obtained and the media are opaque. Still, the VER is limited as a predictive test of postoperative visual function in opaque media.

TABLE 20–8. Ultrasound Findings in Some Posterior Segment Abnormalities in Children

Condition	*Ultrasonographic findings*
Retinal detachment	High echo noted in normally echo-free vitreous; connects at optic nerve
Retinoblastoma	Heterogeneous; often with highly reflective areas of calcification
Medulloepithelioma	Cysts in the anterior part of eye near ciliary body
Early osteoma	Shadowing of scleral and orbital echoes by highly reflective lesion
Vitreous hemorrhage	Does not usually connect with optic nerve; often numerous areas of reflective debris in vitreous

When Is Ultrasound Useful?

Ultrasonography (Table 20–8) is based on the detection of sound waves reflected at an acoustic interface (junction of media with different sound velocities). It is useful in determining the axial length of an eye, detecting posterior abnormalities in opaque media (Fig. 20–5), and characterizing tumor type and size (biometry). The A-scan provides a one-dimensional representation of the acoustic interfaces as sound passes from the cornea to the orbit. In a normal eye, spikes corresponding to acoustic interfaces are seen at the probe tip hiding the corneal spike, the anterior and posterior lens capsules, the retina, sclera, and orbital fat. The B-scan provides a two-dimensional representation of a slice of the eye. By moving the location of the probe and the direction of scanning along an axis, the entire globe can be imaged and analyzed. Ultrasound for posterior segment use is generally 10 MHz.

Medical Diseases in the Pediatric Retina

Mucopolysaccharidoses

About eight types of mucopolysaccharidoses are recognized that are caused by deficient metabolism of protein-polysaccharide complexes secondary to a de-

TABLE 20–9. Neurometabolic Disorders[143]

Name	*Cherry-red spot*	*Retinal Degeneration*
Gangliosidoses		
GO_2 types I, II, III (defect in hexosaminidase)	x	
GO_2 types I, II (defect in beta-galactosidase)	x	
Neuronal ceroid lipofuscinosis (Batten)		Bull's-eye maculopathy
Sphingomyelinases		x
Gaucher (defect in glucocerebrosidase)		Rare degeneration, hemorrhages, neovascularization
Mucopolysaccharidoses, mucolipidoses		x
Farber's disease (defect in ceramidase)	x	

Data from Lang GE, Maumenee IH. Retinal dystrophies associated with storage diseases. In: Newsome DA, ed. *Retinal Dystrophies and Degenerations*. New York: Raven Press; 1988:319–340, with permission.

ficiency of a lysosomal enzyme. Intracellular accumulation of glycosaminoglycans occurs, leading to systemic findings. For example, in type 1 Hurler disease, hepatosplenomegaly, coarse facies, skeletal dysplasia, mental retardation, cardiorespiratory abnormalities, and early death occur at a median age of 5 years.[11] Eye findings include corneal clouding, retinal pigmentary degeneration, and optic-nerve atrophy.

Bone marrow transplantation may be helpful in prolonging survival in Hurler patients and in reducing corneal clouding and optic nerve edema. It is still not known, however, whether this treatment helps prevent retinal degeneration.

Other Metabolic Storage Diseases

Other metabolic diseases associated with storage of abnormal substances can lead to retinal degenerations[143] (Table 20–9). Storage of gangliosides in the neurons of the brain and ganglion cells of the retina occurs in the gangliosidoses (Tay–Sachs, Sandhoff, GO_2 gangliosidoses, type III, GO_2 gangliosidoses, types I and II). Cherry-red spots can occur because of accumulation of the substances in ganglion cells that are absent in the fovea, permitting the red appearance from the underlying choroidal circulation.[143]

Batten disease (neuronal ceroid lipofuscinosis) is associated with retinal degeneration, seizures, and mental deterioration. Retinal degeneration occurs early in life with defects in sphingomyelinase (Niemann–Pick disease), glucocerebrosidase (Gaucher's disease), neuraminidase, and mucolipidoses.

Fabry's disease or angiokeratoma diffusum is inherited as X-linked recessive, affecting males and sometimes heterozygous females. It causes a defect of alpha-galactosidase in leukocytes or cultured fibroblasts and amniotic fluid cells. The presenting finding is the presence of clusters of punctate dark red telangiectases in the skin or bathing trunk area and on the mucous membranes. Eye findings include conjunctival vessel tortuosity, corneal verticillata (whorls), lens opacities, and retinal vascular tortuosity. Ocular findings usually present in the second decade. Vascular occlusions can occur in the eye and systemically. New treatment using recombinant alpha-galactosidase A replacement may offer hope by reversing the accumulation of endothelial deposits of globotriaosylceramide in kidneys, heart, and skin.[144]

Leber's Congenital Amaurosis

This condition includes a group of autosomal recessive hereditary ocular disorders with moderate to severe vision loss beginning at birth or within the first 6 months of life. Several gene defects have been found. Nystagmus and poor pupillary reflexes are present. The fundi may appear normal, have a salt-and-pepper appearance, have pigmentary changes as seen in retinitis pigmentosa, or pigmented spots referred to as *leopard spots*. Also reported in the group constituting Leber's congenital amaurosis are macular colobomas and optic atrophy. The ERG is markedly abnormal or absent. High refractive errors have been reported and should be corrected to optimize visual rehabilitation.[145,146]

Systemic associations include tachypnea, episodic breathing and prolonged apnea, agenesis of the cerebellar vermis and renal abnormalities in Joubert's syndrome, renal abnormalities, childhood hypertension, and skeletal abnormalities.[145]

One mutation causing helser congenital amaurosis is in RPE65. A naturally occurring dog model develops retinal disease. Recently, gene therapy was shown to be effective in restoring visual function in this model.[145a]

Stargardt's Disease (Fundus Flavimaculatus)

Stargardt's disease, or fundus flavimaculatus when macular atrophy is absent, has been associated with

TABLE 20–10. Medical Conditions Affecting the Retina in Infants, Children, and Young Adults

Condition	*Age of Onset*	*Inheritance*	*Central Visual Loss?*	*Peripheral Visual Loss/Night Blindness?*	*Associated Systemic Findings*	*Electro-retinogram (ERG)*	*Other Tests*	*Fundus Appearance*	*Nystagmus*	*Macular Findings*	*Optic Atrophy*	*Photo-phobia*	*Treatment*
Leber's congenital amaurosis[141,145]	Birth to 6 mos	Autosomal recessive	Yes (oculo-digital sign)	Yes	Can have renal, respiratory, musculoskeletal, neurologic	Absent or markedly abnormal		Normal, pigmentary retinopathy, leopard spots, coloboma, or optic atrophy	Yes	Reduced foveal reflex	Some	No	Treat high refractive errors
Rod monochromacy (complete congenital achro-motopsia)[145]	Birth to early in life	Autosomal recessive	<20/200	No		Photopic luminosity curve identical to normal scotopic, absent photopic ERG		Normal or myopic	Yes	Umbo and light reflex reduced pallor secondary to myopia	Relative temporal	Yes red tint to lenses	Treat myopic astigmatism,
Incomplete achromotopsia (blue cone monochromacy)[145]	Birth	X-linked recessive	20/60 to 20/150	No		Small a and b waves in photopic		Normal or myopic	Yes	Umbo and light reflex reduced	Temporal atrophy	Mild to moderate	Neutral density and color filters
Best's disease[145]	First two decades	Autosomal dominant	75% maintain 20/40	No		Normal	EOG abnormal	Egg yolk, breakup of lipofuscin material, pseudohypopyon, sometimes choroidal neovascularization	No	Yellow egg-yolk appearance		No	Treat refractive error, treat choroidal neovasculari-zation
Stargardt's disease[147,148]	5–64 yrs; average 22 yrs	Autosomal recessive; sporadic; occasional autosomal dominant	Loss of central vision varies widely with severity and age	Often normal; can have constriction with widespread atrophy	Case reports (possibly coincidental findings rather than associated)	Normal in 95% of cases		Pisciform lesions around arcades, central foveal atrophy, dark choroid on fluorescein angiography	No	Bull's eye changes		Avoid light, no pain	Reduce exposure to light
Congenital retinoschisis[151]	Birth to school age	Often x-linked, autosomal dominant or recessive	Deter-iorates with age	Visual field loss with schisis		Reduced b/a		Stellate foveal lesion, 50% have peripheral retinoschisis; vitreous veils, occasional preretinal neovascularization elsewhere	May be present in severe cases with onset in infancy	Stellate lesions or pigmentary change		No	Laser and cryo to close NV, surgery (see text)
Bardet-Biedl[140]	Legal blindness by 20 yrs	Autosomal recessive	Yes (oculo-digital sign)	Yes	Obesity, polydactyly, hypogenitalism, mental retardation, renal disease, deafness	Abnormal		Pigmentary retinopathy, white spots, retinitis pigmentosa sine pigmento	Often not	Reduced reflex		Light sensitivity	
Vitamin A deficiency[141]	NA	Autosomal dominant	With severe dry eye	Night blindness	Xerophthalmia, may have cataract or endophthalmitis with keratomalacia	Reduced		Pigmentary retinopathy, white spots	No	No		No	Vitamin A supplementation, may reverse changes in early cases
Retinitis pigmentosa[140,141]	Variable	Dominant, recessive X-linked	Potential central vision loss with cystoid macular edema	Ring scotomas; night blindness	Pigmentary retinopathies associated with vitamin A deficiency; abetalipoproteinemia; hearing loss (Usher disease); cataract	Reduced		Pigmentary disturbance early with later bone spiculing, attenuated arterioles, cataract, Coats'-like response, vitreous cells, neovascularization	No	May have cystoid macular edema	Develops waxy pallor	No	Vitamin A,[157] reduce light

Peroxisomal disorders (adreno-leukodystrophy, Zellweger's Refsum, etc.)[141,143]	Birth	Autosomal recessive (Refsum)	Yes (oculo-digital sign)	Yes	Demyelination of central and peripheral nervous system; liver, adrenal, kidney, and skeletal abnormalities; deafness; ichthyosis	Reduced		Pigmentary abnormalities	Yes	Reduced foveal reflex	Yes	No	Refsum treatable in adults only through dietary restriction of phytanic acid
Congenital stationary night blindness[139]	Birth	Autosomal dominant or recessive; x-linked recessive	Not usual	Prolonged dark adaptation	High myopia	b wave may be abnormal		May have normal appearance or flecked*	Can be present	Reduced foveal reflex with high myopia	No	No	Treat refractive error
Kearns-Sayre syndrome[151†]	Usually before 10 yrs	Mito-chondrial	Can occur	Yes	Ptosis, cardiomyopathy can lead to heart block, external ophthalmoplegia	Variable, usually mildly affected, rarely extinct		Pigmentary retinopathy,rarely optic atrophy, vessels may be attenuated	No	Pigmentary retinopathy, often posterior	Rare	May be observed	Cardiology consultation
Cystinosis[151‡]	6 mos to 1 yr	Autosomal recessive	Not usual	Not ususal	Growth retardation, rickets, acidosis, retinal tubular abnormalities, polyuria, polydipsia, dehydration	Normal	Free cystine in leukocytes, conjunctival biopsy shows crystals	Crystalline retinopathy, pigmentary retinopathy peripherally	No	May have crystals or pigmentary change	No	Photophobia	Renal transplantation, cysteamine
Choroideremia[152]	8 to 10 yrs	X-linked recessive	When visual fields reduced to 5–10 degrees	Visual field constriction with night blindness	Posterior subcapsular cataract	Abnormal		Loss of pigment; later progressive atrophy of retinal pigment epithelium, retina, and choroid	No	Not early on, spared until late	No	Yes	None
Homo-cystinuria[153–155§]	1 yr	Autosomal recessive	Can occur	May occur with pigmentary retinopathy,	Inferior nasal lens subluxation, methylmalonic aciduria, homocystineuria, hypomethioninemia cardiovascular disease, megaloblastic anemia	Subnormal early		Progressive pigmentary retinopathy, slight pallor of optic nerve, retinal artery occlusions and venous thromboses	Yes	Poor foveal reflex, bull's eye	With glaucoma	Light sensitivity	Cobolamin treatment
Albinism[6,7]	Con-genital	Autosomal recessive; x-linked	Yes	No	Abnormal platelets (Hermansky-Pudlak), increased susceptibility to infection (Chediak-Higachi)	Supernormal		Blonde, poor foveal reflex	Yes	Poor foveal reflex	No	May have photo aversion	Correct refractive error
Aicardi's syndrome[156]	Birth	X-linked dominant	Likely	Unknown	Seizure, flexion spasms, psychomotor retardation, hydrocephalus	Normal		Punched out hypopigmented areas of chorioretinal atrophy (lacunae)	Yes	May have lacunae	Lacunae may involve nerve	No	Patients often suffer from aspiration pneumonia

*Oguchi's disease, fundus albipunctatus, fleck retina of Kandori.

†Mitochondrial DNA-related syndromes are divided into two groups: those characterized by the presence of ragged-red fibers in the muscle—including myoclonic epilepsy, mitochondrial encephalmomyopathy with lactic acidosis and stroke-like episodes (MELAS), Kearns-Sayre, chronic progressive external ophthalmoplegia (CPEO), and maternally inherited myopathy and cardiomyopathy—and those lacking ragged red fibers—including include Leber's hereditary optic neuroretinopathy and ataxia-retinitis pigmentosa-dementia complex.

‡There are three types of cystinosis: infantile nephropathic, late-onset juvenile, and adult. All three types have evidence of crystalline deposits in the cornea, conjunctiva, and iris. Crystalline retinopathy occurs in infantile nephropathic and late-onset juvenile, cystinosis; these two types are also associated with renal disease. The infantile form is the most severe.

§Mental retardation and other disabilities (including ectopia lentis, osteoporosis, and thromboembolism) caused by a deficiency of cystathionine beta-synthase; the screening of newborns with measurement of blood methionine, followed by the early treatment, may reduce irreversible brain damage.

RP, retinitis pigmentosa; NV, preretinal neovascularization.

recessive mutations in the *ABCR* gene on chromosome 1.[146] It includes the findings of macular atrophy (bulls-eye appearance) and pisciform, or "fish-like," subretinal lesions. Characteristic findings include mildly subnormal or normal ERG, dark choroid on fluorescein angiography in about 85%, and progressive central vision loss.[147] Age of onset varies. Fundus spectrophotometry detects high lipofuscin in the retina of patients with Stargardt's disease.[148]

Vitamin A Deficiency

This is one of the most important causes of preventable childhood blindness worldwide. It remains a problem in poor communities of Asia, Africa, and Latin America. Children with clinical or subclinical vitamin A deficiency have a significantly increased mortality rate.[149] Treatment is with nutritional replacement.

Albinism

Oculocutaneous albinism is classified as tyrosinase positive as opposed to tyrosinase negative on the basis of tyrosinase enzyme activity. Patients who are tyrosinase positive have some hair pigmentation, whereas individuals that are tyrosinase negative lack pigment in their melanosomes.[6] Other types of albinism include a yellow mutant, Hermansky–Pudlak syndrome (associated with bleeding abnormalities) and Chediak–Higashi syndrome (associated with leukocyte abnormalities and infections). These forms are inherited as autosomal recessive. There is an X-linked form of albinism, Nettleship Falls. Apert syndrome, and Waardenburg-like syndrome have features of albinism.

Ocular findings in albinism include light irides, nystagmus, macular hypoplasia, reduced central vision, myopic, astigmatic or hyperopic refractive errors, strabismus, and visual acuity often poorer than 20/100. PVER may be useful in the diagnosis.[6,7]

Peroxisomal Disorders

Diseases affecting peroxisomes, the intracellular organelles, affect the RPE and lead to retinal degeneration.[141,143] (Table 20–10). Among these are adrenoleukodystrophy, Refsum's disease, Zellweger disease, and olivopontocerebellar atrophy. Peroxisomal disorders may present within the first months of life with abnormal pupillary reactions, nystagmus, and muscle paresis. Abnormalities in fundus pigmentation may be present. Bull's-eye appearances have been described. Optic atrophy and vascular attenuation can occur. There may be abnormalities in the ERG, EOG, and VER, depending on the extent of retinal involvement. There may be elevated serum very long-chain fatty acids.[143]

Other Conditions

Other conditions are described in Table 20–10.[6,7,139–141, 143,145,147,148, 150–157]

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21

Screening for Specific Diseases

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Diabetic Retinopathy

What Is Diabetic Retinopathy and Why Screen for It?

Diabetic retinopathy is the leading cause of blindness in the United States for people between the ages of 25 and 55 years. It is estimated that there are 16 million people in the United States who have diabetes.[1] The incidence of diabetic retinopathy is 29% in people who have had diabetes for fewer than 5 years and up to 78% in those who have had the disease for 15 years or longer.[2] Screening includes the education of patients as to the role of medical control in the prevention of sequelae as well as identifying patients who need treatment (see Chapter 23, Fig. 23–7). The use of laser photocoagulation for macular edema[3] and proliferative disease,[4] combined with current vitreoretinal surgical techniques,[5,6] can reduce the risk of severe vision loss.[1]

Who Is at Risk for Diabetic Retinopathy?

Patients who develop diabetes during pregnancy, or *gestational diabetes*, do not have a significant risk of developing diabetic retinopathy during gestation.[7] Gestational diabetes mellitus, however, is a major risk factor for the subsequent development of non–insulin-dependent diabetes with its associated complications.

Patients with insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes mellitus, have a low risk of retinopathy for the first 5 years following diagnosis.[8] Thereafter, the risk increases. After 5 years, 25% of patients with IDDM have retinopathy. After 10 years, more than 50% have retinopathy, and after 15 years, about 80% have retinopathy. More than 30% will develop retinopathy that requires treatment.[8]

In adult-onset, non–insulin-dependent, or type II, diabetes mellitus, the risk is more difficult to specify because of the variability as to when in the course of disease the individual diagnosis is made. Patients may present with advanced retinopathy at diagnosis. Of type II patients with diabetes for fewer than 5 years, 24 to 40% have retinopathy, and after more than 15 years, 53 to 84% have retinopathy. About 2% of patients with type II diabetes will develop proliferative retinopathy within 5 years of being diagnosed, and 25% of patients will develop proliferative disease after 25 years.[9]

In addition to type and duration of diabetes, the incidence of diabetic retinopathy is dependent on several specific factors. The most important factors are duration of diabetes, level of glycemic control,[2,10,11] control of serum cholesterol,[12] and systemic hypertension. Each of these is an independent risk factor for the onset and progression of diabetic retinopathy. Smoking also adversely affects retinopathy.[1]

Duration of diabetes has long been known to be directly related to the complications. The results of the Diabetes Control and Complications Trial in 1991[2,10,13] proved the role of medical intervention with monitoring and control of serum glucose, blood pressure, and cholesterol. The level of hyperglycemia over time is directly related to the serum HbA1c level. Improving this value from the 9 range to the 7 range can reduce the onset and progression of retinopathy up to 75%.[10] Significant but slightly lower reductions in nephropathy also were found. It was also proven that patients with lowered levels of serum cholesterol and treatment of elevated systemic blood pressure had significantly less severe retinopathy.[13] Patients receiving interferon-beta for hepatitis or leukemia have been reported to be at risk for more rapid progression of retinopathy.[14]

What Is the Pathophysiology of Diabetic Retinopathy?

The pathophysiology of diabetic retinopathy includes hyperglycemia-induced glycosylation of proteins that results in microvascular injury. Hemodynamic changes result from morphologic reticulocyte and leukocyte changes, hyperviscosity, as well as other factors. The injury of the microvasculature, ischemia, and subsequent release of factors cause vascular permeability and angiogenesis. An important growth factor is vascular endothelial growth factor (VEGF), which is thought to be important in the pathogenesis of both macular edema and preretinal neovascularization, both causing loss of vision.[15]

What Are the Types of Diabetic Retinopathy, and How Are They Managed and Treated?

Nonproliferative Diabetic Retinopathy

Nonproliferative diabetic retinopathy (NPDR) is characterized by clinical findings indicative of early injury to the microvasculature. Microaneurysms, intraretinal hemorrhages, cotton-wool spots, venous beading, and intraretinal microvascular abnormalities (IRMA) have been correlated to the patient's risk of progression to proliferative disease.[16] Progressive leakage secondary to compromised barrier function of retinal endothelial cells is believed to cause macular edema. Consequently, retinal thickening and hard exudates can involve or threaten the fovea. Clinically significant macular edema (CSME), defined as retinal thickening within 500 μ of the fovea or hard exudates associated with retinal thickening within 500 μ of the fovea or a disc area of thickening one disc diameter (DD) from the fovea (see Chapter 23, Table 23–2), is identified by biomicroscopic examination of the macula. Diagnosis often requires stereoscopic examination at the slit lamp with a contact lens. The role of focal or grid macular laser photocoagulation has been defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). Treatment to leaking microaneurysms or areas of capillary leakage or nonperfusion identified by fluorescein angiography is recommended once CSME is diagnosed.[3] The study showed 14% of laser-treated eyes versus 33% of untreated eyes had visual loss at 3 years. The use of vitreoretinal surgery and steroids delivered by different methods (for example, subtenon or intravitreal) in the treatment of CSME is also being evaluated. Greater evidence that inflammation may play a role in diabetes mellitus is being discovered through laboratory research.[17]

Estimating the Risk of Progression of Diabetic Retinopathy

Attention is directed to the optic disc to determine whether neovascularization is present and, if so, its size. The macula is examined for neovascularization or macular thickening and exudation. The retinal area covered by the seven standard 30-degree images[17] is important in most screening of diabetic retinopathy. Either biomicroscopic examination or review of the stereoscopic images is performed. To grade the level of NPDR, particular attention is given to quadrants involving the nasal and temporal fields around the optic nerve. Intraretinal hemorrhage, venous beading, and IRMA are identified. Severe NPDR is diagnosed with four quadrants of intraretinal hemorrhages, two quadrants of venous beading, or one quadrant of IRMA, indicating the risk of developing high-risk proliferative disease to be 15% within a year. For patients with very severe NPDR, defined by having any two of the above characteristics, the risk of developing high-risk proliferative disease is 45% within the year.[3]

Proliferative Diabetic Retinopathy

Proliferative diabetic retinopathy (PDR) is defined by neovascularization of the disc (NVD) or neovascularization elsewhere (NVE). NVD or NVE can cause vitreous hemorrhage, retinal detachment, and, if untreated, blindness secondary to retinal detachment or neovascular glaucoma within 2 years in up to 40% of patients.[4,18,19] Panretinal laser photocoagulation is recommended when a level of severity of neovascularization occurs (NVD of about 1:3 DD or greater or NVE of 1:2 DD or greater associated with vitreous or preretinal hemorrhage). Laser reduces the risk of severe vision loss by 50% or more.[18–20]

What Are the Symptoms of Diabetic Retinopathy?

Diabetic patients may be asymptomatic, even when retinopathy is present. Patients may wait until significant visual symptoms develop before seeking ophthalmic care. Therefore, it is important that diabetic patients are educated as to the need for them to have timely ophthalmologic examinations. The American Academy of Ophthalmology (AAO) and American Diabetic Association (ADA) recommend yearly eye examinations for all diabetics unless more frequent examinations are recommended by the ophthalmologist.

With macular edema, the patient may notice blurriness or distortion of vision. The development is often gradual and difficult for the patient to identify. The onset of floaters may indicate vitreous hemorrhage from proliferative retinopathy. Abrupt loss of vision

may reflect vitreous hemorrhage, retinal detachment involving the macula, or sometimes diabetic papillitis.

When Should a Diabetic Patient Have Follow-up Eye Examinations?

An ophthalmologist trained in the examination and treatment of diabetic retinopathy should be consulted for examination of the patient at risk. A history should be taken, noting the regimen of glycemic monitoring, use of hypoglycemic agents, glycosylated hemoglobin levels, blood pressure treatment, and cholesterol control.[1]

The timing of the first examination depends on the type of diabetes. Insulin-dependent diabetics usually have an accurate date of onset of their diabetic state. As it is rare to have significant complications from type I diabetes within the first 5 years of onset, the first ophthalmic examination may be scheduled at 5 years. In contrast, patients with non-IDDM may have had poor glycemic control for an unknown duration prior to diagnosis and should have the first examination closer to the time of diagnosis of diabetes.

The frequency of ophthalmic examinations is determined by the level of severity of retinopathy on the initial examination and on the patient's general health. Patients who are well controlled and expected to maintain appropriate follow-up care can be seen less frequently. Any patient who is poorly controlled, has a record of poor follow-up care, or is recently under stringent control may be seen more frequently. In the interim, the patient should notify the ophthalmologist with any major change in vision, such as reduced vision, distortion, or floaters.

If no retinopathy is found during the initial examination, a follow-up examination may be conducted in 1 year. If there is mild to moderate NPDR present, the patient should be seen in the next 3 to 9 months. The potential for progression to CSME and proliferative changes should be considered.[2]

Patients with mild retinopathy may be seen for follow-up in 9 to 12 months. Patients with moderate retinopathy should be reevaluated in 4 to 6 months as the risk of developing CSME is 23% within 4 years.[3] Patients with severe NPDR should be examined every 4 months and considered for laser therapy if there is concern that follow-up with examinations will be poor. The role of laser and its risks and benefits should be reviewed.

Patients who develop macular edema should be checked every 2 to 4 months. If a patient develops CSME, he or she should be treated with focal or grid laser and followed every 6 to 12 weeks until edema is resolved.[20] If resolution is not present at 4 months, retreatment is recommended.

Patients with early PDR should be examined every 1 to 2 months until the development of high-risk characteristics, such as NVD and NVE. When NVD is 1:3 DD or greater or 1:2 DD of NVE with vitreous hemorrhage occurs, the patient should receive panretinal photocoagulation with close observation until the proliferation has regressed and become quiescent. In questionable cases, such as vitreous hemorrhage obscuring any NVE, an ultrasound is considered to rule out a retinal detachment and laser may be attempted, especially if the fellow eye demonstrates diabetic retinopathy. Patients with vitreous hemorrhage should be followed at least monthly to attempt panretinal photocoagulation and to check for retinal detachment. Patients are instructed to sleep with several pillows to permit settling of the vitreous hemorrhage inferiorly. Once quiescent and stable, examinations every 6 months are recommended.[4]

Patients who develop retinal detachment from fibrovascular membranes causing traction on the retina should be evaluated for possible vitreoretinal surgery.

When Should Pregnant Women Be Screened for Diabetic Retinopathy?

Guidelines regarding screening and follow-up of diabetic retinopathy during pregnancy are presented in Figure 21–1. Patients with gestational diabetes are not at risk for developing retinopathy[7] and therefore do not need to be screened during pregnancy. Diabetic women with no history of diabetic retinopathy who become pregnant should have an eye examination during the first trimester. If no retinopathy is present, annual examinations will suffice unless visual symptoms occur.[7] Forty-seven to 65% of women with preexisting NPDR will show progression of their retinopathy during pregnancy,[7,21] and 5% will progress to proliferative disease at some point during their pregnancy.[7] Therefore, it is necessary to follow pregnant diabetic patients more closely. Patients with mild to moderate NPDR should be examined during the first trimester and again during the third trimester.

