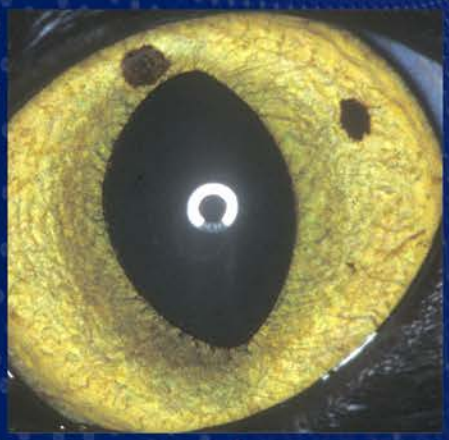
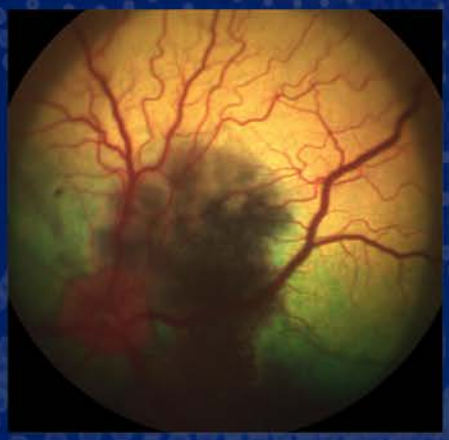
OPHTHALMIC DISEASE IN VETERINARY MEDICINE

SECOND EDITION


CHARLES L. MARTIN
J. PHILLIP PICKETT
BERNHARD M. SPIESS

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The new edition of *Ophthalmic Disease in Veterinary Medicine* is the ideal textbook for trainee and practicing veterinarians needing a quick reference in their daily work. Expert veterinary ophthalmologists will also appreciate this updated completely revised edition, the achievement of a teamwork involving three authors and five contributors, outstanding members of the international veterinary ophthalmology community. Hundreds of beautiful pictures and drawings facilitate a quick, easy, practical consultation and allow direct comparison to clinical cases. For each ophthalmic disease and disorder, the authors provide a detailed description of diagnosis, etiology, clinical signs, prognosis, and therapy. Although the main focus is on small animal species, the readers will appreciate the interesting comparative notes on the horse and the cow, and a section dedicated to presumed inherited eye disorders. *Ophthalmic Disease in Veterinary Medicine* deserves a special space in the library of everyone interested in veterinary ophthalmology. Actually, it is a book to leave on your desk for daily use, so that you can read the notes and show the pictures to owners to help explain what is happening in their pet's eyes.

Prof. Claudio Peruccio, DVM, SCMPA,
Dipl ECVO, Hon Dipl ACVO, MRCVS, EBVS®
European & RCVS Specialist in Veterinary Ophthalmology

The most recent edition of *Ophthalmic Disease in Veterinary Medicine* is a welcome addition to the body of literature in veterinary ophthalmology. This text is certainly straightforward and pragmatic enough to be valuable in the library of the general practitioner. But such a statement belies the 700 pages of depth, detail, and scholarship that the specialist in veterinary ophthalmology will find extremely useful and informative; indeed, this text will become required reading for my ophthalmology residents. It is obvious that this work has fallen under the watchful eye of Dr. Charles Martin, whose attention to detail and ability to piece together not-so-obvious connections are legendary in our specialty. Drs. Martin, Pickett, and Spiess have over 100 years of combined experience in veterinary ophthalmology as clinicians, teachers, and researchers. This text provides abundant evidence that they have maintained a cutting edge in vision science and clinical ophthalmology, and their wealth of experience brings context and perspective to new developments in the specialty. The other contributing authors have followed that lead. Photographs, illustrations, schematics, and flowcharts are particularly useful in enriching the reader's understanding in the specialty of ophthalmology, and this book is loaded with extremely well-done examples of these visual aids. The text is very carefully and thoroughly indexed and cross-indexed, which makes it very user friendly. Without question this work will be referenced daily in my clinical work, classroom teaching, and residency training.

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Ophthalmic Disease in Veterinary Medicine

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Ophthalmic Disease in Veterinary Medicine

Second Edition

Charles L. Martin
J. Phillip Pickett
Bernhard M. Spiess

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PREFACE

Writing a text has often been compared to marriage as it engenders an obligation to keep the covenant intact short of death. When contemplating another edition of the text *Ophthalmic Disease in Veterinary Medicine*, my considerations were how to improve the book as well as updating the text. Updating the information is quite straightforward, while changing the format is more challenging and risky. Previous editions were essentially single authored, which has the advantage of more consistency between chapters in writing style and philosophy, but it also has the disadvantage of limiting the expression of clinical experience to a single author. For this edition, we have chosen to increase the breadth of clinical expertise with a diverse group of authors from many geographic regions of training and practice and who have actively participated in student training and research in veterinary ophthalmology. They have also demonstrated not only great professional skills but a great deal of patience as the timeline for fruition of publication has been greatly extended from the original target date. I would like to thank all the authors for their participation and thoroughness, and we hope that the readers will appreciate the expertise that this diversity has brought to the text.

I would be remiss if I did not recognize Ms. Alice Oven and Pam Tagg and their staff at CRC Press/Taylor & Francis for keeping faith in the project and the contributors. I am sure it has probably been one of their most challenging projects.

Last but not least I thank my daughter Christena Hughes for her help and patience in the copy editing process and my wife Marilyn for her encouragement and advice.

Charles L. Martin

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CHAPTER 1

ANAMNESIS AND THE OPHTHALMIC EXAMINATION

URSULA DIETRICH

ANAMNESIS

Prior to any ophthalmic examination, a thorough history should be obtained including information about the environment of the animal, other pets in the household, diet, previous treatments and medications, but also a complete medical history. Although many ophthalmic diagnoses are anatomic diagnoses, based on direct visual inspection and augmented by known breed-, age-, and species-related syndromes, many systemic diseases may be manifest in the eye and its adnexa as the first and sometimes only clinical symptom (e.g., hypertensive retinopathy, diabetes mellitus, lymphoma).

Breed, age, and occasionally the sex are important data, as many ocular syndromes are inherited or at least have a breed predisposition (see Chapter 15).

The owner's complaints are usually among the following: decreased vision or blindness, ocular discharge, ocular color changes, pain, an opacity or film over the eye, pupillary changes/anisocoria, and exophthalmos/enlarged eye(s). These complaints form the basis for the problem-oriented approach to ophthalmology and are discussed in more detail in subsequent chapters.

Problems observed by the owner

Decreased vision or blindness

Depending on the function of the dog, the environment the animal is kept in, the amount of vision lost, unilateral versus bilateral loss, and the rapidity of development, the historical data may be accurate or misleading. Insidious loss of vision such as progressive retinal atrophy is often diagnosed in an advanced stage when the animal is presented. Most dogs adapt well to vision loss in a familiar environment, and the decrease of vision becomes only noticeable if furniture, and so on, is moved.

Dogs that work by sight are more critically evaluated as to type (moving versus stationary objects) and degree of deficiency. Nonleading questions should be asked regarding night vision, day vision, ability to see moving objects as opposed to stationary objects, and the circumstances under which the visual loss was noted. This information must then be interpreted considering the animal's function and environment and the owner's ability to discriminate. Most animals are not presented with a complaint of decreased vision unless the condition is bilateral and relatively severe.

Ocular discharge

The type of discharge should be noted and historical data regarding chronicity, progression and modification by therapy, season, and environment should be obtained. While ocular discharge is typical of ocular surface and adnexal disease, intraocular disease and the systemic history should not be overlooked.

Ocular color changes

Color changes may be due to conjunctival and episcleral hyperemia associated with conjunctivitis, scleritis, uveitis, or glaucoma. Bulbar conjunctival hyperemia may be diffuse, involving capillaries and large vessels as with conjunctivitis, or selective, involving mainly the larger conjunctival vessels and deeper episcleral vessels with uveitis, glaucoma, and scleritis. Subconjunctival hemorrhage also produces a red bulbar conjunctiva, either in a sector or, occasionally, involving the entire circumference of the conjunctiva. The normal variation of a unilateral or bilateral nonpigmented third eyelid margin may make the eye look redder and, indeed, a nonpigmented third eyelid is probably more susceptible to irritation than the pigmented conjunctival surface.

Corneal opacities may produce red (granulation, intense neovascularization, hemorrhage), white (lipids, calcium, scar, edema, fungal plaques), or black (melanin pigment, corneal sequestrum in cats, dematiaceous fungi) color changes.

Intraocular color changes may arise from the aqueous humor, iris, or lens. Aqueous humor color changes may be red with hyphema, white to gray with hypopyon, fibrin, or lipids, and brown to black when filled with free-floating iris cysts. Iris color changes are usually most dramatic with unilateral involvement and with lightly pigmented irides. The brown iris becomes darker, and the blue iris becomes yellow with uveitis or brown when infiltrated with pigmented tumors. Iridal redness may be observed with

intense neovascularization and engorgement and with petechial/ecchymotic hemorrhage in the blue irides. The latter changes are not often obvious in the darker compact irides. Occasionally, a blue iris may turn green in an icteric animal.

Lens color changes are typically in shades of gray-white with aging and white with cataract formation. Rarely, hemorrhage may occur into the lens associated with congenital vascular anomalies such as persistent hyperplastic primary vitreous (PHPV).

Ocular pain

Blepharospasm and rubbing the eye(s) are obvious signs of pain noted by owners, but ocular pain often manifests in a subtle manner with general malaise, depression, excessive sleeping, and a worsening of the temperament. These signs are often not noted by the owners until improvement occurs and retrospective comparisons are made. In humans, conjunctival pain is described as a foreign body sensation, corneal pain as a sharp ocular pain, and intraocular pain is often a headache pain radiating over the trigeminal nerve distribution. Paradoxically, superficial corneal ulceration is often more painful than deep ulceration due to the concentration of nerve fibers under the corneal epithelium.[1,2] Species variations also exist, as cats and horses are typically more symptomatic with conjunctivitis and corneal disease than dogs.

Opacities

Opacities or film over or in the eye may result from prolapse of the third eyelid, tenacious ocular discharges, corneal opacities, fibrin, blood, inflammatory cells or masses in the anterior chamber, and cataracts. Historical data regarding chronicity, laterality, constant or intermittent occurrence, progression, and precipitating factors should be obtained. Protrusion of the third eyelid is often described by owners as "the eye rolling up into the head."

Pupillary changes

Alterations in pupil size are usually noted when unilateral or when accompanied by another ocular complaint such as blindness, which draws the owner's attention to the eye. Alterations in pupil size are most easily observed in eyes with lightly pigmented irides or against the background of a white cataract. Ocular disease should always be ruled out as the cause for altered pupil size, shape, and mobility before proceeding to neurologic causes.

Exophthalmos/buphthalmos

Enlarged or prominent eyes are most dramatic when unilateral. The condition may be acute or chronic in nature and is often accompanied by another complaint such as red eye, pain, ocular discharge, or a film over the eyes. While buphthalmia is a true enlargement of the globe (most often caused by chronic glaucoma), exophthalmia is forward placement of an otherwise normal-sized globe. Differentiation between exophthalmos and buphthalmos is usually not difficult, but in brachycephalic breeds and animals with only one eye, mild degrees of the problem may be difficult to detect for even the experienced examiner.

General comments

The initial clinical appearance of the problem and its modification with time, therapy, and environmental change should be documented. Measurement of corneal diameters or ultrasonography for measuring globe dimensions may be used to determine subtle differences between eyes. Information on the administration of prior "home" or professional remedies should be obtained, particularly for chronic cases. With new clients, it is necessary to obtain historical data on previous ocular problems and their course and response to therapy. The disease process may have been modified, and the interpretation of the ocular examination, such as pupillary light reflexes and intraocular pressures, may be complicated by prior therapy (such as atropine). Failure of response to previously prescribed therapy should provoke questions to determine the owner's compliance with instructions. Asking to see the remaining medication may allow an assessment of whether the medication has been given as frequently or for as long as was claimed.

Many ocular problems are breed related, and it is often desirable to establish possible inheritance, although the necessary information is often not available. In most instances, genetic syndromes are inferred by the occurrence of a known syndrome in a particular age and breed of animal (see Chapter 15).

As the eye often manifests systemic illness, it is imperative that possible systemic ramifications be considered. In addition, topical medications may have systemic side effects, and, conversely, systemic drugs may have ocular side effects. Candidates for ocular surgery need to be evaluated preoperatively for systemic disease.

Historical data pertaining to environmental factors such as animal exposure, type of housing, bedding, fenced yard, dusts, irritants such as fumes and fiberglass, and function of the animal may help to establish an etiologic diagnosis for a previously unresolved problem.

With experience, the clinician will note that many ocular syndromes have predictable histories, but he/she should always be on the lookout for "red herrings," which are common with historical data.

OPHTHALMIC EXAMINATION

Restraint

The best restraint for ophthalmic examination is usually the least amount possible. The inexperienced examiner usually mistakenly assumes that chemical sedation will facilitate the examination and make up for deficiencies in technique. While sedation is routine in large animal ophthalmic examinations, it is rarely necessary in small animals.

One of the most formidable obstacles to a good ophthalmic examination is protrusion of the third eyelid. Protruding third eyelids can usually be circumvented by keeping the animal alert, off balance, or anxious. Movement of the head, positioning over the edge of the table, or making noises to attract the patient's attention will change the mental status sufficiently so that the eye is exposed for short periods. These maneuvers, combined with exposing the eye to short bursts of light that is no brighter than necessary, allows the experienced clinician enough of a "window of opportunity" to complete most examinations.

In the dog, the muzzle is often held with one hand, and this serves to manipulate the head as well as afford protection to the examiner. Most dogs do not require additional restraint for routine examination, but if there is any doubt as to the examiner's safety, muzzling or, in extreme cases, chemical sedation, is indicated. In the dog, most sedatives or general anesthesia only make the ophthalmic examination more difficult due to protrusion of the third eyelid and infraversion (rolling down) of the eyes.

A gentle and efficient way to restrain a cat during the examination is the "wrap up" method, by gently wrapping the cat into a large, soft towel or small blanket, which is then held by an assistant. The legs and body are securely held, and only the head is exposed with this method. Sedation of a cat is rarely required, but the use of ketamine sedation (10 mg/kg) provides ideal conditions for examination, producing a dilated pupil, eyes straight ahead, and immobilization. The effect of ketamine on the intraocular pressure in cats has been shown to increase by 10%, which needs to be taken into consideration when performing tonometry.[3]

In small animals, speed and utilization of short bursts of light enables an ophthalmic examination to be performed without chemical sedation in most uncooperative patients.

Regional anesthesia/analgesia in the horse

In the horse, whether presented with or without ocular pain, sedation and palpebral nerve akinesia is routinely performed for a thorough examination. Xylazine (0.5–1.1 mg/kg) intravenously (IV) quiets the animal and drops the head for examination. This not only facilitates the examination but is also safer for the examiner. If ocular pain is present, palpebral nerve blocks are routine, easily performed, and facilitate examination even if sedation is used. Blockage of the palpebral branch of the auriculopalpebral nerve (branch of VII cranial nerve) may be performed at several locations, but the most complete akinesis with the least amount of local anesthetic can be produced by injection at the dorsal margin of the highest point of the zygomatic arch (**Figure 1.1**).[4] Firm palpation of the dorsal rim of the arch usually causes the nerve to snap under the examiner's finger. An alternative site is at the base of the ear between the ear and the zygomatic process (**Figure 1.2**). A 25-gauge needle is placed at the site, a syringe is then attached, and 1–3 mL of a local anesthetic is injected. The resultant block gives sufficient akinesis of the orbicularis oculi muscle such that the lids can be opened with minimal force, but the animal can still blink. The dorsal branches of the palpebral nerve can also be blocked at the supraorbital foramen where it mingles with the supraorbital nerve (sensory, V cranial nerve). The supraorbital foramen can be identified by grasping the margins of the dorsal orbital rim and moving medially until it widens (**Figure 1.3**). At this point, the foramen can be palpated in the middle of the rim.[5] Palpebral nerve blocks do not affect the intraocular pressure (IOP), but attempting to measure the IOP in a blepharospastic horse without a nerve block may result in an artificially elevated IOP. Xylazine sedation may lower the intraocular pressure (IOP) by up to 27% in horses.[6]

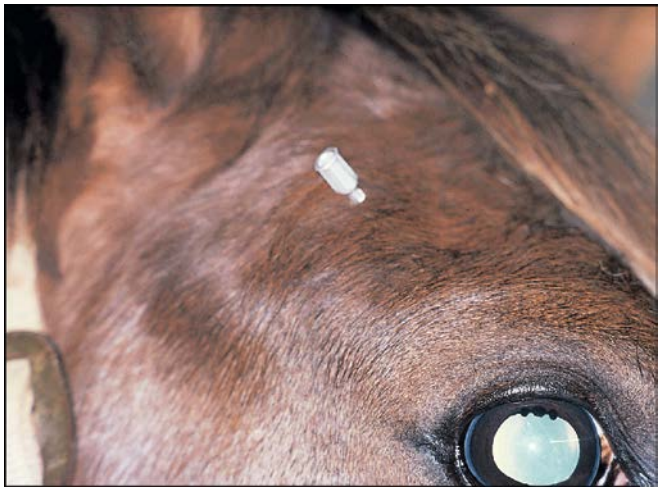

Figure 1.1 **A needle placed subcutaneously above the zygomatic arch for a palpebral nerve block in a horse.**

Figure 1.2 Injection at the base of the ear to block the palpebral branch of the facial nerve in a horse.

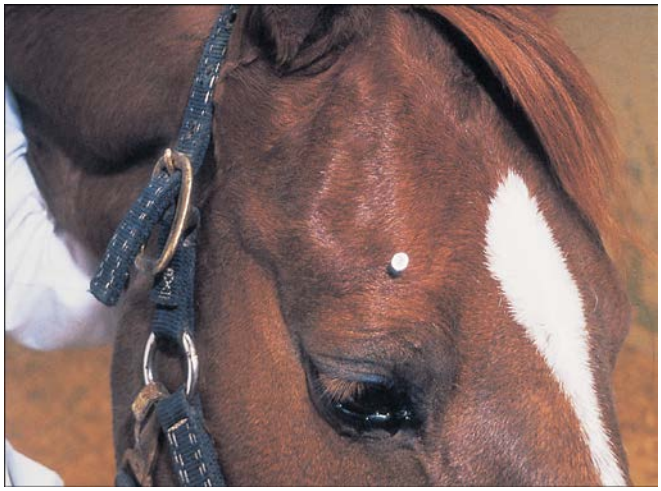

Figure 1.3 A needle in the supraorbital foramen to block the palpebral (motor) and supraorbital (sensory) nerves in a horse.

Diffuse illumination with head unrestrained

Examination with diffuse illumination without head restraint is the initial step in ophthalmic examination and is often ignored in the rush to get a close look at the eye. This is the time to evaluate conformation and symmetry of the eyes and adnexa. It is important to keep the head unrestrained, as simply touching the side of the head will modify lid conformation. In addition, manipulation of the head often precipitates blepharospasm in a dog that is "eye shy" by nature, in pain, or has received prior ocular medication. If some restraint of the head is necessary, the head should be supported under the mandible.

Comparison of ocular and adnexal symmetry is important and should be performed from various angles of observation, that is frontal and dorsal. Palpebral fissures, third eyelid position, globe size and position, iris color, and pupil size should be evaluated for symmetry. This is the time when the orbit should be evaluated, retropulsion of the globes into the orbit compared (**Figure 1.4**), and the patient examined for exophthalmos by comparing the corneal vertices from a dorsal vantage point. Ocular discharges and lid dermatologic lesions such as swellings, alopecia, and erythema should be noted. The cornea should be inspected for its luster, surface irregularities, and opacities. The specular light reflection off the cornea ("*Purkinje images*") superimposed on the pupils allows accurate assessment of ocular alignment, and gross opacities in the anterior chamber and lens may be noted.

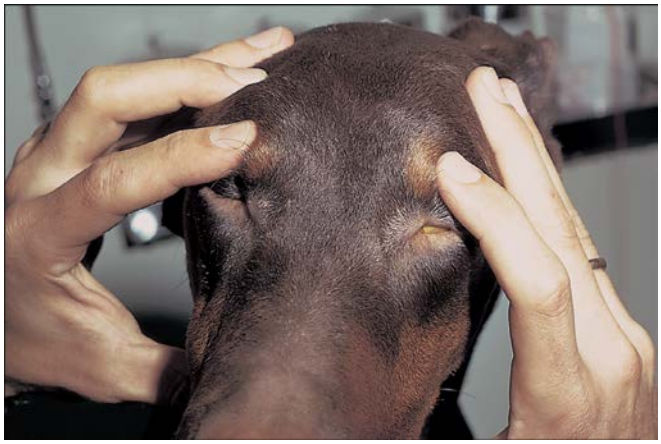

Figure 1.4 Bilateral retropulsion of the globe into the orbit to compare compressibility between orbits. This is different from digital tonometry.

Evaluation for anisocoria (unequal pupils) and the pupillary light reflex (PLR)

The presence of static anisocoria (consistently unequal pupils under varying light conditions) is determined by directing a light at the stop or base of the nose from a distance of 60–90 cm (2–3 feet) in a darkened room. This outlines both pupils simultaneously against the retroillumination of the tapetal reflection. Heterochromia results in a mild anisocoria with the larger pupil in the eye with the blue iris and is considered physiologic. Other forms of anisocoria should be evaluated further.

The PLR is frequently described by authors as either clearly present or absent, but in reality, it is a subjective evaluation that has a great deal of interpretive variation between clinicians of different levels of experience. Pupillary light reflexes should be performed in a darkened room with a bright light, such as a Finoff transilluminator, to produce maximum excursions (**Figure 1.5**). The *swinging light test* employs a bright light shown alternately in each eye for 3–4 seconds at a time. Initial stimulation of the eye elicits the direct response, and the light

Figure 1.5 **Finoff transilluminator used for gross ocular examinations, PLR testing, and mononuclear indirect ophthalmoscopy.**

is quickly shifted to the contralateral eye, and the pupil size observed. The initial observation is evaluation of the indirect or consensual reaction, but as it is maintained, it becomes the direct reflex. This is repeated back and forth at 3–4+ second intervals.

Normally, with a relaxed animal in a darkened room, the PLR responses are brisk, and the degree of contraction is significant on direct stimulation. Due to the presence of the relatively cone-rich area centralis, a focal light directed temporally on the retina stimulates a more complete constriction than a light directed on the nasal retina. When the light is moved to the opposite eye, it may be noted that the initial size of the pupil is slightly larger in this eye and then constricts further. This is due to the unequal pupillomotor input to the consensually responding eye in the dog and cat and is a normal dynamic anisocoria.[7] Sustaining the light in the eye may produce a small amount of redilation due to adaptation of the retina to a weak light. If the sustained illumination results in an obvious dilation, the test is positive (Marcus Gunn pupil) and is the result of a retinal or optic nerve lesion. It is relatively common for patients with retinal/optic nerve blindness to have some degree of pupil reaction to a bright light, as vision is a more complex function than the PLR. It is more common to have vision with dilated nonreactive pupils due to efferent arc lesions of the PLR.

If anisocoria and PLR abnormalities are detected, then special attention in the ocular examination should be devoted to vision testing, fundus examination, and diseases of the iris. The detailed examination should rule out synechiae, iris atrophy, iris hypoplasia, lens displacement, elevated IOP, anterior uveitis, and anterior uveal neoplasia, all of which commonly interfere with pupil mobility and/or shape.

If the iris appears normal, evaluation of the anisocoria in darkness and ambient light should be performed. Anisocoria associated with an afferent arm (usually retina or optic nerve) lesion of the PLR will dilate to equality in a dark room due to an intact sympathetic chain. The anisocoria of Horner's syndrome remains or is more pronounced due to a lack of sympathetic input to the dilator muscle (see section Horner's syndrome, Chapter 4).

Chromatic pupillary light reflex (cPLR)

The physiologic basis of the pupillary light reflex in mammals is a response of the retinal photoreceptor cells (rods and cones) to stimulation with a bright white light source (Finoff transilluminator, slit lamp, or other focused light source). The PLR helps in the assessment of the visual pathway integrity, including the retina, optic nerve, optic chiasm, and anterior visual pathways (optic tracts, midbrain pathways). The phenomenon of a retained pupillary function in rod/cone-less blind mice (by American geneticist Clyde Keeler in 1923) was supported by the more recent discovery of a photosensitive pigment (melanopsin) in the retinal ganglion cells of mammals, which, other than rods and cones, is capable of stimulating nonimage-forming functions, such as a pupillary light reflex.[8–10] This so called intrinsically photosensitive retinal ganglion cell (ipRGC)-mediated PLR activity can be elicited by selective stimulation of the melanopsin pigment with blue light of a narrow wavelength spectrum (480 nm). The commercially available Melan-100 unit is equipped with a powerful diode-based light source and emits blue and red light, which fits the spectral sensitivity of melanopsin (480 nm) and rod–cone opsin (630 nm) (**Figure 1.6**).

The chromatic pupillary light reflex is particularly useful in the diagnosis of retinal disease and optic nerve

Figure 1.6 **Melan-100: the commercially available instrument emits red and blue light which fits the spectral sensitivity of melanopsin (480 nm) and rod–cone opsin (630 nm) which elicits the chromatic pupillary light reflex (cPLR) assisting in the diagnosis of retinal and optic nerve disease.**

disease, as clinical studies in healthy dogs and in dogs with retinal or optic nerve disorders showed.[11,12] Assessment of cPLR is especially helpful in eyes with cataracts, prior to cataract surgery to rule out underlying retinal disease, particularly if an electroretinogram is not available. It could be shown that both blue and red light elicited a strong pupillary light constriction in normal eyes and in cataractous eyes without underlying retinal disease.[11]

Retinal degeneration, retinal detachment

Both the blue and red light cPLR responses are significantly decreased in eyes with cataracts and concurrent underlying retinal disease (degeneration or retinal detachment), with the blue light response showing a higher sensitivity and specificity in the detection of retinal degeneration or retinal detachment.[11]

Sudden acquired retinal degeneration (SARDS)

In dogs with SARDS, the red light cPLR response cannot be elicited, but the blue light response is retained in those eyes. This is explained by the complete loss of photoreceptor function but retained intrinsic melanopsin–retinal ganglion cell mediated chromatic PLR.

Optic neuritis

Blue and red light stimulation both show complete absence of cPLR function in dogs with optic neuritis.

Vision evaluation

Vision evaluation in small animals

Vision testing in animals is based on a combination of behavioral abnormalities and visual reflex testing. In many instances, the owner is not aware of an ongoing vision problem if only one eye is affected, as most dogs can adjust very well to decreased vision or blindness in one eye. In the dog with partial decrease in vision, multiple forms of visual testing are performed to satisfy the examiner that there is a deficit and to characterize it. With complete loss of vision, the result of maze or obstacle course testing is usually dramatic. Cats present a special problem in testing their functional vision because they are often reluctant to explore an area, making it difficult to differentiate a normal shy behavior pattern from a visual deficit. Testing cats in their playing behavior (e.g., pulling a string in front of them) or visual cliff testing can be very useful vision testing procedures in this species.

Menace response

The menace response is a threatening, sudden movement presented near the eye, which elicits a blink. Before testing for a menace response, the examiner must make sure the facial nerve is intact by eliciting a blink reflex through the palpebral or corneal reflex. In dogs with facial nerve paralysis but normal vision, the menace response is subtler, and retraction of the globe may be observed due to contraction of all extraocular muscles and the retractor bulbi muscle.

While menacing can still be performed without an intact facial nerve, the response is subtler. The afferent arm of this response is the visual fibers up to the visual cortex and the efferent arm is the facial nerve. Additional centers involved with the menace response are the cerebellum, the rostral colliculus, and the motor cortex. Cerebellar disease produces an ipsilateral deficit in the menace response with retention of vision (**Figure 1.7**) (see Chapter 4).[13–15] The menace response can be altered by nonvisual influences such as mental status and cerebellar disease.

When trying to elicit a menace response, avoid air currents that may stimulate the blink reflex. Presentation of fingers rather than a broad hand are used to avoid air currents. Complacent or trusting animals should have the eyelids occasionally tapped to make them more alert. The contralateral eye should be closed to determine that it was not a binocular response to the stimulus. Due to

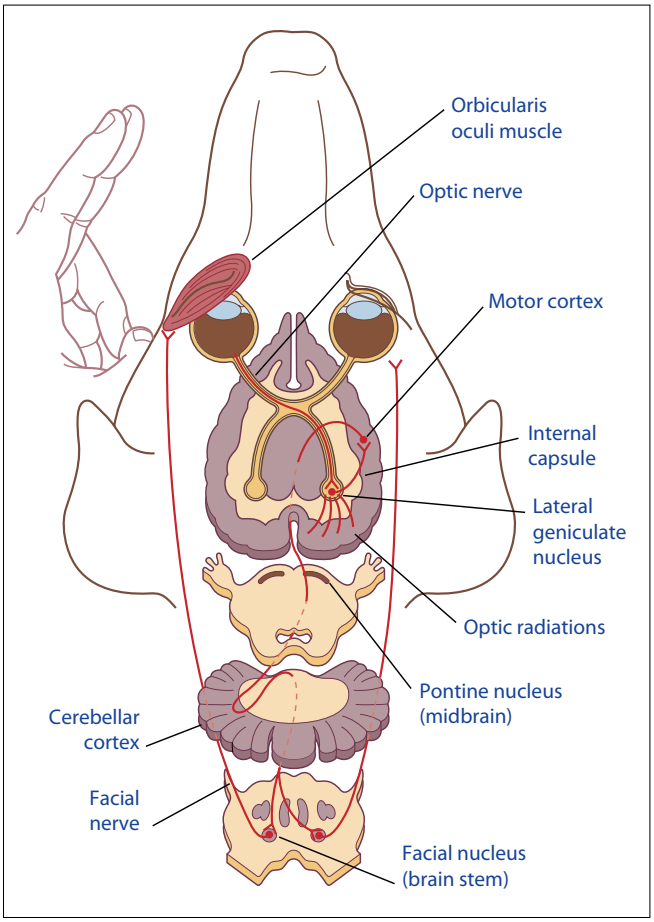

Figure 1.7 **Menace response pathways.**

Table 1.1 **Comparative visual reflexes with unilateral complete lesions within the visual system.**

LESION LOCATION	PLR	ANISOCORIA	MENACE RESPONSE	ERG
Retina	Direct absent, +MG	Mild static	Absent	Extinguished in most cases
Optic nerve	Direct absent, +MG	Mild static	Absent	Normal
Complete chiasm	Absent OU	Dilated OU	Absent	Normal
Optic tract	Present, –MG	Mild static	Homonymous field defect	Normal
Optic radiations/visual cortex	Present	None	Homonymous field defect	Normal

Source: Modified from Goldbaum et al., 1980. *Principles and Practice of Ophthalmology*, vol II. Peyman, G., Sanders, D., and Goldberg, M. (eds). WB Saunders: Philadelphia, PA, pp. 988–1097.

PLR: pupillary light reflex; **ERG**: electroretinogram; **MG**: Marcus Gunn (pupil); Homonymous: right nasal + left temporal field, or left nasal + right temporal field; **OU**: both eyes.

the mixture of ipsilateral and contralateral visual fibers, unilateral lesions above the chiasm do not produce complete blindness in an eye, and a variable menace response may be obtained depending on the visual field stimulated. The predominance of crossed fibers (65%–75%) in higher lesions results in a larger temporal field (nasal retina) defect in the eye contralateral to the defect. Nasal field defects (lateral retina) are more difficult to detect as they are smaller (25%–35%), and it is easier to stimulate the opposite eye inadvertently with movement if it is not closed. **Table 1.1** summarizes the PLR and menace responses with lesions at different anatomic locations.

Dazzle reflex

The dazzle reflex is a subcortical reflex that involves stimulating the retina with a very bright light, resulting in a bilateral narrowing of the palpebral fissure. The reflex requires the retina, optic nerve, chiasm, optic tract, and, probably, the supraoptic nuclei and the rostral colliculi.[13–15] The dazzle reflex persists with cortical blindness. A positive dazzle response helps to establish the intactness of the lower visual system when vision cannot be evaluated (such as with cataracts), and the PLR is altered due to efferent problems (such as iris atrophy, synechia).

Visual placing

Visual placing is a good test for animals with normal motor function and mental status. The animal is held in space and supported under the chest and head while approaching a flat surface such as a table. The normal response is to extend and raise the legs in anticipation of standing on the surface. If the expected response is not forthcoming, then tactile stimulation should be used to establish the normalcy of proprioception and the efferent arm of the reflex. Testing the response with both eyes open and then alternately holding the lids closed evaluates individual eyes. Approaching the surface from the lateral or medial aspect may give an indication of intactness of the visual fields.

Visual cliff

A visual cliff test evaluates not only vision but depth perception. Some cats that are functionally blind will be able to jump off a table.

Maze or obstacle course

An obstacle course in a nonfamiliar environment for the animal is one of the more common methods of evaluating functional vision. The maze test is usually useful with active animals but is often difficult to evaluate with cats that cower or do not move. The examiner usually scatters objects of varying size through the main pathway of the examination room. Most dogs move toward the exit door or the owner's voice. Repeated trials through the maze under ambient room light and with minimal light are performed. Dramatic differences in scotopic (night) and photopic (light-adapted) vision may be observed with maze testing. Patching of individual eyes can be performed; with monocular blindness, most patients become preoccupied with the bandage and remove it when the good eye is patched.

Cotton ball test

Cotton balls dropped into the visual fields of the patient are a common means to evaluate vision. Animals often get easily bored with this, so initial impressions are the most important.

Basic ophthalmic examination techniques

Schirmer tear test

Schirmer tear testing should be performed before any topical medications are placed in the eye and should be considered part of the basic data collection with every ophthalmic examination and certainly with any ocular surface disease. The test used most often in veterinary ophthalmology is the Schirmer tear test I, which measures basal and reflex secretion rate. The test is performed by bending the strip at the notch and hooking the short end

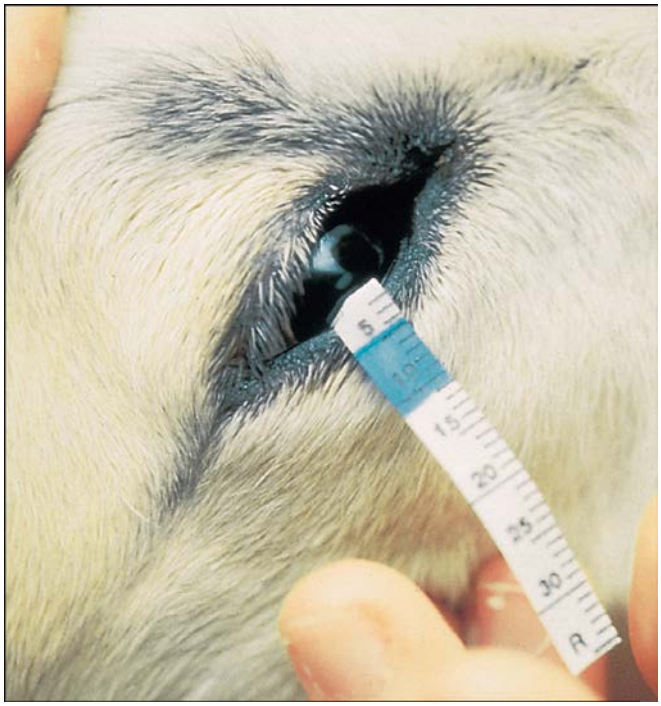

Figure 1.8 **Schirmer tear strips with an integral ruler on the strip and dye in the paper.**

over the medial lower lid into the conjunctival cul-de-sac (**Figure 1.8**). Once the strip is in place, the retention can be improved by closing the lids. The strip is removed after 1 minute, and the amount of wetting, measured in millimeters, is immediately recorded. The normal values of wetting for the dog are 20 ± 5 mm/min and for the cat are 15–17 mm/min.[16,17] The horse has been variably reported to have Schirmer values of 20–30 mm/min and 13 mm/min.[18,19] Schirmer values in the cat may be quite variable, and often a reading of 0 will be found in a perfectly normal eye. Unless there are clinical signs to reinforce the finding of a low Schirmer value, it is prudent to repeat the test later before prescribing medication for a tear deficiency.

Berger and King[20] found a statistical difference over time and between breeds in the Schirmer values of dogs, but while statistically significant, the variation would rarely be significant in making clinical decisions. Large breeds of dogs have higher Schirmer values than small breeds of dogs.[20] Hamor et al.[21] evaluated the Schirmer values in five breeds of dogs and found a difference only in the Shetland sheepdog, where values were 4–5 mm/min lower. In the dog, ocular signs are usually not associated with decreased tear production until values are between 5 and 10 mm. In the past, variations in the readings were attributable to the type of paper used in manufacture of the strips.[22] Newer strips have the measuring rule on the strip and a dye in the paper that is taken up with the tears to delineate the amount of wetting. No clinically significant differences were noted between brands of Schirmer tear test in two studies.[23,24]

The Schirmer tear test II measures the basal tear secretion by eliminating the reflex irritative component with a topical anesthetic. After application of the topical anesthetic, the lower conjunctival cul-de-sac is dried by swabbing with a cotton-tip applicator, and the tear production is measured. The basal secretion in the dog is approximately 12 mm/min.[25]

Mydriasis

PLRs are evaluated before instilling the mydriatic of choice. Most mydriatics take 10–15 minutes to act, so to conserve time, they should be given early in the examination. Mydriasis is necessary for complete ophthalmoscopy and for a thorough examination of the lens.

The mydriatic of choice for diagnostic use should be effective and short in action. Atropine in the normal dog eye lasts for 3 days and in the horse eye for 5–11 days. Tropicamide 1% (0.5% may be preferred in cats) is the preferred mydriatic for diagnostics (**Figure 1.9**).[26,27] The alkaloid drops traverse the nasolacrimal duct and, when licked from the nose, may stimulate profuse salivation in some animals due to the bitter taste. A transient, dramatic enlargement of the submandibular salivary glands has been occasionally

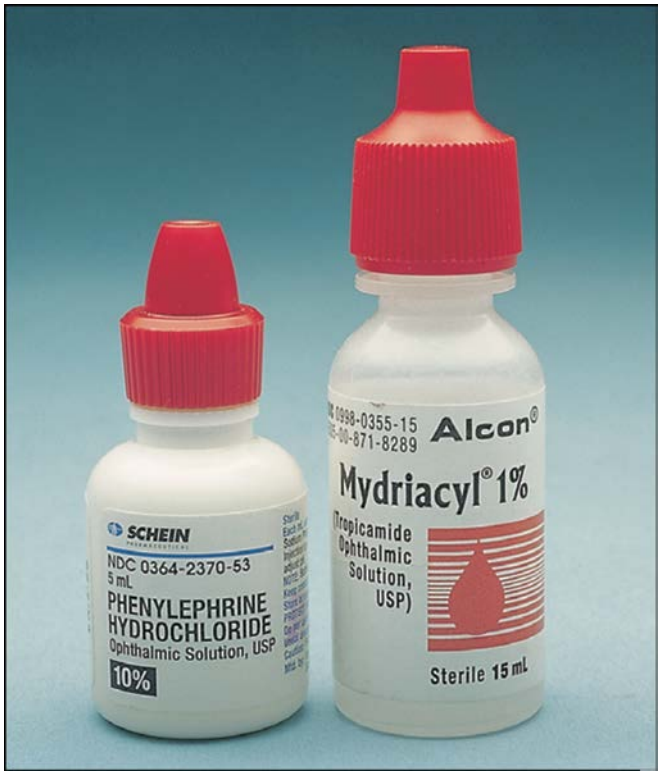

Figure 1.9 **The two common mydriatics used in diagnostic work. Note the red caps, which are typical for any mydriatic solution.**

noted in cats.[28] In young puppies, maximal mydriasis may not be achieved or may be very fleeting. Combining a parasympatholytic drug with a sympathomimetic drug such as 10% phenylephrine may be necessary for good mydriasis. Phenylephrine alone is a poor mydriatic in several species, having minimal effect in the horse and cat.[27,29] A potential systemic side effect of concentrated phenylephrine solution is systemic hypertension.[30] Mydriatics may produce elevations of the intraocular pressure that may be significant in dogs and cats.[31,32] This should be considered when readings are marginally elevated, and tonometry repeated at a later time without mydriatics.[31]

Detailed examination of the anterior segment

Magnification in the form of a loupe or slit lamp is a critical aid in ophthalmic lesion recognition due to the frequently minute nature of lesions and the structures involved. This technique is mainly limited to the anterior ocular segment and adnexa, unless the eye is aphakic. Various head loupes (**Figure 1.10**) or a magnifying lens can be utilized, but the slit lamp or biomicroscope is the most sophisticated means of accomplishing a magnified examination (**Figure 1.11**).[33–37] A simplified slit lamp consisting of a lens and a battery-operated focused light is marketed for about $500 (**Figure 1.12**) (see section Biomicroscopy, for technical details).

A bright light source such as a transilluminator is directed at various angles and may be utilized in conjunction with magnification to examine the lid margin, conjunctiva, third eyelid, cornea, anterior chamber, iris, and lens. In addition to direct illumination, proximal illumination (lighting the region adjacent to the object of regard) and retroillumination (examination against background lighting) are also helpful (**Figure 1.13**).

> Retroillumination is a rapid and sensitive method of detecting opacities in the clear media, that is, lens, cornea, vitreous, aqueous.

Figure 1.10 Examples of head loupes used for magnification.

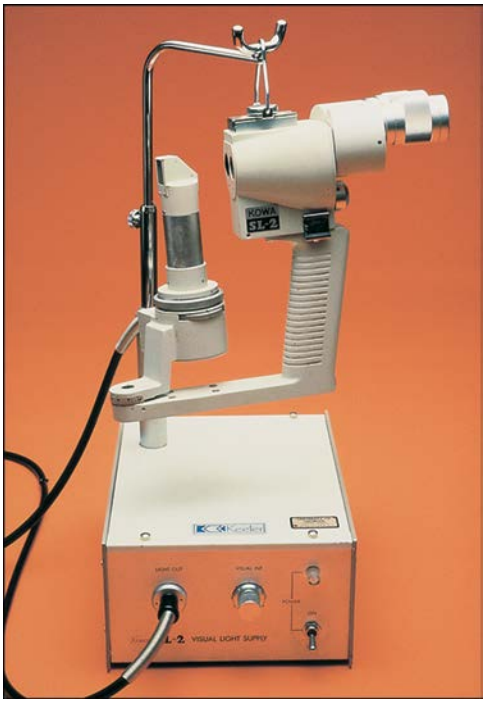

Figure 1.11 Kowa-2 portable slit lamp. It consists of a microscope, focused light, and light source connected to the microscope with a fiber-optic cable.

The lids, lid margins, and canthal regions are examined for abnormalities of the cilia and meibomian glands. The former may be difficult to detect without magnification. Retroillumination of the eyelids may be performed with a transilluminator when searching for imbedded foreign bodies. The conjunctival surfaces are examined for aberrant cilia (palpebral surface), foreign bodies, and presence of follicles, hyperemia, chemosis, symblepharon, and discharges. The cornea is examined by retroillumination of the iris and the fundus (dilated pupil) to detect small opacities and then studied in more detail in direct illumination. Irregularities of the surface, opacities, and

Figure 1.12 Relatively inexpensive portable slit lamp that consists of a 20 D lens and a focused light.

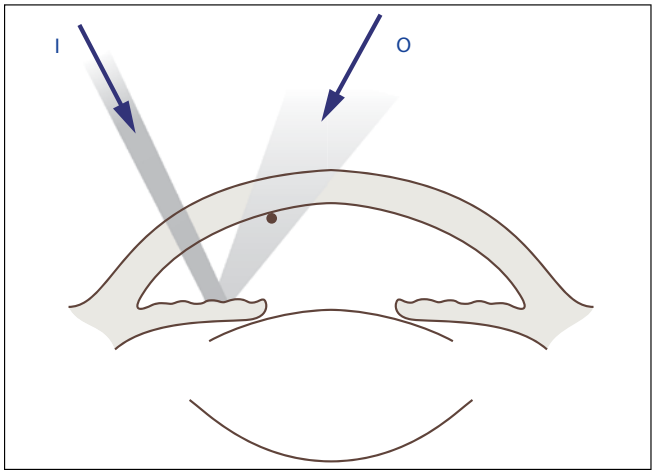

Figure 1.13 **Principle of retroillumination of an object against an illuminated background.**

neovascularization are searched for and characterized based on extent and depth.

The anterior chamber is examined for changes in depth and abnormal contents. The depth is increased with the loss of lens support (aphakia, microphakia, posterior luxated lens, hypermature cataract) and decreased with iris bombe, peripheral anterior synechiae, intumescent lens, or a mass in or behind the iris. Abnormal contents in the anterior chamber such as leukocytes, erythrocytes, fibrin, cysts, the lens, and tumors are noted. Changes in the blood–aqueous barrier can be detected by using a focused light source or thin beam of light to demonstrate the Tyndall effect or "flare" produced by an increased protein content (plasmoid aqueous) and cells in the anterior chamber (**Figure 1.14**).

The iris is examined for texture, masses, color, vascularity, pupillary membrane strands, and stability. With loss of the lens support from a displaced lens or peripheral iris adhesions, the iris trembles on ocular movement (iridodonesis). If the PLRs have not already been examined, they are recorded. The iris, particularly the pupillary region, can be examined in the retroillumination of the tapetum to detect areas of atrophy or hypoplasia. If the PLRs are incomplete or anisocoria is present, sphincter atrophy, hypoplasia, or synechiae may be responsible. The pupil is examined for irregularities in shape that may indicate atrophy or adhesions.

The lens is first examined in retroillumination from the fundus to detect opacities rapidly and then in direct and focal illumination to determine the depth of the lesion. Observed opacities are characterized by their shape, number, color, texture, and location. Irregularities on the lens surface (wrinkled capsule in hypermature cataracts), shape (coloboma, lenticonus), and size (microphakia, intumescent lens) may be observed.

The anterior vitreous can be examined for hyaloid artery remnants, veils, haze (usually protein or cells) and blood clots, and retinal detachment.

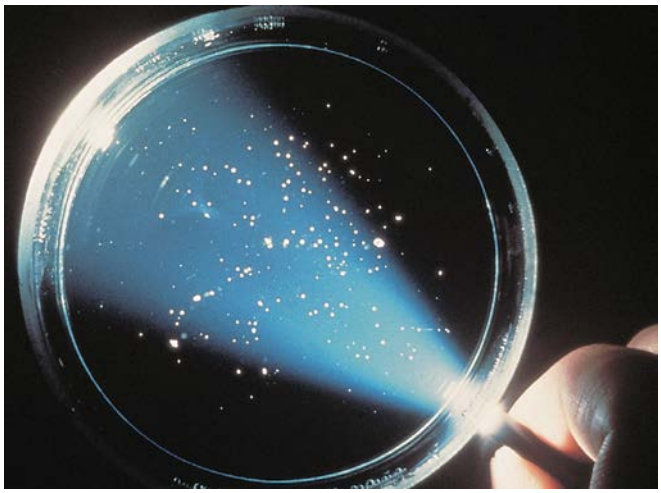

Figure 1.14 **Flare or Tyndall effect present in a petri dish that has a colloidal solution. (Courtesy of Dr. M. Wyman.)**

A magnification source is critical in ophthalmic examination and manipulations, and it is worth the investment to buy a quality instrument that is comfortable, has good optics and a reasonable focal length, and is easily adjusted.

Lacrimal evaluation tests

Schirmer tear test: See previous discussion

Phenol red thread tear test

A test utilizing a 75-mm thread impregnated with phenol red has been developed in Japan and tested in dogs and cats. The end of the thread is hooked and placed in the lower conjunctival cul-de-sac, similar to a Schirmer tear strip. Tears turn the indicator red as they progress down the thread. The small size of the thread does not create as much irritation on insertion as the Schirmer tear strip, and the reading may be more indicative of the basal tear secretion. The wetting is measured after 15 seconds; the mean wetting for normal dogs is 34 ± 4 mm and 23 ± 2 mm in cats.[38,39]

Tear break-up time (BUT)

While previously discussed tear evaluation tests evaluate quantity, the tear BUT test is an attempt to evaluate the quality of the tears. The test is performed by instilling fluorescein on the cornea and not allowing the patient to blink while observing the intactness of the fluorescein in the tear film. The time from instillation of fluorescein to the breaking up of the fluorescein sheet is the BUT. It can be difficult

to perform in animals because while the lids can be held open, the third eyelid cannot be controlled. This test is not performed routinely but may be indicated in various superficial keratopathies. The normal BUT in the dog is reported as 19–20 ± 5 seconds.[40] A recent study in cats showed a significant reduction of the BUT in cats with conjunctivitis and the authors suspect that deficient tear film quality in those cats may predispose to the development of conjunctivitis.[41]

Ocular staining

Fluorescein

Topical sodium fluorescein is an invaluable tool in detecting corneal epithelial defects as well as in monitoring the healing process. Fluorescein is utilized mainly as single-use strips, since it was discovered that the solution was a good culture medium for *Pseudomonas* spp.,[42] although this has recently been brought into question.[43] If used as a 1%–2% solution in multiple-use bottles, care must be taken to avoid contamination. Some clinicians make a fresh solution daily by placing a strip in a 3- to 6-mL syringe and filling it with sterile saline. This may be easier to apply in the horse, but false-negative staining may be encountered with this method because the fluorescein is too dilute.

Hydrophilic fluorescein cannot penetrate the normal lipophilic epithelium, and thus is not normally retained. If intercellular junctions are widened or loss of epithelium occurs, fluorescein is retained by the epithelium or stroma, respectively, and is visible as a bright green stain (**Figure 1.15**).[44] Staining of extensive ulcerations may result in the fluorescein being visible in the aqueous. The corneal staining is transient (about 15–30 min), although in devitalized corneas it may persist for several hours.

If fluorescein strips are used and the ocular surface is not very moist, adding one to two drops of eyewash to the strip ensures an adequate quantity of solution on the eye.

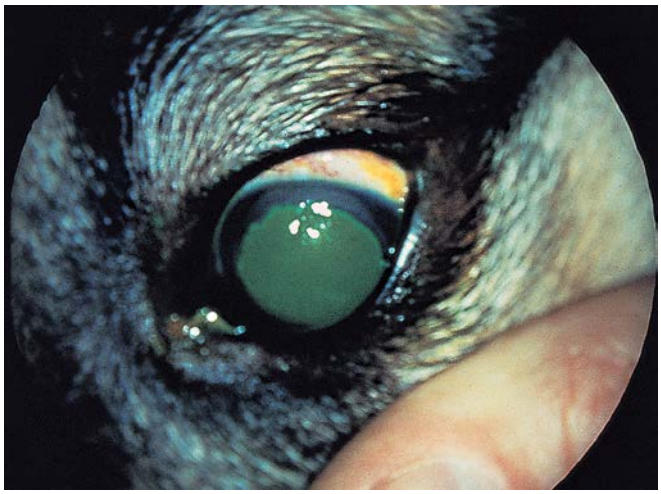

Figure 1.15 **Fluorescein staining of a superficial ulcer.**

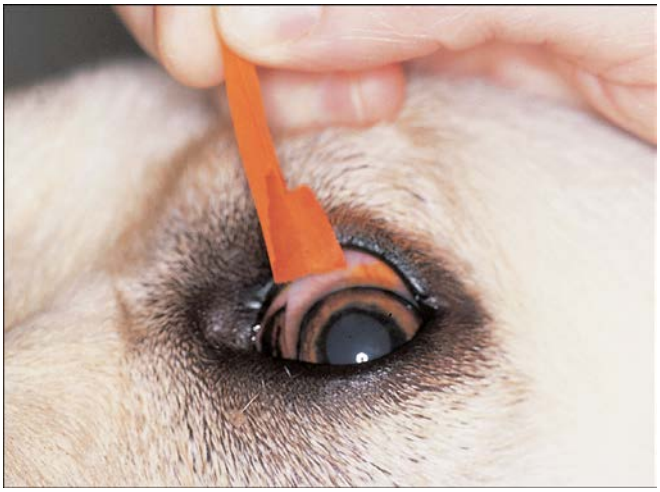

Figure 1.16 **Application of a moist fluorescein strip to the conjunctiva.**

If a dry strip is touched to the eye for moisture, it should be placed on the conjunctiva rather than the cornea (**Figure 1.16**). Touching the cornea with the strip may give a slight positive staining at the point of contact. The eye is rinsed thoroughly with eyewash to remove excess fluorescein and mucus, and the retention of stain is evaluated. With small defects such as herpes epithelial ulcers in cats, the use of an ultraviolet light (Wood's light) or cobalt-blue filter in a dark room causes fluorescence of the fluorescein, making minute stain retention visible.

Other uses for topical fluorescein stain in ophthalmology are to detect aqueous leaks in perforating corneal wounds (Seidel test) and to determine patency of the lacrimal outflow system. The Seidel test is performed by applying a high concentration of fluorescein at the site in question without rinsing. The concentrated fluorescein is orange; if aqueous is leaking from the site, a dark rivulet forms in the orange background. Evaluation of nasolacrimal duct patency with fluorescein is performed by applying fluorescein to the eye and observing its appearance at the nostril (**Figure 1.17**). Fluorescein can normally be observed at the nostrils within a few minutes. A normal test does not ensure the entire lacrimal ductal system is patent, as only one patent lacrimal canaliculus and punctum is necessary for a positive test. The absence of fluorescein may be due to ductal obstruction or an anomalous orifice into the nasal cavity.

Fluorescein may be given IV as a 10% solution to visualize the fundus vasculature or the iris vessels (see section Fluorescein angiography) and to measure limb-to-retina circulation time.