Women who develop or have preexisting PDR need to be followed closely because changes can progress rapidly. If no high-risk characteristics are present, examinations should be performed every month. If high-risk characteristics develop, panretinal photocoagulation should be performed; the patient should then be followed up frequently until the proliferation is quiescent. It should also be noted that proliferative changes in pregnancy can spontaneously regress in the late third trimester and early postpartum period.[22] Patients who develop CSME should be considered for focal laser treatment and followed in 6 to 8 weeks. The

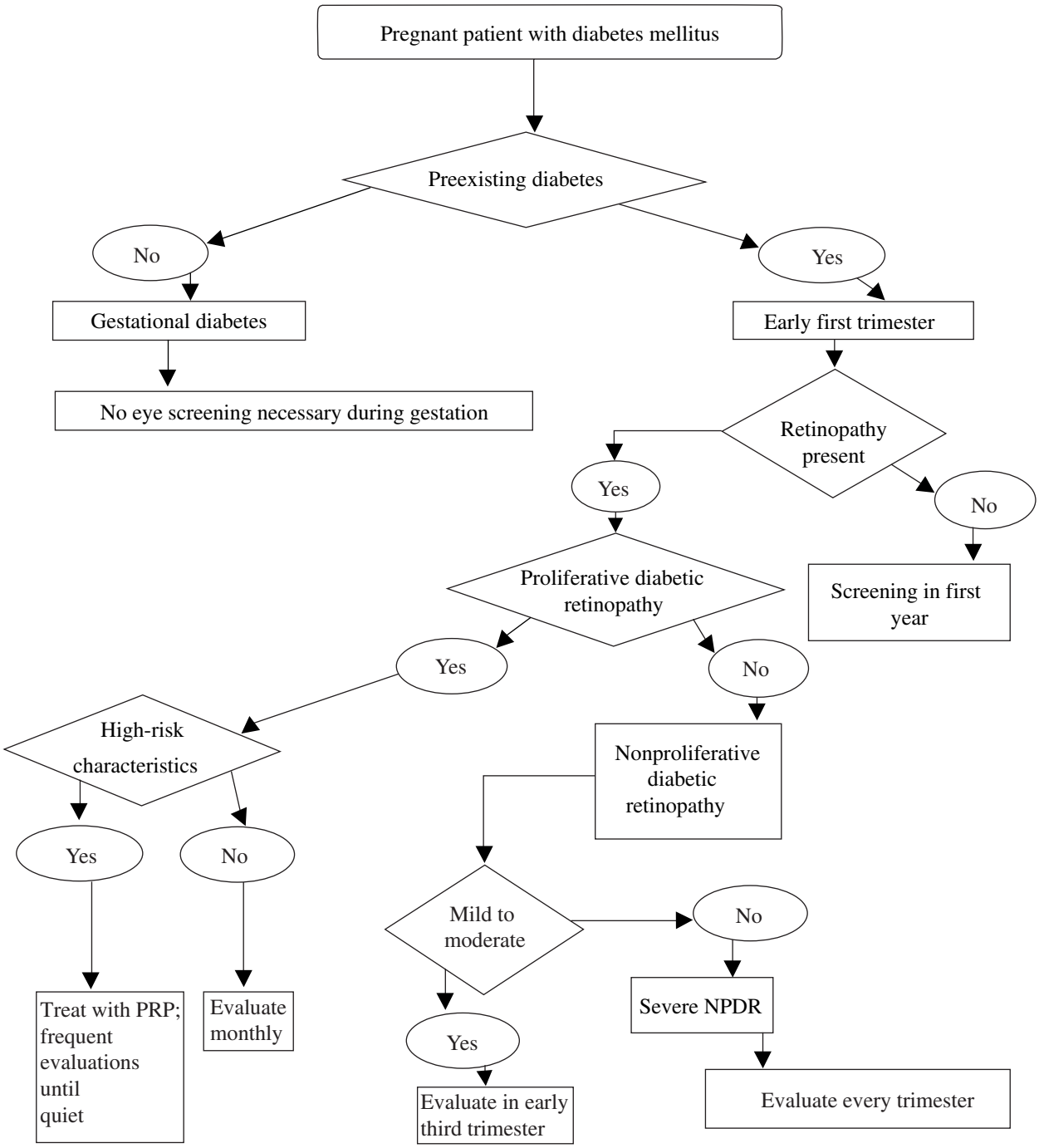

FIGURE 21–1. Clinical pathway: Screening and follow-up of diabetic retinopathy in pregnancy. NPDR, nonproliferative diabetic retinopathy; PRP, panretinal photocoagulation.

macular edema, especially a diffuse type, may improve spontaneously after delivery.[22]

Who Is at Risk for Blindness from Diabetic Retinopathy?

The risk of visual impairment and blindness from diabetic retinopathy increases directly related to control and duration of diabetes. The leading cause of blindness from diabetic retinopathy is macular edema. If visual acuity drops to 20/60 or lower, the patient is likely to have permanent vision loss despite laser treatment. In the absence of treatment or poor response to treatment, vision can continue to decline. Untreated PDR has a risk of progression to blindness within 2 years in 20 to 40% of cases.[4]

Human Immunodeficiency Virus (HIV) and Retinal Disease

For What Retinal Diseases Should the HIV Patient Be Screened?

The HIV virus weakens the immune system and predisposes the eye to a number of opportunistic infections. The most common and visually devastating of these is cytomegalovirus (CMV) retinitis. Screening of the HIV infected patient is primarily directed at identifying CMV retinitis but includes the identification of other diseases that affect the retina and choroid. These include acute retinal necrosis (ARN), progressive outer retinal necrosis (PORN), ocular toxoplasmosis, *Candida* retinitis, *Pneumocystis* choroidopathy, cryptococcal choroiditis, syphilitic chorioretinitis, and mycobacterial infections.[23,24]

What Is HIV Retinopathy?

Human immunodeficiency virus itself can cause retinopathy. Cotton-wool spots are the most common manifestation of HIV retinopathy, but hemorrhages, microaneurysms, capillary nonperfusion, and telangiectatic vessels also occur.[24,25] The retinopathy becomes more prevalent as the systemic disease progresses. HIV retinopathy is found in only about 1 to 3% of patients with asymptomatic HIV infection,[24] whereas more than half of patients with acquired immunodeficiency syndrome (AIDS) have some signs of retinopathy. HIV retinopathy itself has minimal, if any, effects on vision[24] but sometimes causes small scotomata or blind spots. It does need to be differentiated from the early stages of CMV retinitis because of the sometimes similar appearance of cotton-wool spots and early CMV retinitis.

Cytomegalovirus Retinitis

Who Should Be Screened for CMV Retinitis?

Patients who are severely immunosuppressed from HIV, chemotherapy for cancer, or iatrogenic immunosuppression for transplantation are at risk for developing CMV retinitis. Among these, patients with HIV and low CD4 counts are at the greatest risk for developing CMV retinitis.

How Does Cytomegalovirus Retinitis Present?

Typically, when it presents in the posterior pole, CMV retinitis appears as a yellowish white opacification of the retina, sometimes with hemorrhages and exudates. CMV retinitis in the peripheral retina can appear more granular with less hemorrhage. In either case, there is usually little inflammation within the vitreous. Early CMV retinitis can look like cotton-wool spots, but close follow-up with fundus photographs will reveal progressive increase in lesion size associated with CMV retinitis versus the eventual resolution of cotton-wool spots.

What Are the Symptoms of CMV Retinitis?

A patient with active CMV retinitis may notice decreased vision, flashes, floaters, scotomata, or shadows. The patient should seek care immediately if any of these symptoms occur; however, patients may be asymptomatic and harbor CMV retinitis. Therefore, screening asymptomatic patients is considered when the CD4 count is low.

When Should an HIV Patient See an Ophthalmologist?

The CD4 count is the most reliable gauge in determining when patients should be screened and scheduled for follow-up appointments. CMV retinitis rarely occurs in patients with CD4 counts greater than 100. CMV retinitis usually occurs when the count drops below 100, and most cases develop when the CD4 count is less than 50.[25,26] It has been recommended that patients with CD4 counts less than 50 should have an eye examination every 3 to 4 months[25] or immediately if any changes in vision occur. Although there are no specific guidelines for screening patients with CD4 counts greater than 50, patients with CD4 counts in the 50 to 100 range probably should be examined every 6 months because CD4 counts can go down and CMV retinitis can occur with CD4 counts over 50. Patients with CD4 counts greater than 100 should have at least yearly eye examinations.

How Is Cytomegalovirus Retinitis Treated?

Although examinations are scheduled for CMV retinitis screening purposes, other HIV related retinal diseases should be considered in the differential diagnosis. An initial workup and treatment plan should be implemented if any signs of infection develop. Consultation with the patient's infectious disease physician is necessary to assess for systemic infection and decide on appropriate therapy and workup.

Once CMV retinitis is diagnosed, the patient should be treated with antivirals such as ganciclovir or foscarnet to reduce vision loss. Ganciclovir can be given intravenously or as an intravitreal insert. There is also an oral formulation available. Follow-up examinations every 1 to 2 weeks for the first month after intravenous induction therapy is initiated, and then monthly examinations thereafter are recommended.[27,28] Even

after successful treatment of CMV retinitis, patients must be followed up closely because relapse is common,[28] and retinal detachments occur in about 25% of patients within months of developing the disease.[29,30] In general, greater and more peripheral retinal involvement creates a greater likelihood of developing a retinal detachment.[29,30] Active CMV retinitis also is associated more often with retinal detachments. The use of combination therapy is often needed in cases that progress.

What Is Immune Recovery Vitreitis?

With the advent of highly active antiretroviral therapy (HAART), the prevalence of CMV retinitis is lessening. HAART enables the CD4 count to rise and the immune system to recover to some degree. Patients with a history of CMV retinitis who start HAART and have an increase in CD4 count and immune function can develop a condition called *immune recovery vitreitis* or *immune reconstitution uveitis*. In this condition, the CMV retinitis is inactive, but with improved immune function, an inflammatory response to CMV can occur. The larger the area of retina previously involved with CMV retinitis, the greater the likelihood of developing an inflammatory response. If the vitreitis is significant, decreased vision may result.

Visual loss may occur secondary to proliferative vitreoretinopathy, cystoid macular edema, epiretinal membrane formation, or posterior subcapsular cataract.[31,32] Given this, patients with inactive CMV retinitis and CD4 counts above 100 should be examined regularly to evaluate for uveitis as well as retinal tears and detachments. The patient should be told to contact his or her ophthalmologist immediately if any symptoms of uveitis (reduced vision, floaters) or retinal tears and detachment (flashes, floaters, visual field defect, reduced vision) occur between scheduled visits.

Retinopathy of Prematurity

What Is Retinopathy of Prematurity and Why Screen for It?

Retinopathy of prematurity (ROP) initially was described as retrolental fibroplasia for the most severe stage of ROP, stage 5. The International Classification of Retinopathy of Prematurity (ICROP) recognized earlier stages in the pathogenesis, and the term ROP was adopted.[33]

Each year, ROP causes blindness to at least 550 infants and some loss of vision to thousands of others.[34] In about 90% of the early stages 1 and 2, ROP may resolve spontaneously, but in the incompletely vascularized infant retina, ROP can develop, showing characteristic stages. The advanced stages lead to blindness. Screening is crucial in early diagnosis and in detecting threshold disease when the risk of vision loss approaches 50%.[35] With treatment of threshold disease, reduced vision can be prevented in almost 50% of threshold cases.[36]

How Is the Severity Classified?

The Committee for the Classification of Retinopathy of Prematurity (CRYO-ROP) study published an international classification of ROP.[33] This classification uses four parameters: (1) zone, (2) clock hours of involvement (circumferential extent of ROP), (3) stage of disease, and (4) vascular tortuosity and engorgement of retinal vessels (plus disease).

The zone indicates the amount of mature or vascularized retina. *Zone 1* is the most posterior zone, demarcated by a circle centered on the optic disc, the radius of which extends twice the distance from the disc to the fovea. *Zone 2* is a circle centered on the optic disc with the radius corresponding to the distance from the optic disc to the nasal ora serrata. *Zone 3* is the temporal part of peripheral retina not included in zones 1 and 2. Zone 3 ROP is often associated with favorable outcome and rarely requires treatment.[31]

The stage of ROP represents the level of progression of the disease. Stages 1 and 2 have an excellent prognosis and are monitored for progression or resolution. Stage 3 ROP has neovascularization between the avascular and vascularized retina. When threshold disease (see Chapter 20, Table 20–3) occurs, laser or cryotherapy is recommended. *Stages 4 and 5* ROP are partial and total retinal detachment.

The clock hours of involvement indicate the circumferential extent of the worst stage in an eye. The presence of plus disease is indicated in each of the posterior quadrants of an eye.[37]

Who Is at Risk?

Risk factors in the neonatal and antenatal period have been recognized as being associated with the progression of ROP.[33,38] The most important criteria are birth weight and gestational age.[33,38] The likelihood of occurrence of ROP and the severity of disease dramatically increase, the lower the birth weight. Among all risk factors, birth weight is the most significant predictive factor. In infants weighing between 1000 and 1250 g, about half will show some signs of ROP, and only 2% will reach threshold.[33,38] According to Palmer, 65.8% of infants weighing less than 1251 g developed ROP, whereas 81.6% infants weighing less than 1000g developed the disease.[38] The incidence of severe ROP is small in infants weighing more than 1500 g; however, some cases of late-stage ROP have been described in infants with birth weights exceeding the

usual criteria. Gestational age (GA) is another risk factor. Infants with a GA of less than 27 weeks have been reported to have an ROP incidence of 83.4%. As many as 80% of these infants are diagnosed as having prethreshold ROP and 13% with threshold at less than 33 weeks corrected age (gestational age + chronological age); thus, it is recommended that the initial examination be scheduled within 4 to 6 weeks of neonatal life.[35,39]

It has been noted that racial predisposition exists: Caucasians appear more susceptible to developing ROP.[38] High, uncontrolled oxygen is an important risk factor, recognized in the 1950s, especially if inspired oxygen concentration over 70 to 80% is used. Efforts to control oxygen reduced the incidence of ROP. Resurgence has occurred as methods to save lower-birth-weight infants were developed.

The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP) study reported that supplemental therapeutic oxygen to cause a pulse oximetry saturation of 96 to 99% given at prethreshold disease[39] did not cause progression to threshold ROP, nor did it reduce the number of infants requiring ablative surgery. A subgroup of infants with prethreshold ROP without plus disease showed benefit from supplemental oxygen but this was not statistically significant in the study design, and infants on supplemental oxygen had increased pulmonary morbidity.[37,40] Other factors that might increase the risk of ROP include repeated blood transfusions, prolonged parental nutrition, infections, and respiratory distress. Maternal factors include multiple gestation, poor prenatal care, and drug abuse, to name a few.

Some factors may reduce the risk of ROP. Good prenatal care and the use of surfactant, steroids (dexamethasone), and improved neonatal nutritional support may be factors that reduce the incidence and severity of prematurity and ROP.

Who Is at Risk for Blindness from Retinopathy of Prematurity?

Factors involved in the progression and outcome of ROP are age at threshold (the younger the baby, the more complicated the treatment and the poorer the prognosis); rate of progression (rapid transformation to threshold ROP portends a poorer prognosis); and systemic complications, such as sepsis.

Almost all stages 1 and 2 undergo complete resolution. The risk of blindness in infants with stage 3 ROP is reduced with laser[37] or lens-sparing vitrectomy,[41] respectively (see Chapter 20). The goal of management is to prevent stage 5 ROP; however, retinal reattachment in some cases of stage 5 ROP may offer improved visual function.

Mild ROP does not appear to have an impact on visual acuity; however, severe ROP may be associated with impaired visual development and greater risk of high myopia,[42] which emphasizes the necessity of periodic monitoring of early visual acuity in infants with a history of ROP. Even after ROP has regressed, later visual changes, such as myopia, anisometropia, amblyopia, and late retinal detachment,[43] may develop. Follow-up with a pediatric ophthalmologist and a retina specialist is recommended for many patients with residual regressed ROP.

What Are the Symptoms of Retinopathy of Prematurity?

Generally, the premature infant demonstrates few or no symptoms. Therefore, screening is crucial. Later symptoms may indicate that damage has already occurred. Exotropia may indicate an ectopic fovea; leukocoria may indicate a retinal detachment.

When Should a Retinopathy of Prematurity Patient Undergo Screening?

The AAO and the American Academy of Pediatrics (AAP) recommend that infants with a birth weight less than 1500 g or a GA of 28 weeks or less, as well as selected infants between 1500 and 2000 g with unstable clinical courses, undergo screening examinations.[39] The initial examination is often at 4 to 6 weeks of age, regardless of GA.[39] The findings should be recorded according to the ICROP study, indicating stage, zone, and clock hour extent of disease, as well as whether Plus disease is present.[33]

Because of the high medicolegal risk to those who examine for complications of ROP, a protocol for examination should be used, and follow-up of infants is needed; this follow-up should involve the hospital, the neonatal unit, the neonatologist, and the ophthalmologist. The family should be given instructions about the importance of repeat examinations and information about the risks of ROP.

How Is Screening Performed?

The ideal screening should start in the Neonatal Intensive Care Unit (NICU) and follow NICU protocol. Staff and parents have to be informed about the diagnosis and the infants followed up closely. The ophthalmologist should meet with the staff and neonatologist at each NICU to set up a protocol for dilating drops and sterilization of lid specula and scleral depressors. Screening is described in Chapter 20 (also see Fig. 20–11).

During the examination, the vital signs of the infant must be monitored. All findings should be described in the chart using ROP forms. The parents are in-

formed after every examination about follow-up and all possible treatments. Follow-up appointments must be scheduled prior to transferring or discharging the infant. Parents must also be informed about the importance of follow-up examinations on longterm visual acuity.

How Is Retinopathy of Prematurity Treated?

Current therapy for ROP, other than preventing prematurity and judicious neonatal management, consists of cryotherapy and laser therapy. The CRYO-ROP study revealed that visual acuity was better in the threshold eyes treated with cryotherapy than in the control eyes: 44.4% versus 62.1%.[36] Cryotherapy-treated eyes had a lower risk of an adverse anatomic outcome (27.2%) than did control eyes (47.9%).[36] The STOP-ROP study, as well as other studies, demonstrated success after laser treatment.[37] Argon and diode indirect ophthalmoscopic laser systems are becoming more popular because of portability and ease of use. In addition, laser is associated more with iris inflammation, breakdown of the blood-retinal barrier, and later myopia than is cryotherapy. The entire avascular zone is treated with tightly placed laser spots, within one half to one spot size apart or with contiguous cryotherapy. Eyes are monitored closely after treatment (see Chapter 20). Despite timely treatment, vision can be reduced secondary to retinal detachment, posterior pole hemorrhage, high myopia, and strabismus.

Ongoing trials include the Early Treatment for Retinopathy of Prematurity Study, this evaluates whether treatment of some prethreshold disease will result in better visual and anatomic outcome than current management. In the Photo-ROP Study, images obtained from a wide-angle contact camera can be used to screen and monitor.[44]

Hydroxychloroquine Toxicity

What Is Hydroxychloroquine?

Hydroxychloroquine (Plaquenil) is used to treat connective tissue diseases, including systemic lupus erythematosus (discoid, subacute, cutaneous and systemic), rheumatoid arthritis, Sjögren syndrome, polymorphic light eruption, and porphyria cutanea tarda, among others.[45,46] It is effective for long-term maintenance therapy, has a modest incidence of toxicity over time, and can be easily combined with multiple chemically unrelated drugs.[47–49]

Why Screen for Hydroxychloroquine Toxicity?

Generally well tolerated, hydroxychloroquine may cause retinopathy, keratopathy, and myopathy. Exposure to light amplifies the risk of retinopathy in patients treated with anti-malarials. (Dark glasses are recommended for patients who spend much time in sunlight.) The concentration of hydroxychloroquine in plasma and tissue is directly related to daily dosing. The highest concentration is found in melanin-containing tissues, particularly the choroid, ciliary body, and retinal pigment epithelium (RPE) of the eye.[50,51] Therefore, degeneration of the RPE and its effects on the neurosensory retina are major concerns.

Numerous reports indicate a low incidence of retinal toxicity with hydroxychloroquine therapy. The chance of occurrence still exists and appears to depend on dosage.[52] MacKenzie suggests a daily dosage threshold for retinopathy below which the drugs are safe. He has shown that overdosage might occur with a standard dose (400 mg per day) if lean body weight is not taken into account. MacKenzie detected no retinopathy in more than 900 patients treated with less than 6.5 mg per kilogram of lean body weight of hydroxychloroquine, even when total doses exceeded 1000 g.[53] Rynes and colleagues reported the results of a prospective, 7-year follow-up study of 99 patients treated with 400 mg daily.[54] Only four patients developed evidence of early toxicity, which was reversible when therapy was discontinued. They found no relationship between toxicity and total dose. In a study of 1500 patients, Morsman and colleagues found only five cases of toxicity; only one of these patients suffered visual loss.[45] Levy found one case of retinopathy of 1207 patients, and this occurred in a patient treated with high doses (6.98 mg/kg daily) for more than 7 years.[55] The only cases of definite toxicity at doses less than 6.5 mg per kilogram daily of hydroxychloroquine are reported by Mavrikakis and colleagues, who reported two well-documented cases of hydroxychloroquine retinopathy in patients treated for 6.5 and 8 years without exceeding 6.5 mg per kilogram of body weight daily.[56]

The risk of retinal toxicity for long-term use of hydroxychloroquine has been estimated to be between 0 and 4%.[57–59] These studies varied considerably with respect to case definition, sample size, and duration of follow-up. The largest study reported an incidence of retinal toxicity as 0.08% over a median period of 3.3 years.[55]

Overall, hydroxychloroquine toxicity usually does not occur with daily doses below 6.5 mg per kilogram of body weight of lean body weight and continued longer than 10 years.[57] It is generally recommended that regular ophthalmic examinations (every 6 months) be done to detect its occurrence and prevent progression.

What Are the Signs and Symptoms of Hydroxychloroquine Toxicity?

The earliest sign of toxicity, which may occur before the development of any fundus abnormality, is

paracentral visual field loss. The earliest alterations occur in the parafoveal area.[59–61] The patients describe their visual changes as distortion rather than blurriness, and the use of the Amsler grid may be helpful in detecting these early field defects.[59] If the process progresses, the RPE alterations extend into the foveolar area, and the patient will lose central vision. This would be most noticeable while reading or driving, but patients simply may complain of difficulty in focusing.

It is helpful to know reversible side effects of hydroxychloroquine toxicity. These include corneal deposits (verticillata), loss of foveal reflex, and impairment of accommodation.[46,51] Corneal deposits are the most frequent observed lesions. They are dose related, often asymptomatic, and not generally considered a contraindication to continuing treatment.[47,58,62] Loss of the foveal reflex is considered a sign of early reversible maculopathy or premaculopathy.[63] Reevaluation and temporary reduction in dose should be considered.

Retinopathy is the major and most potentially serious irreversible side effect of hydroxychloroquine treatment. Initially, mild pigment stippling of the macula is seen on ophthalmoscopy, and, with time, may result in the classic appearance of bull's-eye maculopathy. On fluorescein angiography, it will appear as a central zone of irregular pigmentation surrounded by a concentric horizontally oval zone of hypopigmentation.[47,50,59,61] If the process progresses, peripheral retinal alterations will be noticeable.

Easterbrook and Bernstein suggest that maculopathy should be defined as the presence of reproducible bilateral visual field defects.[62] These visual-field defects should be present on both Amsler grid and automated visual-field periphery testing. If the patient does have transient or unilateral field defects, he or she does not likely have hydroxychloroquine maculopathy and should not have the therapy discontinued.

How Can Hydroxychloroquine Toxicity Be Prevented?

Overdose can increase the risk of retinopathy. Overdose may be avoided by using an ideal (lean) body weight instead of using the actual weight of the patient when determining daily dosage.[47] If an actual body weight is used for obese patients, patients will be overdosed. Hydroxychloroquine distributes differently through body tissues and is not absorbed well by fat, brain, or bone.[47,49,53] Tissue distribution of drug from areas of lowest absorption to areas of highest absorption is bone, fat, brain, muscle, eyes, heart, kidneys, liver, lungs, spleen, and adrenal glands.

Patients with poor renal function may be overdosed. About 45% of the drug is renally excreted in unchanged form, 8 to 12% is excreted in the feces, and about 5% is sloughed off through the skin.[53] Up to 50% of hydroxychloroquine is biotransformed and broken down, and 30 to 60% of it occurs in the liver. Poor liver function is an additional factor that can contribute to overdose.[47,50,53]

How Is Hydroxychloroquine Toxicity Examined and Treated?

An initial examination is necessary on initiation of hydroxychloroquine treatment. However, retinotoxicity is not diagnosed with less than 9 months of administration, regardless of the dose.[62] If treatment is continued more than 6 months, an ophthalmic examination should be performed regularly.

The patient should be questioned about visual changes because he or she may notice problems when driving or reading. It is recommended that the Amsler grid be used as a monthly self-test for patients.[59,62] It should be confirmed that the patient has had no change in weight, and renal and hepatic function should be established.[49,51]

A baseline examination should include distance and near visual acuity testing in each eye; slit-lamp examination of the cornea and retina; visual-field testing, including automated perimetry (small paracentral scotomas within 10 degrees of fixation appear to be a consistent finding in early maculopathy and correspond to pigmentary changes in the fovea.); and baseline photographs of the macula in both eyes.

Patients should be monitored every 6 months; if no symptoms or signs are revealed, it is safe to continue treatment. Any patient taking hydroxychloroquine in any amount and for any length of time who complains of a disturbance in central vision and has signs of retinal toxicity (such as paracentral scotoma, pigmentary changes, or bull's-eye maculopathy) must discontinue therapy and have follow-up for progression (Fig. 21–2). Severe retinopathy may cause progressive visual loss even after discontinuation of therapy.[49,50,59,61]

Hydroxychloroquine toxicity is rare but serious and often progressive; thus, physicians caring for such patients must be vigilant.