Rose bengal

Rose bengal is a fluorescein derivative of the xanthene group, and it has been used in ophthalmology as a 1%

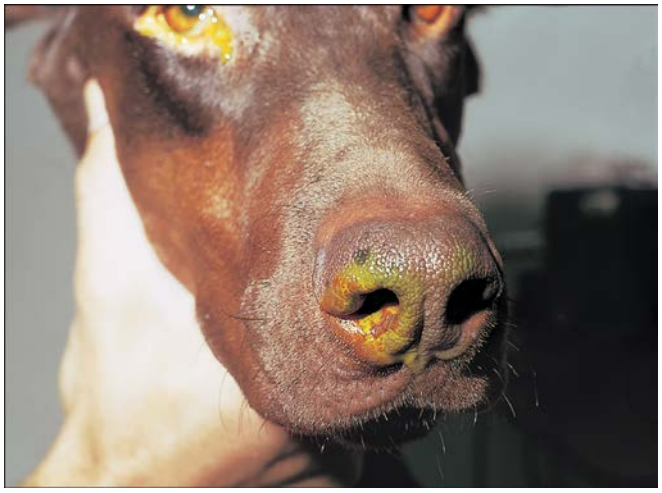

Figure 1.17 **Fluorescein staining visible in the nose after application to the eye of a dog.**

solution. Rose bengal was originally characterized as a supravital stain that only stained degenerate epithelial cells and mucus. Its main use has been in staining devitalized cells in keratoconjunctivitis sicca (KCS), and it is thought to be more sensitive than the Schirmer tear test (**Figure 1.18**).[45] Rose bengal has also been used to stain herpes epithelial ulcers and dysplastic epithelial cells with squamous neoplasia. Recently, the mechanism of action of rose bengal has been questioned. Cell culture evidence indicates that rose bengal stains cells that do not have a mucus layer or the cornea with a deficiency of the preocular tear film.[46] Rose bengal, therefore, stains healthy cells if they are not protected by mucin, and it is intrinsically toxic to cells in concentrations >0.01%. Exposure to light releases oxygen radicals, which are toxic to cells.[46] Rose bengal is also virucidal and bactericidal, and cultures should be obtained before application of the stain. In a mouse herpesvirus model, no virus could be isolated after a single topical application of 1% rose bengal.[47]

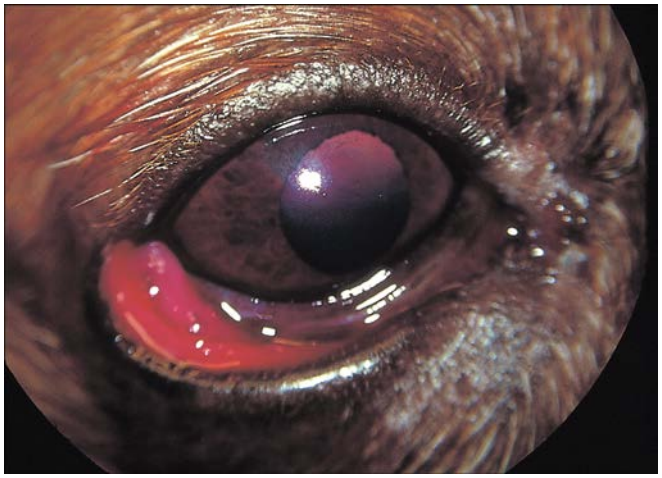

Figure 1.18 **Faint rose bengal staining of the cornea and conjunctiva of a dog with KCS.**

Special ophthalmic examination procedures

Microbiologic cultures of conjunctiva/cornea

If the type of discharge, history of chronicity, lack of response to therapy, or severity of the problem indicates serious or resistant infectious agents are involved, cultures should be obtained early in the examination before the use of topical anesthetics. Topical anesthetics may be bactericidal. Ideally, even if the problem is unilateral, cultures of both eyes are preferred for comparative purposes, but due to the additional expense, this practice is usually not followed. *Staphylococcus* spp. and *Streptococcus* spp. are the most consistent flora of the normal and diseased conjunctiva.[48–53] The swab may be moistened with sterile nutrient broth or saline before use to make the procedure more comfortable and increase the growth rate.[54] Calcium alginate swabs have been reported to yield a higher growth rate.[50] Swabs should be placed in a transport medium or immediately plated to prevent drying of the small samples. Commercial culturettes with transport media and fine tipped swabs are convenient and easy to place on small lesions and avoid contamination from adjacent structures (**Figure 1.19**).

Conjunctival and corneal cytology

Scraping the conjunctiva and/or the corneal surface after topical anesthesia and examining the cells may enable a rapid etiologic diagnosis to be made or may guide initial therapy. The scraping may be performed with various instruments. A metal instrument is used if the surface must be debrided to get to the level of the pathology. A malleable platinum spatula (Kimura) is commercially available but expensive. The author simply uses the noncutting end of a sterile scalpel blade as a convenient disposable sterile scraper (**Figure 1.20**). For surface cytology, a small

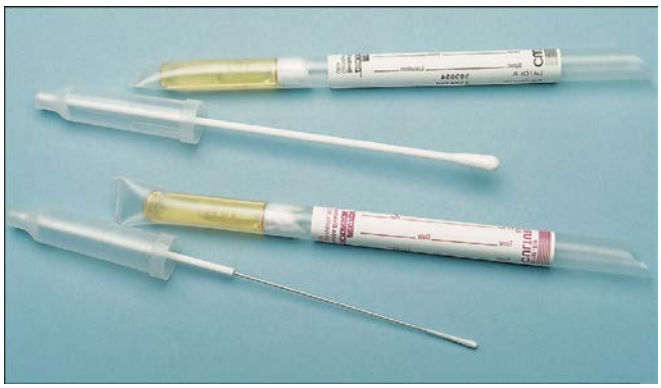

Figure 1.19 **Fine- and course-tipped culture swabs with transport media.**

Figure 1.20 Preparation of #10 Bard Parker blade for use as a scraping instrument to obtain cytology and culture specimen.

disposable nylon bristle brush has given superior preparations and is easier to insert into the conjunctival cul-de-sac of cats (**Figure 1.21**).[55,56] Slide preparations made with the brush have fewer cells, but the cells are scattered and not clumped as with a spatula. The material is transferred to glass slides, air dried and fixed, and can be stained with a variety of stains such as Giemsa and Gram stains. The slides are evaluated for cell type, bacteria, viral and chlamydial inclusion bodies, fungi, and foreign material (see Chapter 8).[57]

Cannulation of the lacrimal outflow system

Cannulation and establishing patency of the lacrimal outflow system is indicated with a problem of epiphora or a resistant or relapsing conjunctival infection. This is readily performed in most dogs with topical anesthesia and using restraint in lateral recumbency. A blunt 22-gauge needle, or a commercial malleable lacrimal needle on a 6-mL syringe, is passed into either the upper or lower punctum. The upper punctum is usually more accessible. Ensuring the lid is kept taut, threading the catheter down the canaliculus, and keeping it parallel to the canaliculus all help to prevent kinking and obstruction by the wall of the canaliculus, thus avoiding a false impression of a pathologic obstruction (**Figure 1.22**).

Resting the hand with the syringe against the animal's head minimizes traumatizing the duct if minor head movement occurs. A fountain of fluid should emerge from the opposite punctum and the nostril. If fluid is not observed at the nostril, the opposite punctum is occluded while flushing to force more fluid down the nasolacrimal duct. Imperfect nasolacrimal ducts result in some dogs in fluid running posteriorly into the pharynx, and the patient often starts to choke, sneeze, and swallow. If an obstruction is present, heavy sedation or general anesthesia may be required, as the force necessary to unblock the obstruction is painful.

Cats are more difficult to cannulate because of the small canaliculus and the animal's temperament. A 25- to 27-gauge blunt needle, ketamine sedation, and a loupe should be used to obtain best results.

The horse's nasolacrimal system is most easily evaluated by retrograde flushing from the nasal end of the nasolacrimal duct. A #8 French urinary catheter or infant feeding tube may be passed in a retrograde direction and

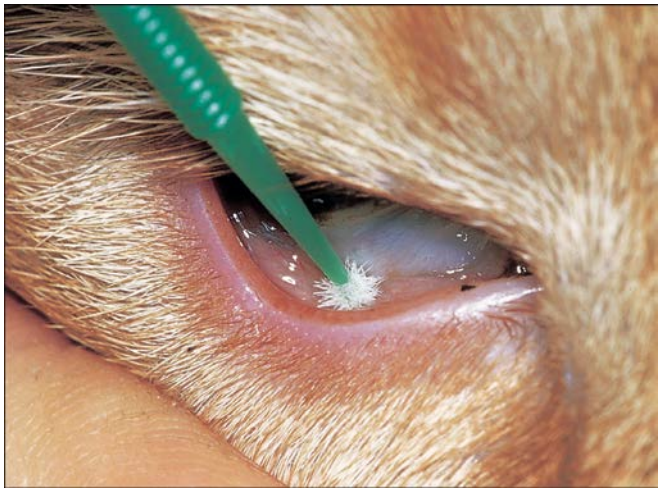

Figure 1.21 Cytobrush used for collecting conjunctival cells. (Courtesy of Dr. M. Willis, The Ohio State University.)

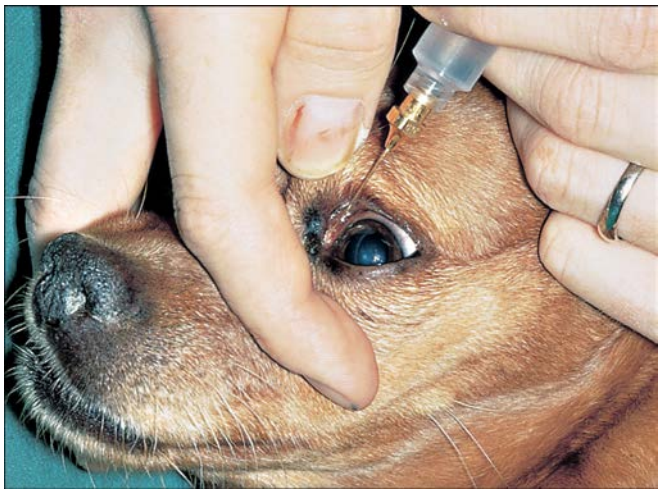

Figure 1.22 Flushing the nasolacrimal duct of a dog through the upper canaliculus, which is usually the easiest to expose and make taut. Note the lateral recumbency of the patient and resting of the examiner's hand on the patient's head.

attached to a syringe for flushing. If the nasolacrimal duct is blocked, the puncta are easily cannulated after sedation.

Double eversion of the eyelids and membrana nictitans

The palpebral conjunctiva and bulbar surface of the third eyelid can be examined by a process of double eversion. Double eversion is performed under topical anesthesia by gently grasping the lid margin with forceps and lifting it up and caudally from the eye, while using an instrument such as a strabismus hook near the base of the lid to push toward the eye. This causes the lid to roll back over the hook, exposing the palpebral conjunctiva (**Figure 1.23**). This maneuver also can be performed on the third eyelid to expose the lymphoid follicles and gland. It is invaluable in searching for hidden foreign bodies and evaluating the tissue pathology.

Tonometry

The measurement of intraocular *pressure* may be made with a variety of instruments, all of which were designed for use on humans. **Indentation tonometry** is exemplified by the Schiotz tonometer, which is of relatively low cost but more difficult to handle and not suitable for all animals. This instrument measures the amount of corneal indention produced by a given weight, and the scale reading is converted to millimeters of mercury with conversion tables (**Figure 1.24**). Conversion tables for dogs and cats have been calculated, and they result in higher IOPs than comparable scale readings on the human conversion table.[58,59] The normal IOP for most species is considered to be <25–30 mmHg (3.3–4.0 kPa) on the human scale.[60–64] The difference in IOP between the two eyes should be ≤8 mmHg (1.07 kPa).[61]

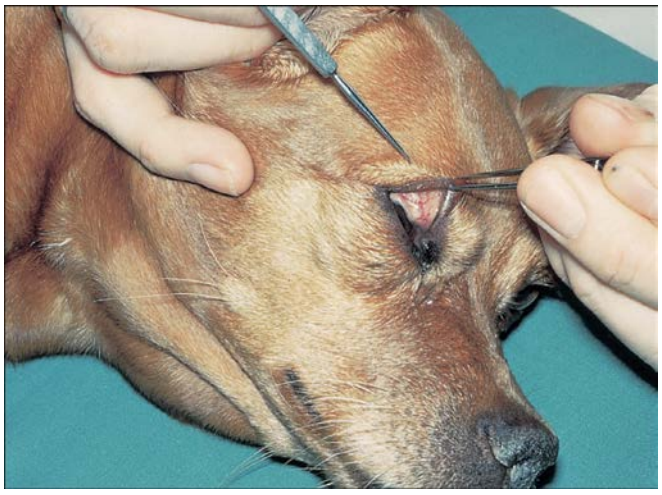

Figure 1.23 **Double eversion of the upper eyelid of a dog to examine the palpebral conjunctiva.**

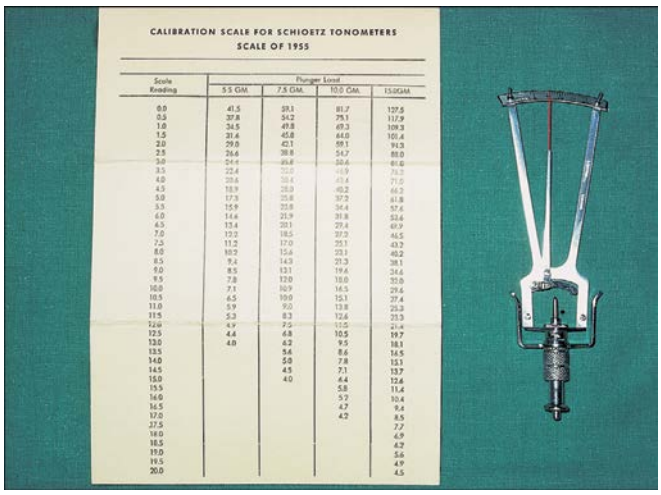

Figure 1.24 **Schiotz tonometer with conversion scale.**

After topical anesthesia is administered, the animal is placed in dorsal to dorsolateral recumbency so that the eye being measured is directed vertically. The tonometer is allowed to rest with its full weight on the central cornea for 1–2 seconds (**Figure 1.25**). The scale reading is noted, and this is repeated three to four times to determine consistency. Although most animals object to being placed on their sides or backs, the sitting patient usually presents with poor eye position because of the vestibular-ocular reflex that often results in the tonometer being placed near or over the limbus. The body position alters the IOP in man and animals. In the dog, dorsal recumbency increased the mean IOP over sternal and sitting positions

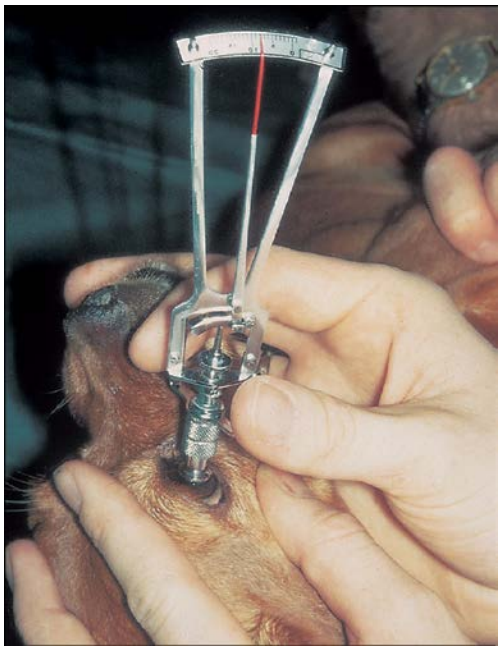

Figure 1.25 **Application of the Schiotz tonometer to the axial cornea with the dog in dorsal recumbency.**

Figure 1.26 **Tono-Pen with cover. The average IOP reading is displayed.**

by 1.5–2 mmHg utilizing the Tono-Pen, but this difference decreased over 3–5 minutes.[65]

Inaccurate or spurious values with the Schiotz tonometer can be produced by dried mucus and tears that have wicked up the plunger, a small corneal curvature (microphthalmos overestimates IOP), a large corneal curvature (such as in buphthalmos, which underestimates IOP), corneal scars, corneal edema, an anterior luxated lens, and transference of pressure to the globe while holding the lids open.

Applanation tonometry measures the force necessary to flatten a given corneal area and may be measured with a variety of instruments. A small handheld electronic applanation tonometer, the Tono-Pen, appears almost ideal for veterinary medicine (**Figures 1.26 and 1.27**). It is portable, consistent, apparently accurate, and easily used on most species including exotics; however, it is expensive. The plunger is 1.5 mm in diameter and is covered with a latex membrane to avoid disease transmission and, more importantly, to avoid tears wicking up the plunger. Light tapping anywhere on the central two-thirds of the cornea perpendicular to the point produces accurate readings.[66] Acceptable readings are indicated by a clicking sound. Three to six acceptable readings are averaged, a tone sounds, and the mean value is displayed in a window with a bar over the coefficient of variance of the readings from 5% to >20%. The Tono-Pen appears to overestimate IOP in the low range, is very accurate in the normal range, and underestimates IOP in the high range in the human, dog, and cat.[67–70] Using the Tono-Pen, mean IOP in the dog was 19 ± 6 mmHg[71] and 17 ± 4 mmHg,[69,70] and in the cat was 20 ± 6 mmHg.[69,70] In the horse, the instrument underestimated the IOP at all pressures, although by a predictable amount. In the horse, wide fluctuations in IOP can be measured that are not eliminated by auriculopalpebral nerve block. In the horse, when the head was above the heart, the IOP was decreased (mean 17.5 mmHg), and when lowered below the level of the heart, the IOP was increased (mean 25.7 mmHg) in 87% of the subjects. The difference was as much as 28 mmHg, with a mean of 8 mmHg.[72] As unsedated horses frequently raise their head when their eyes are being examined and the head is dropped with xylazine sedation, the difference in IOP measurements may be significant.[72] The mean IOP in the normal horse was 23 mmHg with the Tono-Pen.[73]

Rebound tonometry. A new tonometer, marketed as the TonoVet, is based on measuring the deceleration of the impact of a probe when it strikes the cornea, the soft eye producing less or slower rebound than the firmer eye. This principle is termed impact or rebound tonometry. The advantages of rebound tonometry are no topical anesthetic is required, it is slightly more accurate at all IOP levels, the status of the cornea may not be as critical due to the small contact surface, and the instrument is not as subject to operator error. The instrument must be used on the horizontal plane, it is heavier than the Tono-Pen, and the probes or tips are replaced between patients to minimize contamination (**Figures 1.28 and 1.29**).

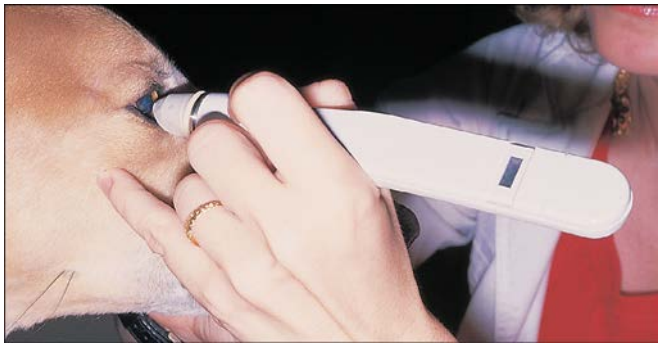

Figure 1.27 **Tono-Pen in use by lightly tapping the cornea.**

Figure 1.28 **Rebound tonometry using the TonoVet in a dog.**

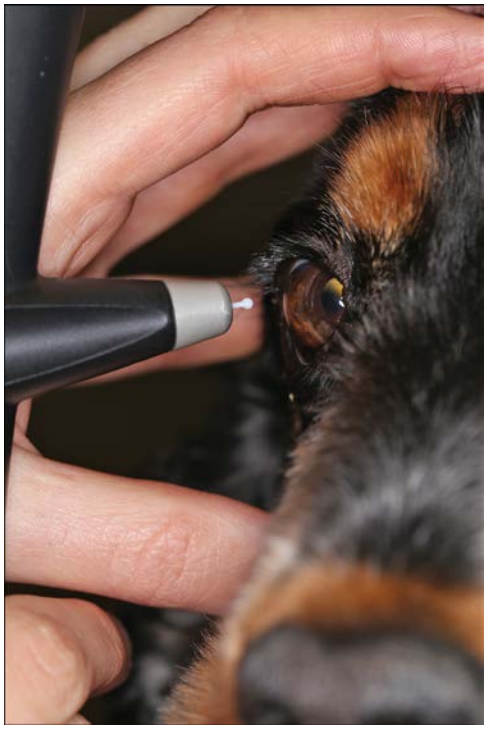

Figure 1.29 **The small steel wire covered with a round plastic tip is expelled from the instrument with high speed onto the cornea.**

Normal intraocular pressure values using a rebound tonometer have been established for dogs and horses and were 10.8 ± 3.1 mmHg (range, 5–17 mmHg) and 22.1 ± 5.9 mmHg (range, 10–34 mmHg) for dogs and horses, respectively. Comparing the mean measurements of IOP of normal dogs and horses using the Tono-Pen and TonoVet, the TonoVet recorded IOP 2 mmHg lower in the dog and 1 mmHg higher in the horse.[74]

In another study comparing the measurements obtained from a rebound tonometer (Icare) and applanation tonometer (Tono-Pen XL) in dogs, the measurements were comparable, although the values obtained with the rebound tonometer were significantly lower.[75]

Rusanen et al.[76] evaluated and compared the values of the rebound and applanation tonometer readings in normal cats and found that the mean IOP readings obtained with the rebound tonometer were 2–3 mmHg higher than measured with the applanation tonometer. The mean IOP with the rebound tonometer and applanation tonometer were 20.74 and 18.4 mmHg, respectively.[76]

Gonioscopy

Gonioscopy is the act of viewing the iridocorneal angle. This region contains the aqueous outflow pathways and thus is important in the pathogenesis of many glaucomas. To view the iridocorneal angle adequately, a contact lens is necessary to allow light to exit the cornea (**Figure 1.30**). Gonioscopy is performed after ophthalmoscopy because the coupling fluid utilized under the lens interferes with ophthalmoscopy. The procedure can be accomplished with topical anesthesia and manual restraint in lateral recumbency or in a sitting position (**Figure 1.31**). A variety of gonioscopic lenses designed for use in human medicine are available, and most are applicable to the dog and the cat (**Figure 1.32**). A strong light and a source of magnification are necessary. This can be provided by an otoscope head, a loupe and transilluminator, or by a slit lamp. In addition to investigating the pathogenesis of glaucoma, gonioscopy is useful in evaluating lesions of the peripheral

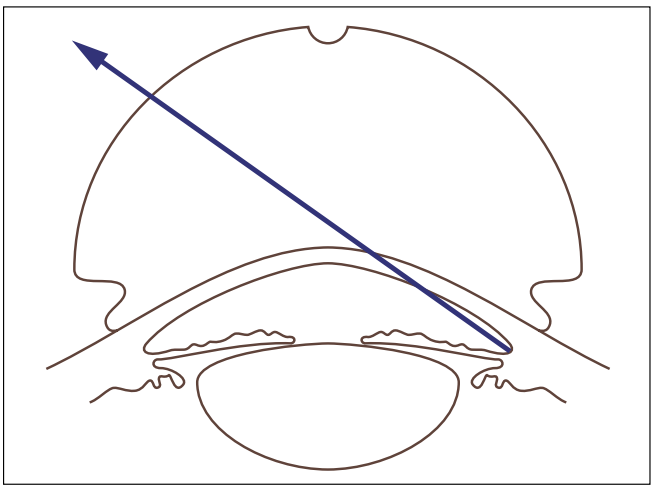

Figure 1.30 **Demonstration of light exiting from the angle when a contact lens is applied for gonioscopy. The light can now exit the cornea because the refractive index has changed from the cornea to plastic (or glass), and the curvature of the lens is different from the cornea, allowing light to exit. Note where the examiner must be positioned to view the opposite angle region.**

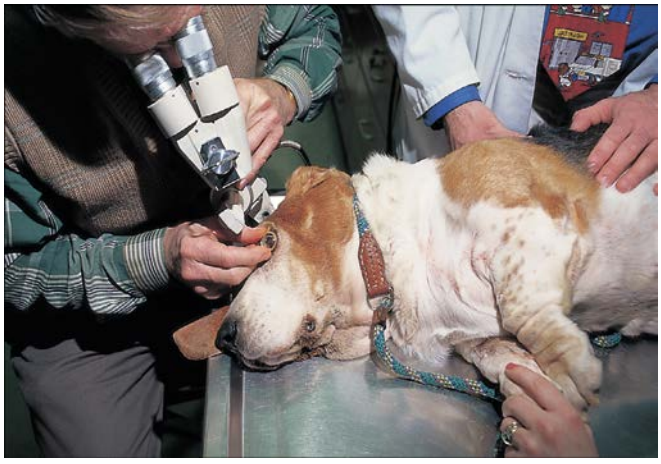

Figure 1.31 **Performing gonioscopy in a nonsedated dog utilizing a slit lamp and a Franklin goniolens.**

Figure 1.32 **Various goniolenses. Left to right are: Cardona-type lens that attaches to a fiberoptic light cable, Franklin lens with sialastic flange, and a three-mirror prism.**

anterior chamber such as iris cysts, foreign bodies, tumors of the region, and traumatic lesions.[61,62,77–79]

The normal iridocorneal region in carnivores is dominated by a well-developed pectinate ligament with a bluish-white trabecular region in the background (**Figure 1.33**). (For further discussion on gonioscopic findings see Chapter 12, Glaucoma.)

Ophthalmoscopy

Ophthalmoscopy is one of the most difficult routine procedures that the veterinarian is asked to master. The traditional direct ophthalmoscope (**Figure 1.34**) is not the instrument of choice in small animal practice because of the inherent magnification and lack of stereopsis. The technique of direct ophthalmoscopy is most applicable in large animals because the larger eye has less inherent magnification (see **Table 1.1**).[80] Binocular or monocular indirect ophthalmoscopy is preferred in the dog and the cat (**Figure 1.35**). The main disadvantage of the binocular indirect ophthalmoscope is the cost, but essentially, all that is necessary for indirect ophthalmoscopy is a condensing lens and a good light source.

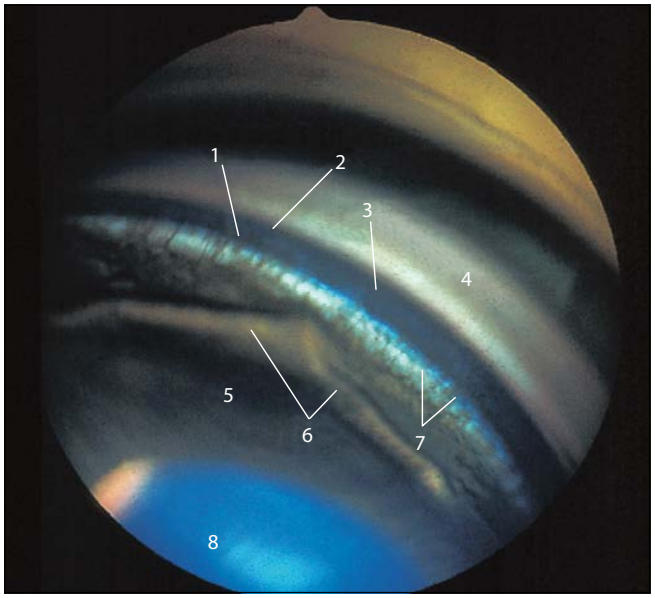

Figure 1.33 **Gonioscopic view of a normal canine iridocorneal angle with various anatomic landmarks. (1: Deep pigmented zone; 2: Superficial pigmented zone; 3: Uveal trabeculae in ciliary cleft; 4: Sclera; 5: Iris; 6: Major arterial circle; 7: Pectinate ligament; 8: Pupil.)**

Figure 1.34 **Direct ophthalmoscope. Power sources may be battery, rechargeable battery, or wall transformer.**

Figure 1.35 **Binocular indirect ophthalmoscope. This unit has a rechargeable battery transformer that allows portability.**

With either technique, the pupil should be well dilated for a thorough examination. Examination of the ocular fundus should include evaluating the optic disc for size, color, elevations, depressions, vascular pattern, and shape. The tapetum, if present, is evaluated for its reflectivity, mosaic detail, color, size, and retinal vascular pattern. The nontapetum is evaluated for pigment density, mottling, and vascular patterns. The normal dog's ocular fundus has more variations than that of other domestic animals and thus can present difficulties for even an experienced examiner in differentiating mild pathology from extremes in normal variations (see Chapter 14).

Direct ophthalmoscopy

Direct ophthalmoscopy is the classical form of ophthalmoscopy and the procedure with which veterinarians are most familiar. The direct ophthalmoscope is often purchased as a set with an otoscope. Many of the principles of direct ophthalmoscopy involving lesion localization and alignment also apply to the indirect ophthalmoscopy.

The direct ophthalmoscope consists of a power source whose light is reflected through a prism into the patient's eye (**Figure 1.36**). The light is then reflected back through the pupil through a movable lens in the ophthalmoscope to the observer. When examining an animal with frontal eyes and a long nose, it is usually mechanically advantageous for the examiner to avoid the patient's nose by using his/her left eye to examine the patient's left eye and his/her right eye to examine the patient's right eye. This is not as important in the horse and cow, which have laterally placed eyes. Alternating eyes in the examination takes practice as most people have a dominant eye that they prefer to use. Some of the principles that Dr. William Havener espoused when teaching ophthalmoscopy are described in the following section.[81]

There are two dials for adjustment in the basic direct ophthalmoscope. The examiner looks through an aperture of the large dial that contains a series of small lenses that can be rotated into viewing position (**Figure 1.34**). The numbers visible on rotating the large dial indicate the strength of the lens that is in place, expressed in diopters. A diopter is the reciprocal of the focal length of the lens in meters, that is D = 1/focal length in meters. The black or green numbers represent plus (+) lenses that are convex or converging lenses. The red numbers represent minus (–) lenses that are concave or diverging lenses.

The second adjustment possible is one that selects the light beam size, shape, and color. Most of the examinations are performed with white light using the large circular aperture. Additional apertures usually available are a smaller circular aperture, a grid aperture, a streak or slit aperture, and often various filters such as blue and red-free filters. The small circular aperture is usually used for proximal illumination, the grid to measure relative sizes of lesions, and the streak to detect irregular contours such as elevations and depressions. The blue filters are used to examine the nerve fiber layer and the red-free filter to examine blood vessels.

Initially the emmetropic (no refractive error) examiner sets the diopter setting on zero with the large circular aperture and places himself about 46–61 cm (18–24 in) from the patient. The examiner must align with two apertures, the aperture of the ophthalmoscope and the aperture of the pupil of the patient. By placing the ophthalmoscope snugly into the brow, the aperture of the ophthalmoscope is steady and constant, and the peripheral view through the aperture is maximized (**Figure 1.37**). The examiner then aligns the ophthalmoscope light with

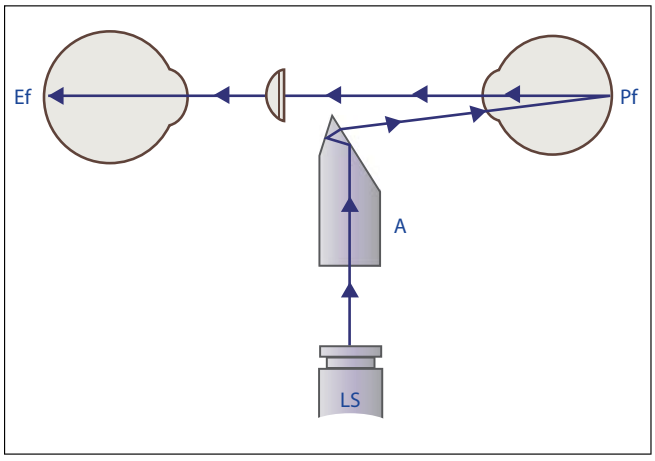

Figure 1.36 **Direct ophthalmoscope light pathways. (Pf: patient's fundus; Ef: Examiner's fundus; LS: Light source; A: Prism or mirror.)**

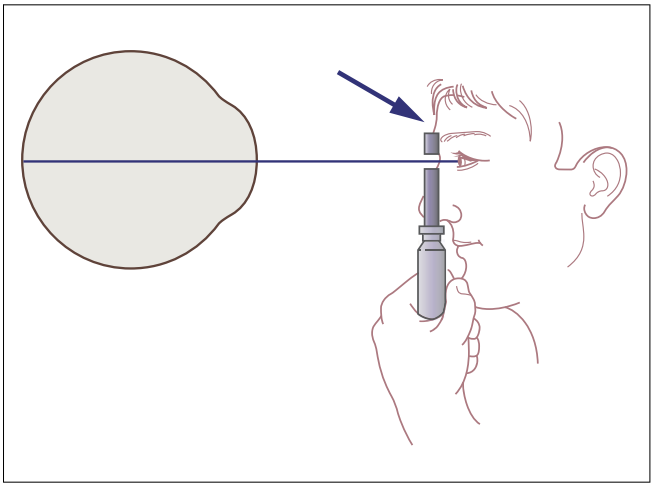

Figure 1.37 **Placement of the ophthalmoscope into the brow to eliminate movement in relationship to the ophthalmoscope and to maximize the observer's field of view.**

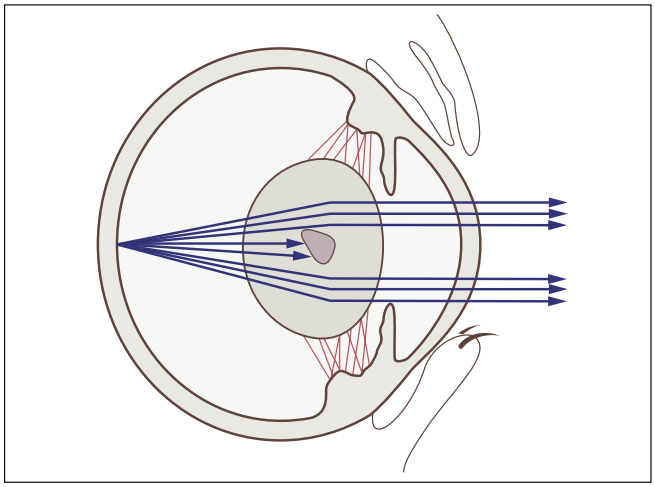

Figure 1.38 **Retroillumination of a lenticular lesion from the fundus reflection.**

the patient's pupil by finding the fundus or tapetal reflection. This usually is a bright, green-yellow tapetal colored reflection through the dog or cat's pupil. This serves to align the light correctly and quickly, and it is a very sensitive means of picking up central opacities in the clear ocular media in front of the retina, that is vitreous, lens, anterior chamber, and cornea by retroillumination. Even small opacities can be detected as darker regions against the fundus reflection due to the blockage of returned light to the observer (**Figure 1.38**). The examiner often cannot localize the opacity in depth with this method but is alerted to the pathology. This technique is a quick screening technique, and with a trained eye, it is a very sensitive test for detecting axial opacities.

One of the difficulties in veterinary ophthalmoscopy is a lack of patient cooperation, with constant head and eye movement causing the examiner to lose the fundic image. The quickest method of regaining alignment with the patient's pupil is to back up 30 cm (12 in) or more, find the tapetal reflection, and then move close again. It is much easier to regain the alignment at a distance, since small variations in the angle of incident light are magnified at the patient level.

Ophthalmoscopy should be performed close to the eye and through a dilated pupil. The closer to the eye and the more dilated the pupil, the greater the peripheral area that can be examined (**Figure 1.39**). Ophthalmoscopy should also be performed in a dark environment to maximize the contrast to the observer's eye.

A bright specular reflection is present from the corneal surface and is often quite annoying. Specular reflections are the light rays being reflected directly back from the cornea to the observer, and they can drown out fundus detail. If the pupil is dilated, this reflection can be displaced by shifting the light slightly off center on the cornea. If the pupil is miotic, this cannot be done as the light will strike the iris (**Figure 1.40**).

In summary, find the fundus reflection, and check for opacities of the clear ocular media (anterior chamber, cornea, lens, vitreous), then move in close to the patient and perform ophthalmoscopy through a dilated pupil and in a dark room.

The optic disc in a dog is about 1.5-mm diameter (1,500 μm). With the 17× magnification of the direct ophthalmoscope, structures approximating 30–90 μm in diameter can be visualized (**Table 1.2**; **Figure 1.41**). Because

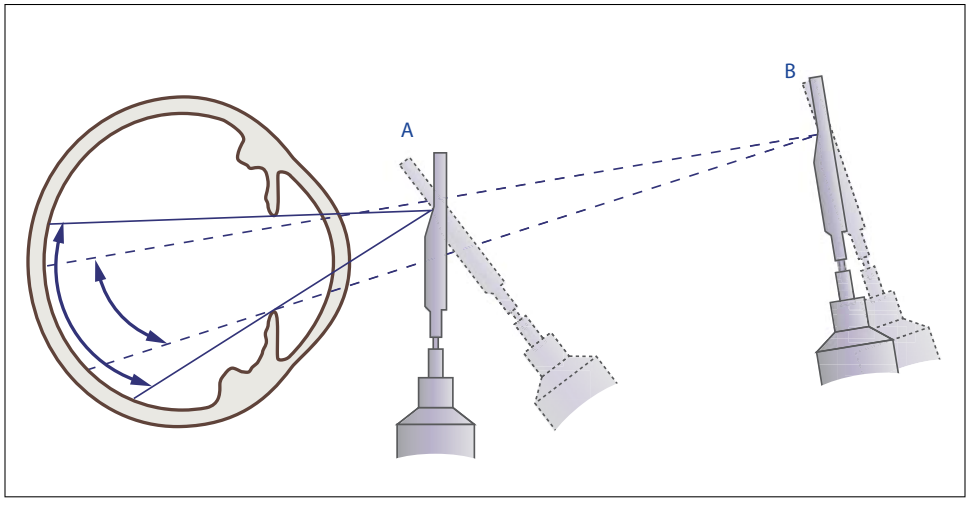

Figure 1.39 **Illustration of how dilating the patient's pupil and moving close to the eye (A) increase the field of observation (compare with B).**

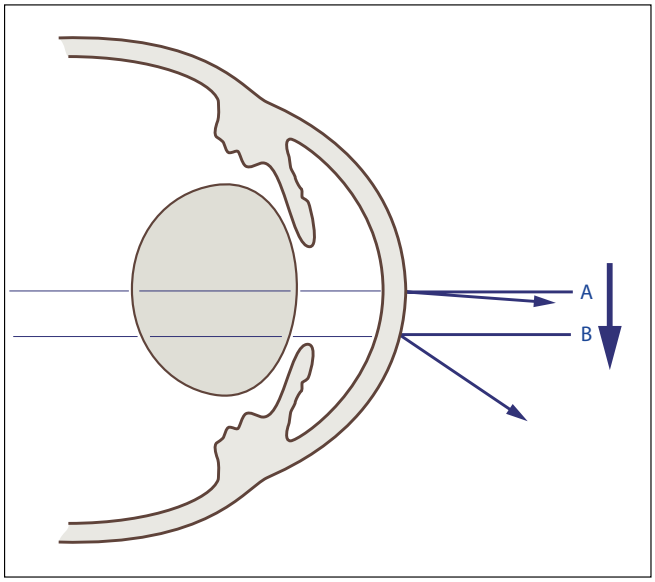

Figure 1.40 **Illustration of how to avoid specular corneal reflections by movement of the light slightly off the axis to point B.**

lesions are often microscopic, it is important to appreciate the histology of the fundus. The normal sensory retina is transparent, and what are visualized are columns of blood (healthy vessels are transparent), pigment, and the optic nerve. In most domestic animals, the tapetum that is in the superficial choroid and in the dorsal half of the fundus is also observed. The retina consists of the pigment epithelium and the neurosensory layers. A potential space exists between the pigment epithelium and the photoreceptors (**Figure 1.42**), which was the cavity of the embryonic optic vesicle before invagination occurred to form a cup and bring the two layers of the neuroectoderm in apposition. It is at this potential space that retinal detachments occur, which technically are retinal separations.

Table 1.2 **Magnification factors for direct ophthalmoscopy.**

SPECIES	LATERAL MAGNIFICATION	AXIAL MAGNIFICATION
Horse	7.9	84
Cow	10.59	150
Sheep	13.89	258
Human	14.66	287
Pig	15.15	307
Dog	17.24	397
Cat	19.50	508
Rabbit	25.25	853
Rat	77.18	7,965

Source: Modified from Murphy and Howland, 1987. *Vision Research* 27: 599–607.

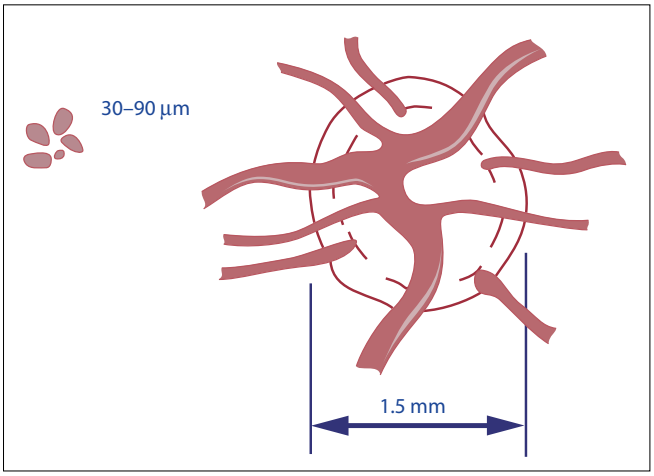

Figure 1.41 **Illustration depicting lesions that are <0.1 of a disc diameter (DD) or in the micron range.**

The holangiotic (retinal blood vessels over the entire retinal surface) fundus has two sources of blood vessels. The superficial vessels are the retinal blood vessels, which supply the inner half of the retina. In the cow, the retinal blood vessels lie on rather than within the retina, where they protrude into the vitreous. The outer half of the retina receives nutrition by diffusion from the choriocapillaris. In pigmented eyes (the norm), the choroidal vessels are obscured by the pigment epithelium and the tapetum

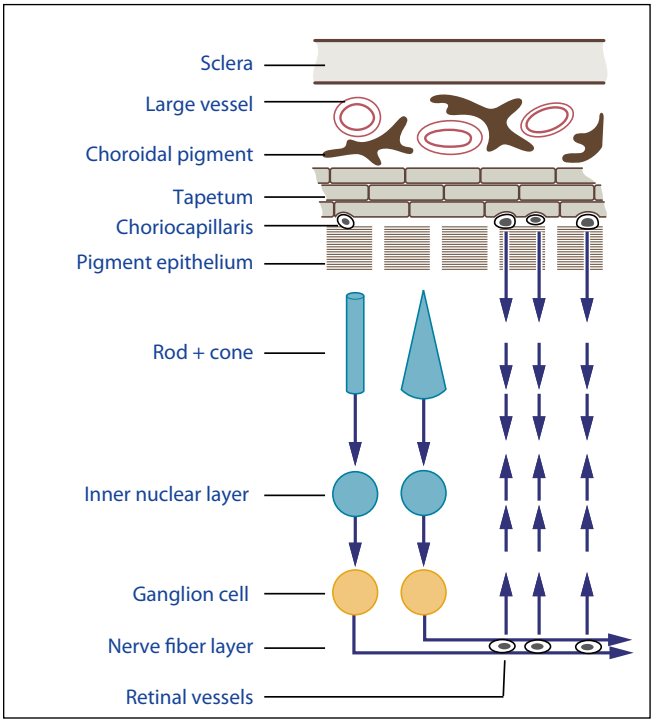

Figure 1.42 **A schematic histology of the fundus. Note the location of pigment, blood vessels, and tapetum. Arrows denote source of nutrition for the retina.**

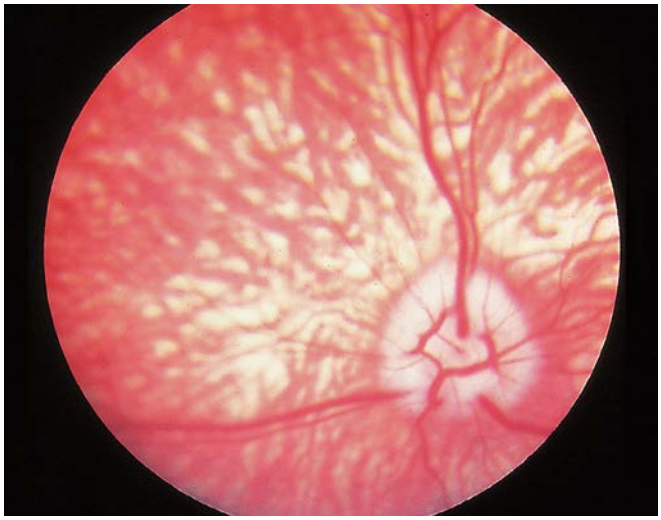

Figure 1.43 **A normal canine albinoid, atapetal fundus. Note the two sources of visible blood vessels.**

(**Figure 1.42**). In albinoid eyes that lack a tapetum and pigment, both vascular systems can be visualized (**Figure 1.43**). Similarly, there are two sources of pigment, retinal and choroidal. In most domestic animals, the tapetal pigmentation is also in the dorsal choroid (**Figure 1.44**).

When performing ophthalmoscopy, as in all examinations, it is desirable to establish a routine to ensure thoroughness. The usual starting point is to find the optic disc (papilla, nerve head) and then to examine each quadrant peripherally from the disc. The optic nerve in the dog is unique in routinely having myelination extending to the level of the retina. In most species, myelination of the optic nerve stops at the level of the sclera (lamina cribrosa). In the dog, varying degrees of myelination of the nerve produce great variation in the shape, size, elevation, and color of the disc (**Figure 1.44**). Of particular importance is the vasculature pattern on the disc, its density, origin, vessel size, and color. The retinal arteries in domestic animals are cilioretinal in origin. Domestic animals lack a central retinal artery (as found in humans), and thus the arteries are found at the disc periphery. The surface of the cat's optic disc is not myelinated, resulting in a small, round, dark optic disc, and the vessels all originate from the periphery of the disc (**Figure 1.45**). (See Chapter 14 for further species variations.)

In the dog, the smaller vessels originating near the periphery are the arterioles. The larger, darker primary and smaller secondary veins go further onto the disc surface, usually to an anastomotic arc (**Figures 1.43 and 1.44**).

The vascular pattern on the disc and how the vessels disappear or originate varies with the species, but variations may be a clue to pathology involving the disc. Fish-hooking of vessels over the edge of the disc and being out of focus are often clues that a depression on the disc, such as a coloboma or glaucomatous cupping, may exist (**Figures 1.46 and 1.47**). Due to the lack of stereopsis or depth perception with direct ophthalmoscopy, the depression may not be appreciated without these visual clues.

The color of the disc is quite variable between individuals and between species, but extremes in pallor or hyperemia are usually significant. The dog, for instance, normally has a pinkish-white disc due to a mixture of myelin and capillaries. With atrophy of the nerve head, it becomes whiter to gray in color (**Figures 1.48 and 1.49**). In addition, the myelination is destroyed, so the fullness, shape, and color are affected in the dog. However, in other species without myelination of the nerve head, color change is the main finding of atrophy.

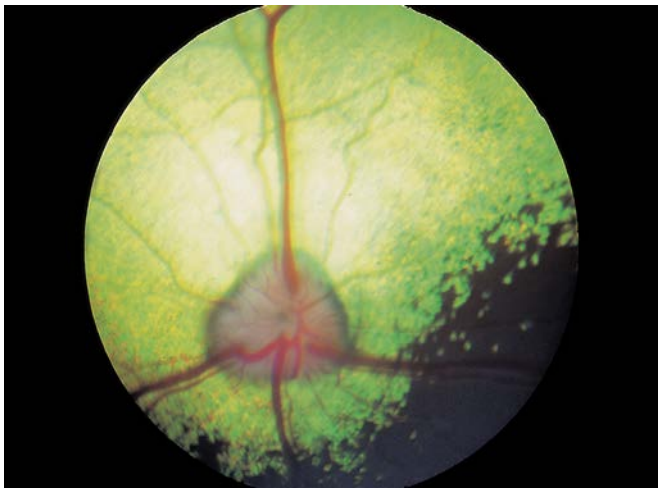

Figure 1.44 **A normal canine pigmented fundus with a tapetum. Note the absence of visible choroidal vessels and a triangular pinkish-white optic disc.**

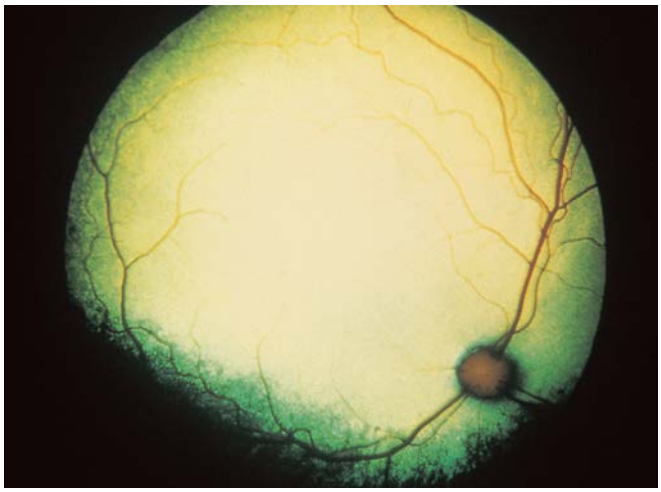

Figure 1.45 **A wide-angle photograph of a feline fundus. Note the small, round, darker disc with vessels only at the periphery.**

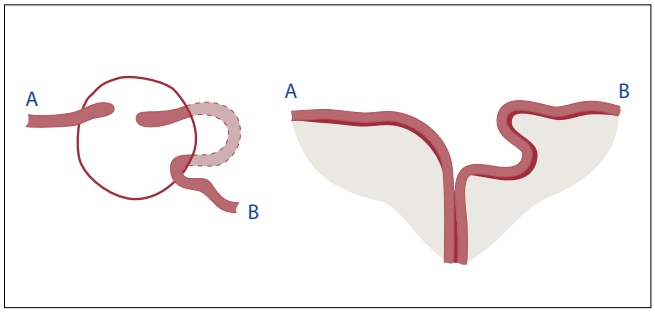

Figure 1.46 **Illustration of two views of retinal vessels on the disc: A vessel that can be followed onto the disc until penetrating the nerve head (A); a vessel that disappears at the edge of a shelf and then reappears without obvious continuity (B); (Left panel: Ophthalmoscopic view; right panel: Sagittal section.)**

An increased redness of the disc is usually from capillary engorgement and may be active as in inflammation (papillitis) or passive as in venous stasis that results in edema (papilledema). With both papilledema and papillitis, the disc is swollen and elevated, causing the vessels to bend to get onto the disc (**Figures 1.48 and 1.50**). The vessels are usually dilated, and mild peripapillary edema may be present. Papillitis usually has a more profound effect on the retinal vessels and optic nerve function than papilledema and is accompanied by blindness.

In summary, changes in disc color, shape, and elevation or depression may be important ophthalmoscopic signs. In the dog, the great breadth of normal variation may make it difficult to diagnose early pathologic changes for even the experienced examiner.

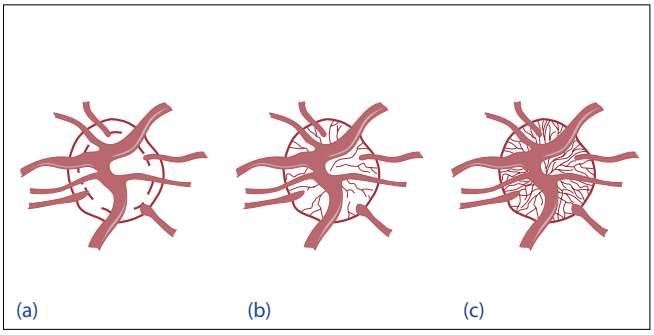

Figure 1.48 **Illustration of pathology of optic disc vasculature: Optic atrophy with no capillaries (a); normal (b); hyperemic disc with inflammation or congestion (papilledema) (c).**

As mentioned previously, the clinician can use the grid aperture to measure the size of lesions, but the size of the grid varies with the working distance. A more consistent and convenient means of describing and locating lesions is to relate the lesions to the disc size and location. This method utilizes the disc diameter (DD) size to describe a lesion's size and distance from the disc, and the hands of a clock to locate the lesion in relation to the disc (**Figure 1.51**). This method allows accurate description of a lesion's size and location to compare with at a later date.