The Age-Related Eye Disease Study

The Age-Related Eye Disease Study (AREDS) is a randomized, placebo-controlled, double-masked clinical trial to study the effects of antioxidants or zinc, in combination or alone, on the risk of age-related macular degeneration (AMD) or age-related cataract.[66–70]

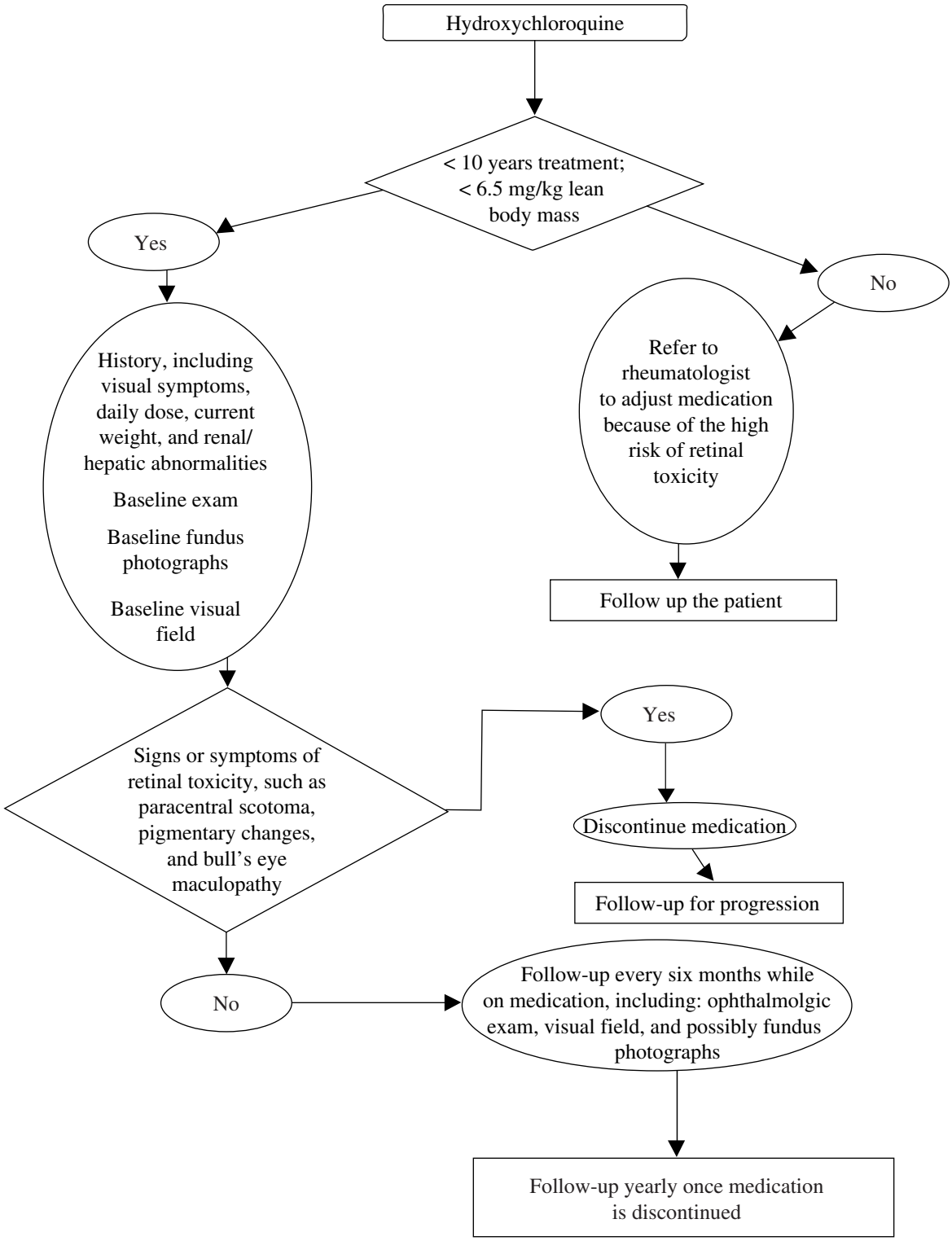

FIGURE 21–2. Clinical pathway: Screening for hydroxychloroquine toxicity.

What Is Age-related Macular Degeneration?

In the United States, United Kingdom, and Australia, AMD is the leading cause of visual impairment and blindness in people aged 65 years or older.[71–73] Vision loss occurs from dry AMD in 90% of cases (drusen and chorioretinal or geographic atrophy) and from wet AMD in about 10% of cases (ingrowth of blood vessels from the choriocapillaris into the subretinal space and into the retina, known as *choroidal neovascularization*, or from pigment epithelial detachments).[74,75] Reported risk factors for AMD include smoking,[76,77] heart disease, hypertension,[78,79] and reduced dietary consumption of vegetables and antioxidants.[80,81]

Treatment of AMD includes laser photocoagulation to choroidal neovascularization outside the fovea[82,83] and, more recently, photodynamic therapy of subfoveal choroidal neovascularization.[84,85] Studies testing the effects of submacular surgery to remove choroidal neovascularization to date have not shown benefit over other less aggressive management.[66–69] Research using antiangiogenic medications and angiostatic steroids is being conducted.

What Is Age-Related Maculopathy?

Age-related maculopathy (ARM) is the presence of at least multiple, small drusen (up to 124 μ) or pigment abnormalities or a combination of both, without geographic atrophy or features of choroidal neovascularization, including subretinal fluid, exudates, and subretinal hemorrhage.

What Are the Symptoms of ARM and AMD?

Patients may describe reduced contrast sensitivity in ARM. Actual blind spots (scotomata) may develop, particularly with chorioretinal atrophy, making it difficult for a patient to read. This is believed to be because letters adjacent to those in direct line of view disappear with a parafoveal scotoma making it difficult for the patient to track words on a line. Parafoveal scotomata can cause significant visual morbidity even when visual acuity is good, for example, 20/30. In these patients, magnification that increases the size of print but not the size of the scotoma can be helpful. Distortion and micropsia are symptoms of subretinal fluid associated with choroidal neovascularization or with pigment epithelial detachments. With these symptoms, the patient should be seen urgently because of the risk of possible choroidal neovascularization.

What Was the Design of AREDS?

Patients were categorized as to their macular findings: In category 1, both eyes had a few small drusen (smaller than 63 μ) or no drusen within a 125-μ circle and no pigment abnormalities. Category 2 had several small drusen or a few medium-sized drusen (63- to 125-μ drusen) or pigment abnormalities or any combination of these in one or both eyes and vision better than 20/32 (also included one eye as described for category 2 and the fellow eye as category 1). Category 3 had an absence of advanced AMD in both eyes and at least one eye with vision of 20/32 or better. Category 3 also had at least one large druse (125 μ), extensive intermediate drusen, or geographic atrophy that did not involve the center of the macula or any combination of these. Category 4 had a visual acuity of 20/32 and no advanced AMD (geographic atrophy involving the center of the macula or features of choroidal neovascularization) in the study eye. The fellow eye had either lesions of advanced AMD or visual acuity less than 20/32 and AMD abnormalities sufficient to explain reduced visual acuity as determined by examination of photographs at the reading center.

Patients were randomized to one of four treatment interventions: (1) total daily dose of antioxidants (500 mg vitamin C, 400 IU vitamin E, 15 mg beta carotene); (2) zinc (80 mg of zinc oxide with 2 mg crupic oxide); (3) combination of antioxidants and zinc; or (4) a placebo.[70] Outcomes were photographic assessment to show progression of AMD, and vision loss (≥15 letters on ETDRS chart).

What Was Found in AREDS?

The probability of one eye progressing to advanced AMD over 5 years by category was 0.5% for category 1; 1.3% for category 2; 18% for category 3; and 43% for category 4 (Table 21–1). Within the category 3 eyes, those with large drusen in each eye or noncentral geographic atrophy were four times as likely to progress to advanced AMD (27%) than the remaining other category 3 participants (6%).

In categories 1 and 2 (patients with no or early age-related macular changes), the progression to advanced AMD was too low to assess treatment effects.

TABLE 21-1. Probability of Developing Advanced Age-Related Macular Degeneration in an Eye Over Five Years

Category	*Percent*
1	<0.5
2	1.3
3	18
Including only eyes with large drusen or noncentral geographic atrophy	27
Remaining category (3 eyes)	6
4[a]	43

[a]Age-related macular degeneration event occurred in fellow study eye.

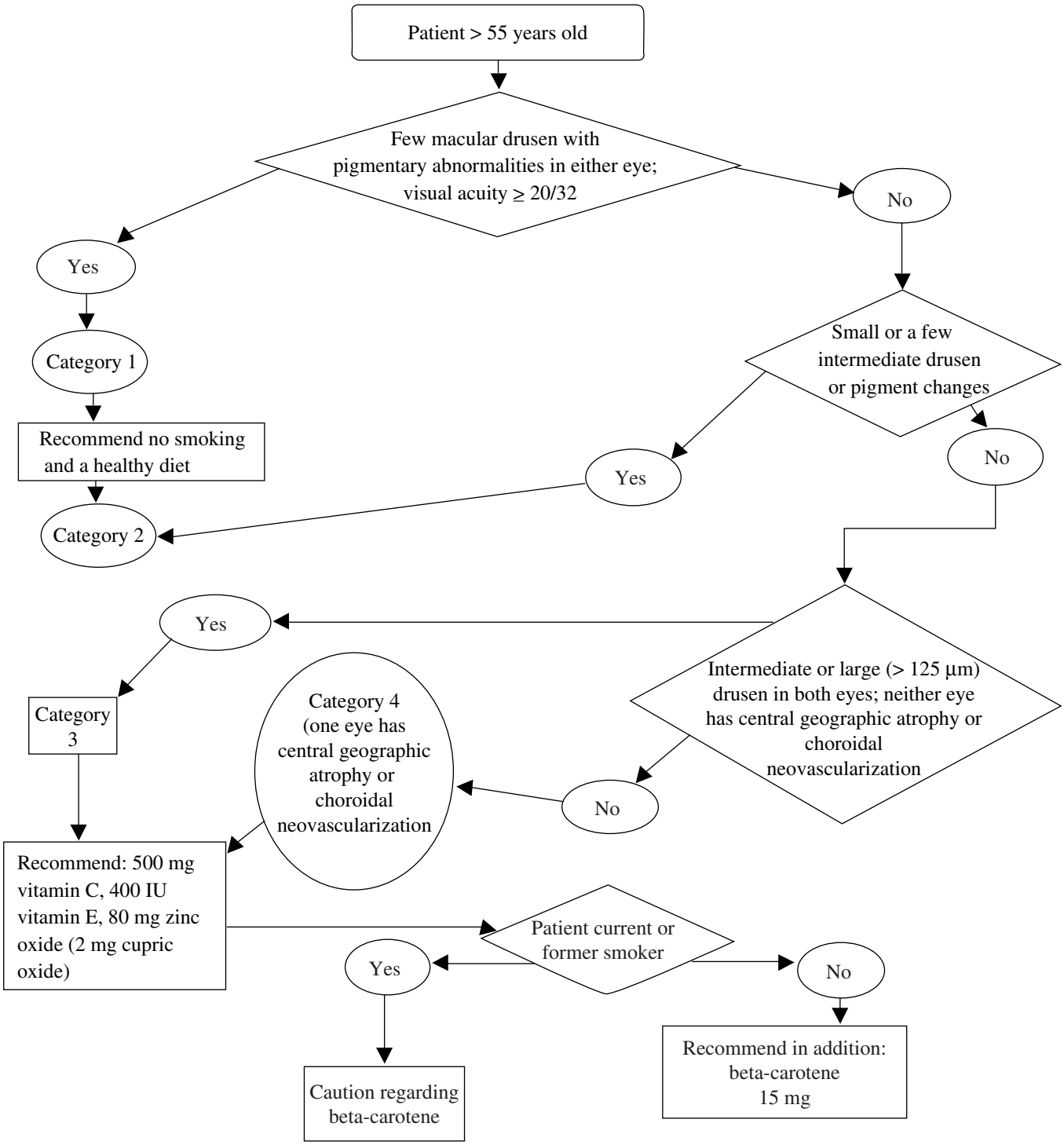

FIGURE 21–3. Clinical pathway: Screening for age-related macular degeneration (AMD) and age-related maculopathy (ARM) based on the Age-Related Eye Disease Study (AREDS).

No benefits from the trial were seen in these groups. These groups constitute the majority of patients under age 70.[70]

In category 3 and 4, in patients who took nutritional supplements of antioxidants and zinc, there was a reduction in the odds of developing advanced AMD (20%) compared with those who received placebo (28%). There was a significant reduction in vision loss from advanced AMD in patients who received zinc and antioxidant treatment compared to placebo.[70]

The high-dose formulation of vitamin C, vitamin E, and beta-carotene had no apparent effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss in a relatively well-nourished adult sample.[70] Approximately 70% of patients in the study opposed the use of a multi-vitamin.

What Are the Recommendations from AREDS Regarding Screening?

Because AMD is the leading cause of vision loss in patients over age 65, all people over age 55 years (Fig. 21–3) should have regular dilated eye examinations with their ophthalmologists to determine their risk of developing advanced AMD.

Patients with category 3 [at least one large druse (>125 μ) or noncentral geographic atrophy in one or both eyes] or category 4 (advanced AMD in one eye) should consider taking vitamin C (500 mg), vitamin E (400 IU), zinc oxide (80 mg zinc oxide) daily, copper to reduce the risk of copper deficiency that can occur with high-dose zinc (2 mg as cupric oxide), and beta-carotene (15 mg). Smokers may be at risk for developing lung cancer with high-dose beta-carotene.[86] Therefore, beta-carotene supplementation is not recommended for smokers or former smokers.

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22

Retinal Disease and the Anterior Segment Surgeon

JOEL PEARLMAN AND JULIA HALLER

Endophthalmitis

What Is Endophthalmitis?

Endophthalmitis is a severe ocular condition involving infection of the internal structures of the eye by replicating microorganisms. Most often, these organisms are bacteria, but fungi, protozoa, and viruses can produce this disease. Most endophthalmitis follows surgery or trauma, at which time these organisms gain access to the inside of the eye. This is known as exogenous endophthalmitis. Less commonly, infectious organisms enter the eye through a hematogenous route, producing *endogenous* endophthalmitis, a disease more typically found in debilitated or immunosuppressed patients, intravenous drug abusers, and patients with indwelling catheters.

Postoperative endophthalmitis can be acute (within 6 weeks of surgery) or delayed onset (more than 6 weeks). The onset of endophthalmitis has diagnostic and prognostic implications and directly impacts the initial management of the patient.

What Is the Incidence of Endophthalmitis?

The incidence of postoperative endophthalmitis has been studied in several large series. In the United States, the incidence was reported as 0.072% in a series of 23,625 cases.[1] The estimates are somewhat higher for secondary intraocular lens (IOL) implants and penetrating keratoplasty (0.3%). It is distinctly unusual after vitrectomy surgery (0.02%). After penetrating trauma, the incidence varies between 3 and 30%, depending on the setting (nonrural is lower compared with rural) and whether an associated intraocular foreign body is present.

What Are the Symptoms of Endophthalmitis?

The most common symptom is decreased vision, noted in 94% of patients in the endophthalmitis vitrectomy study (EVS), a randomized controlled clinical trial assessing the efficacy of intravitreal antibiotics, intravenous antibiotics, and vitrectomy in postsurgical endophthalmitis.[2,3] Pain is not universal but was reported in 75% of patients. Unlike the typical postoperative course, the pain may become progressively worse rather than progressively better with time.

What Are the Signs of Endophthalmitis?

The major signs of endophthalmitis are hypopyon and vitreitis (Fig. 22–1). Signs of periocular inflammation, such as eyelid and conjunctival erythema and corneal edema, may also be present and are typically more fulminant than that typically seen postoperatively. In the EVS, hypopyon was reported in 85.7% of patients. Membrane formation can occur around the IOL implant. A variable vitreitis is present, sometimes completely obscuring a view of retinal detail. A red reflex was present in only 32% of patients. Bleb-associated endophthalmitis can occur anytime after filtering surgery and is more common in blebs located inferiorly. Pus in the bleb may be the presenting sign. In chronic endophthalmitis caused by *Propionibacterium acnes*, a white plaque may be seen on the posterior capsule. Chronic granulomatous uveitis is often present. The distribution of signs and symptoms is summarized in Table 22–1.

What Microorganisms Are Responsible for Endophthalmitis?

Bacteria are the most common cause of endophthalmitis, with gram-positive organisms accounting

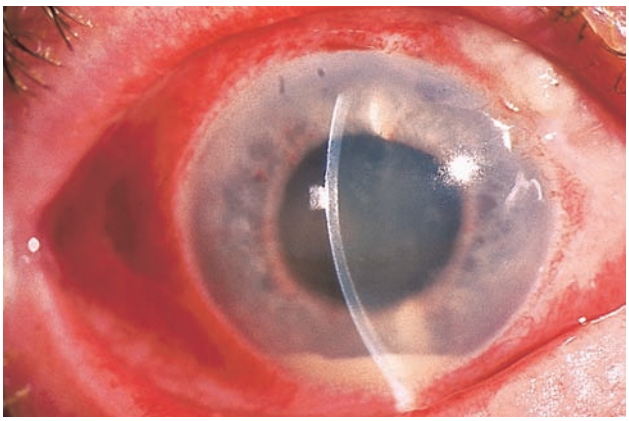


FIGURE 22–1. Hypopyon is one of the common signs of endophthalmitis. See Table 22–1 and the text for full details.

for 60 to 80% of acute infections. Generally, the organisms involved in acute postoperative endophthalmitis derive from the normal lid flora. *Staphylococcus*, particularly coagulase-negative varieties (70%), *Staphylococcus aureus* (10%), and *Streptococcus* species (11.5%) are the most common of these. Gram-negative bacteria accounted for 6% of cases in the EVS and are considerably more virulent than the coagulase-negative *Staphylococcus*. Delayed-onset endophthalmitis is typically due to *P. acnes*, a gram-positive bacillus, but can be caused by *Candida parapsilosis*, *Staphylococcus epidermidis*, and *Corynebacterium* species. Bleb-associated endophthalmitis is often a streptococcal infection; and these organisms can be particularly virulent. Traumatic endophthalmitis, in which organic foreign material is involved, has a greater likelihood of involving *Bacillus cereus*, which can have a dramatically virulent course. Fungal infection is reported in 10 to 15% of cases. Endogenous endophthalmitis is more commonly associated with fungal infection, particularly *Candida* and *Aspergillus*, but it can be bacterial, with *Neisseria meningitidis*, *S. aureus*, and *Haemophilus influenzae* being important causes. A thorough investigation for a systemic source should be undertaken in any suspected case of endogenous endophthalmitis and any infection addressed.

TABLE 22–1. Incidence of the Signs and Symptoms of Endophthalmitis in the Endophthalmitis Vitrectomy Study

Signs and Symptoms	*Percent*
Visual acuity <5/200	90
Visual acuity LP	26
Pain	75
APD	12
Corneal infiltrate	5
Hypopyon	86
Inability to visual retinal vessels	80
Red reflex present	23

LP, light perception; APD, afferent pupillary defect.

How Do You Categorize Endophthalmitis?

Endophthalmitis can be grouped into several categories with prognostic and therapeutic importance. These categories help determine the responsible organism and guide the initial choice of medical or surgical therapy. The most common form is acute postoperative endophthalmitis, which occurs within 6 weeks of intraocular surgery. *Delayed-onset* postoperative endophthalmitis occurs more than 6 weeks to several months after surgery and often presents with chronic indolent inflammation. *Bleb-associated* endophthalmitis can follow filtering surgery (or occur in eyes with inadvertent blebs) anytime. Infection isolated to the bleb (i.e., without endophthalmitis) can often be managed with intensive topical or periocular antibiotics. *Traumatic* endophthalmitis can follow penetrating or perforating eye injuries. In a rural setting, endophthalmitis has been reported in as many as 30% of cases, with a substantial portion of these being *Bacillus* species. In a nonrural setting, the incidence is considerably lower. Visual recovery is often limited by associated traumatic damage to ocular structures as well as the virulence of the microorganisms involved. *Endogenous* endophthalmitis refers to the hematogenous spread of microorganisms from a distant site. Patients are typically debilitated or immunosuppressed. Infections are generally fungal in nature but can be bacterial from a variety of sources.[4]

What Has the Endophthalmitis Vitrectomy Study Taught Us about Optimizing Treatment for Endophthalmitis?

The EVS was a randomized, multicenter clinical trial sponsored by the National Eye Institute to help determine the optimal management of acute postoperative endophthalmitis.[2,3] The efficacy of vitrectomy versus vitreous tap, both with intravitreal antibiotic injection, was assessed. The effect of concomitant intravenous antibiotics was also studied. Patients with endophthalmitis within 6 weeks of cataract surgery or secondary IOL implantation were included. Vision between 20/50 and light perception was allowed, and some clarity of the cornea and anterior chamber sufficient to visualize part of the iris was required. Vitre-

ous or anterior chamber opacity obscuring visualization of second-order arterioles was required. Study patients were randomized to one of four groups, all of whom received intravitreal antibiotics: (1) initial vitrectomy with intravenous antibiotics, (2) initial vitrectomy without intravenous antibiotics, (3) initial tap with intravenous antibiotics, and (4) initial tap without intravenous antibiotics.

All patients were treated within 6 hours of presentation. An anterior chamber tap and culture were performed. In the vitrectomy group, a standard three-port pars plana vitrectomy was performed, taking an undilated vitreous specimen at the start of the procedure. In the tap groups, a vitreous specimen was obtained either with a needle introduced through the pars plana or a vitrectomy instrument introduced through a single port. The aqueous and vitreous samples were cultured. Intravitreal amikacin (0.4 mg in 0.1 mL) and vancomycin (1 mg in 0.1 mL) were administered. Vancomycin (25 mg in 0.5 mL), ceftazidime (100 mg in 0.5 mL), and dexamethasone (6 mg in 0.25 mL) were given subconjunctivally. Amikacin (25 mg in 0.5 mL) was substituted for ceftazidime in penicillin-allergic patients. Topical vancomycin 50 mg per milliliter alternating with amikacin 20 mg per milliliter was administered. Topical cycloplegics and steroids were given as well as oral prednisone 30 mg twice daily for 5 to 10 days.

For patients randomized to receive intravenous antibiotic therapy, ceftazidime 2 g every 8 hours was administered intravenously (or ciprofloxacin 750 mg twice daily administered orally for penicillin-allergic patients) and amikacin 7.5 mg per kilogram of body weight load then 6 mg per kilogram every 12 hours was administered.

Patients were reevaluated 36 to 60 hours after the initial procedure; 10.5% of patients required an additional procedure, of which 70.5% were reinjection of intravitreal antibiotics. Further intervention was recommended if the eye was clinically worsening and the following criteria were met: (1) vision 5/200 to light perception; (2) worsening media opacity; 3) at least equivocal growth from the initial cultures; and (4) 1-mm increase in hypopyon, corneal ring infiltrate, or worsening pain.

The primary study endpoints were visual acuity and clarity of the ocular media. No statistically significant difference in final visual acuity or media clarity was observed in patients treated with systemic antibiotics versus those without systemic antibiotics. No difference was observed in patients treated with initial tap and injection versus initial pars plana vitrectomy if the presenting vision was hand motions or better. An important difference in outcome occurred in patients who presented with vision of light perception only. Initial vitrectomy yielded a three times greater likelihood of achieving better than 20/40 final vision (33% versus 11%). Patients treated with vitrectomy in this group were twice as likely to achieve better than 20/100 (56% versus 30%) and less likely to have worse than 5/200 (20% vs. 47%) compared with the group of patients subject to initial vitreous tap and intravitreal antibiotic administration. A clinical pathway for the treatment of endophthalmitis from a variety of causes is shown in Figure 22–2.

What Is the Role of Cultures in Endophthalmitis?

Cultures yielded positive results in 69.3% of cases, 12.8% were equivocal, and 17.9% yielded no growth. Cultures from the anterior chamber were positive in only 4% of cases. Importantly, gram-positive organisms were isolated in 94.2% of eyes. Coagulase-negative organisms were seen in 68%. All gram-positive organisms were sensitive to vancomycin. Six percent of eyes had gram-negative infections. Of these, 89% were sensitive to both amikacin and ceftazidime. Eleven percent were resistant to both of these antibiotics. Gram-negative organisms were never cultured from eyes in which a second-order retinal vessel was visible on initial examination.

What Drugs Are Indicated for the Treatment of Endophthalmitis?

Initial antibiotic therapy should cover a broad spectrum of microorganisms, have efficacy at concentrations achieved by intravitreal injection, and have low toxicity. Bactericidal agents are preferred over bacteriostatic drugs because the eye is an immune privileged site. Coverage to include methicillin-resistant *Staphylococci* and *Bacillus* species in trauma is necessary. Some antibiotics exhibit considerable retinal toxicity when introduced into the vitreous cavity. Aminoglycosides, particularly gentamicin, can cause vascular occlusion and retinal necrosis. The most commonly administered drugs are listed below:

Cephalosporins are synthetic penicillins. Cefazolin, a first-generation drug, has a relatively broad gram-positive coverage but weak activity against gram-negative, methicillin-resistant organisms and enterococci. Ceftazidime 2.25 mg in a 0.1 mL volume is typically administered.

Vancomycin is a bactericidal agent effective against most gram-positive bacteria, including Bacillus. It is generally regarded as first-line empiric therapy and is given as a 1 mg injection in a 0.1 mL volume.