There are various clues available for localizing the depth of a lesion with the ophthalmoscope. One useful clue for localization of fluid lesions such as hemorrhages is the morphology of the lesion. Fluid lesions must conform to the anatomy involved and, as a result, have a variety of shapes and sizes. Due to the loose attachment of the vitreous to the retina, the neurosensory retina to the pigment

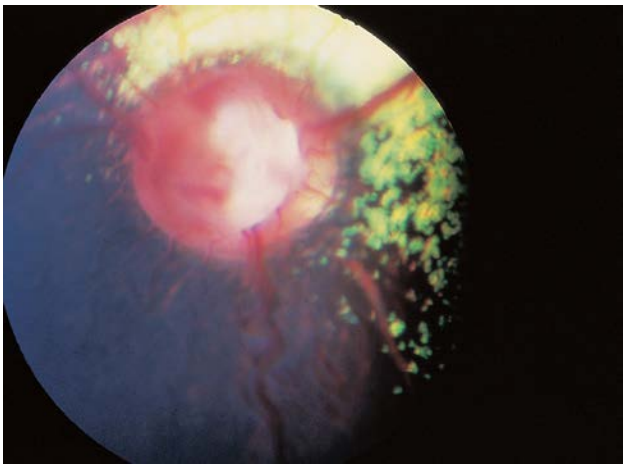

Figure 1.47 ***Clinical correlate of 1.46.*** **The dog has a coloboma of the disc (white area) with vessels falling into this recess. Retinal vessels on one side do not proceed onto the disc as they do on the opposite side.**

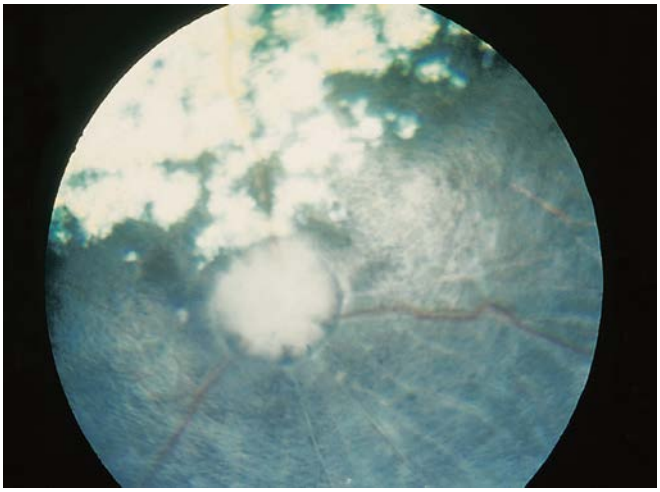

Figure 1.49 **Optic nerve atrophy in a dog with advanced progressive retinal atrophy. Note the gray flat disc with scalloped edges.**

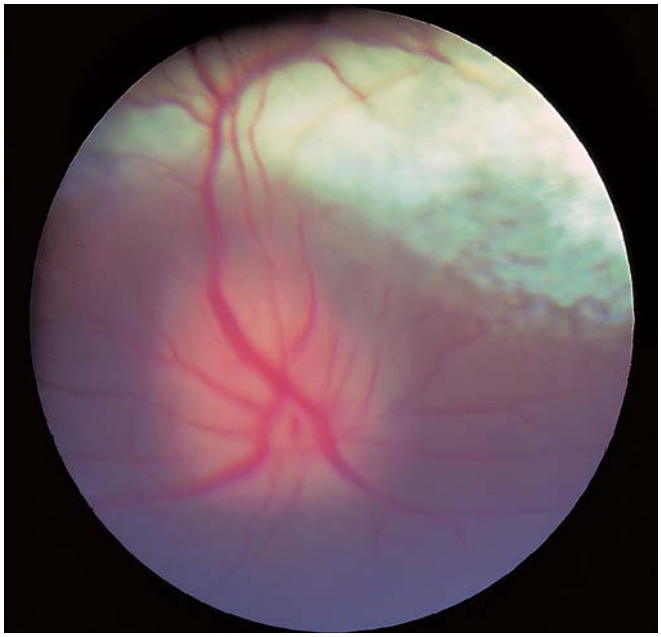

Figure 1.50 **Papilledema in a dog with an engorged, elevated disc. Mild peripapillary edema is present.**

epithelium, and the loose structure of the choroid, hemorrhages of large size may occur in these three spaces. Intraretinal hemorrhages are confined by the axons, dendrites, and Müller cell processes, which run mainly in a vertical manner, so these tend to be small, round hemorrhages. A hemorrhage in the nerve fiber layer has to insinuate between the fibers so it is typically flat and striated with feathered borders and is often called a flame-shaped hemorrhage (**Figure 1.52**). Preretinal hemorrhages with a formed vitreous are typically large and red, and the

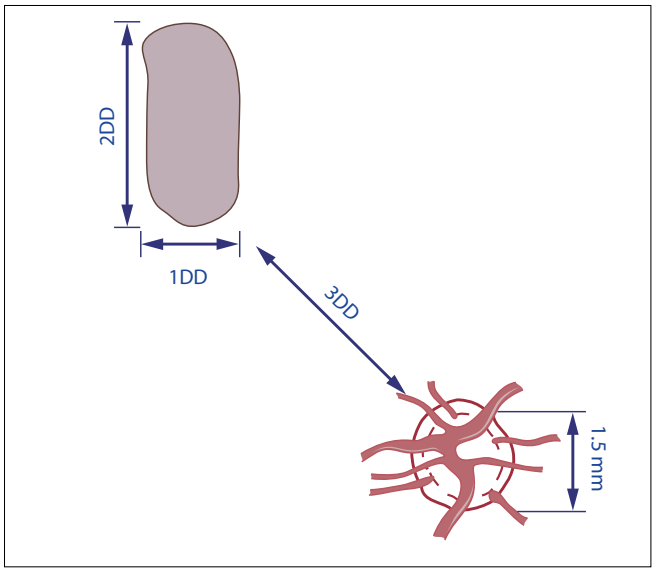

Figure 1.51 **Illustration of locating and describing lesions in relationship to the disc and disc diameter (DD).**

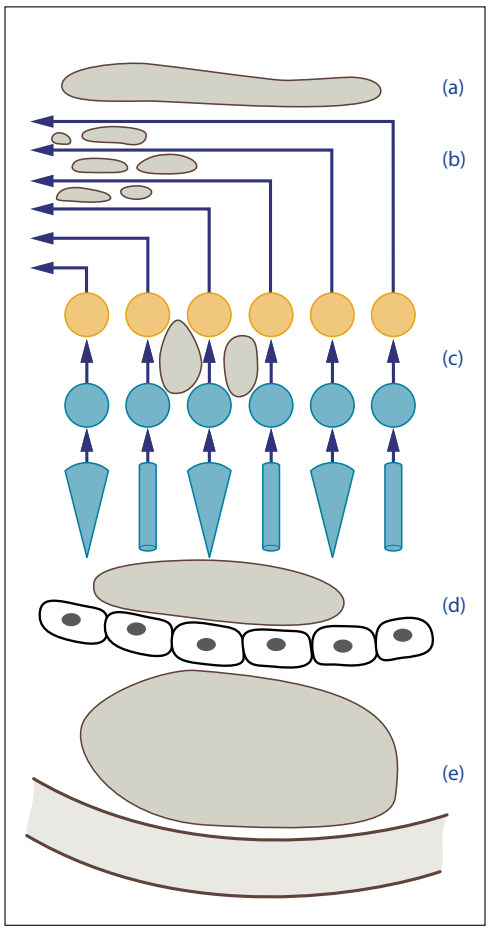

Figure 1.52 **Morphology of fluid lesions based on area of fundus: preretinal/subhyaloid area (a); nerve fiber layer (b); intraretinal (c); sub-neuroretina (d); choroidal (e).**

erythrocytes may settle out, producing a flat top or keel-boat-shaped hemorrhage (**Figures 1.53 and 1.54**). If the vitreous is liquefied, the preretinal hemorrhage becomes diffuse within the vitreous.

- The first principle of lesion location is that the morphology of fluid lesions is determined by the adjacent anatomy. Familiarity with the tissue architecture can help in localizing the lesion.
- A second principle in lesion localization is to find a structure of known depth and relate it to the lesion.
- The usual structures sought for lesion localization are a retinal or choroidal blood vessel. Other structures such as pigment and the tapetum may also be related to the lesion (**Figure 1.55**).
- A third method of lesion localization is utilizing the phenomenon of parallax. This is a very sensitive method of determining if two points are in apposition or separated. This works well in determining low retinal detachments (**Figure 1.56**).

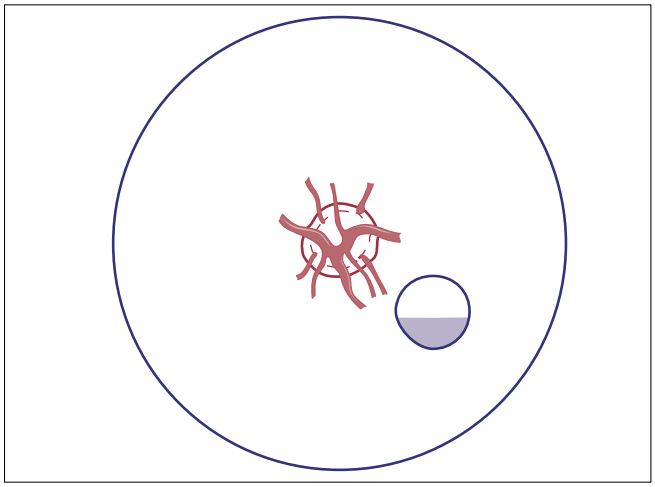

Figure 1.53 **Illustration of preretinal hemorrhage that has settled, giving a flat top. The clear top portion may be overlooked by the examiner.**

Parallax is looking at the structure in question against the background from two different observation points and determining if the structure moves in relation to the background. This will establish whether the two points are separated.

- The fourth method of lesion localization, unique to the direct ophthalmoscope, is the use of various lenses to focus on the object. Most animal's fundi will be in focus at 0 to –2 diopters (D). A lesion that is blurred can be assumed to lie either in front of or at the back of the plane of the fundus. The plus (black or green numbers) lenses converge light, allowing lesions elevated from the surface to come into focus. The negative lenses (red numbers) bring into focus lesions that are below or beyond the level of the normal fundus (**Figure 1.57**). Approximately 4 D is equivalent to 1 mm in the canine eye. This varies by species due to the inherent magnification of the eye.

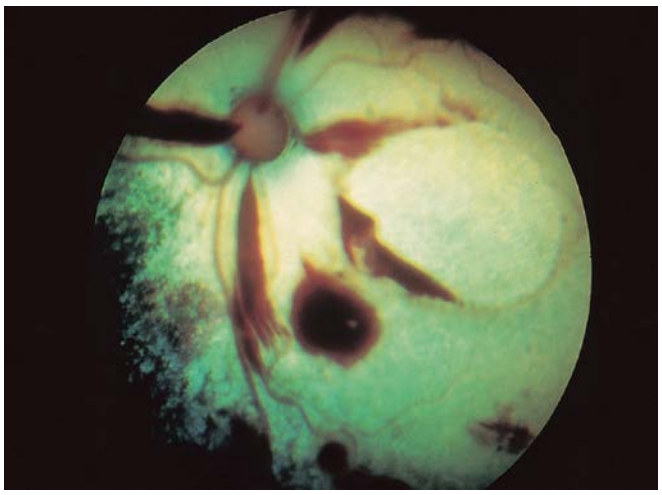

Figure 1.54 **Cat fundus with multiple hemorrhages at different levels of the fundus. Preretinal hemorrhages with flat tops (is the packed cell volume normal?) and striated nerve fiber hemorrhages are present.**

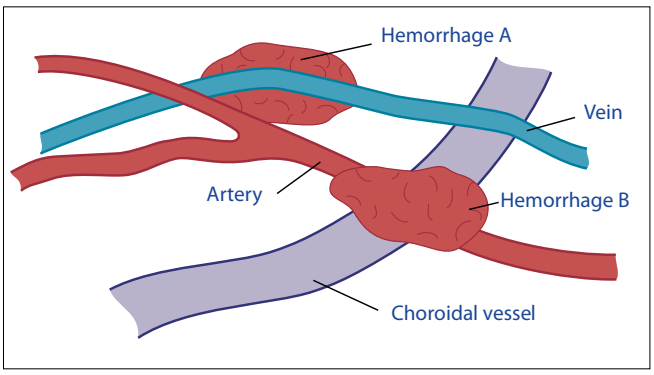

Figure 1.55 **Illustration relating the depth of lesions to the two vascular systems.**

Summary

The four methods of lesion localization with the direct ophthalmoscope are:

1. Lesion morphology
2. Relating to structures of known depth
3. Utilizing the parallax phenomenon
4. Diopter settings

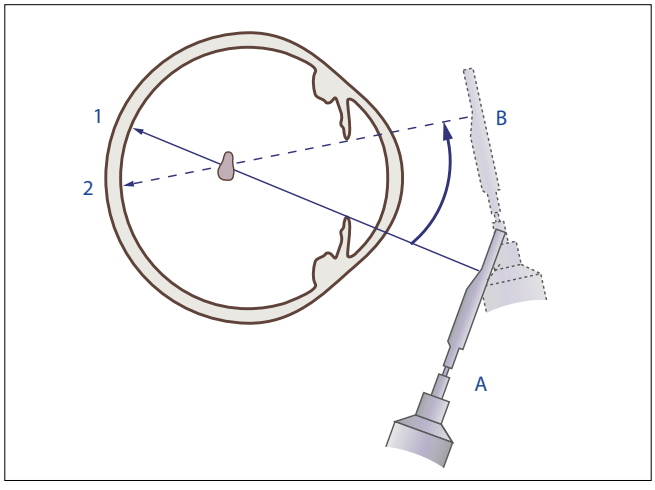

Figure 1.56 **Illustration of the principle of parallax by observing the lesion from two perspectives and noting whether the lesion moves against the background. If the lesion moves, it is located in front of the retina and not on it.**

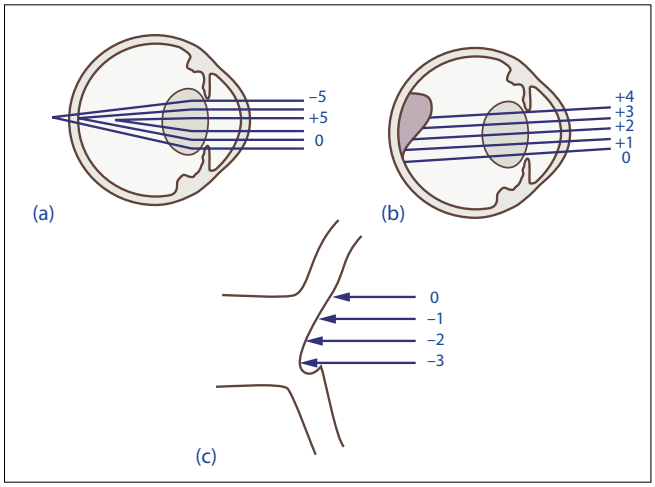

Figure 1.57 **Illustration of using the ophthalmoscope lenses to focus on raised or depressed lesions: emmetropic eye focused on 0 (a); + lenses used to focus on a raised lesion (b); − lenses focusing on a depressed lesion (c).**

Proximal illumination is a technique whereby the area in question is illuminated by shining the light adjacent to the area being examined. The small circular aperture is used in this instance. This may yield information regarding the structural nature of the lesion. If the lesion is cystic, fluid, or of a low density, the lesion transmits light which is reflected back to the observer's eyes. A dense or heavily pigmented lesion absorbs the light (**Figure 1.58**).

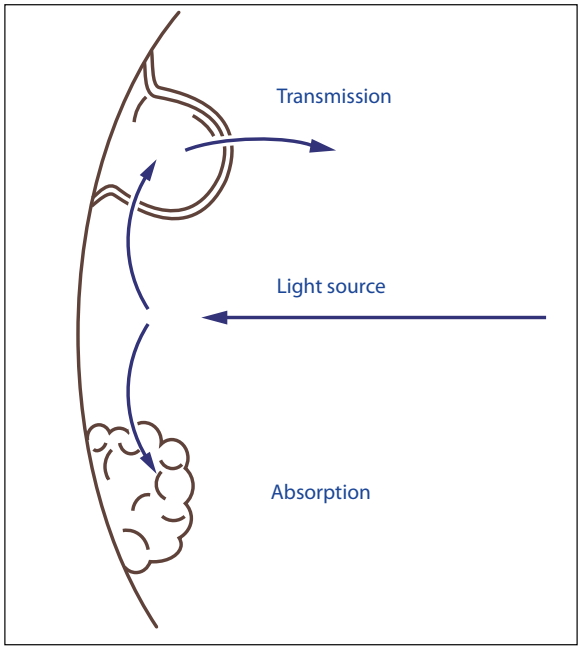

Figure 1.58 **Illustration of the technique utilizing proximal illumination.**

As with most techniques, competence comes only with practice, practice, and more practice!

Indirect ophthalmoscopy

Although the image may be confusing with the indirect ophthalmoscope because it is upside down and reversed, the technique is easily learned.[82,83] The necessary components of indirect ophthalmoscopy are an adequate light source and a converging lens. The light source with the binocular indirect ophthalmoscope (BIO) is on a headband or fits on spectacle frames, thus freeing the examiner's hands to hold the lens and the patient (**Figure 1.59**). The function of the headset is not only to provide light but to narrow optically the examiner's interpupillary distance (PD) of 60–15 mm (**Figure 1.60**). Narrowing the PD allows both eyes plus the light to be projected through the patient's pupil; this allows the observer binocular vision and stereopsis (**Table 1.3**). Many scopes now have a small pupil feature that narrows the PD to as small as 6 mm. **Table 1.4** gives the minimum pupil size of the patient that is necessary with three different strengths of condensing lenses for binocular observation. The lens strength selected alters the magnification and size of field of the image, the size of pupil that the fundus can be visualized through stereoscopically, and the inherent stereopsis (**Table 1.5**). The higher the diopter strength of the lens, the smaller the image but the larger the field of view, the smaller the pupil that can be examined, and the less the stereopsis.[84,85]

Most of the time when utilizing the BIO, the examiner can handle the animal without having an assistant to restrain the head (**Figure 1.59**). A teaching mirror is also

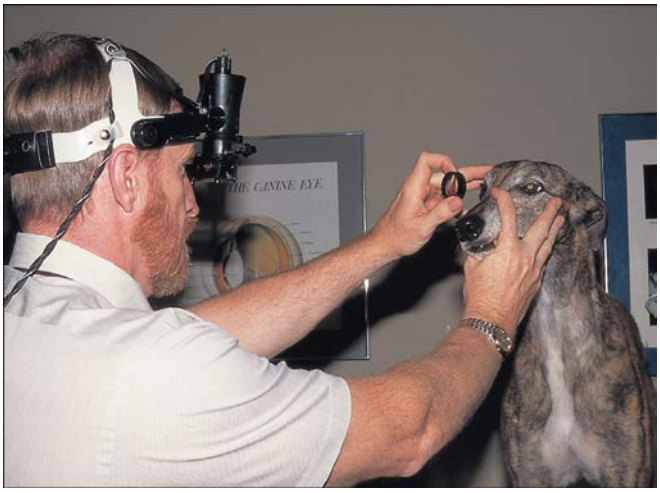

Figure 1.59 **Binocular indirect ophthalmoscopy being performed. Note the working distance and lack of an assistant to hold the animal.**

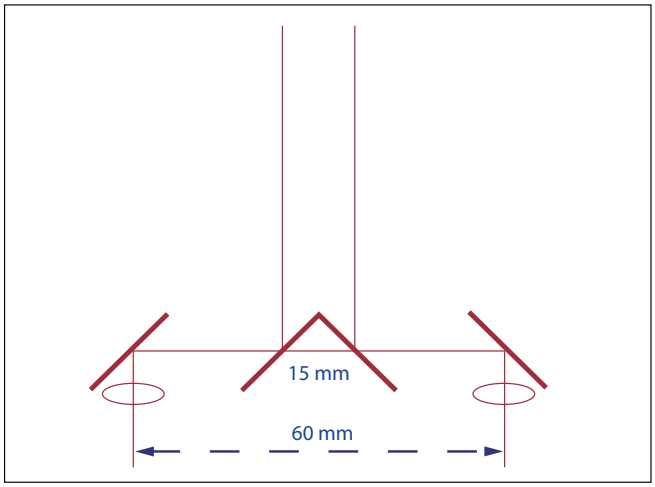

Figure 1.60 **Optics of the binocular indirect ophthalmoscope and narrowing the interpupillary distance of the examiner.**

available for most models, and video indirect scopes are available.

Before using the BIO, a few adjustments are necessary. The headset band tension is adjusted so that it is firm enough to keep from slipping and allow subtle movement of the light by contraction of the brow, but loose enough to avoid a headache. If the headset is not in front of the examiner's eyes, the headset is moved up or down. The PD is adjusted for each eye by sliding the optics of each eyepiece horizontally. The light should fall in the center of the observation field for that eye, and the two fields should be fused. The adjustment of the light on a vertical basis is performed using the hand as a target. With the hand at the usual, comfortable, bent-arms working distance, the light is adjusted to fall in the upper half of the examiner's field.

The usual binocular indirect ophthalmoscope has three main adjustments to be made before use. They are:

1. Adjustment of the tension of the headband
2. Adjustment of the interpupillary distance of the eyepieces
3. Vertical adjustment of the light in the eyepieces

The light source can be made very bright with a BIO, as it is usually powered by 110 volts from a transformer with a rheostat. In addition, the indirect image is inherently brighter due to all light returning to the observer's eye. The bright light may allow observation through hazy media with the BIO that was previously unsuccessful with the direct form.[83] The light should be no stronger than necessary, as this washes out detail and creates patient discomfort with a resultant lack of cooperation. Anesthetized patients that cannot move may develop retinal burns due to the strong light. The strength of the light must often be decreased for the tapetum and increased for the nontapetal region.

The image formed with a BIO is an aerial image which is upside down, reversed, and formed between the patient and the examiner (**Figure 1.61**).[82]

The lenses used in indirect ophthalmoscopy are biconvex or converging lenses, usually ranging from +14 D lenses to +30 D in strength. When used with the binocular headset, additional magnification is built into the headset, and magnification increases fourfold with the +14 D to twofold with the +28 D lens, although this varies with the species (see **Tables 1.3** and **1.5**). The magnification of the retina is equal to the diopter strength of the eye divided by the diopter strength of the lens used.[84,85] The strength of the lens affects not only the magnification but the amount of stereopsis or depth perception of the

Table 1.3 **Magnification factors for indirect ophthalmoscopy.**

	LATERAL MAGNIFICATION				AXIAL MAGNIFICATION			
SPECIES	**14 D**	**20 D**	**30 D**	**40 D**	**14 D**	**20 D**	**30 D**	**40 D**
Horse	1.18	0.79	0.51	0.38	1.86	0.84	0.35	0.19
Cow	1.58	1.06	0.68	0.50	3.34	1.50	0.62	0.34
Sheep	2.07	1.39	0.90	0.66	5.74	2.58	1.07	0.58
Human	2.19	1.47	0.95	0.70	6.39	2.87	1.19	0.65
Pig	2.26	1.52	0.98	0.72	6.83	3.07	1.28	0.70
Dog	2.57	1.72	1.11	0.82	8.85	3.97	1.65	0.90
Cat	2.91	1.95	1.26	0.93	11.31	5.08	2.11	1.15
Rabbit	3.77	2.53	1.63	1.20	18.99	8.53	3.55	1.93
Rat	11.52	7.72	4.98	3.68	177.44	79.65	33.15	18.06

Source: Modified from Murphy and Howland, 1987. *Vision Research* 27:599–607.

Table 1.4 **Minimum patient pupil size for stereopsis with varying power of condensing lenses using binocular indirect ophthalmoscopy.**

INTERPUPILLARY DISTANCE (MM)	STRENGTH OF CONDENSING LENS (D)	INTERPUPILLARY DISTANCE OF VIEWER'S EYES AS PROJECTED ON THE PATIENT'S EYE (MM)
15	30	1.5
15	20	2.25
IS	15	3.0

Source: Modified from Goldbaum et al., 1980. *Principles and Practice of Ophthalmology*, vol II. Peyman, G., Sanders, D., and Goldberg, M. (eds). WB Saunders: Philadelphia, PA, pp. 988–1097.

Table 1.5 **Ocular characteristics of lenses.**

LENS POWER (D)	APPROXIMATE MAGNIFICATION	FIELD OF VIEW	APPROXIMATE STEREOPSIS
28–35	× 2	60°	× 0.5 normal
20	× 3	51°	× 0.75 normal
14	× 4	30°	× 1 normal

Source: Modified from Goldbaum et al., 1980. *Principles and Practice of Ophthalmology*, vol II. Peyman, G., Sanders, D., and Goldberg, M. (eds). WB Saunders: Philadelphia, PA, pp. 988–1097.

examiner. The higher the diopter strength of the lens, the less the depth perception (**Table 1.5**).

An additional factor in selecting a lens is the size of the patient's pupil. The higher diopter lens can project the examiner's pupil onto a smaller patient pupil (**Figure 1.62**, **Tables 1.1** and **1.4**[84]). When examining the peripheral fundus, the patient's pupil becomes optically

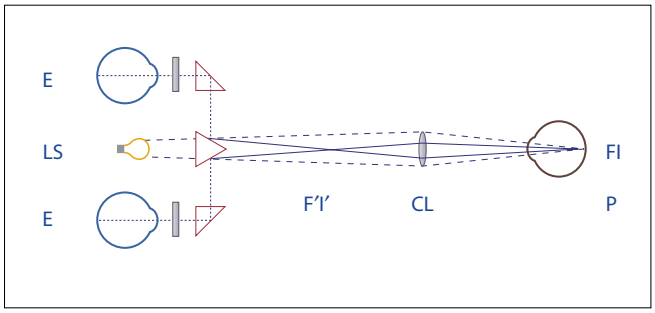

Figure 1.61 **Optics of binocular indirect ophthalmoscopy. Note how the examiner's pupil distance is narrowed by the prisms and that a real aerial image is formed between the examiner and the patient. (E = examiner's eyes; LS = light source; P = patient; Ff = patient's fundus; Cl = corrective lens; F′I′ = image patient's fundus in space.) (With permission from Rubin, 1960. *Journal of the American Veterinary Medical Association* 137:648–651.)**

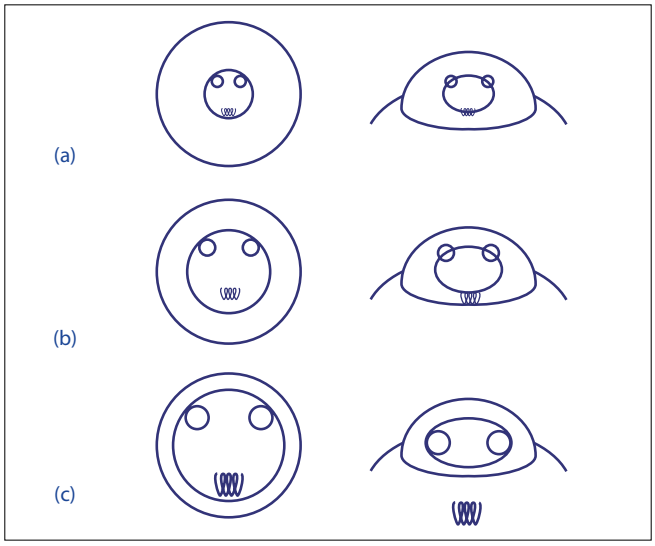

Figure 1.62 **Optics comparing pupil size needed for various strengths of condensing lens and the difficulty in projecting the light and viewer's eyes obliquely through the pupil to view the peripheral fundus: 30 D lens image of examiner's eyes and light projecting into a small pupil and when viewing the peripheral fundus (a); 20 D lens image; note the larger pupil size required and that the peripheral fundus can still be examined if the pupil is large (b); 14 D lens; the pupil must be very large and oblique viewing effectively cuts the light out so the peripheral fundus cannot be visualized (c). (With permission from Goldbaum et al., 1980. *Principles and Practice of Ophthalmology*, vol II. Peyman, G., Sanders, D., and Goldberg, M. (eds). WB Saunders: Philadelphia, PA, pp. 988–1097.)**

compressed or narrow, so to maintain binocular function, the examiner may have to use a higher diopter lens but lose some depth perception in the process (**Figure 1.62**). A good compromise if only one lens is available is a +20 D lens. The size of the field of view is dependent on the diopter power of the lens and the diameter of the lens. The higher diopter lens produces a more panoramic view, and, for a given lens strength, increasing the diameter of the lens increases the field of view.[84,85] The more recently developed Keeler 2.2 panretinal lens uniquely combines magnification of nearly a +20 D lens with the wider field of view of a +30 D lens and is suitable for the fundic examination through wider and smaller pupils.

Selection of the strength of the lens depends on the patient's pupil size and the amount of stereopsis (depth perception) and magnification desired.

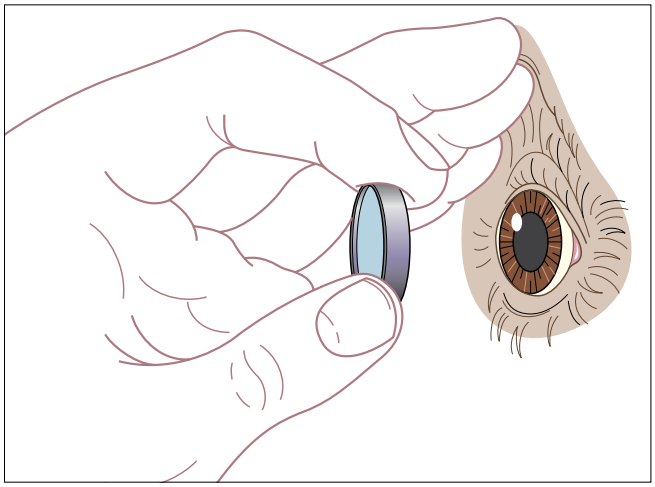

Figure 1.63 **Technique of holding the lens so that the upper lid is held open, the lens is aligned, and the hand and the lens move with the head.**

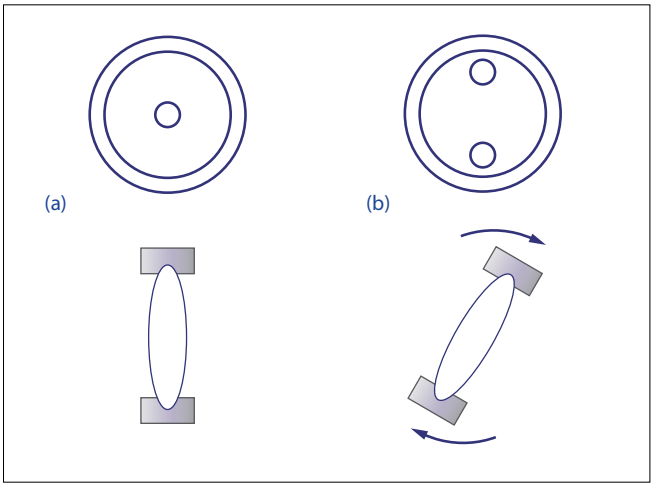

Figure 1.64 **Illustration of specular reflections off the handheld lens: specular reflex from each surface is centered in the lens that distracts from viewing (a); slight tilting of the lens pushes the specular reflections to the side leaving the central area clear (b).**

The lens is held with the thumb and the forefinger, and the remaining fingers are used to retract the upper lid and steady the lens in space (**Figure 1.63**). The strongest convex surface of the lens should be facing the observer for the best image. Many lenses have an identifying dot or a white ring that identifies the side towards the patient. When using the lens, it will be noted that a bright specular reflection is present from the anterior and posterior lens surface and is located in the center of the lens when the lens is held perpendicular to the light beam. These bright specular reflections are often annoying, as they obscure the area of interest that is usually centered. These specular reflections can be decentered by tilting the lens slightly, which pushes the reflections to the side (**Figure 1.64**).[86] Excessive tilting of the lens creates a prismatic effect, bending the light so that it is not directed through the pupil.

One of the difficulties in learning indirect ophthalmoscopy is created by the reversed image. This confuses the beginner as to the direction to move to bring the object of regard into better view.

> Note: To bring an object into the central view, the observer's head and the hand lens move in the same direction as the area to be viewed in the aerial image.

Movement of the head to bring objects in the image to the center is a simple concept, but it is counterintuitive and requires practice (**Figure 1.65**).

Parallax can be demonstrated with indirect ophthalmoscopy by tilting or shifting the hand lens or the head to observe the object from a slightly different angle. If the object is separated from the background, it then moves in relationship to the background (**Figure 1.66**).

Due to the expense of a BIO, many other light sources can be used instead. Any light source that does not diffuse out excessively can be utilized. If the light source is battery operated, it allows easy portability. The light sources can be as varied as a good penlight, a strong otoscope or direct ophthalmoscope, or any fiber-optic bundle. If the direct ophthalmoscope is used as the light source, more magnification can be produced by adding 1–2+ D of lenses than if it is set at 0 D. Beyond 2 D, the image becomes blurred. Because there is no optical narrowing of the examiner's PD without a headset, the 60 mm (average PD) must

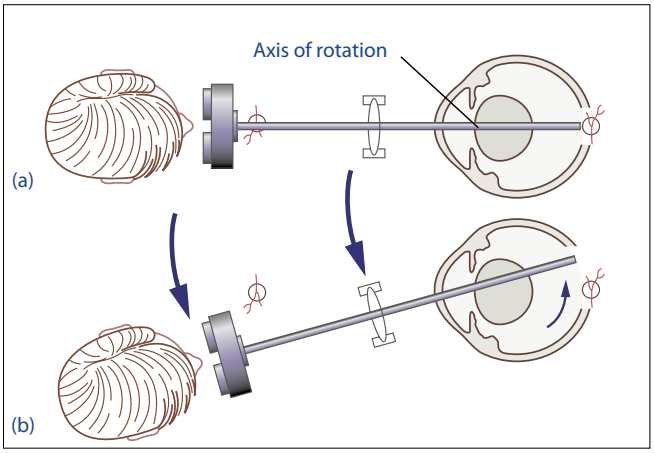

Figure 1.65 **The area to the side of the branching vessels in the fundus can be observed by the examiner moving in the direction the vessels are seen in the image.**

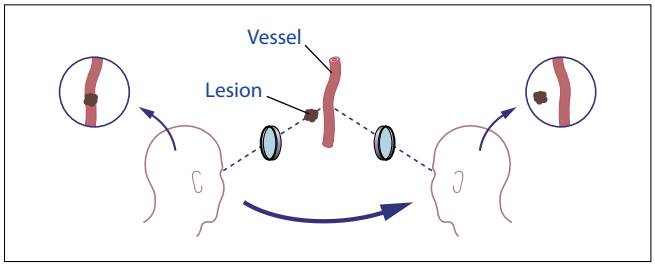

Figure 1.66 **Demonstration of parallax of a lesion with a BIO. The lesion when viewed from one perspective is observed against a background vessel; if the lesion is separated from the background vessel, the lesion will move in relation to the vessel by slight rotation of axis of observation.**

be projected onto the patient's pupil, and the technique requires a much larger pupil to acquire binocular examination (**Table 1.5**). Consequently, it is termed monocular indirect ophthalmoscopy (**Figure 1.67**). Another form of monocular indirect ophthalmoscopy is available in which the instrument optically rights the reversed and inverted image, thus avoiding this source of confusion. The image is smaller, but there is a wider field than with direct ophthalmoscopy (**Figure 1.68**). The instrument is expensive but extremely easy to use.

Indirect ophthalmoscopy gives a lower magnification but a larger field than direct ophthalmoscopy, and it gives the examiner a better overall picture. With less magnification, the patient's ocular movements are less troublesome. Most forms of indirect ophthalmoscopy utilize both of the examiner's eyes, and thus, stereopsis with depth perception is an important advantage. With good mydriasis, the extreme peripheral retina can be examined. The ora ciliaris retina is routinely visualized temporally and ventrally, less commonly nasally, and rarely dorsally without scleral indention. Peripheral examination requires practice in positioning and manipulating the hand lens to get a prismatic bending of light.

Figure 1.67 **Monocular indirect ophthalmoscopy being performed with a Finoff illuminator. Note an assistant is necessary to hold the dog's head.**

Figure 1.68 **Monocular indirect scope that optically corrects the image for the observer.**

In veterinary medicine, an important advantage of the BIO is that the examiner's head is a distance from the patient. This is important from the standpoint of physical trauma and, occasionally, contagious diseases in laboratory animals. It is always important to compare eyes in the examination, and the BIO allows this to be done quickly and thus to be more valid. Most BIOs have a teaching mirror available, so colleagues or students can gain firsthand observations with an experienced examiner.

> Most texts emphasize the difficulty of using a BIO, but in practice, it is routinely more gratifying to the novice to finally see the overall picture, so that it encourages ophthalmoscopy rather than discourages it.

The most important disadvantage of the usual BIO is the cost. This is not prohibitive for the practitioner, but it is for the student. The monocular version of indirect ophthalmoscopy only requires a lens that may cost from $20 to $300. The magnification with this form of indirect ophthalmoscopy is usually not as much as the BIO, and depending on the source of light, both of the examiner's hands are used, so an assistant is necessary. The patient's pupil must be larger to have binocular vision and stereopsis (**Table 1.6**).

Table 1.6 **Ocular characteristics of lenses.**

AVERAGE INTERPUPILLARY DISTANCE OF HUMANS (MM)	POWER OF CONDENSING LENS (D)	SIZE OF PATIENT'S PUPIL (MM)
0	30	6
0	20	9
0	15	12

Source: Modified from Goldbaum et al., 1980. *Principles and Practice of Ophthalmology*, vol II. Peyman, G., Sanders, D., and Goldberg, M. (eds). WB Saunders: Philadelphia, PA, pp. 988–1097.

Electrophysiologic tests

Electroretinography, visually evoked responses, and electro-oculography are electrophysiologic responses that may be utilized in clinical investigations. While initially limited to institutions, computerization has made the electroretinography equipment less expensive, and it is usually available in specialist practices.

The electroretinogram (ERG) is an action potential that occurs when a sudden change of illumination falls on the retina. The potential is divided into three major components: A-, B-, and C-waves. The A-wave is the first negative deflection and arises from the photoreceptors; the B-wave follows and is the first positive deflection and arises from nonneuronal glia in the inner nuclear layer; and the C-wave is a slow positive potential arising from the pigment epithelium of the retina (**Figure 1.69**).[87–89] **Figure 1.69** is typical of a flash-induced ERG with white light under dark adaptation (rod-dominated response). Fundus photography or indirect ophthalmoscopy reduces the dark adapted ERG amplitudes, and up to 60 minutes of dark adaption may be necessary to return to comparable ERG amplitudes of 20 minutes of dark adaption without previous light stimulation.[90] The usual flash ERG is generated by the outer half of the retina, and diseases that preferentially affect the ganglion cells or optic nerve, such as glaucoma, may result in a normal ERG in a blind animal.

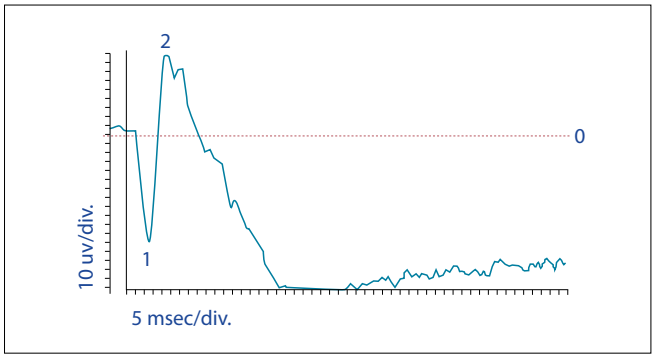

Figure 1.69 ERG from a normal dog: A-wave (1); B-wave (2); no C-wave is recorded. Performed with blue light in a dark room. Note two oscillatory potential wavelets on the B-wave.

A retinal electrical potential evoked with an alternating patterned grating (patterned ERG, PERG) evokes responses that may have optic nerve and ganglion cell origins.[91] The PERG has also been utilized to estimate the visual acuity of animals.[92]

Oscillatory potentials (OPs) are small oscillations that are superimposed on the B-wave, and there may be up to four to five wavelets. They are observed best during dark adaptation; their origin is the inner retina, and they are thought to be from the amacrine cells. Wavelets O3 and O4 are most easily observed (**Figure 1.69**).[93,94] In humans, alterations in the OPs are observed with alterations in retinal circulation, most notably in diabetes mellitus.

Visual evoked potentials (VEPs) are measured over the occipital cortex after stimulating the retina with light. The potentials are small and require computer averaging and general anesthesia. VEPs measure the integrity of the optic nerve, optic tracts, and occipital cortex.

Fluorescein angiography

Fluorescein angiography is used to study the retinal, choroidal, and iris vasculature. After injection of 10–25 mg/kg of fluorescein IV, the circulation is observed through a camera equipped with an exciter filter (500 nm) to stimulate the fluorescence of fluorescein, a barrier filter that selects light at the peak emission for fluorescein (550 nm), a motorized film advancer, and a rapid strobe recharging unit. The flow of dye through the vessels is sequentially observed as the choroidal, retinal arteriolar, capillary, and venous phases (**Figure 1.70**).[95,96] The tapetum fluoresces at similar wavelengths as fluorescein, thus reducing the contrast, but this can be minimized by a barrier filter that transmits wavelengths over 530 nm.[97]

Ultrasound

Ultrasonography in A and B modes has become routine in most centers for studying ocular lesions when the medium is opaque. It is particularly helpful in detecting neoplasia, phacoclastic uveitis, lens abnormalities and posterior lens rupture, foreign bodies, vitreous pathology, and retinal detachment with opaque media.[98–100]

Ultrasonography detects acoustic interfaces or differences in the density of tissue. The more dramatic the acoustic interface, the more the ultrasound waves are reflected back to the probe. A-mode ultrasonography gives an image of the amplitude of reflections in one spatial dimension (anterior–posterior), whereas B-mode ultrasonography consists of two spatial dimensions. A-mode is best suited for biometric measuring of ocular dimensions, whereas B-mode is usually used for diagnostic imaging,

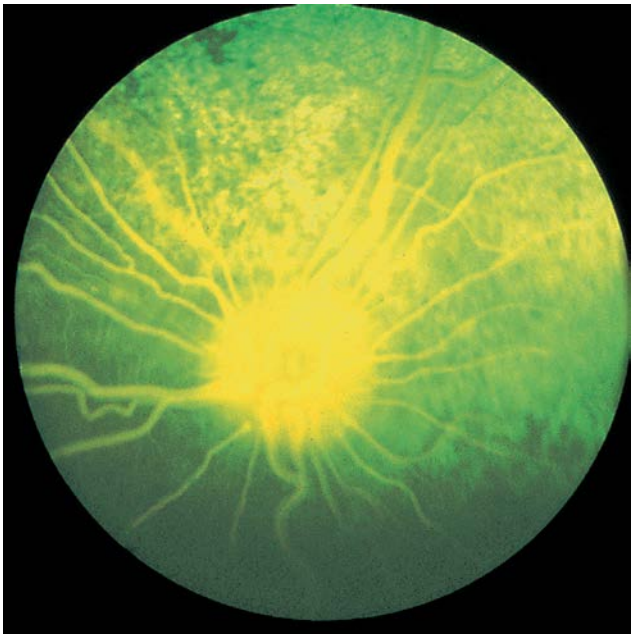

Figure 1.70 **Fluorescein angiogram in a dog in the late venous phase. Note the arteries and veins are both filled. (Courtesy of Dr. K. Gelatt.)**

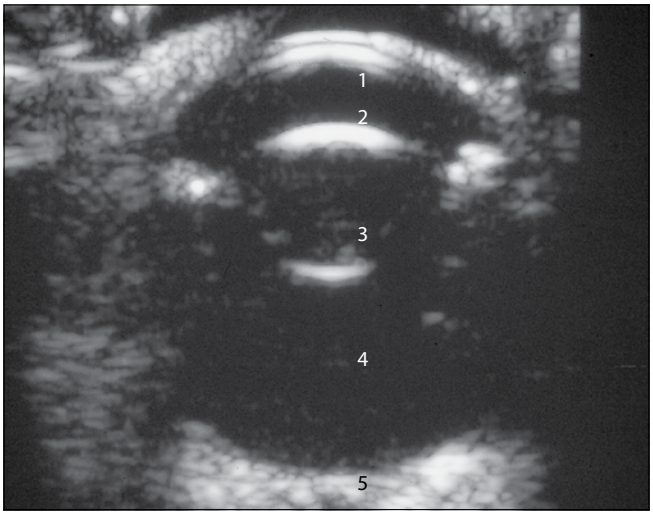

Figure 1.71 **B-mode ultrasound image of a normal 11-year-old dog with a 10-MHz probe and direct contact with the cornea. (1: Cornea; 2: Anterior chamber; 3: Lens; 4: Vitreous; 5: Optic nerve.)**

although B-mode has been reported to be as accurate as A-mode for biometric measurements.[100,101] The method of probe placement may be through a water bath (surgical glove filled with water) offset on the closed lids, or, more commonly, directly on the cornea utilizing an ultrasound coupling gel. Typical probe frequencies used in ophthalmic ultrasound are 7–10 MHz.

New instruments with probes that can focus at different focal lengths have improved visualizing the anterior segment without an offset (**Figure 1.71**).

The development of high-frequency ultrasound in recent years (with probe frequencies ranging from 20–50 MHz) allows a detailed examination of the anterior ocular segment, including sclera, cornea, anterior chamber, iris, and iridocorneal angle. Although the tissue penetration depth is limited to about 4–5 millimeters, the resolution of the imaged ocular structures is very high and comparable to a low-power sagittal histologic section through the tissue[102] (**Figure 1.72**). Ultrasound biomicroscopy, which uses even higher frequencies of 50–100 MHz, is particularly useful in the examination of the iridocorneal angle and ciliary cleft.[103]

B-mode ultrasonography has greatly expanded our diagnostic capabilities in eyes with opaque media.

Ultrasound biometry is particularly useful for the measurements of intraocular dimensions and determination of the axial length of the eye.[100,101] The reported axial lengths of the dog eye vary with the head type. Mesocephalic dogs have a mean axial length of 19.9 mm and dolichocephalics have a mean of 21.2 mm.[101] Sedated Samoyeds have a mean of 22 mm,[104] and an overall mean of 20.4 mm was found when a variety of breeds was examined.[105] Ultrasound biometry has also been used for accurate measurement of the axial length to calculate

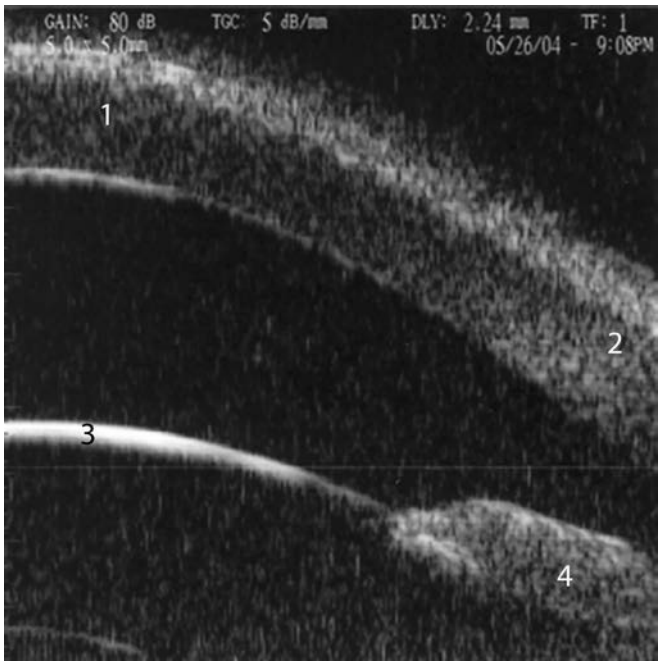

Figure 1.72 **Ultrasound biomicroscopy (50-MHz probe). (1: Cornea with epithelium, stroma, and Descemet's membrane; 2: Sclera; 3: Anterior lens capsule; 4: Iris.)**

the refractive power for intraocular lens implants in dogs,[105] cats,[106] and horses.[107]

An extension of the use of ultrasound has been color flow Doppler studies of the eye and orbit to study blood flow[108] and ultrasonic pachymetry to measure corneal thickness.[109]

Ocular centesis

Aqueous and vitreous centesis is performed frequently for cultures and cytology of intraocular disease.[110,111] Aqueous centesis can be performed under topical anesthesia in a cooperative patient, but most clinicians feel more comfortable using sedation. Aqueous humor centesis is performed with a 25- to 30-gauge needle entering the anterior chamber at the limbus, with the needle passing parallel with the iris (**Figure 1.73**). The "seal" on the syringe should be broken prior to passing the needle into the eye to avoid awkward movement when aspirating fluid. Unless the anterior chamber is collapsed, about 0.3 mL of aqueous humor can usually be aspirated. Centesis is used not only to obtain aqueous humor but may be used to vacuum cells off lesions on the iris and aspirate cystic lesions. Centesis of the anterior chamber is usually safe, but with opaque corneas or marked iris bombe, trauma to the iris, endothelium, or lens is more likely. (See **Table 1.7** for aqueous humor laboratory values.[110])

Cultures obtained from the aqueous may be negative with septic conditions because of the dilution and turnover of fluid. Vitreous is a more reliable culture media for septic endophthalmitis, but vitreous centesis has more inherent complications (hemorrhage and creation of retinal holes) and so is reserved for seriously diseased eyes. A 22-gauge needle is used due to the difficulty in aspirating formed vitreous. The needle is passed 6–8 mm posterior to the limbus in the lateral to dorsolateral quadrant where the pars plana is widest. The needle is pointed to the center of the eye (**Figure 1.74**) utilizing extreme care to avoid hitting the lens. The needle frequently needs repositioning to find pools of liquified vitreous.

Table 1.7 **Baseline values for aqueous humor for the dog and cat.**

FACTOR	DOG	CAT
Refractive index	1.335	1.335
Protein content (mg/100 mL)	24–54	15–55
	11–55	–
Anterior chamber volume (mL)	0.4–0.6	0.6–0.9
	–	0.72
Cytology	Occasional mononuclear cell or melanocyte	

Source: Modified from Olin, 1977. *Journal of the American Veterinary Medical Association* 171:557.

Biomicroscopy

The advent of portable slit lamps has made biomicroscopy the standard for examination of the anterior segment. Otto Ueberreiter, an Austrian veterinarian, pioneered the use of the slit lamp in veterinary ophthalmology.[33,34,112]

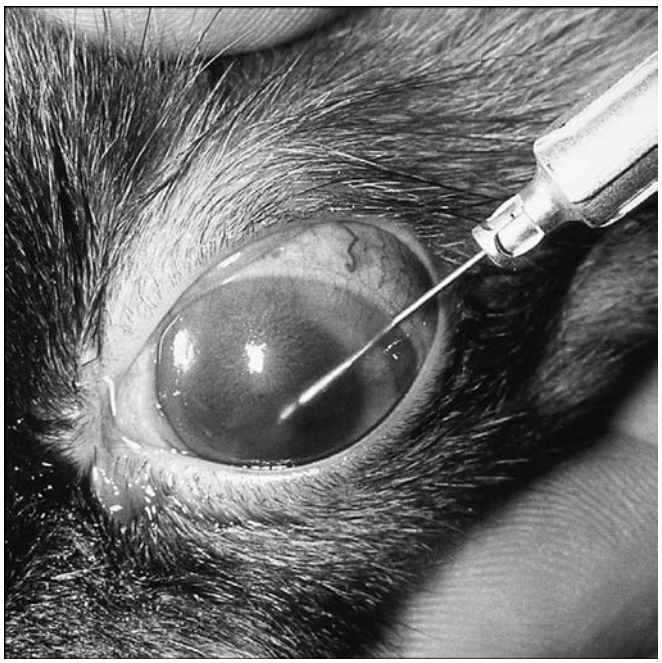

Figure 1.73 Aqueous centesis from a cat with uveitis.

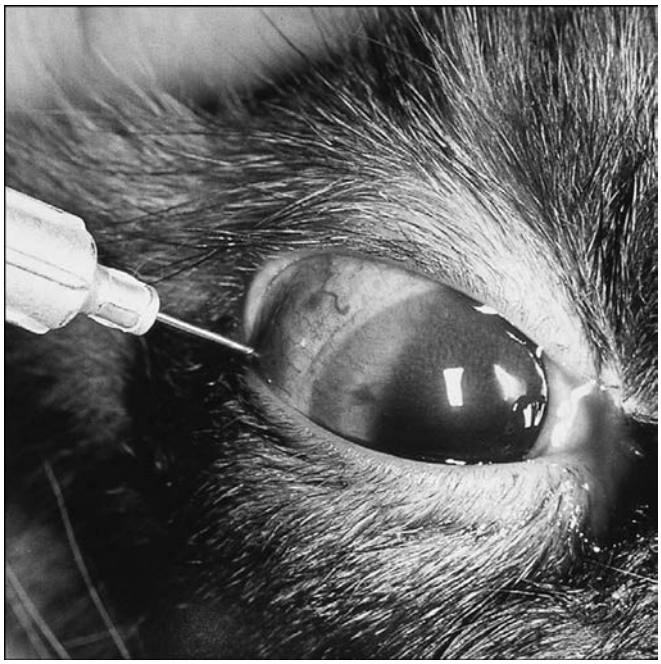

Figure 1.74 Vitreous centesis of a cat eye. Special care should be taken to avoid the lens.

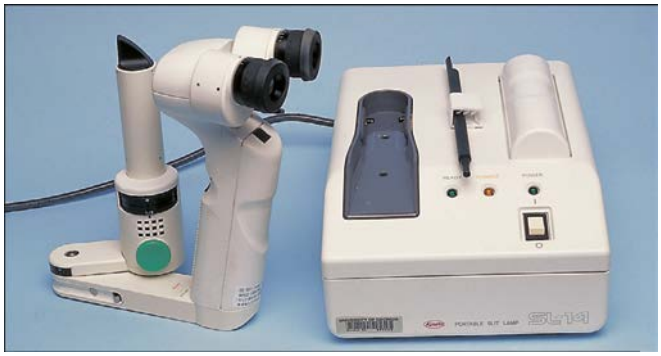

Figure 1.75 **Kowa SL-14 slit lamp with recharging stations.**

A variety of portable slit lamps are in use today; they range in price from $500 to $3500 (**Figure 1.75**). In veterinary medicine, where patient movement is inherent, a disadvantage of the newer slit lamp models is that the lowest magnification is often 10×, which is too high.

Biomicroscopic techniques

Slit lamps come in many variations, but all consist essentially of an illuminating system with a focused light that usually has various apertures to modify the color and the shape of the light beam and a microscope. The light can be rotated at various angles around the point of observation with the microscope. The slit lamp is unique in that the microscope and the light source have the same focal length (about 7–10 cm [2.8–4 in]). Before using, the oculars of the microscope should be adjusted for the PD of the examiner and the focus of the oculars adjusted by observing the light on a target rod. Some instruments have lines within the oculars to focus on. Because the light is focused, it is important to adjust the oculars for each individual so that the microscope and the light focus coincide. The target rod is located at the focal point of the light source, and the oculars are adjusted so that the margins of the light image are sharp in each ocular. In general, the clinician should utilize the least magnification possible and wider beam widths for preliminary examinations and should selectively utilize higher magnifications for minute lesions. The light beam is placed 20–30° from the axis of the microscope, and in most dogs, it is oriented from the temporal side of the eye because the nose interferes with placement of the light. The light can be utilized from either side in brachycephalic dogs, cats, and horses.

Most common illumination techniques

Direct focal illumination This is the most common form of slit lamp examination with the microscope and light beam focused on the same point. The advantage of the focused light beam is that the sharp demarcation of illuminated and nonilluminated surfaces reduces scattered light that drowns out detail. When observing the cornea and lens, this produces a parallelepiped or a three-dimensional block of light as it traverses the tissue (**Figure 1.76**). Examination of solid structures such as the iris simply gives a magnified view with minimal glare. The parallelepiped of the cornea and lens allows visualization of the two surfaces of the tissue as well as the intervening tissue. As the surfaces of the cornea and lens are curved, specular reflections are produced. Specular reflections appear as bright reflections near the center of the vertical axis of the light beam. Examination with a broad light beam producing a parallelepiped gives a preliminary or overall impression. This is followed with the optic section, which is produced by narrowing the width of the light so that the block of light becomes two dimensional, namely length and depth (**Figure 1.76**). Coincidentally, the strength of the light usually must be increased. Examination of the tissue with the optic section allows exact localization in depth of lesions. When examining with an optic section, various zones of optical discontinuity can be observed in the cornea and lens.[35–37] The optic section is an *in vivo* histologic section at low magnification.