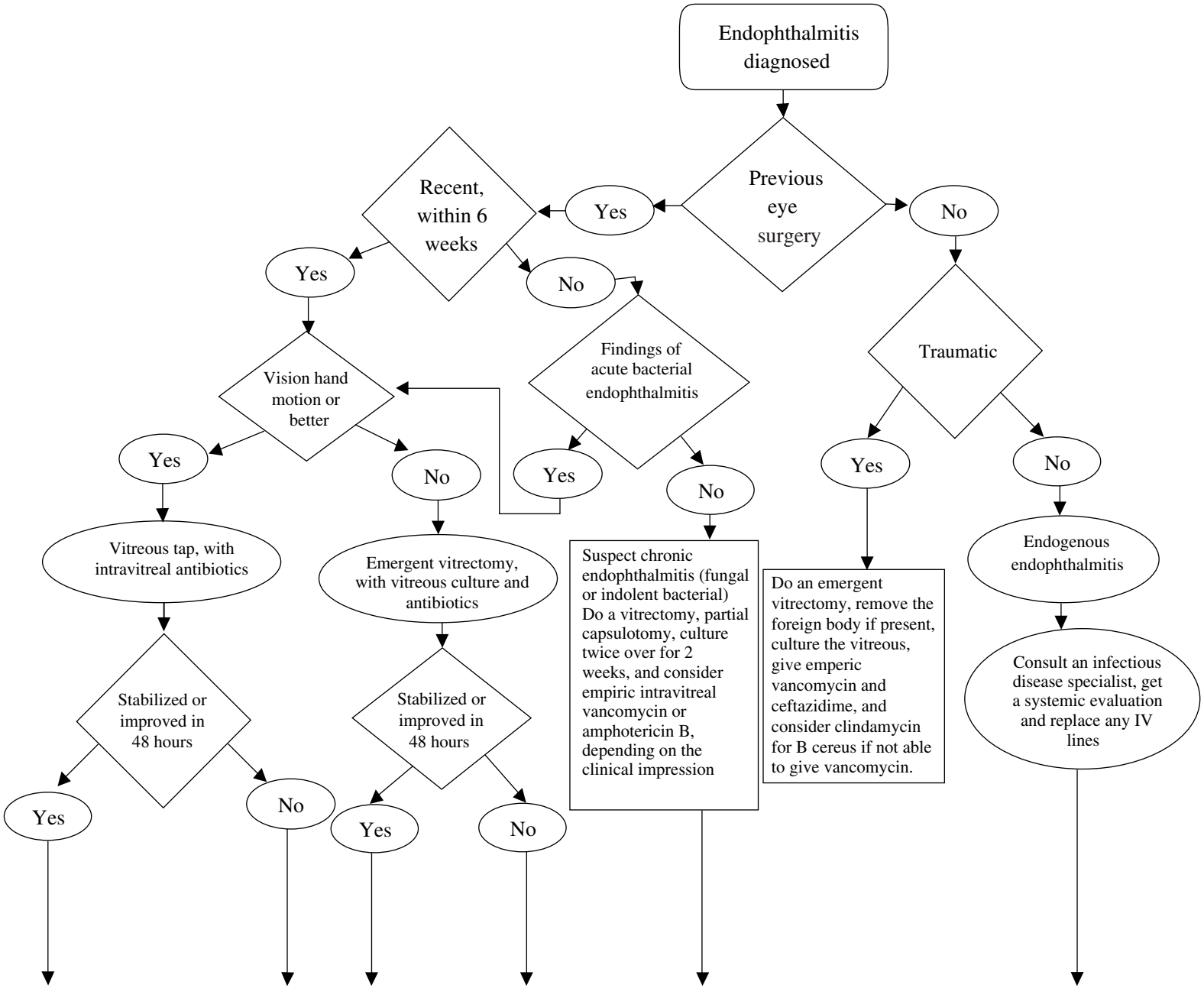
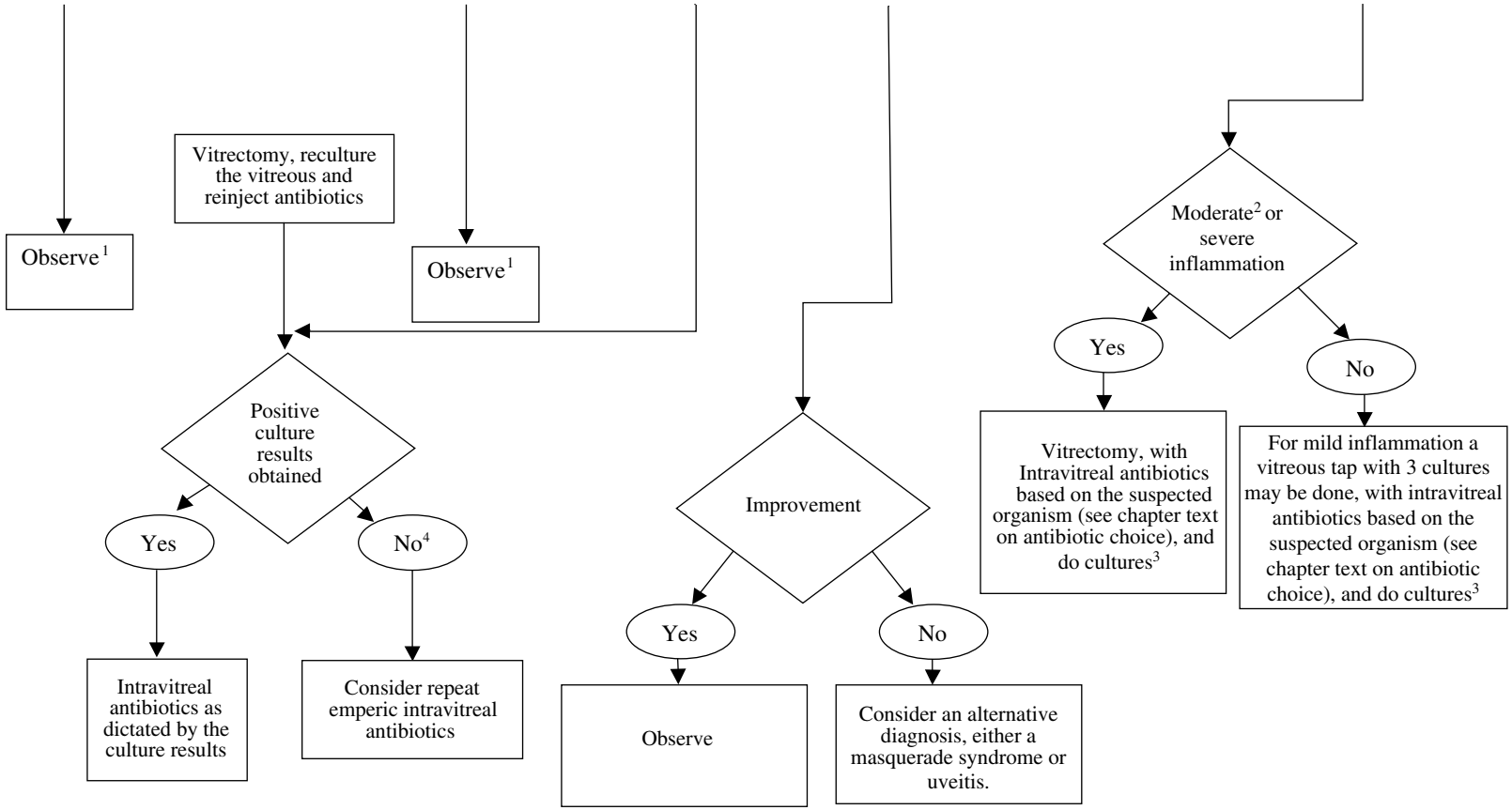


FIGURE 22–2. Clinical pathway for endophthalmitis. IV, intravenous.



1. Follow every 1 to 3 days for 1 to 2 weeks depending on level of improvement.
2. While there is no consensus on levels of inflammation, moderate to severe vitritis obscuring the second order retinal vessels or worse is a reasonable measure.
3. Please see Table 22–2 and the associated text for details of dosing.
4. Worsening vision or vitreous opacification in the setting of a negative culture may warrant further intervention, such a reculturing and reinjection.

FIGURE 22–2. *Continued*

Aminoglycosides inhibit protein synthesis and have some gram-positive but excellent gram-negative coverage. Unfortunately, their therapeutic window is quite narrow, and severe retinal toxicity can be seen with intravitreal injection. In the EVS, amikacin was used as a 400-μg injection in a 0.1-mL volume.

Quinolones inhibit DNA synthesis and have broad-spectrum activity against numerous microorganisms. Anti-*Streptococcal* and anti-anaerobe activity is somewhat weak. Intravitreal administration can result in retinal toxicity, however. Ciprofloxacin administered systemically does achieve significant levels in the vitreous cavity.[5]

Antifungal drugs include amphotericin B and the azoles. Amphotericin B dosed at 5 to 10 μg in 0.1 mL has been used intravitreally with reasonable success in cases of fungal endophthalmitis. Moreover, in some instances of *Aspergillus* endophthalmitis, amphotericin B can be combined with 5-fluorocytosine.

A common initial approach to the treatment of bacterial endophthalmitis is the administration of intravitreal vancomycin 1 mg in 0.1 mL and ceftazidime 2.25 mg in 0.1 mL. Subconjunctival vancomycin and ceftazidime might be given as well. A postoperative drop regimen consisting of topical vancomycin, ceftazidime, and a steroid such as prednisolone acetate is commonly used.

Intravitreal antibiotics and antifungal agents commonly used in the treatment of endophthalmitis and their doses are summarized in Table 22–2.

What Are the Routes of Administration?

Antibiotics can be given topically, subconjunctivally, intraocularly (either intracameral or intravitreal), and systemically. Intraocular administration, particularly intravitreal injection, achieves therapeutic dosing for a period of approximately 24 to 48 hours. Systemic administration generally does not achieve therapeutic levels in the vitreous cavity, with the exception of ciprofloxacin.

TABLE 22–2. Intravitreal Antibiotic and Antifungal Agents Commonly Used in the Treatment of Endophthalmitis

Antibiotic	*Dose (in 0.1 mL)*
Vancomycin	1.0 mg
Amikacin	0.4 mg
Ceftriaxone	2.0 mg
Ceftazidime	2.25 mg
Clindamycin	0.5 to 1.0 mg
Amphotericin B	5 or 10 μg

How Do You Follow Up on Endophthalmitis?

Successful treatment often results in a dramatic improvement in pain by the first postoperative day. Worsening inflammation in the face of persistent pain may indicate active infection and the need for further intervention. Repeat tap and injection or vitrectomy surgery would be warranted for eyes that are clinically worsening. If cultures suggest resistance to the antimicrobial agent used, repeat injection with an appropriate antibiotic is necessary. Difficulty assessing the retina is a frequent problem because of media opacity; so serial ultrasounds are sometimes needed to identify retinal detachment, which was observed in 8% of eyes in the EVS. Additionally, membrane formation and traction detachment resulting from severe intraocular inflammation can result. Persistent corneal edema might require eventual penetrating keratoplasty. Elevated intraocular pressure, however, often can be managed medically. More difficult to control is postoperative hypotony. Vigorous control of intraocular inflammation can be helpful. A through evaluation for a wound leak is necessary.

When Would You Consider Re-Treating?

Retreatment of endophthalmitis is indicated for cases where stabilization or improvement is not noted after the first 36 to 48 hours. Signs of worsening include increased hypopyon, decreased vision, and an increase in vitreous opacification (which can be documented on ultrasound in situations where the vitreous is not ophthalmoscopically visible). In eyes previously treated with tap and injection, consideration of pars plana vitrectomy and reinjection should be given. In eyes previously vitrectomized, repeat vitrectomy or reinjection of antibiotics should be performed. If possible, retreatment should be guided by culture results from the initial vitreous or aqueous specimen.

How Can Endophthalmitis in Silicone-Filled Eyes be Treated?

Endophthalmitis in the silicone-filled eye can be difficult to detect because the eye may seem quieter than expected; however, successful treatment of endophthalmitis in this setting has been reported. The technique involves removing the silicone oil, washing the vitreous cavity with antibiotic for 15 minutes, performing an 80% fluid–air exchange, so that approximately 20% of the antibiotic solution remains in the eye, then replacing the oil.[6] Oil itself may have some intrinsic antimicrobial activity against some bacteria and fungi.[7]

When to Remove a Cataract in the Face of Retinal Disease

What Are the Considerations for Removing a Cataract in a Patient with Retinal Disease?

The management of the lens in patients with underlying retina disease depends on the visual potential of the eye and how readily the goals of retina surgery or laser can be achieved. In some cases, it may be perfectly reasonable to leave a relatively dense cataract untouched in a patient with an underlying disciform scar and little chance of significant visual improvement, particularly if the fellow eye is in good condition. On the other hand, extracting a clear lens may be indicated if an anterior dissection of membranes is necessary to reattach the retina. Whether cataract extraction worsens preexisting retinal disorders is known for only a few conditions and is discussed here. Studies are under way to help address this issue for other diseases. Some investigators believe that the lens may serve as a barrier to diffusible substances such as vascular endothelial growth factor and may protect against rubeosis in proliferative retinopathies.[8] There is always, of course, concern for the development of cystoid macular edema (CME) following cataract surgery. Macular edema may be particularly exuberant and aggressive in some patients with underlying retinal vascular disease. A second consideration is the likelihood of worsening cataract after a vitreoretinal procedure such as pars plana vitrectomy and membrane peeling for epiretinal membrane. In selected cases, simultaneous cataract extraction and IOL implantation concurrent with the posterior segment surgery are advisable.

There are a variety of techniques for the removal of the lens, and limited data are available to suggest which of these might be the best approach. Intracapsular cataract extraction (ICCE) was associated with a high incidence of CME and progression of diabetic retinopathy in the series reported by Aiello and colleagues.[9] ICCE is decreasing substantially in popularity, however, and may produce problems with visual rehabilitation. Moderate levels of progression of retinopathy (20%) and macular edema (8%) have been reported in a small uncontrolled series after extracapsular cataract extraction (ECCE) with nuclear expression.[10] Data from phacoemulsification cases have been reviewed in number of series. Mittra and colleagues reported similar postoperative findings after phacoemulsification in a retrospective series of 150 patients, compared with other modalities of cataract extraction.[11] Seventy-eight percent had improvement in visual acuity of two or more lines. One quarter had progression of retinopathy. Risk factors for progression included preexisting nonproliferative or proliferative retinopathy and longer surgical times. Zaczek and colleagues reported similar data.[12] Additionally, manipulation of anterior structures in patients with severe diabetic retinopathy can lead to the formation of a postoperative fibrin reaction that can be quite aggressive, sometimes leading to synechiae formation and hypotony.

Finally, pars plana lensectomy should be considered in specialized circumstances, for example, when anterior dissection of membranes is needed. In some situations, it is possible to leave the anterior capsule intact and place an IOL in the sulcus, either at the conclusion of surgery or as a second procedure. Figure 22–3 summarizes these considerations and how one might approach concurrent cataract and retinal disease.

The decision as to whether to implant a lens and the type of lens use is an important issue with little in the way of data to support one type over another in the literature. We recommend using a large-diameter optic (at least 6.5 mm) acrylic foldable lens for cases where small incision phacoemulsification is performed or an all polymethylmethacrylate (PMMA) lens with similar dimensions. Silicone lenses and plate-haptic lenses are not recommended. Silicone lenses are incompatible with silicone oil, which may be adsorbed onto the surface or absorbed into the lens resulting in irregular refractive changes.

How Does Retinal Surgery Impact on Cataract Formation?

Cataract formation is common after vitrectomy surgery; the incidence of progressive nuclear sclerosis at 2 years is 70 to 80%. The exact cause is unknown, but numerous hypotheses exist, including changes in the lens due to the infusion, local alterations in oxygen concentration, and ultraviolet or heat exposure from the operating microscope. Some "feathering" of the posterior lens capsule is common with intravitreal gas tamponade and is sometimes reversible. Eyes requiring silicone oil tamponade, for example, for complicated retinal detachments or the repair of macular holes where appropriate postoperative positioning cannot be achieved, inevitably develop cataracts. The incidence approaches 100% between 6 and 18 months postoperatively and can develop even after silicone oil removal.[13–18]

In cases of retinal disease with good visual prognosis, such as some epiretinal membranes and macular holes, it is reasonable to consider concurrent cataract extraction, IOL implantation, and vitrectomy surgery. We often extract the lens in eyes with relatively mild cataract, particularly if protracted gas or oil tampon-

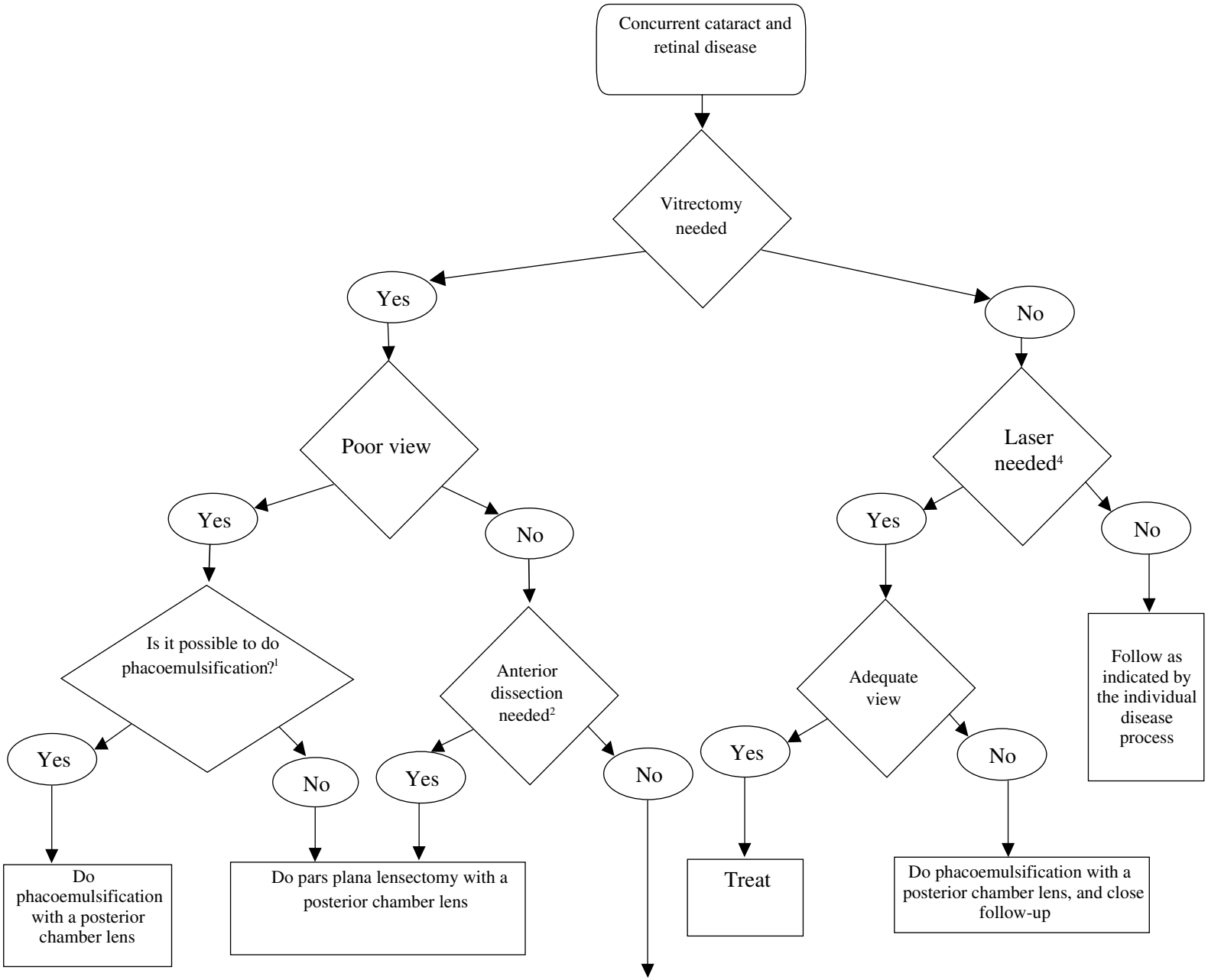
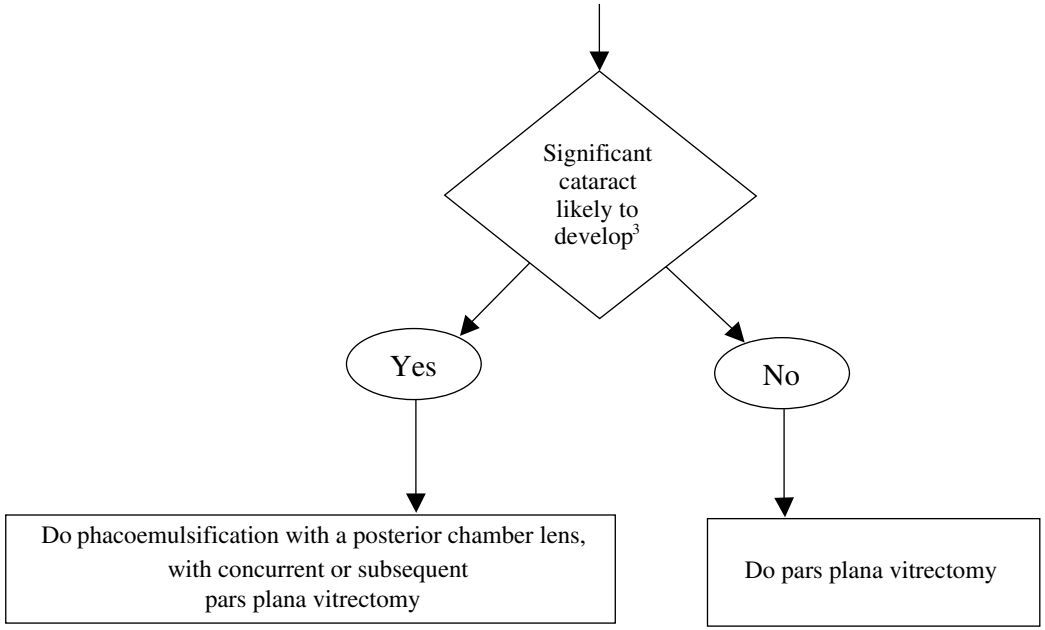


FIGURE 22–3. Clinical pathway for concurrent cataract and retinal disease.



1. Phacoemulsification is preferred by some surgeons as it is felt to allow a more physiologic positioning of the intraocular lens. In cases where extensive posterior dissection is not needed (e.g., macular hole and epiretinal membrane surgery) concurrent phacoemulsification, intraocular lens implantation, and vitreous surgery is reasonable. If more extensive retina surgery is needed, consideration should be given to separate operations, allowing the cornea and anterior segment to recover, or lensectomy, preserving the anterior capsule followed by intraocular lens implantation in the sulcus.
2. Anterior dissection, such as removal of membrane in anterior hyaloidal fibrovascular proliferation may be quite difficult in a phakic or pseudophakic patient.
3. The development of a visually significant cataract may be expected in a patient with pre-existing cataract and a high likelihood of good macular function, such as in epiretinal membrane surgery or in cases where extending gas or oil tamponade is needed. In such situations, it is reasonable to consider phacoemulsification and intraocular lens implantation at the time of vitrectomy surgery. Some surgeons, however, prefer to delay the anterior segment surgery.
4. The clarity of the ocular media required for laser treatment of retinal lesions varies. In general, panretinal photocoagulation for retinal neovascularization in proliferative retinopathies can often be achieved through significant cataract. Focal laser treatment for clinically significant macular edema or cystoid macular edema in branch retinal vein occlusion may require more optical clarity and be an indication for earlier phacoemulsification and intraocular lens implantation. This should be balanced against the possible development of post-operative cystoid macular edema (Irvine-Gass syndrome).

FIGURE 22–3. *Continued*

ade is anticipated, expecting the lenticular opacity to worsen rapidly in the postoperative period and become visually significant. The approach to the cataract varies between surgeons and sometimes involves collaboration between the anterior segment specialist and the vitreoretinal surgeon. In many cases, phacoemulsification and IOL implantation are performed first, followed by vitrectomy and membrane peeling. The cataract surgery may be performed through a scleral tunnel approach or a clear-cornea approach. We have found that suturing the wound, even if it appears self-sealing, greatly facilitates further manipulation of the posterior segment and maintains a formed anterior chamber. One disadvantage is that the anterior chamber may become somewhat turbid and the cornea mildly edematous following the lens extraction, occasionally compromising the view for the posterior-segment work. We have not found this to be a particularly significant problem, however. It has the advantage of allowing in-the-bag placement of an IOL. An alternative is to perform the cataract surgery as a separate procedure before vitrectomy, but this of course has the disadvantage of exposing the patient to two surgeries and doubling the anesthetic risk. Finally, pars plana lensectomy, sparing the anterior capsule allows for sulcus placement of the IOL.

How Does Cataract Extraction Impact on Retinal Disease?

The effect of cataract surgery on diabetes has been evaluated in a number of retrospective and case series. Overall, cataract surgery can worsen preexisting retinopathy and macular edema; however, a relatively high level of visual improvement has been reported in diabetics undergoing cataract extraction. If possible, treatment and stabilization of retinopathy are desirable before considering cataract extraction. In cases where the lenticular opacity precludes reasonable laser treatment, cataract surgery with lens implantation followed closely by treatment of the retina is indicated.

The incidence of retinal detachment after cataract extraction ranges between 0.66 and 3.6% and is higher in complicated cases where there has been vitreous loss.[5] Prophylactic treatment of retinal breaks is helpful in reducing the postoperative risk of detachment. Prophylactic treatment of asymptomatic lattice degeneration and atrophic holes is generally not recommended.

The effect of cataract surgery on other forms of retinopathy is less well studied. Good results have been reported in patients with retinitis pigmentosa.[19] Even less data are available for patients with age-related macular degeneration. Reports in the literature regarding visual improvement or worsening and progression of the retinal disease are conflicting. This is currently the focus of a pilot study (RACS) at the Wilmer Eye Institute.

What Are Special Refractive Considerations in the Retina Patient?

A variety of vitreoretinal techniques can temporarily or permanently alter the refractive state of the eye. Encircling elements tend to induce myopia, sometimes as much as 3.00 diopters or more, which can lead to substantial anisometropia and aniseikonia. Such issues may be addressed secondarily by the cataract surgeon or by contact lens or refractive surgery procedures in appropriate cases. Silicone oil produces a refractive change due to its higher index of refraction (1.400) compared with vitreous (1.336). The shape of the oil bubble at its anterior surface creates a lens effect, however, so that a hyperopic shift is observed in phakic eyes and a myopic shift in aphakic eyes. The extent of the shift depends on the size of the oil bubble and averages +6.00 in phakic eyes and −7.00 diopters in aphakia. IOLs with plano-posterior surfaces minimize the refractive changes associated with oil. These changes only become significant in cases where extended or permanent silicone oil tamponade is necessary. Contact lens correction is appropriate for selected patients with good visual potential.[20]

What Special Conditions Guide the Approach to Cataract Surgery in the Retina Patient?

Subluxated lenses and traumatic cataracts occasionally are seen accompanying severe ocular trauma. Sometimes these lenses are completely dislocated into the vitreous cavity. Cases range from mild lenticular changes, with little if any phacodonesis to complete zonular disruption. Indications for surgery include visual dysfunction associated with the cataract or subluxation, phacomorphic glaucoma, or phacoanaphylactic uveitis. The surgical approach to these cataracts depends on the stability of the lens, the presence of vitreous in the anterior chamber, and associated ocular injuries that might require surgical intervention such as scleral compromise or retinal detachment. If the lens is relatively stable and no vitreous is present anteriorly, a standard phacoemulsification approach is reasonable. Care should be taken to perform a thorough hydrodissection to reduce zonular stress. Some surgeons advocate a "chopping" technique because this may reduce further zonular compromise. A large

optic IOL is placed. In situations where the zonular dehiscence is more substantial, an anterior approach with a stabilizing Morcher ring might be appropriate, depending on the level of comfort the surgeon has with such systems. If there is anterior herniation of vitreous and concern for vitreoretinal traction, or if the lens is completely dislocated, a three-port pars plana vitrectomy and lensectomy is indicated. Care should be taken to perform as complete a vitrectomy as possible. Perfluorocarbon (PFC) liquid injected over the optic-nerve head may be used to protect the retina from falling nuclear fragments expelled from the fragmatome and also may help to stabilize the retina in cases of concurrent retinal detachment. In these cases, it is probably best to leave the eye aphakic and, depending on the visual potential of the eye, consider secondary IOL placement, either sutured to the sclera or iris or placed in the anterior chamber.