Retroillumination Retroillumination can be categorized as direct and indirect. Direct retroillumination examines structures or lesions against the background of the retroilluminated light (**Figure 1.13**); indirect retroillumination examines the retroilluminated structure against the adjacent dark background (**Figure 1.77**). The technique of retroillumination uses light that is reflected from deeper intraocular structures such as the iris or the fundus, while focusing the microscope on the nearer structures studied such as the cornea or the lens (**Figure 1.13**).[35–37] Retroillumination is an extremely sensitive and rapid method of detecting opacities

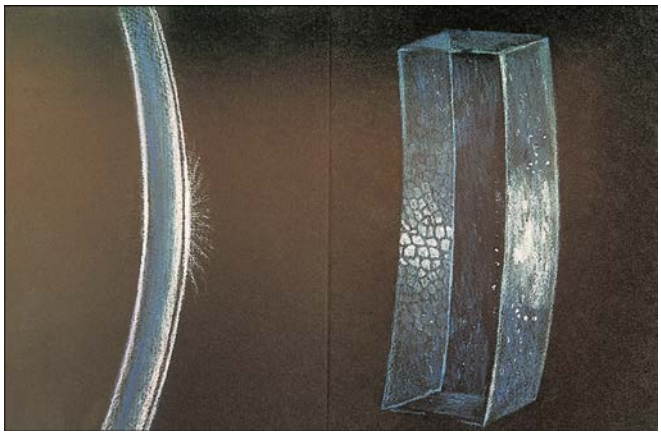

Figure 1.76 **Optic section and parallelepiped of cornea. Note the specular reflections. The endothelium can be visualized with a quiet patient utilizing specular reflections.**

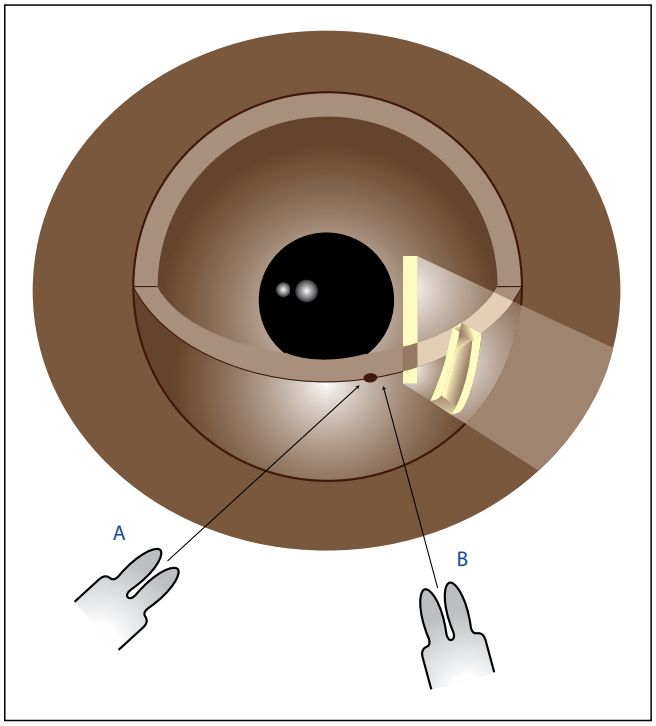

Figure 1.77 Direct and indirect retroillumination of a corneal lesion. At position A, direct retroillumination views the object in the cornea against the retroilluminated iris; at position B, the object is illuminated by the light but is examined against the dark nonilluminated iris. (Modified from Berliner, 1966. *Biomicroscopy of the Eye: Slit Lamp Microscopy of the Living Eye*, vol 1. Hafner Publishing: New York.)

of the clear media. Objects are observed because they obstruct, refract, or reflect light. Structures studied that obstruct light appear darker in direct retroillumination.

Oscillatory illumination Oscillatory illumination is a minor variation of direct focal illumination and retroillumination that utilizes the movement of the light source to study the dynamics of changing illumination on the structure or lesions.

Proximal or indirect illumination Proximal illumination utilizes a focused beam directed adjacent to the object being studied. Proximal illumination may determine the density of the lesion, that is solid versus cystic.

Focal pinpoint illumination The newer generations of slit lamps allow the examination of the anterior chamber with a pointed, focal light, which is a highly specific feature on the slit lamp dial settings. This pinpoint light source allows the detection of aqueous flare within the anterior chamber as a pathognomonic sign of intraocular inflammation. Aqueous flare is an accumulation of cells, causing the physical phenomenon of light scattering ("Tyndall effect") (**Figure 1.14**).

Examination of the posterior segment In an eye with a lens, the slit lamp can only focus as far posteriorly as the anterior vitreous cavity. Contact or noncontact lenses may be used to neutralize the cornea and allow the fundus to be examined with the slit lamp.[113]

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CHAPTER 2

OPHTHALMIC PHARMACOLOGY

BERNHARD M. SPIESS

ROUTES OF ADMINISTRATION

Topical

Topical administration is the usual route associated with ophthalmic drugs. Some of the many factors to consider when selecting a drug for topical therapy are: what is the target tissue and can the drug reach the targeted tissue in therapeutic levels; is the drug available in ophthalmic form; what form of topical drug to use if it is available in more than one form; what is the desired frequency of administration and practicality of it being administered; owner compliance; patient cooperation; comparative cost of medications; and potential side effects and toxicities.

Ability to penetrate the intact cornea

The intact cornea consists of the epithelium, which has a high lipid content; the stroma, which has a high water content; and the endothelium, which also has a high lipid content. Most drugs penetrate the cornea by a process of passive diffusion, which depends on concentration gradients, solubility characteristics, and for ionizable molecules, the dissociation constant.[1] A drug applied topically must have a differential solubility in water and lipid to penetrate the intact cornea.[2,3] Many drugs do not possess this characteristic; for instance, antibiotics are mainly water soluble, with the notable exception of chloramphenicol and the sulfonamides. The solubility of a drug may sometimes be improved by combining it with certain organic salts (glucocorticoids with acetate) or by producing a prodrug, or chemical derivative of the drug, manipulated to improve a certain characteristic such as solubility, which once absorbed is regenerated into the parent compound (dipivalyl epinephrine to epinephrine). Surfactants, such as benzalkonium chloride, which is a frequent preservative in ophthalmic solutions, also enhance absorption through the epithelial barrier by their epithelial toxicity. The main lipid barrier is broken with ulcerations and lacerations so that in these conditions the water-soluble antibiotics may attain therapeutic concentrations. In conditions such as corneal abscesses, the epithelium may be debrided to enhance drug penetration. In rabbits, removal of 25%–50% of the corneal epithelium increases the drug concentration in the cornea and aqueous ninefold. Defects larger than 50% do not further increase the drug concentrations.[4] In general, topical therapy achieves therapeutic drug levels only on the ocular surface and as far posteriorly as the iris–ciliary body. Topical therapy should not be relied on for posterior segment diseases.[5,6] An exception may be the newer nonsteroidal anti-inflammatory drugs such as nepafenac, the pharmacokinetics of which suggest a potential use in the treatment of posterior disease.[7]

Frequency of application

The frequency of therapy varies with the severity of the condition, the vehicle used, and the duration of action of the drug administered. For instance, one instillation of atropine in the normal eye can maintain mydriasis for 3–4 + days, whereas in an eye with iritis, mydriasis may require instillation three to four times per day. Antibiotics used for minor infections or prophylaxis may be given every 8–12 hours, but for an infected corneal ulcer, the concentration may be increased, and it may be used hourly or by constant infusion.

Placement of topical drugs

Most containers are multiple use and may be used on different patients. Care must be taken so that the container nozzle does not touch the hair or the cornea and become contaminated. A solution should be applied so that the drop falls onto the eye rather than have the container held into the eye and squeezed. The amount of fluid that the conjunctival cul-de-sac can accommodate is about 30 μL, and this is often exceeded by one drop from an ordinary bottle. The moral is that one drop, if it hits the eye, is more than enough, and two drops are excessive, wasteful, and increase the potential for systemic side effects from nasolacrimal absorption.[1] To minimize washout by subsequent drops, if more than one preparation is being given to a patient, a 5- to 10-minute interval should be observed between drops.

Ointments are harder to quantitate but a 1-cm (0.25– to 0.5-in) ribbon of ointment is adequate. After application, it is almost a reflex action to rub the ointment over the

cornea, but this should be avoided as it is traumatic, particularly if an ulcer is present.

Vehicle

The vehicle chosen for topical therapy may be a solution, a suspension, an ointment, or a solid ocular insert. The advantages and disadvantages of solutions and ointments are outlined in **Tables 2.1 and 2.2**. Comparable preparations in different vehicles are usually quite acceptable, and it is often a matter of personal preference.

Excipients of topical drugs

Excipients are the therapeutically inactive ingredients in drugs, but they are often critical to the success of the preparation. Excipients in topical medications are used to buffer, maintain sterility, prevent oxidation, and increase absorption. The pH of the preparation may be buffered by products such as acetic, boric, or hydrochloric acid or bicarbonate, borates, citrates, and phosphates to increase the nonionized form of the drug to improve lipid solubility, to increase the drug's stability, and to improve ocular comfort. The viscosity of the solution may be altered by vehicles such as polyvinyl alcohol, polyvinylpyrrolidone, and various forms of methylcellulose; in general, the goal is to increase the corneal contact time with the drug by slowing lacrimal drainage. Surfactants such as benzalkonium chloride are frequently found in ophthalmic solutions, and they act as antibacterial agents or preservatives, increase the solubility of hydrophobic agents, and enhance corneal penetration by their epitheliotoxic action. Other preservatives used are chlorhexidine, chlorobutanol, and thiomersal.

Agents such as dextrans, glycerine, and sodium chloride are added to solutions to bring the tonicity to a physiologic range of approximately 0.9% to minimize ocular discomfort. Antioxidants such as sulfites and EDTA are added to prevent degradation of many drugs to an inactive form by sunlight and oxygen (e.g., epinephrine, proparacaine). In suspensions, the particles that hold the active ingredient are excipients.[11,12]

Table 2.1 **Advantages and disadvantages of solutions and suspensions.**

Advantages

- Less disturbance of vision (questionable importance in veterinary medicine).
- Lower incidence of contact dermatitis.
- Less toxic to interior eye if an unsealed perforating corneal injury is present.
- May be easier to apply for some owners, especially in small animals.

Disadvantages

- Very short contact time (30 seconds), necessitates frequent application.[8,1] Important when considering owner compliance, as the more frequent the application, the less likely it is to be performed.
- Diluted out in irritated eyes with epiphora.
- Often more expensive for short-term therapy when compared with a comparable ointment.
- Suspensions often need excessive shaking to mix and deliver the intended dose.
- Systemic absorption from nasolacrimal duct drainage is greater than ointments.[8]

Table 2.2 **Advantages and disadvantages of ointments.**

Advantages

- Longer contact time, which means less frequent therapy and higher drug concentrations are usually delivered.
- Not diluted out by epiphora.
- Protects the cornea from exposure and keeps it moist better than solutions.
- Softens crusts and discharges.
- Easier to apply in large animals.
- Often less expensive than the comparable solution.

Disadvantages

- Add to the amount of discharge material from the eye.
- More difficult for some owners to apply.
- Higher incidence of contact dermatitis.
- More toxic to the endothelium if a penetrating injury is present.
- Interfere with epithelial healing more than solutions. However, this is controversial, and some studies have found no significant difference, or, if present, it is not clinically significant.[9]
- Imprecise dosage.
- More difficult to sterilize.
- Drug release from the vehicle is variable so that prolonged contact time may be negated, that is, 0.1% sodium dexamethasone phosphate solution penetrates better than the ointment.[10,9]

Packaging of topical medications

To avoid confusion in identifying topical solutions, by convention they are coded by cap colors: mydriatics and cycloplegics are red; miotics are green; carbonic anhydrase inhibitors (CAIs) are orange; β blockers are yellow or blue; glucocorticoids are pink; nonsteroidal anti-inflammatory drugs (NSAIDs) are gray; and anti-infective agents are tan or brown.[6]

Alternative topical delivery systems

Membrane-controlled delivery system

A polymeric membrane containing a reservoir of drug can be placed into the conjunctival cul-de-sac, and this allows the drug to diffuse out at a predictable rate. The rate and duration vary depending on the design. Such delivery systems are commercially available for a few drugs such as pilocarpine and epinephrine, which are used in glaucoma treatment, and these allow placement only once a week into the eye. The drug release is small, but the effect is equal

to or better than the pulsed therapy of a drop at intervals. Because of the lower concentration of drug released, the undesirable side effects are not noted.[13] The commercial designs have not been satisfactory in the dog or cat as the third eyelid usually catches on the reservoir and flips it out of the cul-de-sac. It is also a relatively expensive means of therapy, particularly for its main use in treating glaucoma, which is a lifetime therapy.

Pellets

Solid pellet-like particles of methylcellulose that dissolve slowly in the conjunctival cul-de-sac are commercially available. The main purpose is to give a slow continuous release, but in domestic animals, the third eyelid often flips them out of the cul-de-sac.[14]

Collagen inserts

Antibiotics impregnated into collagen inserts designed as rings to be inserted into the conjunctival cul-de-sac have been experimentally utilized in cattle. Mechanical design and physical properties of the collagen produce difficulties that have prevented successful application.[15] Collagen shields, which when hydrated appear as soft contact lenses, are on the market for the cat and the dog. They slowly dissolve over 3–5 days and may act as a drug reservoir when soaked in water-soluble drugs such as antibiotics. The pharmacokinetics vary with each drug and cannot be anticipated but in general are comparable to frequent topical applications. Caution should be exercised as the preservatives in the preparation are often toxic, and they will also be increased in concentration.

Soft contact lens

A soft contact lens can be soaked in water-soluble drugs and used as a drug reservoir. Caution should be taken with preparations containing preservatives as these may reach toxic levels if there is prolonged contact.[16]

Continuous and intermittent irrigation

A tube placed into the conjunctival cul-de-sac and brought out through either lid (subpalpebral lavage, SPL) or placed in the nasolacrimal duct and exiting through the false nostril can be used as a means of applying drops to an uncooperative patient.[17,18] In the past, when the tubes and footplates had to be fashioned individually, there were significant complications with the tube or the footplate rubbing on the cornea when the tube was placed in the upper lid.[19] As a result of the complications, clinicians advocated utilizing the lower medial lid (**Figure 2.1**) where the third eyelid would protect the cornea or the nasolacrimal duct.[18,20] With the advent of a commercial source of SPL sets (Mila International,),

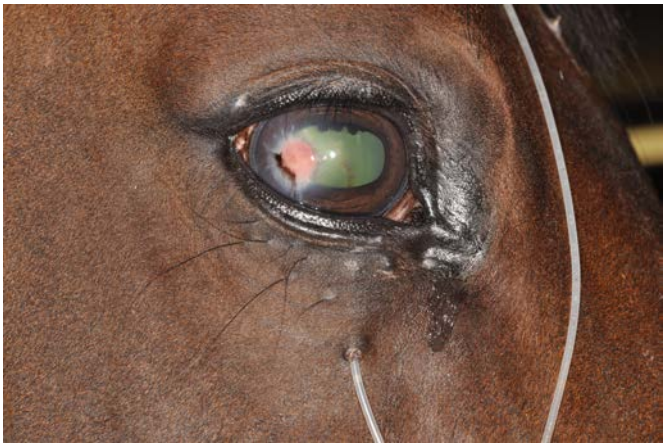

Figure 2.1 **Right eye of a horse with a subpalpebral lavage system inserted through the inferior eyelid. The footplate of the tube rests between palpebral conjunctiva and third eyelid to avoid corneal irritation.**

corneal ulcerations from rubbing of the footplate on the cornea have become uncommon. The placement of a SPL has become routine in treating horses with painful ocular disease that requires therapy over a prolonged period. Medication is placed in the tube (0.1–0.2 mL) and then pushed through with a bolus of air. Some horses object to the passage of air into the cul-de-sac and may require larger amounts of medication or a flush with saline to push the medication onto the eye. These latter methods increase the volume of drug and the expense or run the risk of diluting the medications.

When administering multiple medications, it is tempting to combine them in one solution. *In vitro* antimicrobial testing of solutions combining gentamicin, tobramycin, miconazole, and atropine for 6 hours did not demonstrate any decrease in effectiveness against *Pseudomonas* spp. or *Aspergillus* spp.[21]

Two basic techniques exist for applying SPL. The first is a two-hole system where the tubing is looped into and back out of the conjunctival cul-de-sac, with one or more holes placed in the portion of the tube exposed to the cul-de-sac. Placing the tube is difficult and requires two punctures by a needle trocar (**Figure 2.2**); this technique was popular before the advent of commercial SPL kits. The second technique is a single-hole SPL system that utilizes a silicone tube with a footplate. Both types of SPL require placement of the holes at the fornix or furthest extreme of the conjunctival cul-de-sac of the upper or preferably the lower eyelid to avoid ulceration. The injection end of the tubing is placed on a braided portion of the mane with a tongue depressor and tape. The tubing is held in place with taped "butterflies" that are sutured to the skin. The placement of the first butterfly close to the eye is the most critical in keeping the tube pulled up away from

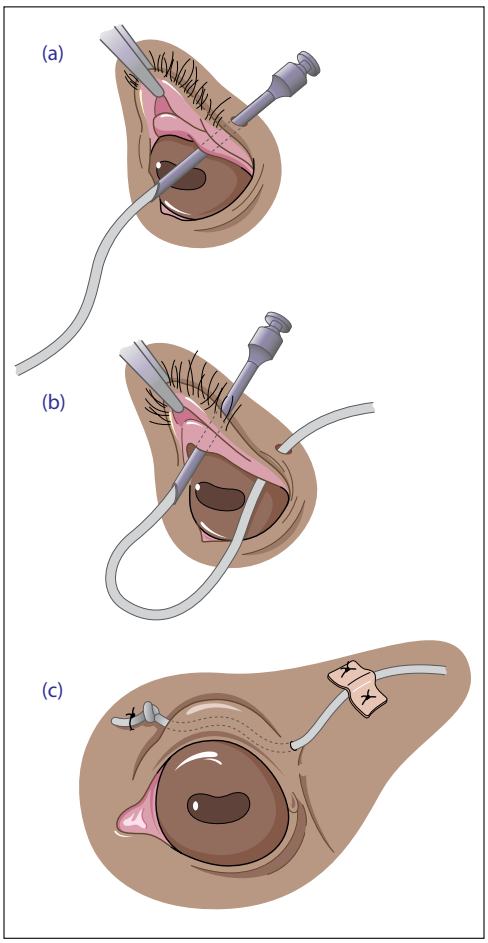

Figure 2.2 **Two-hole method of placing a subpalpebral lavage in the horse. The initial hole is created by a 14 gauge needle to thread tubing through (the direction can also be reversed) (a). Placement of a second hole to thread tubing through back onto the lid (b). A knot is tied at the end of the tubing to secure with a suture, and a hole made in the tubing traversing the conjunctival cul-de-sac; taped butterflies are sutured to the skin (c).**

the cornea. The tubing is slipped through the barrel of a tuberculin syringe and a blunt 22-gauge catheter threaded onto the tubing. The catheter is seated snugly into the barrel of the tuberculin syringe and a catheter cap placed on the catheter (**Figure 2.3**).

Commercial SPL kits are now available, so they do not have to be custom made. SPL units can be applied for several weeks, but they must be monitored for placement, infection, and function. In a series of 156 SPL placements of a custom-made tube, serious complications requiring premature removal developed in 16% of the placements.[19] One of the most common complications, subconjunctival migration of the footplate, is minimized by using a commercial SPL kit with a larger footplate, which also decreases the rate of corneal ulceration.

Alternatively, in the horse it is easy to place a tube in the nasolacrimal duct and flush retrograde with medications, although the tube is not as well tolerated. Nasolacrimal catheters require larger volumes of medication to reach the eye, and more of the medication is likely to reflux back as the tube does not reach the conjunctival cul-de-sac.

A micropump hooked to the subpalpebral unit delivers medications in a continuous manner. The micropump may be mechanical, for example, the Cormed ambulatory infusion pump (Medina, NY), elastomeric, or osmotic. The osmotic pump may be implanted subcutaneously and connected to a SPL or placed subconjunctivally after priming with medication. Tissue fluids are drawn around the drug reservoir, resulting in pressure that pushes the drug out at a calculated rate for up to 7 days. The amount and duration of medication varies depending on the size of the pump.[22–24] An external elastomeric pump is commercially available that delivers 0.5 mL/h and avoids the need for dissection (Mila International). The pump holds up to 125 mL of medication, but the calculated delivery rate is affected by the temperature and the viscosity of the medication. Pumps are a great work saver when only giving one medication or if several medications are to be given at the same high dosing rate. However, when using multiple medications, drugs are often given on varying dosing schedules. Also, even inexpensive drugs may become expensive when administered in the quantities necessary for continuous infusion.

Subconjunctival

Injection of a drug under the bulbar conjunctiva is also usually under Tenon's capsule, and consequently, the drug is deposited against the sclera, thus bypassing the lipid barrier that the intact cornea presents. Penetration of the drug is mainly by simple diffusion through the sclera, although leakage through the needle hole and topical absorption does occur.[5,6] The use of repositol or long-acting products can produce a prolonged therapeutic effect, but there is nothing inherent in the route that allows the drugs to last for long periods of time. Most animals can have the injection performed under topical anesthesia (**Figure 2.4**). Injection in the usual anterior location achieves therapeutic levels only in the anterior segment, although if injected posteriorly, therapeutic retinal levels may be achieved.[25] Injection of a drug subconjunctivally in the palpebral conjunctiva, as is frequently performed in food animal medicine, loses the advantage of being absorbed through the sclera. Drug uptake is probably topical through leakage from the needle hole and systemic from vascular uptake.

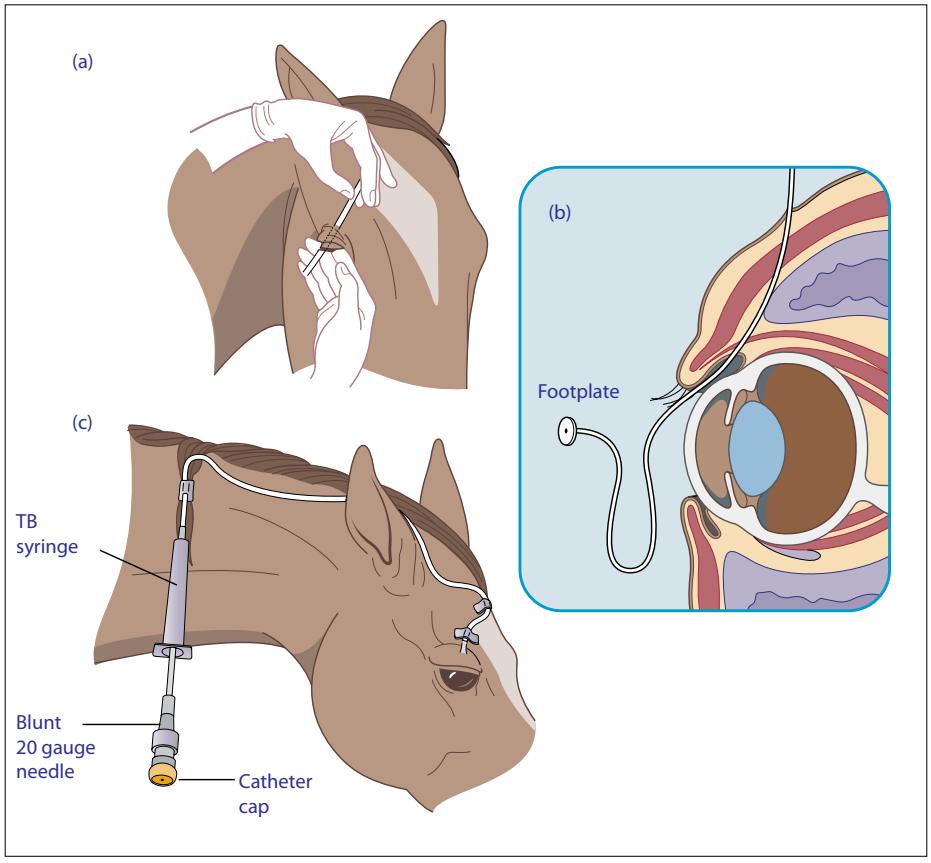

Figure 2.3 **Single-hole method of placing subpalpebral lavage system in the horse. A hubless needle trochar is placed in the fornix and through the lid (a). Tubing is threaded into the trochar and pulled through the lid. A cross-section illustration to show placement of tubing in the fornix or as high up in the conjunctival sac as possible (b). The footplate is pulled up to the fornix, taped, and sutured in place and a tuberculin syringe used to stabilize the distal end of the tubing (c). The tubing is threaded into the needle end of a tuberculin syringe barrel, and a blunt 22-g cannula is threaded into the tubing; the hub of the cannula seats or fits snugly into the tuberculin syringe. A catheter cap is added to the cannula; the syringe is then taped to a tongue depressor, and the unit is taped to a piece of braided mane.**

Advantages

- Aqueous products can be absorbed into the eye.
- If repositol-type products are used, a prolonged drug level can be obtained without the bother of frequent topical medication.

Disadvantages

- Perforation of the globe with the needle can occur.
- Many drugs are irritating.
- If repositol products are used, it is difficult to discontinue therapy, for instance to stop steroids if they become contraindicated.
- Increased systemic absorption and potential side effects.

Intraocular or intracameral administration

Intraocular injections are given when heroic means are needed to control a problem. The dangers of the trauma of injection plus the toxicity of many drugs to the corneal endothelium, lens, and retina must be balanced against the therapeutic benefit. The concentration of drugs is drastically reduced when intraocular injections are utilized. The injection can be in either the anterior chamber (intracameral) or the vitreous, or both, depending on the condition (see section Ocular centesis, for site). Intravitreal injections are often the only means of achieving significant drug levels in the vitreous.

The most common drugs administered intracamerally are antibiotics for endophthalmitis and tissue plasminogen activator for fibrin formation. Intravitreal implants of polymers surrounding an antiviral drug have been used in humans to treat cytomegalovirus retinitis. Experimentally in horses, cyclosporine intravitreal implants have been used to treat recurrent uveitis (ERU), and implants have been designed to achieve therapeutic cyclosporine levels for up to 10 years.[26,27] Because of serious side effects, a suprachoroidal cyclosporine-releasing device has since been developed and implanted successfully in many horses with ERU.[28]

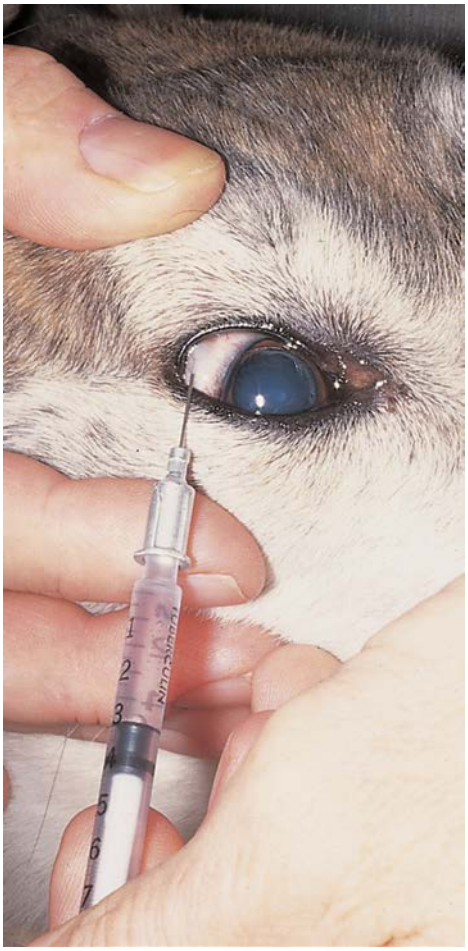

Figure 2.4 **Subconjunctival injection being administered in a dog under topical anesthesia with a 25-gauge needle.**

Retrobulbar injection

Retrobulbar injection is an infrequent route of drug administration, although this may be a route to obtain good drug levels in the optic nerve, vitreous, and posterior pole.[29] Systemic absorption is significant, with serum drug levels comparable to levels given by systemic routes.[30] Air or positive contrast material may be injected retrobulbarly for radiographic studies of the orbit. With the availability of computed tomography (CT) and magnetic resonance imaging (MRI), these contrast techniques are now rarely utilized. In the horse, retrobulbar local anesthesia is used to position the eye better and decrease ocular movements, thus allowing lighter general anesthesia, or to facilitate surgical procedures in standing horses.[31,32] Retrobulbar injections of anesthetics have also been shown to decrease postoperative pain after enucleation in dogs.[33] However, this is not without possible complications.[34]

Systemic

The systemic route is usually used to achieve therapeutic drug levels in the posterior segment and the optic nerve. Just as in the cornea, the posterior and anterior segments have barriers in the normal eye that limit the penetration of many drugs. A blood–aqueous humor barrier exists in tight cellular junctions of the ciliary body nonpigmented epithelium[35] and iris vascular endothelium, and a blood–retinal barrier exists due to tight junctions in the retinal vascular endothelium and the retinal pigment epithelium.[36,37] These barriers require lipid-soluble drugs to penetrate in the healthy eye, but with inflammation, the barriers become more permeable. Systemic therapy is given when the drug is needed in the posterior segment, severe anterior segment disease is present, or it is the only route available for the desired drug.