What Are the Considerations for Intraocular Choice?

A variety of IOL materials, shapes, and sizes are available to the cataract and vitreoretinal surgeon. Limited data exist on the optimal lens type to use in the face of retinal disease. For retinal vasculopathies, control of the underlying disease process is likely more important than the type of lens implanted. In vitreoretinal surgical cases, we have tended to use a large optic (6.5 mm) acrylic foldable lens. The larger optic tends to reduce prolapse into the anterior chamber in gas and oil-filled eyes. Acrylic lenses retain less silicone oil than silicone lenses. An all-PMMA lens is a reasonable alternative, although it requires a larger limbal incision to insert and is difficult to insert through a small clear corneal incision. One experimental model of silicone adhesion suggests that Raysoft (HEMA) lenses have a lower affinity for oil than do PMMA or acrylic IOLs.[21] Heparin surface modified (HSM) PMMA lenses have been demonstrated to behave similarly to acrylic lenses in terms of postoperative inflammation in diabetic patients.[22] Generally, silicone IOLs are avoided in cases where silicone oil might be used, even in a future surgery. Oil adheres tightly to these lenses and may diffuse into the lens substance, changing its refractive power.[23]

Intraocular lenses can be placed in the capsular bag if sufficient support remains or in the ciliary sulcus if sufficient anterior capsular remnants are present. In the absence of adequate capsular support, the lens can be sutured to the sclera[24] or to the iris, as has been previously described.[25] Alternatively, an anterior-chamber IOL can be placed or the eye left aphakic and corrected with spectacles (if bilaterally aphakic) or contact lenses.

How Is the Biometry of the Silicone-Filled Eye Assessed?

As noted previously, the refractive index of silicone oil is higher than that of the vitreous. Similarly, the speed of sound in oil differs from that in vitreous. This change in speed must be taken into account when measuring the eye ultrasonically. For a phakic eye, the anterior-chamber depth and lens thickness can be measured in the standard fashion. The posterior-segment depth must be corrected for the speed of sound in oil, 986 m per second compared with that in vitreous, 1552 m per second). For example, if the anterior chamber depth is 2.5 mm, the lens measures 5 mm, and the posterior segment depth is 17 mm, then the apparent axial length of a silicone-filled eye would be 34.3 mm compared with the true axial length of 24.5 mm. Measuring the axial length of such eyes in the upright position should be considered to minimize the size of the preretinal aqueous layer, which would otherwise further complicate this measurement.[12]

Management of the Dropped Nucleus

What Is the Optimal Management of the Dropped Nucleus?

The optimal management of the dropped nucleus (Fig. 22–4) depends on the amount of posteriorly dislocated nuclear material, the degree of intraocular inflammation, the intraocular pressure, and the adequacy of the view. The optimal method of aphakic correction depends on the amount of remaining capsular support and the level of expertise of the surgeon. This section reviews some of these considerations and

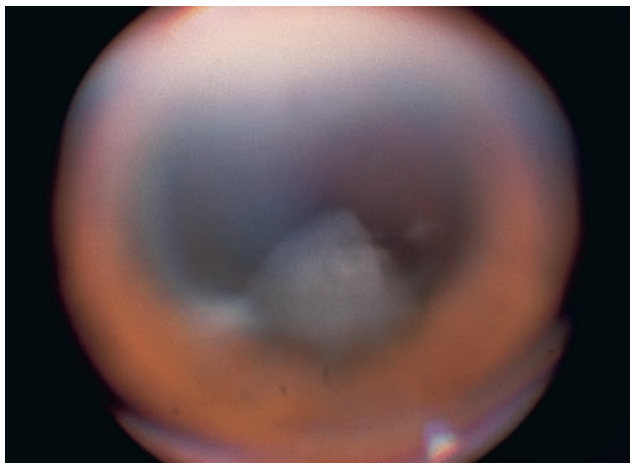


FIGURE 22–4. Retained lens material.

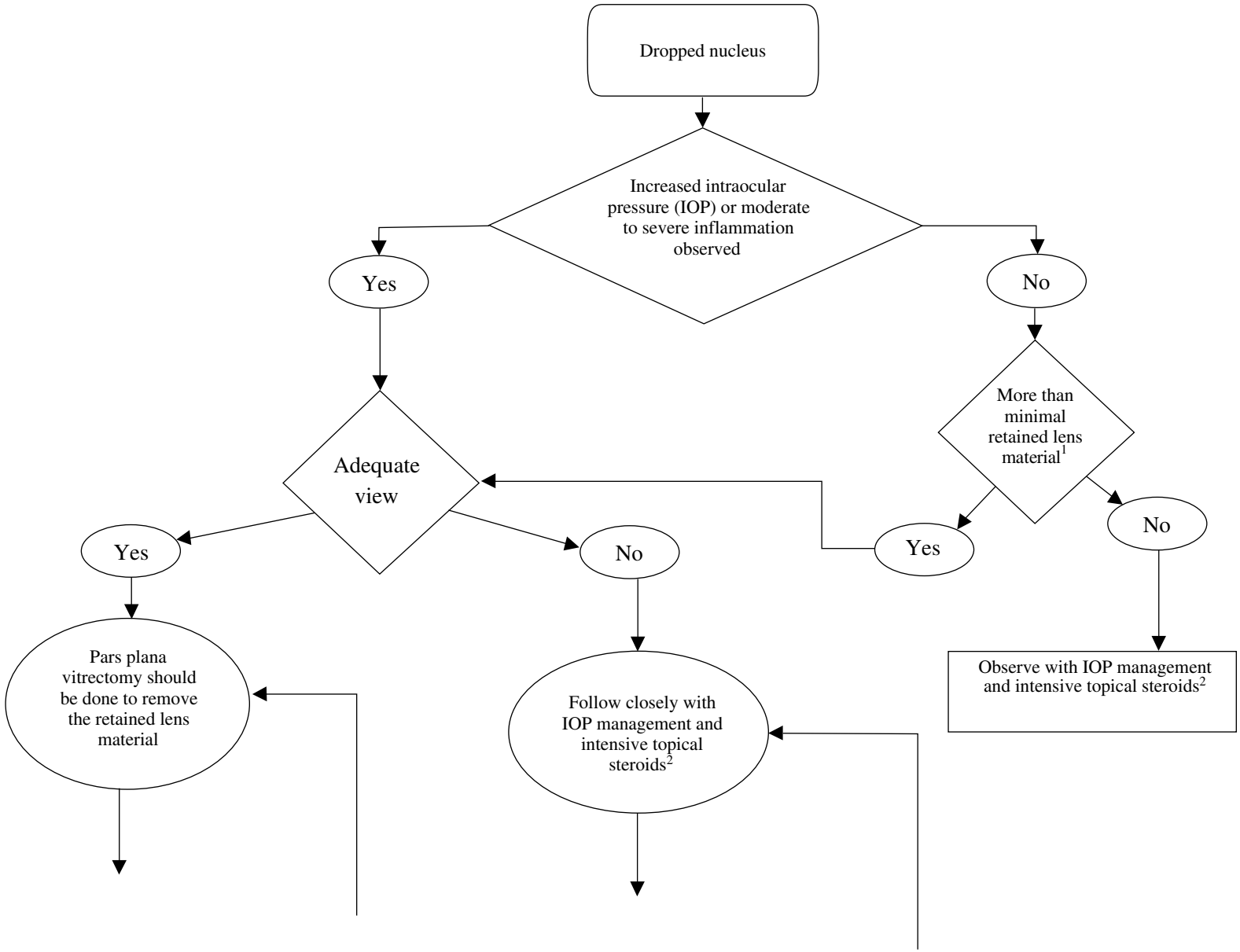
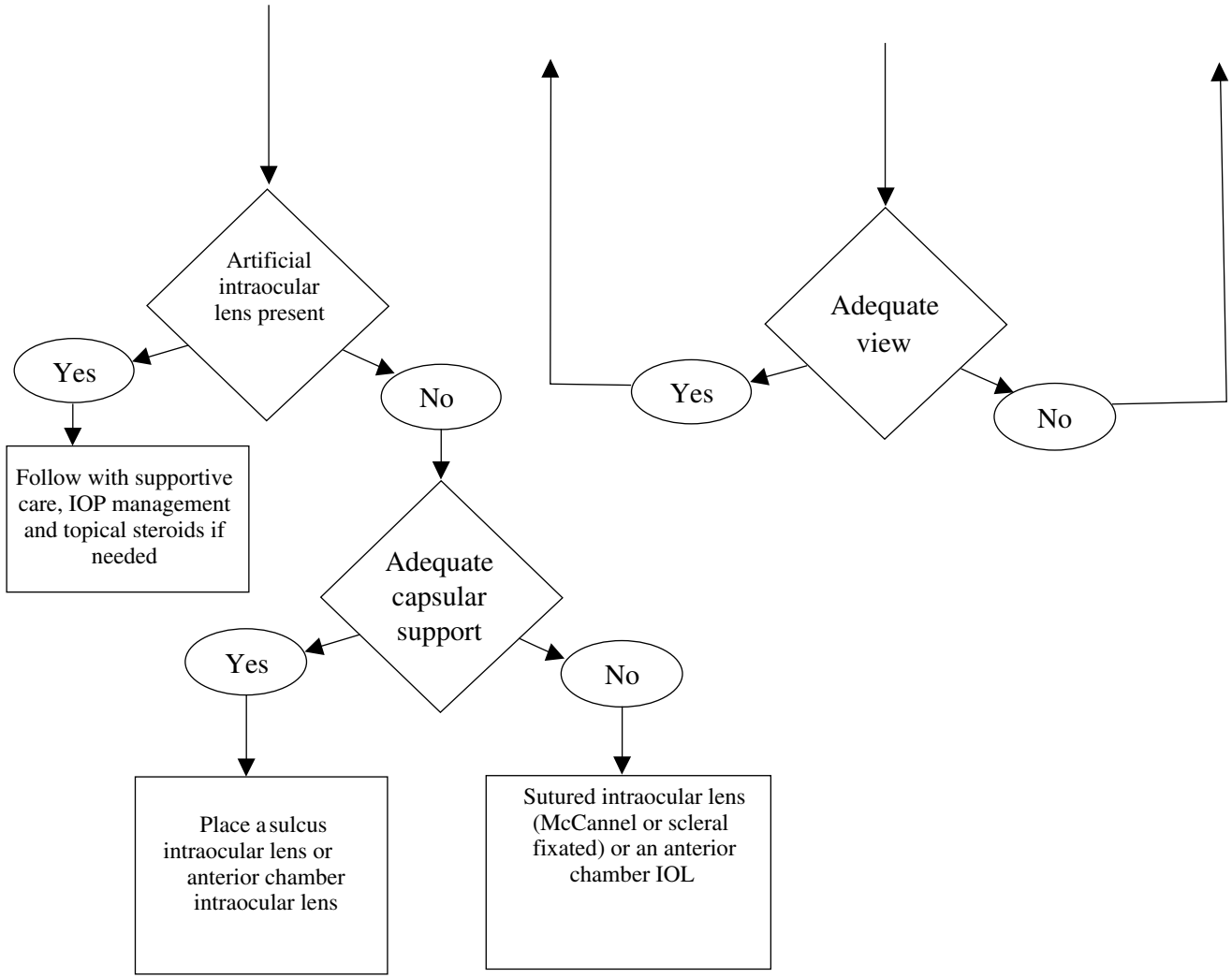


FIGURE 22–5. Clinical pathway for dropped nucleus.



1. There is lack of universal agreement on the amount of retained lens material that constitutes "minimal." However, more than 5% of retained nucleus or cortex is a general indication for vitrectomy. Nuclear material tends to cause more inflammation than does cortex. Additionally, the amount of retained material is correlated with the degree of inflammation and intraocular pressure rise. Please see the text for details.
2. There is similar lack or universal consensus on the route of steroid administration. Topical steroids are often sufficient. Some practitioners prefer a subtenons route, which can achieve a continual dosing for several months. This has a disadvantage in steroid responders, who could require intraocular pressure control. Intravitreal kenalog or decadron has been used in anecdotal reports.

FIGURE 22–5. *Continued*

recommendations for management. Figure 22–5 offers one approach to this problem.

What Is the Incidence of Dropped Nuclei?

Retained lens fragments are thought to occur in 0.3 to 1.0% of cataract extractions.[26,27] The incidence appears higher in small-incision phacoemulsification cases, compared with nuclear expression techniques. Small pupils, hard nuclei, trauma, deep orbits, pseudoexfoliation, and hereditary syndromes associated with zonular weakness are all associated with an increased risk of this problem.

What Should the Anterior-Segment Surgeon Do in These Cases?

A wide range of techniques has been proposed for managing lens fragments dislocated in to the vitreous cavity, including viscoelastic-mediated elevation of lens fragments, cryoextraction, and needle extraction. None of these is as effective as vitrectomy surgery, however. The main initial decisions that need to be made are whether an IOL can be placed and whether further surgery is needed. An effort not to attempt retrieval of displaced fragments reduces the risk of complications such as vitreous hemorrhage, retinal tears, retinal detachments, and corneal decompensation.

The best course of action is to perform an anterior vitrectomy, removing as much of the residual cortex as possible and ensuring that no vitreous is present at the wound. If there is adequate residual capsular support, an IOL can be placed in the ciliary sulcus. We recommend a large optic foldable acrylic lens or an all-PMMA lens. Silicone lenses are poor choices because of the potential future need for the use of silicone oil to repair a recurrent retinal detachment, as previously discussed. Silicone lenses have a strong affinity for silicone oil, which may lead to retained oil droplets and a change in the refractive status of the IOL. Without adequate capsular support, an IOL can be placed in the anterior chamber or alternatively sutured to the iris or scleral wall. Posterior dislocation of an IOL inserted without adequate support further complicates the subsequent vitrectomy. The surgical wound should be closed tightly, with several interrupted sutures, to facilitate maintenance of the anterior chamber during pars plana vitrectomy. Control of postoperative inflammation and intraocular pressure should be optimized with the use of frequent topical steroids and ocular hypotensives.

What Are the Indications for Pars Plana Vitrectomy?

In situations where only a small amount of residual lens fragments are present and there is no significant intraocular inflammation or elevation of IOP, observation may be warranted. The level of intraocular inflammation correlates to some extent to the amount of retained lens material.[28] The picture may be further confounded by concomitant endophthalmitis, which has been reported in two of six patients with hypopyon of 62 with dislocated lens fragments.[29] Other issues, such as glaucoma, presumably with a phacolytic component, retinal tears and detachments from vitreous manipulation, and vitreous hemorrhage, also may require vitreoretinal evaluation and treatment.

The timing of vitrectomy is somewhat controversial, but there is some suggestion that early vitrectomy may be beneficial, generally within the first 2 weeks of cataract extraction. There is no strong evidence that immediate vitrectomy has any better visual outcome than vitrectomy delayed for a short time.[30–33] In some cases, it may be necessary to wait until corneal edema resolves to pursue vitrectomy.

How Are Posteriorly Dislocated Lens Fragments Removed?

A standard three-port pars plana vitrectomy setup is installed. The infusion cannula is visualized. A core vitrectomy is performed, and then any residual capsular material is carefully removed. The vitreous associated with each lens fragment is carefully dissected,

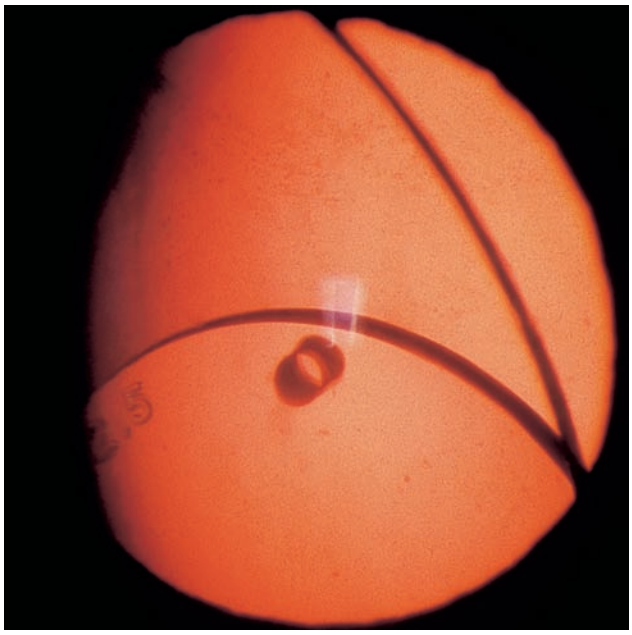
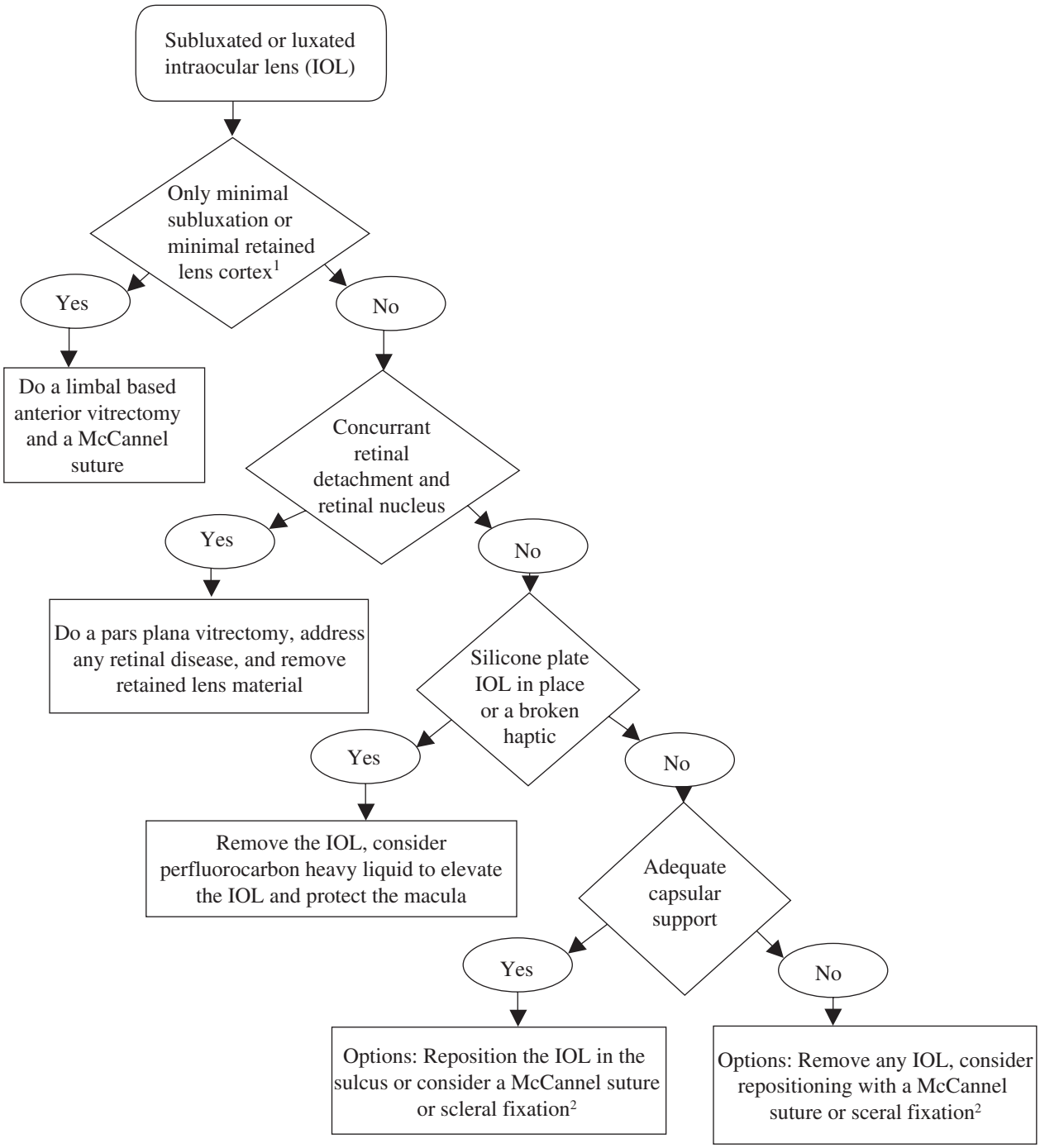


FIGURE 22–6. Subluxated intraocular lens (IOL). A subluxated IOL can be explanted, sutured to the iris or sclera.



1. Minimal retained cortex is approximately 5% or the original lens volume. Please see the text for details.
2. Respositioning the IOL may require one method of suture fixation if the implant is to be kept in the posterior chamber without adequate capsular support. A McCannel suture can be placed to fixate one or both haptics to the iris. Briefly, a 10–0 prolene suture is passed through the clear cornea and iris to "capture" the haptic. The ends of the suture are brought out a small paracentesis and tied. Scleral fixation is an alternative in which the prolene can be first attached to the haptic, then brought out the ciliary sulcus through the sclera and tied. The knots are often buried under a partial thickness scleral flap.

FIGURE 22–7. Clinical pathway for subluxated intraocular lens (IOL).

and then the fragments themselves are aspirated with the cutter or fragmatome in the midvitreous cavity. Care is taken to avoid excess traction on the retina and expelling hard nuclear fragments toward the retina. Low ultrasound levels are recommended. Some surgeons prefer to instill a small bubble of PFC to protect the macula during sonication; however, visual outcomes appear to be the same whether or not PFCs are used during surgery.[30] PFC also may be useful to elevate posteriorly luxated IOLs and facilitate their repositioning or explantation.

How Is Aphakia Corrected in These Patients?

Aphakic correction may be achieved with a contact lens, anterior-chamber IOL, posterior-chamber IOL in the sulcus with or without suture fixation. Margherio and colleagues reported better visual outcomes in patients with posterior chamber lenses compared with anterior chamber lenses, but other studies have not demonstrated a statistically significant improvement.[34] Posterior-chamber IOL fixation can be achieved suturing the haptics to the iris or to the sclera. Some surgeons prefer 3- or 4-point fixation to minimize IOL tilt and dislocation.

What Are the Visual Outcomes of Eyes with Posteriorly Dislocated Lens Material?

About 60 to 68% of such eyes achieve 20/40 or better.[30,33,35] Those with retinal detachment fare more poorly.

Management of Subluxated and Luxated Intraocular Lenses

What Are the Principles for Managing Dislocated Intraocular Lenses?

The general principles for managing dislocated IOLs (Fig. 22–6) are similar to those just discussed for dropped lenses. Subluxation generally refers to an off-center IOL, but still in the pupillary space, whereas luxation generally refers to an IOL that is completely dislocated from the pupil. In cases of minimal subluxation, it is often possible to correct the vision best with refraction. For somewhat more substantial dislocation, repositioning the lens, possibly with a stabilizing suture through the iris to "capture" either one or both haptics ("McCannel suture") may be warranted. If vitreous is present anteriorly, a limited anterior vitrectomy is performed concurrently with IOL repositioning. More complex dislocations, particularly those associated with other retinal pathology such as detachment or retained nuclear or cortical material, require a more extensive surgical approach, as outlined here for retained lens material. A completely dislocated (luxated) IOL requires posterior vitrectomy and either explantation or repositioning of the lens. Some surgeons use PFC liquids to help elevate the IOL from the retinal surface. IOLs with broken haptics and plate haptic IOLs generally require explantation.

Depending on the amount of capsular support and the likelihood of recurrent dislocation, a variety of options are available for positioning the IOL. In cases where adequate anterior capsular support is present, simply placing the IOL in the ciliary sulcus may be feasible. Without adequate support, the IOL can be placed in the anterior chamber, sutured to the iris with one or two 10–0 Prolene sutures ("McCannell sutures"), or sutured to the sclera. An approach to the management of dislocated IOLs is offered in Figure 22–7.

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23

Clinical Trials in Retina

KAREN GEHRS AND SHARAM DANESH

Treatment of Choroidal Neovascularization (Macular Photocoagulation Study and Others)

Why Was the Macular Photocoagulation Study Conducted?

Choroidal neovascularization (CNV) is a significat cause of severe visual loss in patients with age-related macular degeneration (AMD) and ocular histoplasmosis syndrome (OHS). The Macular Photocoagulation Study (MPS) was a randomized, controlled clinical trial designed to determine whether laser photocoagulation of CNV prevents severe visual loss (SVL). Several clinical trials were conducted. These included (1) extrafoveal CNV in patients with AMD, OHS and idiopathic CNV (ICNV); (2) juxtafoveal CNV in patients with AMD, OHS, and ICNV; and (3) new and recurrent subfoveal CNV in patients with AMD only.

How Was the Extrafoveal Choroidal Neovascularization Trial Conducted?

Three trials investigated the role of laser treatment to extrafoveal CNV in patients with AMD, OHS, and ICNV. To be eligible for these trials, patients were required to have angiographic evidence of a choroidal neovascular membrane (CNV) with the foveal edge 200 to 2500 μ from the center of the foveal avascular zone (FAZ). The visual acuity was 20/100 or better in the study eye. Eyes with peripapillary membrane were included, if the laser treatment spared at least 1.5 clock hours of peripapillary nerve fiber layer adjacent to the temporal half of the disc. Patients enrolled in the AMD trial had evidence of drusen. Patients in the OHS trial had at least one atrophic scar (histo spot). Patients in the ICNV trial had no drusen, histo spots, or other clinical findings that could account for the CNV.

Eligible eyes were randomly assigned to argon-laser photocoagulation or no treatment. Argon blue-green laser was used to obliterate the entire neovascular complex, including any areas of blood or blocked hyperfluorescence. Treatment resulted in uniform whitening of the overlying retina. Treated patients were seen at 3 to 9 weeks to assess the adequacy of treatment. Treated patients were encouraged to monitor their vision with an Amsler grid and report any new distortion or enlargement of scotoma. Additional treatment was promptly applied when persistence or recurrence of a treated membrane was found.

The primary outcome measure for the MPS was occurrence of SVL, defined as a loss of six or more lines of visual acuity (equivalent to a quadrupling of the visual angle).

Does Laser Photocoagulation Preserve Vision in Patients with Extrafoveal Choroidal Neovascularization?

Age-Related Macular Degeneration Trial

The AMD trial enrolled 236 eyes. Compared with observation, laser photocoagulation significantly reduced the risk of SVL during the entire follow-up period: 47% versus 62% at 3 years and 46% versus. 64% at 5 years.[1–3] After 5 years, the mean visual acuity was 20/125 in the laser-treated eyes and 20/200 in untreated eyes. The recurrence rates for the treated eyes were high: 24% at 6 months and 52% at 2 years.[4]

Ocular Histoplasmosis Trial

The OHS trial enrolled 232 eyes. Laser photocoagulation significantly reduced the risk of SVL during the entire follow-up period: 10% versus 45% at 3 years and 12% versus 42% at 5 years.[2,3,5] After 5 years, the mean

visual acuity was 20/40 in the laser-treated eyes and 20/80 in untreated eyes. The recurrence rates for treated eyes were 22% at 6 months and 28% at 2 years.[4]

Idiopathic Choroidal Neovascularization Trial

Sixty-seven eyes were enrolled in the ICNV trial. There was a trend for laser photocoagulation to reduce the risk of SVL: 20% versus 36% at 3 years and 23% versus 48% at 5 years.[2,3,6] These results were not statistically significant because of the small sample size. After 5 years, the mean visual acuity was 20/64 in the laser-treated eyes and 20/80 in untreated eyes. The recurrence rates for treated eyes were 15% at 6 months and 28% at 2 years.[4]

How Was the Juxtafoveal Choroidal Neovascularization Trial Conducted?

Three trials investigated the role of krypton laser treatment to juxtafoveal CNV in patients with AMD, OHS, and ICNV. Krypton-red laser was used for treatment within the FAZ because the red wavelength is not absorbed by the xanthophyll in the inner retina. To be eligible for these trials, patients were required to have angiographic evidence of neovascularization with foveal edges between 1 and 199 μ from the center of the FAZ or between 200 and 2500 μ from the center if associated blood or blocked fluorescence extended within 200 μ of the FAZ center. These lesions could have blood or blocked fluorescence due to pigment that extended through the entire FAZ. The visual acuity was 20/400 or better in the study eye. Eyes with peripapillary membranes were included if the laser treatment spared at least 1.5 clock hours of peripapillary nerve-fiber layer adjacent to the temporal half of the disc. Patients enrolled in the AMD trial had evidence of drusen. Patients in the OHS trial had at least one atrophic scar (histo spot). Patients in the ICNV trial had no drusen, histo spots, or other clinical findings that could account for the CNVM.

Eligible eyes were randomly assigned to krypton-laser photocoagulation or no treatment. Treatment required a fluorescein angiogram taken within 72 hours and retrobulbar anesthesia. Krypton-red laser was used to obliterate the area of hyperfluorescence and obtain uniform whitening of the overlying retina. Unlike the extrafoveal trials, treatment of blood or blocked fluorescence associated with neovascularization was not required. Treatment extended 100 μ beyond the edge of neovascularization except when closer than 100 μ to the fovea.

Treated patients were seen at 2, 4, and 6 weeks following treatment. Fluorescein angiography was obtained to assess the adequacy of treatment. Treated patients were encouraged to monitor their vision with an Amsler grid and report any new distortion or enlargement of scotoma. If persistence or recurrence of a treated membrane was found and met the initial treatment criteria, additional treatment was promptly applied.

Does Krypton Laser Photocoagulation Preserve Vision in Patients with Juxtafoveal Choroidal Neovascularization?

Age-Related Macular Degeneration Trial

The AMD trial comprised 496 eyes. There was a trend for laser photocoagulation to reduce the risk of SVL: 49% versus 58% at 3 years and 52% versus 61% at 5 years.[7,8] After 5 years, the median visual acuity was 20/200 in laser treated eyes and 20/250 in untreated eyes. The benefit of laser was greater in patients who were not hypertensive.[7] For these patients, 38% of the treated eyes lost six or more lines of visual acuity at 5 years compared with 70% of untreated eyes. For the hypertensive patients, there was no apparent benefit for treatment. The estimated rate of persistence or recurrence for treated eyes was 78% at 5 years.[8] The treatment benefit for these eyes might have been greater if subfoveal recurrences had been treated.

Eyes with only classic CNV benefitted more than the other subgroups in the study.[9] At 3 years, this subgroup showed severe visual loss in 48% of the treated eyes and 71% of the untreated eyes. When occult CNV was present, treatment of only the classic CNV was not beneficial. The study recommended treatment of juxtafoveal lesions with classic CNV but no occult CNV with laser photocoagulation.[9]

Ocular Histoplasmosis Trial

The OHS trial comprised 288 eyes. Laser photocoagulation significantly reduced the risk of SVL during the follow-up period: 5% versus 25% at 3 years and 12% versus 28% at 5 years.[8,10] After 5 years, the median visual acuity was 20/40 in the laser treated eyes and 20/64 in untreated eyes. The rate of persistence or recurrence for treated eyes was 33% at 5 years.[8]

Idiopathic Choroidal Neovascularization Trial

The ICNV trial comprised 49 eyes. Laser photocoagulation appeared to reduce the risk of SVL: 10% versus 37% at 3 years and 21% versus 34% at 5 years.[8,11] These results were not statistically significant because of the small sample size. After 5 years, the mean visual acuity was 20/50 in the laser-treated eyes and 20/80 in untreated eyes. The rate of persistence or recurrence for treated eyes was 22% at 5 years.[8]

How Was the Recurrent Subfoveal Choroidal NeovascularizationTrial for Age-Related Macular Degeneration Conducted?

This trial investigated the role of laser treatment for recurrent neovascularization extending under the fovea that developed adjacent to the scar caused by earlier laser treatment. To be eligible, patients were required to have angiographic evidence of subfoveal CNV with well-demarcated borders that were contiguous to the scar from earlier juxtafoveal or extrafoveal treatment. Lesions were eligible only if some portion of retina within one disc diameter (1.5 mm) of FAZ center remained untreated. The size of new and old treated areas could not exceed six standard MPS disc areas (one standard area: 1.77 mm^2). Eligible eyes were randomly assigned to laser photocoagulation or no treatment. Eyes in the treatment group were randomized to receive krypton-red or argon-green laser. Laser treatment covered the entire neovascular lesion and extended 100 μ beyond the edge of the lesion and 300 μ into the old treatment scar.

Treated patients were seen at 3 and 6 weeks following treatment and fluorescein angiography was obtained. Additional treatment was promptly applied when persistence or recurrence of a treated membrane was found and met the initial treatment criteria.

Does Laser Photocoagulation Preserve Vision in Patients with Recurrent Subfoveal Choroidal Neovascularization

The study comprised 206 eyes. Immediately following treatment, treated eyes lost more vision than untreated eyes.[12,13] At 3 months, the rates of SVL were 14% for the treated eyes and 9% for the untreated eyes. After the 3-month follow-up visit, treated eyes had relatively stable visual acuity, and the untreated eyes continued to lose visual acuity. The rates of SVL were 9% at 2 years and 12% at 3 years for the treated eyes, compared with 28% at 2 years and 34% at 3 years for the untreated eyes. The rate of persistence or recurrence for treated eyes was about 50% at 3 years.[14] There was no difference between the argon-green and krypton-red treated eyes.[15]

How Was the New Subfoveal Choroidal Neovascularization Trial for Age-Related Macular Degeneration Conducted?

This trial investigated the role of laser treatment for new neovascularization directly under the fovea. Patients with well-demarcated subfoveal CNV smaller than 3.5 standard MPS disc areas were randomized to laser photocoagulation or no treatment. Eyes in the treatment group were randomized to receive krypton-red or argon-green laser. Laser treatment covered the entire neovascular lesion and extended 100 μ beyond the edge of the lesion.

Treated patients were seen at 3 and 6 weeks following treatment and fluorescein angiography was obtained. If persistence or recurrence of a treated membrane was found and met the initial treatment criteria, additional treatment was promptly applied.

Does Laser Photocoagulation Preserve Vision in Patients with New Subfoveal Choroidal Neovascularization?

The study enrolled 373 eyes. Initially, treated eyes lost more visual acuity than the untreated eyes.[16,17] At 3 months, the rates of SVL were 20% for the treated eyes and 11% for the untreated eyes. By 1 year after study entry, however, treated eyes had lost less visual acuity than untreated eyes. This benefit persisted for at least 3 additional years.[13] The rates of SVL were 20% at 2 years and 22% at 4 years for the treated eyes compared with 37%% at 2 years and 47% at 4 years for the untreated eyes. The rate of persistence or recurrence for treated eyes was about 50% at 3 years.[14] No difference was found between the argon-green and krypton-red treated eyes.[15]

Patterns of Visual Acuity

When subgroups of patients with different combinations of initial visual acuity and lesion size were analyzed, four distinct patterns of visual acuity loss were identified and are rated by group[18] (Fig. 23–1).

Group A

Group A eyes were characterized by less loss of visual acuity in treated eyes than in untreated eyes at every follow-up examination. These eyes were excellent candidates for treatment.

Group B

Group B was characterized by more loss of visual acuity in treated eyes than untreated eyes at 3 months but less loss of visual acuity in treated eyes than untreated eyes at 12 months and thereafter. It was found that eyes treated 1 year after the initial treatment maintain a visual acuity benefit. Alternatively, these eyes may be followed up and treated when the vision starts to decrease or the lesion size starts to increase.

Group C

Group C was characterized by relatively low proportions of large decreases in visual acuity in both treated and untreated eyes and by slightly less loss of visual

	Small (≤ 1 MPS DA)	Medium (>1 to ≤2 MPS DA)	Large (>2 MPS DA)
≥20/100	Group B	Group B	Group D
20/125–20/160	Group A	Group B	Group D
≤20/200	Group A	Group A	Group C

FIGURE 23–1. Patterns of visual loss in eyes with new subfoveal neovascularization. MPS, Macular Photocoagulation Study; DA, disk area.

acuity in treated eyes during follow-up. These lesions are good candidates for treatment because the risk of further loss with treatment is low and there is a small treatment benefit.

GROUP D

Group D was characterized by substantially more visual acuity loss in treated eyes than in untreated eyes at 3 months through 18 months and little difference between the two groups thereafter. These lesions are poor candidates for treatment.

Is Photodynamic Therapy with Verteporfin Effective in Treatment of Subfoveal Choroidal Neovascularization in Age-Related Macular Degeneration?

The Treatment of AMD with Photodynamic Therapy (TAP) Study Group reported the 1- and 2-year results of two multicenter randomized clinical trials investigating the role of photodynamic therapy (PDT) in treatment of subfoveal CNV secondary to AMD. Eligible patients had subfoveal CNV caused by AMD measuring 5400 μ or less in greatest linear diameter with evidence of some classic CNV and best-corrected visual acuity of about 20/40 to 20/200. Six hundred nine patients were randomly assigned to PDT with Verteporfin or placebo.

Eyes treated with PDT were significantly more likely to lose fewer than 15 letters of visual acuity than untreated eyes: 61% versus 46% at 1 year and 53% versus 38% at 2 years. In subgroup analysis, the eyes with 50% or more classic CNV had a significant treatment benefit, but those with greater than 0% and less than 50% had no benefit from treatment.[19,20]

What Are the Recommendations for Treatment of Choroidal Neovascularization?

Eyes with extrafoveal and juxtafoveal CNV secondary to OHS or idiopathic causes are treated with laser photocoagulation according to the MPS guidelines. Subfoveal CNV secondary to OHS or idiopathic causes is not treated with laser photocoagulation. The Submacular Surgery Trial is investigating the role of surgical removal of CNV for these lesions. Some physicians may consider treating these lesions with PDT.

Eyes with extrafoveal or juxtafoveal CNV secondary to AMD that are 100% classic are treated with laser photocoagulation according to MPS guidelines. Generally, lesions containing nearly 100% occult CNV are not considered for PDT based on the verteporfin in PDT (VIP) Study.[20a] For subfoveal CNV secondary to AMD, there may be more than one treatment option. Laser photocoagulation may be used to treat well-defined subfoveal CNV with smaller size and poorer visual acuity according to MPS guidelines, but many consider PDT may be used to treat subfoveal CNV with more than 50% classic component according to the TAP study guidelines.

Branch Retinal Vein Occlusion Study

Why Was the Branch Retinal Vein Occlusion Study Conducted?

The Branch Retinal Vein Occlusion Study (BRVOS) was a multicenter, randomized clinical trial designed to investigate efficacy of (1) scatter-laser photocoagulation in the management of neovascularization and vitreous hemorrhage and (2) focal laser for the treatment of macular edema in patients with branch retinal vein occlusions (BRVO).

How Was the Trial of Focal Laser for Treatment of Macular Edema Conducted?

To be eligible, patients must have had a BRVO 3 to 18 months earlier, macular edema reducing visual acuity to 20/40 or worse, sufficient clearing of intraretinal hemorrhage to permit evaluation of fluorescein angiography and safe laser photocoagulation, and absence

of hemorrhage directly in the fovea. Eligible patients were randomized to focal laser photocoagulation or observation.

Treatment consisted of argon-laser photocoagulation applied in a grid pattern over the area of capillary leakage in the macular region identified by fluorescein angiography. Photocoagulation was not extended closer to the fovea than the edge of the foveal avascular zone (FAZ) and not peripheral to the major vascular arcades.

Patients were evaluated at the time of entry into the study and every 4 months thereafter. Additional photocoagulation was applied at each 4-month visit if untreated leaking areas and foveal edema persisted with continued loss of visual acuity. The primary outcome measure for this part of the study was a gain of two or more lines of visual acuity at two or more consecutive 4-month follow-up visits.

Can Photocoagulation Improve Visual Acuity in Eyes with Macular Edema Reducing Vision to 20/40 or Worse?

Between July 1977 and February 1984, 139 eligible eyes from 139 patients were recruited: 71 randomized to laser and 68 to observation. The average duration of follow-up was 3.1 years.

Treated eyes with macular edema were more likely to gain two or more lines of visual acuity than control eyes.[21] At 3 years, 65% of treated eyes gained two or more lines of visual acuity compared with 37% of control eyes. Treated eyes were more likely to have visual acuity of 20/40 or better (60% versus 34%), and less likely to have visual acuity of 20/200 or worse (12% versus 23%). The average visual acuity was 20/40 to 20/50 in the treated group and 20/70 in the control group. Treatment was beneficial for all eyes regardless of the duration of occlusion.[21]

How Were the Trials of Laser Photocoagulation for Prevention of Neovascularization and Vitreous Hemorrhage Conducted?

Eyes at risk for development of neovascularization were enrolled in group I and those at risk for vitreous hemorrhage were enrolled in group II. To be eligible, patients must have had a BRVO 3 to 18 months earlier with at least five disc areas of retinal involvement and sufficient clearing of intraretinal hemorrhage to permit safe laser photocoagulation. In addition, group I eyes were required to have no neovascularization, and group II eyes were required to have disc or peripheral neovascularization. Eligible eyes in each group were randomized to scatter laser photocoagulation or to observation.

Treatment consisted of argon laser to the involved segment to achieve "medium" white burns (200 to 500 μ in diameter) spaced one burn width apart, extending no closer than two disc diameters from the center of the fovea.

Patients were evaluated at the time of entry into the study and every 4 months thereafter. The outcome measure for group I was neovascularization, defined as any amount of surface or preretinal new vessel formation. The outcome measure for group II was vitreous hemorrhage, defined as any amount of preretinal or vitreous hemorrhage.

Can Photocoagulation Prevent the Development of Neovascularization and Vitreous Hemorrhage?

From July 1977 to February 1985, 319 eligible eyes from 316 patients were recruited to group I; 160 eyes were randomized to laser and 159 eyes to observation. The average duration of follow-up was 3.7 years. Treated eyes were less likely to develop neovascularization than the control eyes.[22] Retinal neovascularization developed in 19 (12%) of the treated eyes compared with 35 (22%) control eyes. The probability of neovascularization was greater in eyes with nonperfusion on fluorescein angiography. All eyes that developed neovascularization had at least five disc diameters of capillary nonperfusion on initial or follow-up fluorescein angiography.

Eighty-two eligible eyes from 82 patients were recruited to group II from July 1977 to February 1985. Forty-one eyes were randomized to laser and 41 eyes to observation. The average duration of follow-up was 2.8 years. Treated eyes were significantly less likely to develop vitreous hemorrhage.[22] Vitreous hemorrhage developed in 29% of the treated eyes opposed to 61% of the control eyes.

These results suggested similar rates of vitreous hemorrhage whether laser treatment is applied before or after development of neovascularization. Application of laser after development of neovascularization would obviate unnecessary treatment to many eyes that never would develop these complications.

What Were the Recommendations of the Branch Retinal Vein Occlusion Study for Management?

For patients who have a decreased visual acuity of 20/40 or worse following a BRVO, the study recommended waiting for sufficient clearing of retinal hemorrhages to obtain high-quality fluorescein angiography. If macular nonperfusion is the cause of visual loss, no treatment is offered. If macular edema is the cause of visual loss, and vision continues to be 20/40 or worse without spontaneous improvement, grid macular photocoagulation is recommended.

For patients who have a BRVO with retinal involvement larger than five disc diameters, the study recom-

mended waiting for sufficient clearing of retinal hemorrhage for high-quality fluorescein angiography. If more than five disc diameters of nonperfusion are present, patients should be followed at 4-month intervals for development of neovascularization. If neovascularization develops and is confirmed, scatter-laser photocoagulation treatment is recommended in the involved quadrant. General guidelines for management of patients with BRVO are outlined in Figure 23–2.

Central Retinal Vein Occlusion Study

Why Was the Central Retinal Vein Occlusion Study Conducted?

The Central Retinal Vein Occlusion Study (CRVOS) was a multicenter, randomized clinical trial designed to evaluate (1) the timing of panretinal photocoagulation (PRP) for ischemic central vein occlusion; (2) the role of macular grid-pattern photocoagulation for macular edema with reduced visual acuity resulting from CRVO; (3) the natural history of eyes with CRVO. This study was not designed to evaluate the efficacy of PRP in the treatment of anterior segment neovascularization, that is, neovascularization of the iris or angle (NVI/NVA), in patients with CRVO.

How Was the Trial of Panretinal Photocoagulation for Ischemic Central Retinal Vein Occlusion Study Conducted?

To be eligible, patients must have had CRVO of less than 1 year in duration with at least 10 disc areas of retinal nonperfusion. Visual acuity of light perception or better and intraocular pressure lower than 30 mm Hg were required. Eligible eyes were randomized to either immediate PRP or laser only if NVI/NVA developed. Prophylactically treated eyes received additional PRP if NVI/NVA developed.

Treatment consisted of 1000 to 2000 evenly spaced laser spots applied to achieve moderately intense white burns (500 to 1000 μ in diameter) spaced 0.5 to 1 burn apart, avoiding retinal hemorrhage or retinal vessels. Treatment was applied no closer than two disc diameters from the center of the fovea and no closer than 500 μ nasal to the disc.

Patients were evaluated at the time of entry in the study and monthly for the first 6 months after entry. After the first 6 months, patients were seen at 2 months and every 4 months thereafter. At each visit, undilated slit-lamp examination and gonioscopy were performed to examine for anterior segment neovascularization. The primary outcome of the study was anterior segment neovascularization defined as two clock hours of NVI or any NVA.

Should Panretinal Photocoagulation for Ischemic Central Retinal Vein Occlusion Be Performed at Diagnosis or Only When Anterior Segment Neovascularization Develops?

From August 1988 to August 1992, 181 eligible eyes from 180 patients were recruited. Ninety eyes were randomized to prophylactic PRP and 91 eyes to PRP when anterior neovascularization developed. The follow-up period was 3 years, except for patients recruited after February 28, 1991, who were followed up until February 28, 1994.

After adjusting for baseline variables, there was a trend for decreased risk of anterior segment neovascularization in the early treated group that was not statistically significant.[22] Anterior segment neovascularization developed in 18 (20%) of 90 eyes treated prophylactically and in 32 (35%) of 91 untreated eyes.

Regression of anterior segment neovascularization within 1 month was more than four times as likely in response to treatment in previously untreated eyes than in response to retreatment in prophylactically treated eyes.[22] Four (22%) of 18 eyes in the early treatment group showed prompt regression within 1 month, compared with 18 (56%) of 32 eyes in the group that did not receive early treatment. Long-term regression of neovascularization occurred in about 90% of eyes in both groups. Only four eyes in each group had neovascular glaucoma with persistent anterior segment neovascularization.

The most important risk factor for both occurrence and persistence of anterior segment neovascularization was the amount of nonperfused retina measured at study entry.[22] The risk of anterior segment neovascularization ranged from 16% in eyes with 10 to 29 disc areas of nonperfusion to 52% for eyes with 75 or more areas of nonperfusion at baseline.

In all but two patients, anterior segment neovascularization occurred in the first year of follow-up, usually within the first 3 months. In most eyes, NVI was present at the time anterior segment neovascularization was discovered. NVA without NVI was present in three patients.

How Was the Trial of Grid-Pattern Laser Photocoagulation for the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion Conducted?

To be eligible, patients must have had CRVO of at least 3 months in duration with visual acuity between 20/50 and 5/200 as a result of macular edema without capillary nonperfusion involving the fovea and documented by fluorescein angiography. Eligible eyes were randomized to either grid-pattern laser treatment or to observation.

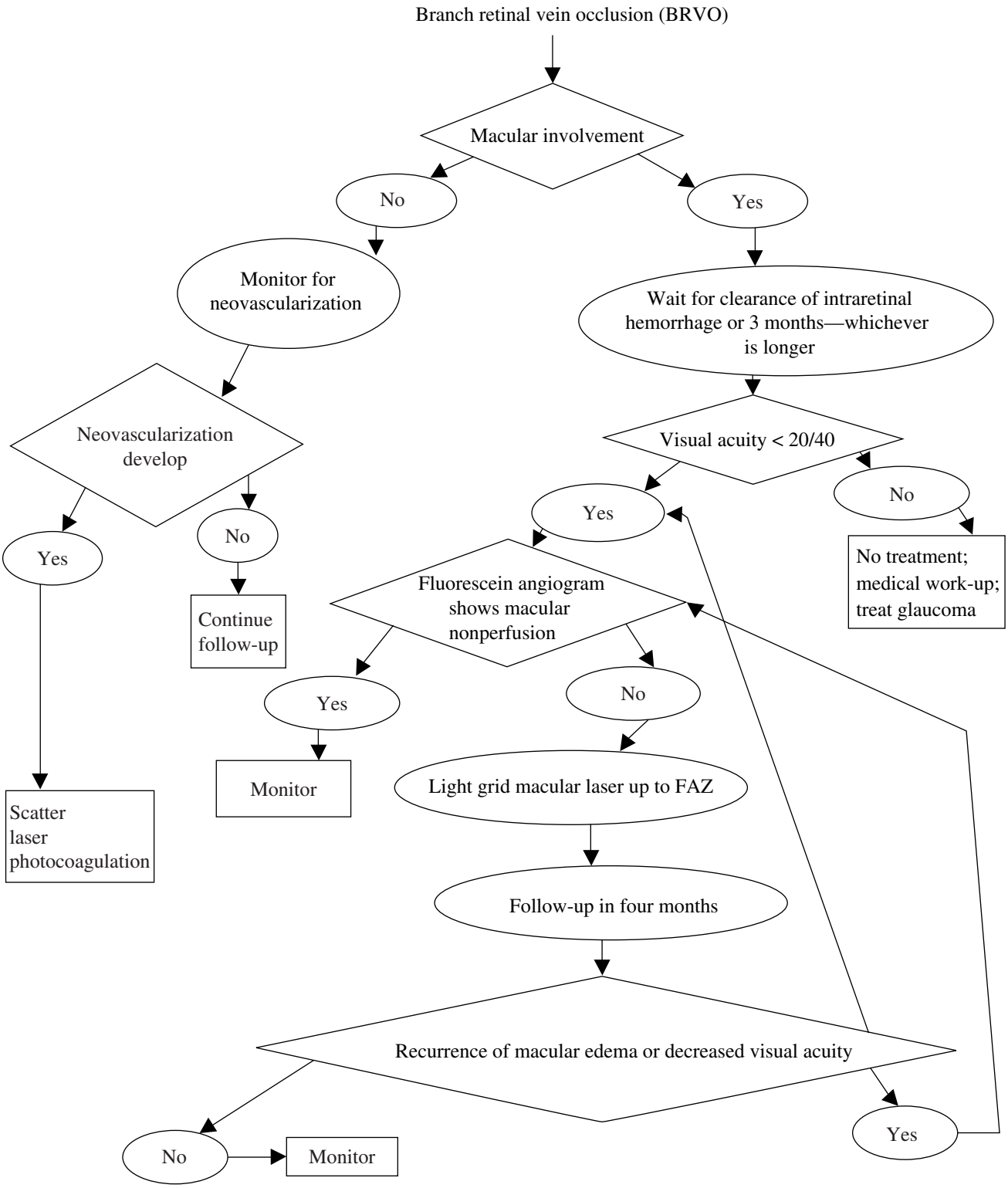

FIGURE 23–2. Clinical pathway: Management of the patient with branch retinal vein occlusion. FAZ, foveal avascular zone.

Treatment consisted of argon-green laser, with spot size 100 μ, applied in a grid-pattern spaced 0.5 to 1 burn width apart to the areas of leaking capillaries outside of the foveal avascular zone and within two disc diameters of the center of fovea. Patients were evaluated at the time of entry in the study and every 4 months for 3 years or until the end of the study. Treatment was repeated in eyes with persistent macular edema without capillary nonperfusion and improvement in visual acuity of nine letters or less.

What Is the Role of Grid-Pattern Laser Photocoagulation in the Treatment of Macular Edema Secondary to Central Retinal Vein Occlusion?

From August 1988 to August 1992, 155 eyes of 155 eligible patients were recruited; 75 were randomized to grid-pattern laser treatment and 78 to observation. The follow-up period was 3 years, except for patients recruited after February 28, 1991, who were followed up until February 28, 1994.

Although treatment significantly reduced the amount of macular edema present on fluorescein angiography, there was no significant difference between treated and untreated patients in level or change in visual acuity.[23] The mean visual acuity score at baseline was 42 letters for the treated eyes and 44 letters for untreated eyes. The mean visual acuity score at 36 months was 39 letters for treated eyes and 43 letters for the untreated eyes. The mean change in visual acuity score, from baseline to the 36-month visit, was a loss of four letters in treated eyes and a loss of three letters in untreated eyes. The visual acuity improved by two or more lines in 17 (23%) of the treated eyes. Eleven of these 17 eyes came from patients younger than 60 years. There was a trend for treatment to be more beneficial in patients younger than 60 years of age, but this finding was not statistically significant when adjusted for potential interactions.

Treatment significantly reduced the amount of macular edema measured on fluorescein angiography.[23] At the 12-month annual visit, no measurable macular edema was present in 21 (31%) of 68 treated eyes, whereas all of the 72 untreated eyes showed some macular edema ($p < 0.0001$).

What Is the Natural History of Eyes with Central Retinal Vein Occlusion?

To determine their natural history, 547 perfused eyes (defined as fewer than 10 disc areas of nonperfusion on fluorescein angiography) were monitored to determine their natural history. About one third of these eyes (185 of 547, or 34%) developed ischemia (defined as greater than 10 disc areas of nonperfusion) at 3 years.[24] Conversion to ischemia was most rapid in the first 4 months after enrollment[25]; 81 (15%) progressed to nonperfusion by the 4-month visit.

Most eyes with sufficient intraretinal hemorrhage to prevent determination of perfusion status were determined to be ischemic.[25] At the 4-month visit, 38 (83%) of 46 such eyes demonstrated at least 10 disc areas of nonperfusion (28 eyes) or developed NVI/NVA before the retinal status could be determined (10 eyes).

In the CRVOS population of 714 eyes, NVI/NVA developed in 117 eyes (16%) during the course of the follow-up. In 10 eyes, new vessels failed to regress in response to photocoagulation. For eyes initially categorized as nonperfused or indeterminate, NVI/NVA developed in 35% (61/176), whereas 10% (56/538) of eyes initially categorized as perfused developed NVI/NVA. The risk of NVI/NVA increased in relation to the number of disc areas of nonperfusion and initial visual acuity.

In patients with recent (less than 1 month) onset of vein occlusion, visual acuity of less than 20/200 alone contained virtually all the predictive information. The eyes with better initial visual acuity had a greater chance of having better final visual acuity. Visual acuity worse than 20/200 was highly correlated with the presence and development of ischemia.

The annual risk of any vascular occlusion in an unaffected fellow eye was about 0.9% per year.

What Were the Recommendations for the Clinical Care of Patients with Central Retinal Vein Occlusion?

At the initial examination, it is important to perform undilated slit-lamp examination and gonioscopy to evaluate for NVI/NVA. If NVI/NVA is present at the initial examination, PRP should be considered. Intraocular pressure should be measured because of the reported association of CRVO and glaucoma. Patients are recommended to be under general medical care, with yearly measurement of blood pressure. Color photography and fluorescein angiography are not essential but might be useful in providing a good baseline and identifying the perfusion status. In patients with bilateral simultaneous CRVOs, the possibility of hyperviscosity should be considered. Patients with unilateral CRVO are notified that the risk of a vascular occlusion in the fellow eye is about 1% per year.

Visual acuity is the most important factor in determining a prognosis and follow-up plan. If the patient's initial visual acuity is 20/40 or better, there is a good likelihood of retaining good acuity. If the visual acuity is 20/50 to 20/200, the visual acuity is variable; the visual acuity may improve (19%), remain unchanged (44%), or deteriorate (37%). If the initial visual acuity is worse than 20/200, prognosis for vision is poor (80% remain at that level or worse). Visual acuity is more important than the initial fluorescein

angiogram in determining prognosis and clinical management of the patient, because more than one third of initially perfused eyes develop nonperfusion and NVI/NVA. If the visual acuity is 20/40 or better, the patient is seen every 1 to 2 months for 6 months, tapering the interval to annual follow-ups as the patient's condition stabilizes. Patients with visual acuity of less than 20/200 are seen every month for the initial 6 months. Patients with visual acuity of 20/50 to 20/200 are seen either monthly or bimonthly, depending on the level of visual acuity and the progression or improvement of the CRVO. If the visual acuity drops to less than 20/200, it is likely that nonperfusion has developed and the patient should be followed monthly for 6 months.

Treatment with PRP is instituted only at the first sign of neovascularization. After PRP, the patient is monitored closely every 2 to 4 weeks to ensure that the NVI is not advancing. If NVI recurs, photocoagulation should be added in untreated areas of the retina.

Focal laser photocoagulation is not recommended for patients with decreased visual acuity secondary to macular edema. Some investigators consider this treatment in patients younger than 65 years. General guidelines for management of patients with CRVOs are outlined in Figure 23–3.

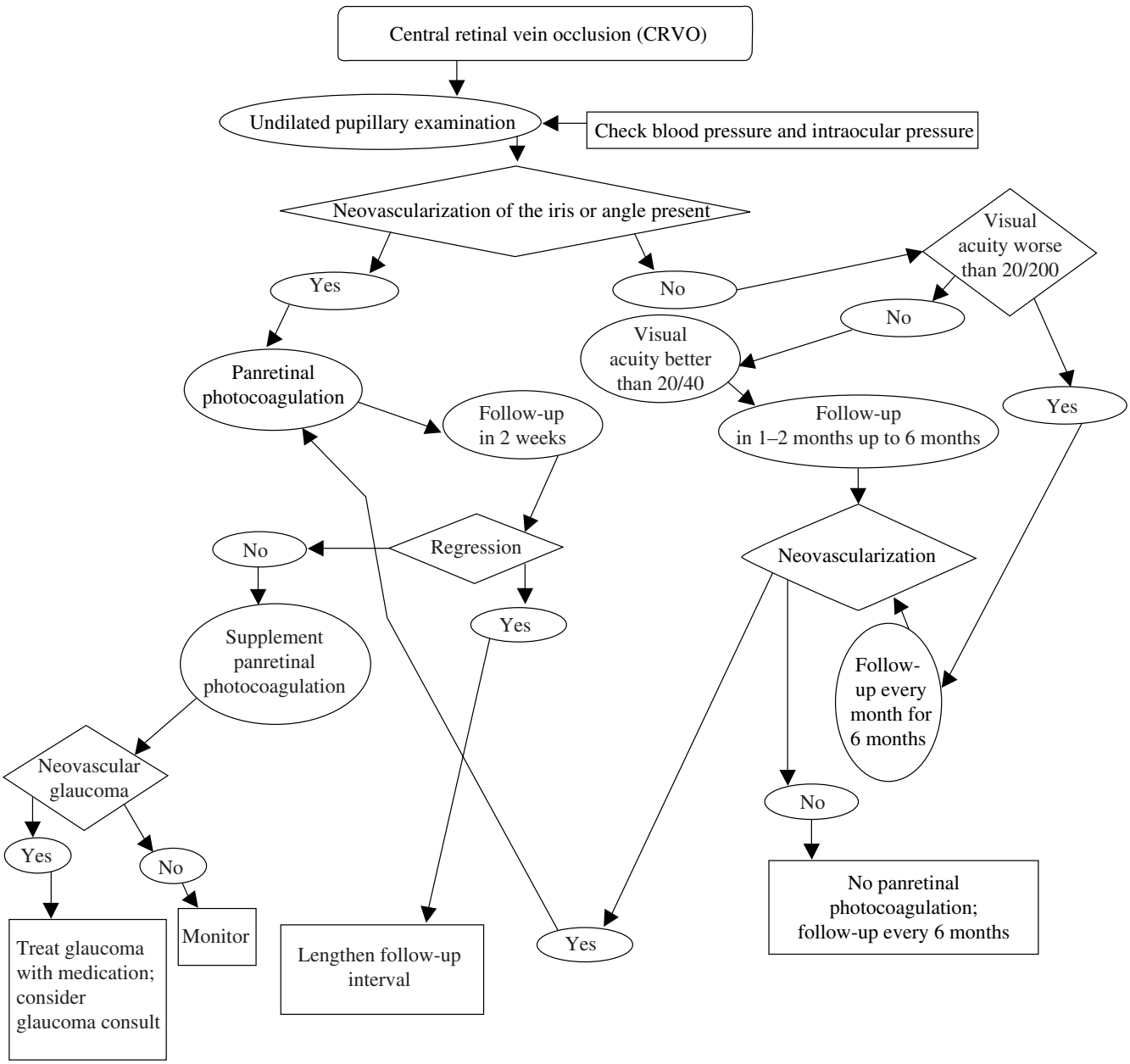

FIGURE 23–3. Clinical pathway: Management of the patient with central retinal vein occlusion.

Diabetic Retinopathy Study

Why Was the Diabetic Retinopathy Study Conducted?

The Diabetic Retinopathy Study (DRS), a randomized, controlled clinical trial was designed to determine whether photocoagulation benefits vision in patients with proliferative diabetic retinopathy (PDR).

How Was the Diabetic Retinopathy Study Conducted?

To be eligible for this study, patients were required to have diabetic retinopathy in both eyes, either proliferative changes in at least one eye or severe nonproliferative changes in both eyes. Severe nonproliferative retinopathy was defined as presence of at least three of the following: cotton-wool spots, venous beading, intraretinal microvascular abnormalities (IRMA), and extensive retinal hemorrhages. Visual acuity of 20/100 or better in both eyes was required. One eye of each patient was randomized to PRP and the other eye to observation. One of two treatment modalities, xenon arc or argon laser, also was chosen randomly. Both treatment techniques included extensive scatter photocoagulation and focal treatment of new vessels on the surface of retina. Focal treatment of new vessels on the disc was required in argon-treated eyes.

Patients were evaluated at the time of entry in the study and every 4 months thereafter. The primary outcome measure for the DRS was occurrence of severe visual loss defined as visual acuity of less than 5/200 at two or more consecutive 4-month follow-up visits.

Does Panretinal Photocoagulation Preserve Vision in Patients with Proliferative Diabetic Retinopathy?

From 1971 to September 1975, 1,758 eligible patients entered the study. Laser photocoagulation significantly reduced the cumulative risk of severe visual loss by 50% or more[26,27] (Fig. 23–4). After 2 years, SVL had occurred in 15.9% of all untreated eyes and 6.4% of all treated eyes, including 7.1% in the argon treated group and 5.8% for the xenon treated group. After 3 years, the rates were 26.4% in untreated eyes and 10.5% in treated eyes.[27]

The risk of developing neovascularization in eyes with nonproliferative diabetic retinopathy (NPDR) was significantly decreased with treatment.[27] At 1 year, 50.2% of all untreated eyes without new vessels at baseline remained free of new vessels, compared with 78.8% of all treated eyes. Neovascularization of the disc (NVD) had developed in 24.2% of all untreated eyes, compared with 7.5% of all untreated eyes. Treatment also resulted in more regression of neovascularization.[27] At 1 year, 61.8% of eyes with moderate or severe NVD randomized to treatment showed some degree of regression of neovascularization, compared with 26.7% of control eyes.

Side effects of treatment included decreased visual acuity and peripheral visual field loss.[27,28] Six weeks after treatment, 22.8% of xenon-treated eyes, 9.8% of argon-treated eyes, and 5.6% of all untreated eyes lost two to four lines of visual acuity. With longer follow-up, the treated eyes had a more favorable visual acuity outcome than untreated eyes because of an increased rate of visual loss in the untreated eyes. The argon-treated eyes had only small visual-field losses, but in xenon-treated eyes, the reduction in visual field was substantial. In patients with severe fibrovascular proliferation and retinal elevation, xenon-arc treatment was associated with a higher risk of significant visual loss and extension of areas of retinal detachment. Argon laser treatment demonstrated no significant adverse effects.

What Were the Risk Factors for Severe Vision Loss in the Diabetic Retinopathy Study?

Four risk factors were found to increase the 2-year risk of developing SVL: (1) the presence of vitreous or preretinal hemorrhage; (2) the presence of NVD; (3) the

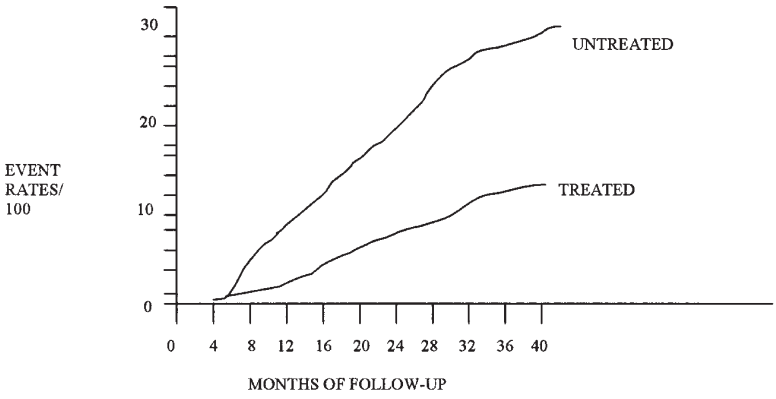

FIGURE 23–4. Cumulative event rates of visual acuity less than 5/200 at two or more visits for all patients. (Reproduced with permission from Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings. *Ophthalmology*. 1978;85:82–106.)

severity of NVD (greater than shown in standard photograph 10A with at least one fourth to one third of the optic disc covered by neovascularization); (4) in the absence of NVD, neovascularization elsewhere in the retina (NVE) greater than one-half disc area.[27,29]

The presence of three of these high-risk characteristics carried a substantial risk for development of SVL. As the number of risk factors increased from two to three, the 2-year risk of SVL jumped from 8.5 to 26.7%. To simplify the detection of high-risk characteristics, they may also be defined as one of the following: (1) any NVD with vitreous hemorrhage; (2) moderate to severe NVD (equal to more than one-fourth to one-third disc area) with or without vitreous hemorrhage; and (3) moderate (one-half disc area) NVE with vitreous hemorrhage.

What Were the Recommendations of the Diabetic Retinopathy Study for the Treatment of Patients with Diabetic Retinopathy?

The DRS recommended treatment of eyes with high-risk PDR with PRP.[30–32] The results of the DRS demonstrated that PRP treatment reduces the occurrence of severe visual loss and the rate of retinopathy progression. The study defined the high-risk characteristics for development of SVL. The beneficial effects of photocoagulation clearly outweighed the adverse effects in patients with high-risk characteristics.

In eyes without high-risk characteristics, the adverse effects of photocoagulation are more important. Delaying treatment defers these risks or avoids them entirely in eyes that do not progress. For eyes with less than high-risk PDR, the DRS did not provide a clear choice between prompt treatment and observation followed by treatment when high-risk characteristics occur. Therefore, the DRS investigators recommended a randomized prospective study to investigate these treatment options.

Early Treatment Diabetic Retinopathy Study

Why Was the Early Treatment Diabetic Retinopathy Study Conducted?

The Early Treatment Diabetic Retinopathy Study (ETDRS), a randomized, controlled clinical trial, was designed to investigate (1) the optimal timing of PRP in the course of diabetic retinopathy; (2) the role of focal laser photocoagulation in the treatment of diabetic macular edema; and (3) the role of aspirin in the course of diabetic retinopathy. From April 1980 to July 1985, the ETDRS enrolled 3,711 eligible patients.

TABLE 23–1. Definitions of Stages of Diabetic Retinopathy

Mild nonproliferative diabetic retinopathy (mild NPDR)
A least one microaneurysm, but not as severe as "moderate" NPDR
Moderate nonproliferative diabetic retinopathy (moderate NPDR)
Extensive intraretinal hemorrhages or microaneurysms or cotton-wool spots, venous beading, or intraretinal microvascular abnormalities (IRMA) definitely present but not so severe as "severe" NPDR
Severe nonproliferative diabetic retinopathy (severe NPDR)
Cotton-wool spots, venous beading, and IRMA, all present in at least two quadrants; or two of them present in at least two quadrants with intraretinal hemorrhages and microaneurysms present in all quadrants.
Early proliferative diabetic retinopathy (early PDR)
PDR without DRS high risk characteristics
High-risk proliferative diabetic retinopathy (high-risk PDR)
PDR with DRS high risk characteristics

How Was the Trial of Panretinal Photocoagulation for Eyes with Less than High-Risk Characteristics Conducted?

Eligible eyes had mild, moderate, or severe NPDR or early PDR[33,34] (Table 23–1). Patients with high-risk PDR were not eligible for the study because the DRS had already recommended immediate PRP. One eye of each patient was randomized to early mild or full-scatter PRP, and the other eye was assigned to deferral of photocoagulation until high-risk characteristics developed.

Scatter photocoagulation was performed using argon laser. Mild and full-scatter PRP consisted of 400 to 650 and 1200 to 1600 spots of moderately intense white burns, respectively. For eyes assigned to deferral, full-scatter photocoagulation was applied as soon as high-risk PDR was detected. For eyes assigned to early scatter photocoagulation, additional scatter treatment was performed if high-risk characteristics developed during the follow-up.

The primary outcome measure for this part of the study was the occurrence of SVL, defined as visual acuity of less than 5/200 at two or more consecutive 4-month follow-up visits. Other outcomes included rate of progression to high-risk PDR, vitrectomy, and complication rates.

When in the Course of Diabetic Retinopathy Is It Most Effective to Initiate Photocoagulation Therapy?

The risk of SVL was low for both the early treated eyes and the eyes assigned to deferral of photocoagula-

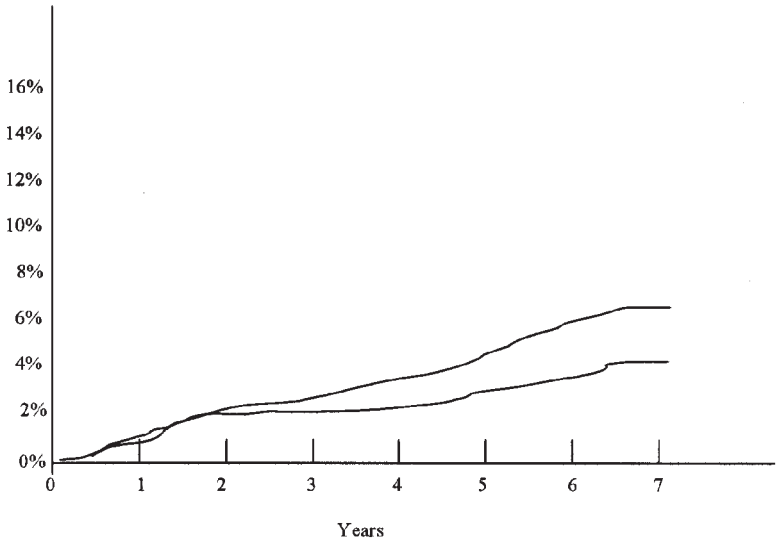

FIGURE 23–5. Cumulative rates of the development of severe visual loss for all eyes assigned to immediate photocoagulation (aqua) or deferral of photocoagulation (black). *(Reproduced with permission from Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy: ETDRS report number 9.* Ophthalmology. *1991;98:766–785.)*

tion.[35] The 5-year rates of SVL were 3.7% for eyes assigned to deferral of photocoagulation, 2.7% for eyes assigned to early mild scatter, and 2.4% for eyes assigned to early full-scatter photocoagulation. The cumulative rates of the development of SVL for all early treatment eyes and the eyes assigned to deferral of photocoagulation are shown in Figure 23–5. Although there was a small reduction in the incidence of SVL for the early treated eyes, this difference was not statistically significant.

The rates of vitrectomy were also low for both groups.[35] The 5-year rates of vitrectomy were 3.9% and 2.2% for deferral and early photocoagulation, respectively.

Early scatter photocoagulation in eyes with NPDR and early PDR reduced the risk of progression to high-risk PDR by about 25% in the mild scatter group and about 50% in the full-scatter group, compared with deferral of photocoagulation.[35]

Side effects of early scatter photocoagulation included significant visual field loss and moderate visual loss (MVL) at 6 weeks. These occurred more frequently in the early treated eyes, particularly in those treated with full scatter photocoagulation.[35]

How Was the Trial of Focal Photocoagulation for the Treatment of Diabetic Macular Edema Conducted?

To assess the role of photocoagulation for treatment of diabetic macular edema, one eye of each patient with macular edema was randomized to focal laser treatment and the other eye was assigned to deferral of photocoagulation. Macular edema was defined as retinal thickening at or within one disc diameter of the center of the macula or definite hard exudates in this region. Macular edema was defined as clinically significant (CSME) if any of the characteristics listed in Table 23–2 were present.

The initial treatment of macular edema consisted of focal argon-laser photocoagulation of all leaking microaneurysms and grid-pattern treatment of areas of diffuse leakage or nonperfusion within 500 to 3000 μ from the center of the macula (Fig. 23–6). A pretreatment fluorescein angiogram was used to identify treatable lesions. At the 4-month follow-up, retreatment of persistent CSME was considered. In addition, treatment of lesions from 300 to 500 μ from the center of fovea was recommended if the vision was less than 20/40 and retina edema and leakage persisted.

The primary outcome measure for this part of the study was occurrence of MVL, defined as a doubling of visual angle or visual acuity loss of 15 or more letters on the ETDRS eye chart (equivalent to three lines) between the baseline and follow-up visit.

Is Focal Laser Photocoagulation Effective in the Treatment of Diabetic Macular Edema?

Focal laser photocoagulation was effective in reducing the rate of MVL at all levels of retinopathy.[36–40] In

TABLE 23–2. Definition of Clinically Significant Macular Edema (CSME)

CSME is defined as one or more of the or more of the following:
1. Retinal thickening at or within 500 mm of the center of the macula
2. Hard exudates at or within 500 mm of the center of the macula associated with adjacent retinal thickening
3. A zone or zones of retinal thickening one disc area in size, at least part of which is within one disc diameter of the center of the fovea

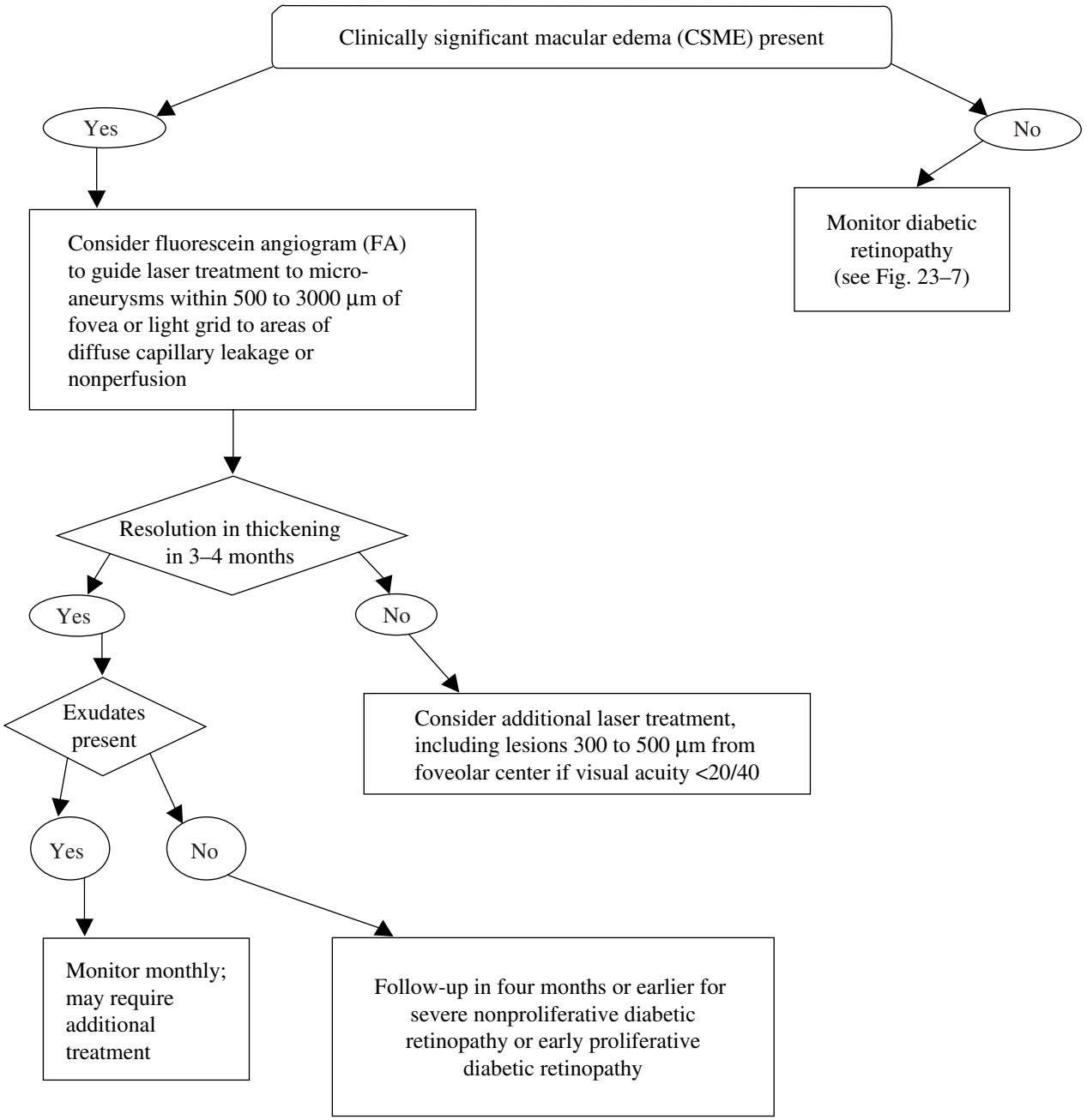

FIGURE 23–6. Clinical pathway: Clinically significant macular edema.

eyes with mild to moderate NPDR and CSME, laser reduced the rate of occurrence of MVL significantly: 5% versus 8% at 1 year, 7% versus 16% at 2 years, and 12% versus 24% at 3 years.[36] When only eyes with CSME were considered, the beneficial effect of treatment was more pronounced: 1% versus 8% at 1 year, 6% versus 16% at 2 years, and 13% versus 33% at 3 years. There was no benefit in treating eyes with diabetic macular edema before the development of CSME. The treatment benefit for eyes with CSME was observed regardless of the level of baseline visual acuity. The best strategy for eyes that also received scatter photocoagulation was immediate focal laser with delayed scatter when more severe retinopathy developed.

The benefit of laser photocoagulation for treatment of CSME was also observed in eyes with severe nonproliferative and mild proliferative retinopathy.[36] The best strategy for eyes that also received scatter photocoagulation was immediate focal laser combined with immediate mild scatter; however, immediate focal with delayed scatter was not evaluated in these eyes.

Is Aspirin Effective in Altering the Course of Diabetic Retinopathy?

To assess the effect of aspirin, patients meeting eligibility requirements in both eyes were assigned randomly to aspirin 650 mg per day or matching placebo. Aspirin had no effect on the progression of diabetic retinopathy or the occurrence and severity of vitreous/preretinal hemorrhages.[41,42]

What Are the Treatment Guidelines for Diabetic Retinopathy Based on the Results of the Early Treatment Diabetic Retinopathy Study?

For most eyes with less than high-risk PDR, the ETDRS recommended deferral of treatment until high-risk characteristics develop. For such eyes, the side effects of scatter photocoagulation must be balanced with the possible small benefit of early photocoagulation in reducing the risk of SVL. In eyes with severe nonproliferative or early proliferative retinopathy, prophylactic PRP may be performed if reliable follow-up is not possible or rapid progression of retinopathy is expected.

The ETDRS recommended focal laser treatment only for eyes that meet the criteria for CSME (Table 23–2). CSME is diagnosed with magnified stereo examination of the macula to detect retinal thickening. Focal laser photocoagulation is performed based on the ETDRS treatment guidelines. If the vision is normal or the center of macula is not thickened, an initial period of close observation (such as every 2 or 3 months) may be preferable to immediate treatment. Patients should be monitored 4 months after treatment, and if persistent CSME and treatable lesions are present, retreatment is recommended.

If both high-risk characteristics and CSME are present, focal laser is performed first to minimize exacerbation of macular edema. If the retinopathy is very aggressive, however, both treatments should be performed simultaneously.

The ETDRS concluded that aspirin had no effect in the course of diabetic retinopathy, and there are no ocular contraindications to aspirin when required for cardiovascular disease or other medical indications. General guidelines for management of patients with diabetic retinopathy are outlined in Figure 23–7.

Diabetic Retinopathy Vitrectomy Study

Why Was the Diabetic Retinopathy Vitrectomy Study Conducted?

The Diabetic Retinopathy Vitrectomy Study (DRVS) was a multicenter, randomized clinical trial designed to evaluate the risks and benefits of performing early pars plana vitrectomy in eyes with severe PDR and vitreous hemorrhage. When the DRVS was designed, vitrectomy was usually reserved for eyes with severe vitreous hemorrhage of at least 1 year's duration or for eyes with traction retinal detachment involving the center of the macula.

The DRVS comprised three studies: a natural history study and two randomized clinical trials. The natural history study defined a subgroup of patients with severe PDR in which prognosis with conventional management was poor enough to justify a randomized trial of vitrectomy in eyes retaining useful vision.[43] This trial aimed to determine whether the visual prognosis might be improved by removal of severe fibrovascular proliferations before their contraction led to distortion or detachment of the macula. The second randomized clinical trial was a trial of early vitrectomy in eyes with severe vitreous hemorrhage.

How Was the Trial of Early Vitrectomy for Severe Proliferative Diabetic Retinopathy Conducted?

To be eligible for this trial, patients were required to have extensive, active neovascular, or fibrovascular proliferation and best corrected visual acuity of 10/200 or better. Patients with this level of neovascular or fibrovascular proliferation were found to have poor visual outcome with conventional management by the DRVS natural history study, which justified enrollment in this trial. Eligible eyes were randomized to early vitrectomy or conventional management. The conventional management group received vitrectomy if they developed a macular detachment with poor visual acuity or severe vitreous hemorrhage of at least 6 months' duration. The goals of vitrectomy were removal of vitreous opacities, excluding those in the peripheral vitreous anterior to the equator, and division and removal of all preretinal membranes. Follow-up visits were scheduled 3, 6, 12, 18, 24, 36, and 48 months after randomization. Between July 1979 and May 1983, 381 eyes of 345 eligible patients entered the study.

Is Vitrectomy Beneficial for Eyes with Severe Fibrovascular Proliferation and Good Visual Acuity?

The eyes that underwent early vitrectomy had a clear advantage in achieving good vision, defined as visual acuity of 10/20 or better.[44,45] More eyes in this group had a visual acuity of 10/20 or better at every follow-up visit after the 3-month visit: 41% versus 31% at 2 years, 47% versus 25% at 3 years, and 44% versus 28% at 4 years.

Early vitrectomy did not affect the proportion of eyes with poor outcome.[44] The percentage of eyes

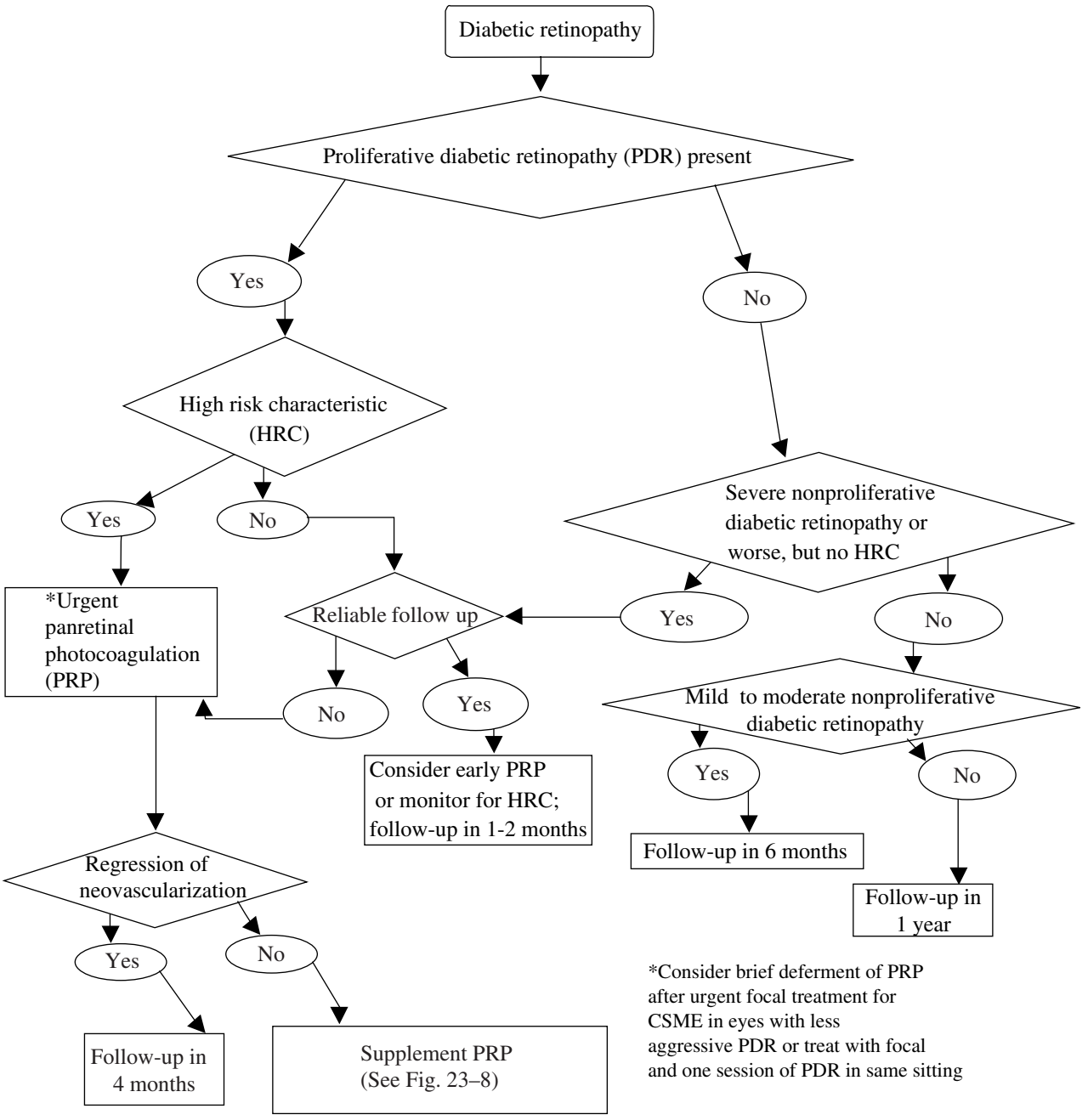

FIGURE 23–7. Clinical pathway: Laser photocoagulation in the management of clinically significant macular edema (CSME) and neovascularization secondary to diabetic retinopathy.

with visual acuity of 5/200 or less was not significantly different at any of the follow-up visits. Although the eyes in the early vitrectomy group had a higher percentage of NLP vision at all follow-up visits, this difference was not statistically significant.

The visual outcomes at 4 years were better in patients with type 1 diabetes mellitus, those whose eyes had better initial vision, and those who had previous PRP. The advantage of early vitrectomy was not affected by any of these factors, however. Early vitrectomy was more beneficial as the severity of new vessels increased. A subgroup analysis of eyes with varying severity of new vessels showed no benefit of early vitrectomy in eyes with the least severe neovascularization.

How Was the Trial of Early Vitrectomy for Severe Diabetic Vitreous Hemorrhage Conducted?

To be eligible for this trial, patients were required to have a severe vitreous hemorrhage within 6 months before randomization and visual acuity from 5/200 to light perception. Eligible eyes were randomized to

early vitrectomy or deferral groups. The early group received vitrectomy within several days of randomization. The deferral group received vitrectomy after 12 months if there was persistent vitreous hemorrhage with decreased visual acuity to 5/200 or worse. Follow-up visits were scheduled 3, 6, 12, 18, 24, 36, and 48 months after randomization. From November 1976 to May 1983, 616 eyes from 594 eligible patients entered the study.

Is Early Vitrectomy More Beneficial than Vitrectomy at 1 Year for Eyes with Severe Vitreous Hemorrhage?

A greater number of early vitrectomy eyes achieved visual acuity of 10/20 or better throughout the follow-up period.[46,47] At the 2-year visit, 24.5% of early vitrectomy eyes and 15.2% of the deferral group had visual acuity of 10/20 or better. This advantage of early vitrectomy in recovery of good vision at 2 years was most apparent in patients with type I diabetes (35.6% versus 11.7%). Patients with type II diabetes had the same rate of achieving 10/20 visual acuity in early vitrectomy and deferral groups. Patients with type I diabetes had more extensive new vessels, fibrous proliferation, and vitreoretinal adhesions.

More eyes in the early vitrectomy group recovered a visual acuity of 10/100 for up to 18 months after randomization. At 3 months, 50% in the early vitrectomy group compared with 17% in the deferral had this level of acuity. After 18 months, however, there was no difference between the two groups in the number of eyes with visual acuity of 10/100.

There was no significant difference in the percentage of eyes with visual acuity of no light perception (NLP) at 2 years when comparing early vitrectomy and deferral groups (24.9% versus 19.3%, respectively). Eyes in the early vitrectomy group, however, had an increased risk of losing light perception within the first 18 months.[46]

In patients with type I diabetes, the early vitrectomy group had the same 2-year rates of untoward events of corneal edema, epithelial abnormalities, neovascular glaucoma, and increased intraocular pressure as the deferral group but a lower risk of retinal detachment. In patients with type II diabetes, the rate of these untoward events were higher in the early vitrectomy group, and the rate of retinal detachment was the same in both groups.[46]

What Were the Recommendations of the Diabetic Retinoopathy Vitrectomy Study for Vitrectomy in Eyes with Diabetic Retinopathy?

Vitrectomy should be considered in eyes with advanced, active PDR and good vision. Early vitrectomy can improve the prognosis for good vision without increasing the risk for poor vision.

Early vitrectomy is also recommended for eyes with severe vitreous hemorrhage from PDR. The advantage of vitrectomy was clearly present in patients with type I diabetes. The great severity of new vessels, fibrous proliferation, and vitreoretinal adhesions in patients with type I diabetes may explain the benefit of early vitrectomy in this group. In both groups, early vitrectomy provides a better chance for prompt recovery of useful vision but also carries a greater risk of early loss of light perception. General guidelines for surgical management of patients with PDR are outlined in Figure 23–8.

Cryotherapy for Retinopathy of Prematuriy Study

Why was the Cryotherapy for Retinopathy of Prematurity Study Conducted?

The Cryotherapy for Retinopathy of Prematurity (Cryo-ROP) study was a multicenter, randomized clinical trial designed to evaluate the risks and benefits of transscleral cryotherapy to the avascular peripheral retina of premature infants with retinopathy of prematurity (ROP).

How Was the Cryo-ROP Study Conducted?

Infants who weighed less than 1251 g at birth underwent serial eye examinations starting 4 to 6 weeks after birth. Eyes that developed threshold disease were randomized to transscleral cryotherapy or observation. Threshold ROP was a level of severity at which the risk of blindness was predicted to approach 50% and was defined as at least five contiguous or eight cumulative 30-degree clock hours of stage 3 ROP in zone 1 or 2 in the presence of plus disease. Plus disease was defined as dilation and tortuosity of posterior retinal vessels.

Cryotherapy was performed with the patient under topical anesthesia, local infiltration, or general anesthesia based on the discretion of the treating physicians. The avascular peripheral retina anterior to the fibrovascular ridge was treated with contiguous applications of cryotherapy. Conjunctival incisions were made only when necessary to treat more posterior retina.

The primary outcome for this study was presence or absence of unfavorable structural outcomes defined as (1) a retinal fold involving the macula, (2) a retinal detachment involving zone 1 of the posterior pole, or (3) retrolental tissue or "mass."

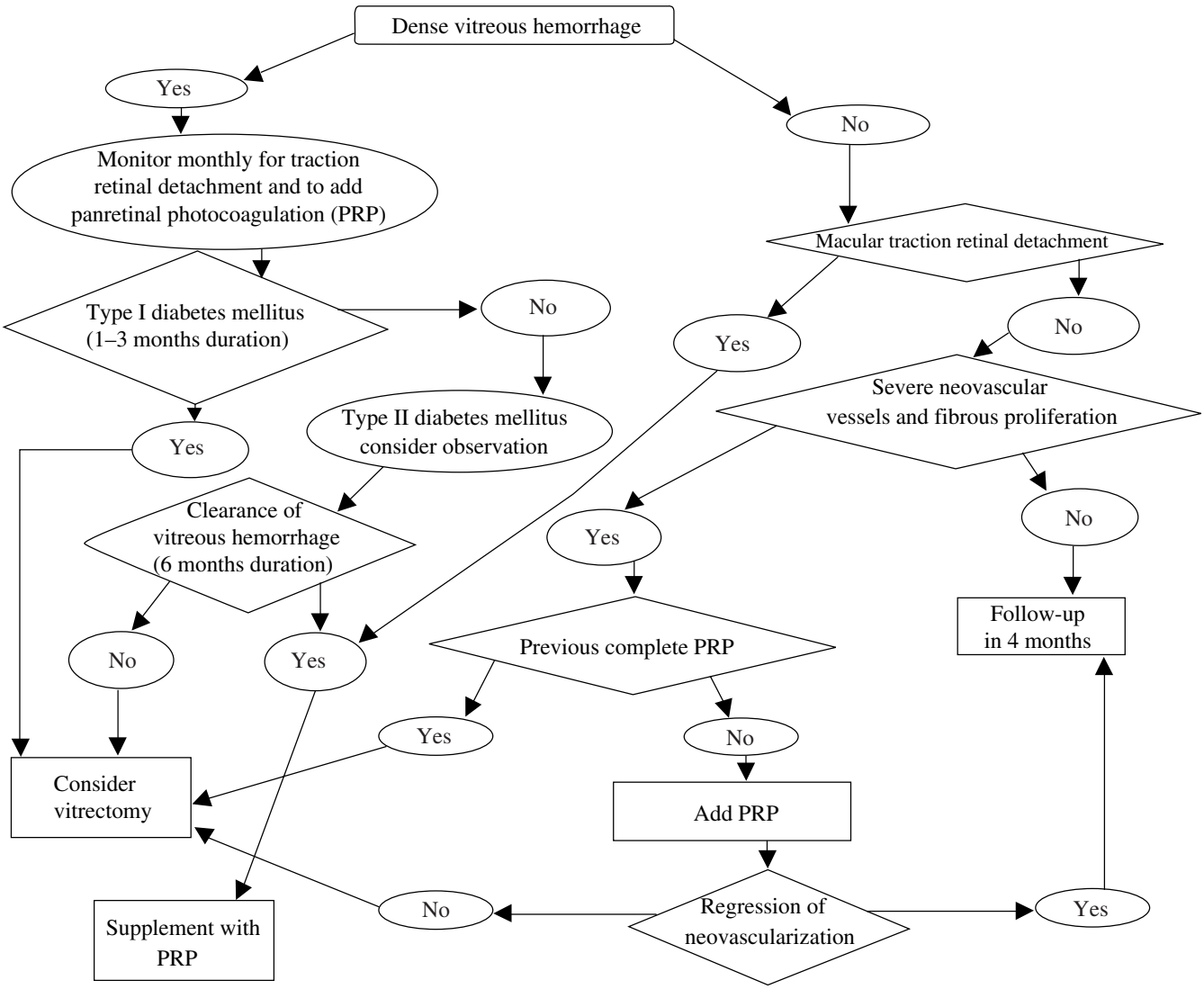

FIGURE 23–8. Clinical pathway: Vitrectomy in the management of severe proliferation and vitreous hemorrhage secondary to diabetic retinopathy.

Is Cryotherapy Effective in Reducing the Rates of Unfavorable Outcomes in Patients with Retinopathy of Prematurity?

In this study, 291 infants were randomized. The mean birth weight of randomized infants was 800 g, and the mean gestational age was 26.3 weeks. Infants were randomized at a mean of 11.3 weeks after birth. Most of infants (82.5%) had bilateral threshold disease at the time of randomization. On average, about 50 separate spots were required for treatment. About 10% of the infants died during the first 12 months of the follow-up.

Cryotherapy reduced the risk of unfavorable structural outcomes, based on fundus photographs, throughout the follow-up by approximately 40 to 50% compared with untreated eyes: 31.1% versus 51.4% at 3 months and 25.7% versus 47.4% at 12 months.[48–51] Similarly, the risk of unfavorable outcomes as determined by evaluation of the examining physician was reduced by almost 40% at both 3.5, 5.5, and 10 years.[52–54] Lower birth weight and more severe retinopathy at randomization increased the risk of unfavorable outcomes. The difference between the treated and control eyes remained significant regardless of birth weight or severity of retinopathy.

Functional outcomes were significantly better in cryotherapy eyes than in untreated eyes. Treated eyes performed significantly better on assessment of grating visual acuity using the Teller Acuity Card Procedure at 12 months and 3.5 years and better on assessment of recognition letter acuity measured with HOTV testing at 3.5 years.[51–53] Results of the Snellen visual acuity at 5.5 years showed fewer cryotherapy

eyes than control eyes had visual acuity of 20/200 or worse (47.1% versus 61.7%) or blindness (31.5% versus 48%). A trend was noted, however, for control eyes to have higher rates of vision, 20/40 or better, than the treated eyes (13% versus 17%, p = 0.19). This trend was not present at the 10-year outcome.[54] Therefore, the benefit of cryotherapy in preventing unfavorable outcomes may be accompanied by a decrease in the rates of best visual acuity.

What Is the Role of Laser Photocoagulation in the Treatment of ROP?

Laser photocoagulation was not available when the Cryo-ROP study was conducted. Since then, argon and diode-laser photocoagulation have been shown in several studies to be as effective as cryotherapy in reducing unfavorable outcomes in ROP.[55–57] Complication rates are also lower with laser than cryotherapy. Laser photocoagulation has gained widespread acceptance and replaced cryotherapy in the treatment of ROP. Diode-red laser is preferable to argon laser in the treatment of ROP because argon green-laser can be absorbed by a persistent tunica vasculosa lentis. Whereas peripheral transient lens opacities have been reported with diode-red laser,[58] permanent cataracts have been described with argon laser.[59]

Does Supplemental Therapeutic Oxygen for Infants with Prethreshold ROP Reduce Probability of Progression to Threshold ROP?

In the supplemental therapeutic oxygen for ROP (STOP-ROP) Study, infants with prethreshold ROP were randomized to receive conventional oxygen therapy with pulse oxymetry targeted at 89 to 94% saturation and supplemental oxygen with pulse oxymetry targeted at 96% to 99% saturation. The results showed a small trend toward improved outcomes with higher targeted oxygen saturation.[60] The rate of progression to threshold was 48% in the conventional arm, 41% in the supplemental arm. In subgroup analysis, eyes without plus disease benefited more from supplemental oxygen therapy (progression rates of 32.3% versus 45.6%); however, the supplemental group had slightly higher rates of systemic complications such as exacerbations of chronic lung disease. These data did not support supplemental oxygen therapy for all infants with prethreshold ROP.

Does Reducing Ambient Light in the Nursery Reduce Occurrence of Retinopathy of Prematurity?

Hospital-nursery lighting had been suggested as a risk factor for developing ROP. The Light-ROP study was a randomized clinical trial investigating the effects of light reduction on the occurrence of ROP. Premature infants weighing less than 1251 g and with gestational ages less than 31 weeks were randomized to a group wearing goggles to reduce light exposure after birth or to no intervention. The results showed that a reduction in ambient-light exposure does not reduce the incidence of ROP.[61]

What Are the Guidelines for Screening Examinations for ROP?

The latest American Academy of Pediatrics screening guidelines for ROP recommend screening of all infants with birth weight of 1500 g or lower or gestational age of 28 weeks or less.[62] Screening of infants with birth weight greater than 1500 g or gestational age greater than 28 weeks is discretionary based on these recommendations; however, screening infants as old as 32 weeks may potentially avoid missing any instances of more advanced ROP.[63] Initial examination is performed at 4 to 6 weeks after birth or 31 to 33 weeks postconceptional age, whichever is earlier. Examinations are performed at intervals based on the severity of ROP until ROP regresses with vascularization to zone III or progression to threshold disease occurs. Eyes with threshold disease should be treated with laser photocoagulation or cryotherapy. Long-term follow-up is recommended for detection and management of myopia, strabismus, and other ocular conditions associated with ROP.

Vitrectomy for Treatment of Idiopathic Macular Holes

Why Were the Studies of Vitrectomy for Prevention and Treatment of Macular Holes Conducted?

The pathogenesis of macular holes is proposed to involve tangential vitreous traction by a layer of cortical vitreous. Tangential vitreous traction causes foveal detachment and impending or stage 1 macular holes. About half of stage 1 macular holes resolve spontaneously after posterior vitreous detachment and release of vitreous traction; however, persistent vitreous traction results in a small full-thickness macular hole (stage 2), followed by development of a round full-thickness macular hole with a vitreofoveal separation (stage 3). In some cases, the vitreous detaches completely, causing a stage 4 macular hole.[64]

Three randomized multicenter clinical trials were conducted by the Vitrectomy for Prevention of Macular Holes Study Group to investigate the benefit of vitrectomy in (1) preventing full-thickness macular holes in patients with impending (stage 1) macular holes, (2) eyes with stage 2 macular holes, and (3) eyes with stage 3 or 4 macular holes.

Does Vitrectomy Surgery Prevent Full-thickness Macular Holes in Patients with Impending Macular Holes?

Eyes with impending macular holes were randomized to vitrectomy with removal of cortical vitreous or to observation. To decrease the chance of misdiagnosis, the fellow eyes of eligible patients were required to have a full-thickness (stage 3 or 4) macular hole. The outcome measures for the study were the rate of progression to full-thickness macular holes and visual acuity.

The study was terminated early because of low recruitment. Twenty-seven patients were randomized to vitrectomy and 35 patients to observation. The risk of progression to a full-thickness macular hole was the same in both groups[65]; a full-thickness macular hole developed in 10 vitrectomy eyes (37%) and in 14 control eyes (40%). The final visual acuity was not significantly better in vitrectomy eyes, which was explained by appearance or progression of nuclear sclerotic cataract.

Although this study was terminated before the required sample size was reached, it ruled out a substantial benefit from vitrectomy for stage 1 macular holes. If a true benefit exists, it is not significant. A conservative approach for treatment was recommended in view of the high incidence of nuclear sclerotic cataracts and a possibility of retinal complications.

Is Vitrectomy Surgery Beneficial in Eyes with Stage 2 Macular Holes?

Eyes with stage 2 macular holes were randomized to surgery for closure of macular hole or to observation. The surgical procedure included pars plana vitrectomy, induction of posterior vitreous detachment, removal of epiretinal membranes, and internal gas tamponade with a nonexpansile mixture of perfluoropropane gas. Following surgery, patients assumed a face-down position for a minimum of 2 weeks. The outcome measures included (1) macular hole size and (2) four standardized measures of vision: best corrected visual acuity using ETDRS chart; contrast sensitivity reading test, and Potential Acuity Meter (PAM) test.

Thirty-six eyes with 12 months of follow-up were studied. Compared with eyes that underwent surgery, significantly more eyes assigned to observation progressed to stage 3 or 4 macular holes.[66] At 12 months, 15 (71%) of 21 observation eyes and 3 (20%) of 15 surgery eyes progressed to stage 3 or 4 macular holes. At 6 and 12 months, the average hole size in the observation group was significantly larger than that in the surgery group. Eyes that underwent surgery had significantly better visual outcome at 6 and 12 months in terms of word reading and PAM visual acuity.[66] The two groups did not differ in ETDRS visual acuity or contrast sensitivity measurements. The discrepancy in visual results was believed to be because of the high rate of development of nuclear sclerotic cataracts in the surgery group.

In summary, this study showed that surgery in stage 2 macular holes resulted in a significantly lower incidence of hole enlargement compared with observation and appeared to be associated with a better outcome in some measurement of visual acuity.

Is Vitrectomy Surgery Beneficial in Eyes with Stage 3 or 4 Macular Holes?

Patients with stage 3 or 4 macular holes with visual acuity worse than 20/50 were randomized to surgery or to observation. The surgical procedure included pars plana vitrectomy, induction of posterior vitreous detachment, removal of epiretinal membranes, and internal gas tamponade with a nonexpansile mixture of perfluoropropane gas. Following surgery, patients assumed a face-down position for a minimum of 2 weeks. The outcome measures included hole closure, cataract formation, and four standardized measures of vision: (1) best corrected visual acuity using the ETDRS chart, (2) contrast sensitivity, (3) reading test, and (4) PAM test.

The study comprised 129 eyes with 6 months of follow-up. Eyes that were operated on had a higher rate of hole closure than eyes that were observed (69% versus 4%). Operated eyes had significantly better visual outcome at 6 months as measured by ETDRS visual acuity, word reading, and PAM visual acuity.[67] The groups did not differ in terms of contrast sensitivity. The risk of progression of nuclear sclerosis was greater in the operated eyes than in observed eyes.[67] Other complications of surgery included macular pigmentary changes, subretinal neovascularization, cystoid macular edema, and endophthalmitis. In summary, the results of this study indicated that some visual measures indicated improvement after vitrectomy surgery for macular holes, despite a notable incidence of adverse events.

Endophthalmitis Vitrectomy Study

Why Was the Endophthalmitis Vitrectomy Study Conducted?

The Endophthalmitis Vitrectomy Study (EVS) tested the role of vitrectomy versus vitreous tap and the role of systemic antibiotics in the treatment of postopera-

tive endophthalmitis within 6 weeks after cataract surgery or secondary intraocular lens implantation.

How Was the Endophthalmitis Vitrectomy Study Conducted?

No postoperative patients from other surgical procedures, postcataract patients seen more than 6 weeks after surgery, or patients with endophthalmitis associated with trauma or endogenous spread were included in the study. All patients received intravitreous antibiotics. The main outcome measures were visual acuity using the ETDRS chart and media clarity. The study comprised 420 patients randomly assigned to vitrectomy or tap and to treatment with systemic ceftazidime and amikacin or no systemic antibiotics. Analysis was completed after a 9-month follow-up.[68]

What Were the Results?

The study results showed that the use of systemic antibiotics on endophthalmitis patients did not have an effect on measured outcomes. In nondiabetic patient eyes with hand motion vision or better, there was no difference in final visual acuity or media clarity whether vitrectomy or vitreous tap was performed; however, nondiabetic patients with only light perception vision benefited from vitrectomy over tap.

In diabetic patients, regardless of initial visual acuity, vitrectomy and intravitreous antibiotics resulted in a better final visual acuity than vitreous tap and intravitreous antibiotics, but the results were not statistically significant. This was thought to be because of low numbers of patients.[69] There was no benefit found in using intravenous antibiotics in diabetic patients with endophthalmitis within 6 weeks of cataract extraction or secondary intraocular lens.

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