ANTIMICROBIAL AGENTS

Considerations in selecting an antimicrobial agent

Spectrum of activity and mode of action of the drug

When the infectious agent is unknown, a broad-spectrum agent or combination product is often used. A preliminary selection of antibiotics is made based on the presence and morphology of bacteria in scrapings or aspirates, combined with previous experience or published studies on sensitivity patterns.[38–40] Devastating intraocular infections require a bactericidal antibiotic to stop the infection as quickly as possible. Antimicrobial antagonisms are theoretically possible, but due to the very specific timing and dose relationships that are required, clinical antimicrobial antagonism is uncommon.[41]

When used prophylactically or for mild surface infections, potent antibiotics should not be used because drug resistance is encouraged.

Where is the agent needed?

The target area for the antimicrobial agent determines the route, the frequency of administration, and often the drug used, based on its known ability to penetrate the various barriers.

Patient comfort

Some preparations such as sulfonamides routinely sting and result in poor owner compliance. Cats are unpredictable in their tolerance to a particular topical antibiotic (gentamicin drops are often not tolerated), and inflammation may increase the irritation for many drugs.

Potential hypersensitivity to an antibiotic

Patients potentially may develop a systemic hypersensitivity to an antibiotic that is used topically and thus preclude future systemic use of that antibiotic. This is a major consideration in humans but less of a concern in animals. Alternatively, certain antibiotics such as neomycin are

prone to produce topical hypersensitivity reactions or, rarely, a systemic anaphylactic reaction.

> Development of a severe keratitis and/or blepharitis after initiating therapy should prompt the clinician to consider that the reaction is drug induced.

Indications for antimicrobial agents

Topical antibiotics are used for infections or suspected infective processes involving the lids, conjunctiva, cornea, anterior chamber, iris, and ciliary body. The number of antibiotics commercially available as ophthalmic preparations is limited, particularly for resistant Gram-positive organisms. In these cases, it is necessary to formulate topical preparations (often cephalosporins) from systemic antibiotics. The frequency of administration should be at least three to four times a day and may be hourly, depending on the severity and consequences of the infection (blindness with intraocular infection, progressive ulceration). In severe infections, the commercial topical solution may be fortified with the systemic form of the antibiotic to increase the antibiotic concentration. Experimental infections have confirmed the increased efficacy of fortified preparations; for instance, tobramycin and gentamicin have been recommended at a fourfold increase from the commercial topical preparations.[42,43]

The antibiotic selected depends on the sensitivity (known or suspected) of the organism and where the drug is needed. (See **Table 2.3** for intraocular penetration of antibiotics in the nonulcerated, noninflamed eye.) The fluoroquinolone antibiotics have become popular antibiotics when a broad-spectrum and bactericidal antibiotic is needed either systemically or topically. Ofloxacin has become the topical fluoroquinolone of choice because it penetrates the intact cornea better than other fluoroquinolones.[44] The main therapeutic weakness of the fluoroquinolones is their lack of effectiveness against Streptococci. The fourth-generation fluoroquinolones (moxifloxacin and gatifloxacin) have improved their efficacies against Gram-positive organisms while maintaining the similar effectiveness of older fluoroquinolones to Gram-negative organisms. Moxifloxacin penetrates the ocular barriers two to three times better than gatifloxacin and the older generations of fluoroquinolones.[45,46] The fluoroquinolones are also reported to inhibit keratocyte proliferation and produce cytotoxicity in tissue culture preparations.[47] Systemic fluoroquinolones, specifically enrofloxacin, have been associated with acute blindness in cats[48] (see Chapter 14). The toxicity affects the outer half of the retina and appears to be dose dependent. Risk factors are IV dosing, long-term administration, and aged animals.[49]

Table 2.3 **Intraocular penetration of antibacterial agents.**[50–57,59–70]

AGENT	SYSTEMIC	TOPICAL	SUBCONJUNCTIVAL
Penicillin	Fair	Poor	Good
Ampicillin	Poor	Poor	Good
Amoxicillin	Good	Poor	Good
Ciprofloxacin	Good	Poor	–
Ofloxacin	Good	Poor	–
Methicillin	Good	–	Good
Erythromycin	Poor	Good	Good
Cephalosporin	Poor	Poor	Good
Colistin	Poor	Poor	Good
Gentamicin	Poor	Poor	Good
Tobramycin	Poor	Poor	Good
Kanamycin	Poor	Poor	Poor
Amikacin	Good	?	? probably
Lincomycin	Good	–	–
Neomycin	–	Poor	Poor
Chloramphenicol	Poor/fair	Good	Good
Tetracycline	Poor	Good	Good
Minocycline	Good	?	? probably
Bacitracin	–	Poor	Poor
Rosacin	Poor	Good	Good
Polymyxin	–	Poor	Poor
Trimethoprim/ Sulfadiazine	Good	–	–
Sulfonamide	Good	Good	Good

Sources: Compiled from Bloome, M.A. et al. 1976. *Archives of Ophthalmology* 83:78–8350; Rowley, R.A., and Rubin, L.F. 1970. *American Journal of Veterinary Research* 31:43–49; Axelrod, A.J., and Peyman, G.A. 1973. *American Journal of Ophthalmology* 76:584–588; May, D.R. et al. 1974. *Archives of Ophthalmology* 91:487–489; Pohjanpelto, P.E.J. et al. 1974. *British Journal of Ophthalmology* 58:606–608; Purnell, W.D., and McPherson Jr., S.D. 1974. *American Journal of Ophthalmology* 77:578–582; Rieder, J. et al. 1974. *Albrecht von Graefes Archiv fur Klinische und Experimentelle Ophthalmologie* 190:51–61; Faigenbaum, S.J. et al. 1976. *American Journal of Ophthalmology* 82:598–603; Zachary, I.G., and Forster, R.K. 1976. *American Journal of Ophthalmology* 82:604–611; George, F.J., and Hanna, C. 1977. *Archives of Ophthalmology* 95:879–882; Barza, M.B. et al. 1978. *American Journal of Ophthalmology* 85:541–547; Kluge, R.M., and Zimmerman, T. 1978. *Annals of Ophthalmology* 10:1248–1251; Hillman, J.S. et al. 1979. *British Journal of Ophthalmology* 63:794–796; Saunders, J.H., McPherson Jr., S.D. et al. 1980. *American Journal of Ophthalmology* 89:564–566; Sigel, C.W. et al. 1981. *Veterinary Medicine/Small Animal Clinician* 76:991–993; Borden, T.B., and Cunningham, R.D. 1982. *American Journal of Ophthalmology* 93:107–110; Hulem, C.D. et al. 1982. *Archives of Ophthalmology* 100:646–649; Tabbara, K.F. et al. 1983. *Archives of Ophthalmology* 101:1426–1428; Wingfield, D.L. et al. 1983. *Archives of Ophthalmology* 101:117–120; Jay, W.M. et al. *Archives of Ophthalmology* 102:430–432.

In addition to topical antibiotics, systemic and subconjunctival antibiotics may be used in severe anterior segment infections, and the systemic route is indicated for posterior segment infections. **Table 2.4** presents appropriate antibiotic dosages for subconjunctival injections. Fluoroquinolones, specifically enrofloxacin, should be used cautiously in cats and avoided when other antibiotics would be just as effective. When utilized, a dose of 2.5 mg/kg every 12 hours is recommended, and fundus examination should be performed on a weekly basis.

Intraocular antibiotics are given for intraocular infections or to destroy the aqueous humor secreting capacity of the eye. The concentration of antibiotic is critical and must be supported by research data rather than estimates (**Table 2.5**). Gentamicin can be tolerated at a maximum dose of 350–400 μg inside the eye. The larger dose is given for bacterial endophthalmitis and may save the eye if given early. Intravitreal injection is the only route that produces high vitreous drug levels, and therapeutic levels may remain for 48–72 hours.[53,70] Higher doses destroy the retina and produce cataracts. Doses of 25–35 mg of gentamicin injected into the vitreous destroy the ciliary epithelium and result in decreased, or cessation of, aqueous humor production. Intravitreal gentamicin has been used as a chemical means of treating some forms of advanced glaucoma with permanent blindness,[71] but it should not be used in the functioning eye because this concentration will also destroy the retina. In one series,[72] 9% of injected eyes developed phthisis an average of 15 months post injection, and in 65% of the eyes, glaucoma was controlled. In eyes that required a second injection, the success rate was 50%.

Table 2.4 **Subconjunctival antibiotic dosages.**

AGENT	DOSAGE
Ampicillin	50–250 mg
Amphotericin B	125 μg
Bacitracin	10,000 U
Carbenicillin	100 mg
Cefazolin	50 mg
Cephaloridine	100 mg
Cephalothin	50–100 mg
Chloramphenicol	50–100 mg
Colistin	15–37.5 mg
Erythromycin	100 mg
Gentamicin	10–20 mg
Tobramycin	10 mg
Lincomycin	150 mg
Methicillin	150–200 mg
Neomycin	250–500 mg
Penicillin G	0.5–1.0 × 106
Polymixin B	10 mg
Streptomycin	50–100 mg
Tetracycline	2.5–5.0 mg

Table 2.5 **Intraocular antibiotic dosages.**[52,53,70,74,108,109]

AGENT	DOSAGE
Amikacin	500 μg
Amphotericin B	1–5 μg
Cefazolin	2.25 mg
Cephalothin	2 mg
Cephaloridine	250 μg
Ciprofloxacin	100 μg
Gentamicin	350–400 μg
Methicillin	<10 mg
Moxalactam	1.25 mg

Sources: Compiled from Axelrod, A.J., and Peyman, G.A. 1973. *American Journal of Ophthalmology* 76:584–588; ; May, D.R. et al. 1974. *Archives of Ophthalmology* 91:487–489; Zachary, I.G., and Forster, R.K. 1976. *American Journal of Ophthalmology* 82:604–611; Rutgard, J.J. et al. 1978. *Annals of Ophthalmology* 10:293–298; Fisher, J.P. et al. 1982. *Archives of Ophthalmology* 100:650–652; Fett, D.R. et al. 1984. *Archives of Ophthalmology* 102:435–438; Talamo, J.H. et al. 1986. *Archives of Ophthalmology* 104:1483–1485.

Intravitreal aminoglycoside antibiotics vary in toxicity: gentamicin > tobramycin > amikacin = kanamycin.[73] Due to the emergence of Gram-negative organisms resistant to gentamicin and the lower retinal toxicity of amikacin, 400–500 μg of amikacin intravitreally has been recommended over gentamicin for treating endophthalmitis.[74]

Paromomycin, an aminoglycoside antibiotic that is poorly absorbed from the gut and used to treat enteric protozoal infections, produced acute renal failure, cataracts, and deafness in cats after a 5-day course of oral therapy.[75] Three of four cats developed severe cataracts, which were noted by the owners a few weeks after antibiotic therapy.

Due to the limited effectiveness of aminoglycosides against Gram-positive organisms, a cephalosporin is often concurrently injected.

The selection of topical antibiotics is not as varied as one might anticipate, resulting in the need to improvise in concentration and compounding of systemic preparations when resistant organisms are encountered. Fortunately, many disease processes break down the barriers to drug absorption, allowing therapeutic levels of antibiotics to be achieved that might otherwise not be effective.

Antibiotic prophylaxis

Topical antibiotics are frequently administered for 1–3 days after lid, conjunctival, and corneal surgery. Also, whenever there is a break in the corneal epithelium (ulcer or laceration), whether or not it is associated with infection, it is routine to use prophylactic topical antibiotics to prevent the native bacterial flora from becoming established in traumatized tissue.[76] Newer antibiotics should not be used indiscriminately for routine prophylaxis to help avoid the development of resistant organisms to the drug. In the horse, which is predisposed to fungal keratitis after corneal ulceration, prophylaxis is often extended to the use of antifungal antibiotics. Subconjunctival and systemic prophylactic antibiotics are also given before and after intraocular surgery by some surgeons.

Antifungal preparations

Topical ophthalmic antifungal preparations are in the "orphan drug" category as fungal ophthalmic conditions are relatively uncommon, and thus it is not economically feasible for companies to develop such products. The only commercially available product marketed in the United States and Europe for ophthalmic use is natamycin 5% suspension. As natamycin (pimaricin) is quite expensive and not widely available, off-label use of topical and systemic antifungal preparations has become almost universally accepted. Systemic antifungal drugs may be formulated for topical therapy, and topical antifungal agents for use on other surfaces may be used for ocular use. Antifungal drugs fall into several categories: polyenes, pyrimidines, imidazoles, and miscellaneous drugs.[77]

The selection of an antifungal drug is difficult because of the lack of choice in commercially available products and often the lack of knowledge regarding the drug sensitivity of the organism. Performing mycotic sensitivity testing is expensive and time consuming, with the results often returning after the patient is cured (which usually takes several weeks)! Knowledge of the local fungal flora and their susceptibility to various antifungal drugs may help in the choice of the initial therapy.[78]

Polyene antifungals

Polyene antifungals increase the cell wall permeability of fungi by binding irreversibly to ergosterol.

- Natamycin 5% (pimaricin): Natamycin is the only commercially available ophthalmic drug marketed for topical therapy. Natamycin is a white suspension that is water insoluble and is effective against filamentous fungi and yeast such as *Candida* spp.[77] An ophthalmic ointment preparation (Infectomyk®) is available but penetrates the intact cornea poorly and leaves a white precipitate on ulcerated surfaces, lids, and inside SPL tubes.
- Amphotericin B: Amphotericin B is best known as an antifungal used in treating systemic mycoses. It has been used in topical ophthalmic therapy as a 0.1%–1.0% solution where it appears to be tolerated but, unless the surface is ulcerated, corneal penetration is poor. Topical 1% amphotericin B solution exhibits the most corneal toxicity and interference with corneal healing of a variety of antifungal agents.[79] Amphotericin B has also been injected subconjunctivally and intravitreally, but these routes have significant problems. Subconjunctival amphotericin B is very irritating, and it is questionable whether there is a safe dose with intravitreal injection. Axelrod and Peyman[52] and Axelrod et al.[80] recommended a very low dose of 5–10 μg in the middle of the vitreous cavity to avoid retinal toxicity. Souri and Green[58] found that even 1 μg of intravitreal amphotericin B was toxic to the retina and the lens in the rabbit.

Imidazoles

Imidazoles alter the fungal cell membrane by inhibiting ergosterol synthesis, resulting in increased permeability of the cell wall. Some may also interfere with mitochondrial oxidation and cause cell death by an accumulation of toxic substances. In one series of fungal sensitivities, *Aspergillus* sp. was the prevalent species, and the imidazoles were the most effective group of antifungals against this organism.[81] The latest *in vitro* sensitivity testing concluded that voriconazole was the most effective antifungal agent for the species of *Aspergillus* isolated from equine mycotic keratitis.[78]

- Miconazole has a broad spectrum of activity against yeast, filamentous fungi, and dermatophytes.[77] It penetrates moderately well, especially if corneal ulceration is present.[82] The IV form of miconazole has been used extensively as a topical 1% solution for equine keratomycosis; 2% vaginal and dermatologic creams have also been used for topical ocular therapy. The IV form has also been administered subconjunctivally.

Intraocular injection of miconazole is of questionable safety due to the toxicity of the vehicle as well as the drug. If injected intraocularly, the dose should not exceed 40 μg in a small eye, such as in a dog;[83] the safe dose for the larger equine eye is unknown. Intravenous miconazole has been taken off the market in the United States, but

compounding pharmacies have been formulating a preparation. When compounding, it has been difficult to keep the drug in solution.

- Clotrimazole has been used for topical ophthalmic therapy using 1% vaginal and dermatologic creams.
- Ketoconazole penetrates the cornea well, and dermatologic preparations have been used on the cornea. Ketoconazole has a broad spectrum of activity, and isolates from equine keratomycosis have been susceptible.[40,81] It has been used extensively for treating systemic mycoses in the dog, where cataracts have been a complication of long-term therapy.[84]
- Thiabendazole paste has been used historically for equine keratomycosis but has been supplanted by the newer imidazoles.[85]
- Fluconazole is a newer imidazole that has been used systemically, topically, and intracamerally. It is a triazole and has the advantage of enhanced tissue penetration because it has minimal protein binding. Like miconazole, the IV preparation of fluconazole is used as a topical solution and penetrates very well with corneal debridement.[86] While anecdotal reports are promising, fungal sensitivity testing indicates that most of the isolates are resistant.[40] Systemic therapy has been advocated for deep keratomycosis or corneal abscesses because of the drug's excellent tissue penetration,[87] starting with a loading dose of 2 mg/kg followed by 1 mg/kg every 12 hours by mouth for 2 weeks. With improvement, the dose can be decreased to 1 mg/kg every 24 hours.[88] Latimer et al.[89] studied the pharmacokinetics of fluconazole in the horse and calculated that the loading dose should be 14 mg/kg by mouth, followed by 5 mg/kg every 24 hours. This is a very expensive therapy for a horse. Fluconazole has also been administered intracamerally at 100 μg/0.1 mL.[88]
- Itraconazole is a triazole, and it has improved activity against filamentous fungi.[40] It has poor water solubility; Ball et al.[90] enhanced corneal penetration by dissolving the drug in dimethyl sulfoxide and creating a 1% ointment, with excellent clinical success. Itraconazole (5 mg/kg) is also being used systemically with equine keratomycosis. Systemic itraconazole has been the treatment of choice for systemic mycoses.
- Itraconazole/DMSO 1% ointment was formulated by dissolving 1 g of ultramicronized itraconazole in 33.3 mL 90% DMSO, heated to 80°C (176°F) while agitated, and the heated mixture combined with 66.6 mL of petrolatum that had been heated to 80°C (176°F). The mixture was allowed to cool while agitated until it solidified.[90]
- Voriconazole belongs to the triazoles and inhibits ergosterol synthesis causing cell membrane disruption. A 1% solution is prepared from the commercially available IV solution by reconstituting the lyophilized powder with sterile water for injection.[91] Voriconazole has been shown to have the best efficacy against equine fungal isolates.[78]

Miscellaneous antifungals

- Betadine solution has been used in topical therapy of keratomycosis.
- Silver sulfadiazine has been used as a topical cream for equine and human mycotic keratitis. It generally is well tolerated, is inexpensive, and moderately effective.[92]
- Chlorhexidine gluconate 0.2% has been used as an effective and inexpensive antifungal preparation in humans.[93]

Initiation of antifungal therapy in the horse is often accompanied by a clinical worsening of the condition. This worsening is probably due to the sudden death of fungi. Therapy is monitored by frequent corneal cytology if the condition is superficial. If healthy fungal hyphae continue to be observed on cytology despite therapy, the antifungal drug should be changed.

ANTIVIRAL AGENTS

The topical antiviral agents are mainly directed against the herpesvirus in man, and they are relatively specific for DNA viruses. Their use in veterinary medicine is mainly for ocular herpesvirus in cats and horses. The topical commercial agents are nucleic acid analogs, and they interfere with nucleic acid synthesis. They are virostatic and do not have an effect on viruses that are latent and are not multiplying. There are several commercial topical ophthalmic antiviral preparations available in the United States:

- Idoxuridine (IDU): A first-generation antiviral agent. IDU substitutes for thymidine in the purine building block of the DNA virus and is toxic to other mammalian cells as well. IDU was available as a solution and an ointment. Therapy is frequent: ointment is every 4 hours and solution every hour or every 2 hours. IDU is the least expensive of the antiviral agents. Individuals may experience irritation from the solution, and this is most likely if the product has become oxidized, as evidenced by a brown discolorization.[94] IDU has been discontinued in the United States but can be obtained through compounding pharmacies.

- Adenine arabinoside (Ara-A or vidarabin): Also a structural analog for adenosine. Vidarabin is available as a 3% ointment, given every 4 hours. Vidarabin is less toxic to mammalian cells and more effective than IDU.[94]
- Trifluorothymidine (TFT) (trifluridine): A thymidine analog inhibitor against the DNA virus. It is a 1% solution, administered every 4 hours. It is less toxic and more effective than other antivirals but more expensive. Based on a rabbit herpes keratitis model, it has been suggested that the application of trifluridine might be reduced to as infrequently as every 24 hours.[95]
- Acyclovir (acycloquanosine): An analog for guanosine that becomes a potent inhibitor of viral DNA polymerase. Acyclovir is selectively activated by phosphorylation by viral thymidine kinase but not by cellular thymidine kinase. This concentrates the active form in viral-infected cells and so minimizes toxicity to other mammalian cells.[94] Acyclovir may be given both systemically and topically, although it is not available in the United States as an ophthalmic preparation.
- Ganciclovir has been shown to be effective in a rabbit herpes simplex keratitis model.[96] It is commercially available as an ophthalmic gel preparation (Virgan®).
- Cidofovir (Vistide®) is commercially available as a 7.5% solution for injection. Diluted with 0.9% saline to a 0.5% solution, it can be used topically for the treatment of FHV-1 keratitis in cats.[97] It has the advantage of a twice-daily application only.

The relative efficacies of the antiviral agents are usually quoted for human herpesvirus in man or rabbit. The efficacy with other species of herpesvirus may vary as well as between strains of the same species. A limited *in vitro* study of feline herpesvirus sensitivities indicated that TFT was most effective, followed by IDU, vidarabin, and acyclovir.[98] This has been expanded to: trifluridine > idoxuridine = ganciclovir > cidofovir = penciclovir > vidarabine > acyclovir = foscarnet.[99,100]

Systemic acyclovir has been used in cats but, due to its limited bioavailability and feline herpesvirus resistance, it is of questionable benefit. Attempts at increasing the bioavailability of acyclovir by using valacyclovir, which is converted in the liver to acyclovir, result in systemic toxicity. Cats given valacyclovir exhibited clinical signs of dehydration and lethargy associated with hepatic necrosis and renal tubular necrosis after 12 days of therapy.[101] This toxicity is apparently species specific. Despite the report of systemic toxicity to valacyclovir, ophthalmologists and internists have been using famciclovir orally for several years without apparent toxicity. The dose and duration has been quite varied, but some caution is in order. Ophthalmologists have been giving between 1/4 of a 125 mg tablet to 1/4 of a 250 mg tablet for an adult cat for 3–6 weeks and 1/4 of a 125 mg tablet for kittens.[102] Some individuals have used famciclovir indefinitely to treat relapsing syndromes. Thomasy et al.[103] evaluated the toxicity and efficacy of famciclovir (90 mg/kg every 8 hours for 21 days) in experimental herpes infection in cats. They detected no adverse affects in the physical or biochemical parameters, and the clinical signs were attenuated with the drug.

The use of topical antiviral therapy with feline herpesvirus infections raises questions of cost/benefit ratio and accuracy of diagnosis. The clearest indication for therapy is with active corneal epithelial ulcers that are characteristic of herpesvirus.

Intravitreal injection of the systemic antiviral cidofovir at a dose of 100–500 μg has been advocated as a treatment for glaucoma. Unlike intraocular gentamicin, cidofovir apparently is not toxic to the retina or the lens.[104] It was originally noted that individuals given systemic cidofovir developed marked hypotony. The safety and efficacy of cidofovir for intraocular injections need further investigation.

Miotics (cholinergic agonists)

Pharmacology

The cholinergic miotics are classified into direct and indirect according to their action. The direct acting miotics, for example, pilocarpine, act directly on the cell to produce an acetylcholine-like action. They maintain their effect upon denervated structures. Pilocarpine has muscarinic action (stimulation of smooth muscle and glands) but not nicotinic action (stimulation of striated muscle). By convention, miotic solutions have a green cap.

The indirect acting miotics are cholinesterase inhibitors, and they act by preserving acetylcholine at the nerve endings. They have no effect on denervated structures where acetylcholine is not released. They are also categorized by their reversible or irreversible binding ability with acetylcholinesterase (**Table 2.6**). The indirect, nonreversible drugs are very potent drugs, and severe side effects from systemic absorption are possible.

Miotic preparations constrict the pupil (miosis), cause contraction of the ciliary muscle that produces accommodation, open the aqueous humor outflow channels, and increase vascular permeability. A transient breakdown of the blood–aqueous humor barrier may occur that resolves after about 48 hours.[109] Miotics are used in man almost exclusively for glaucoma therapy, where the important action is not the outward miotic effect but the contraction of the ciliary muscle, which increases aqueous humor

Table 2.6 **Parasympathomimetic miotics used in ophthalmology.**

DRUG	CONCENTRATION	FORMS	ACTION
Pilocarpine	0.5%–10%*, 4%**	Solution*, gel**, inserts	Direct cholinergic, muscarinic action
Carbachol	0.75%–3%	Solution	Direct and indirect cholinergic muscarinic and nicotinic actions
Echothiophate iodide	0.03%–0.25%	Solution	Cholinesterase inhibitor; irreversible, muscarinic and nicotinic actions
Isoflurophate (DFP)	Withdrawn	–	Cholinesterase inhibitor; irreversible, muscarinic and nicotinic actions
Demecarium	Withdrawn	–	Cholinesterase inhibitor; reversible, muscarinic and nicotinic actions

Note: *Solution; ** Gel.

outflow.[110] Miotics are usually not very effective for glaucoma therapy in animals because of the typical high intraocular pressure (IOP) when the condition is recognized and the physical obstruction present in the outflow pathway. The miotic and pressure lowering effectiveness also decreases with long-term therapy.[111–113]

Indications for use

Glaucoma

Miotics are used in glaucoma therapy and work most effectively with open-angle glaucoma, which is relatively rare in the dog. Carrier and Gum[111] found a statistically significant decrease in IOP in normal and glaucomatous beagles with 4% pilocarpine gel every 24 hours. However, the animals were only treated for 3 days, and during this time, IOPs drifted back to baseline values. Mean IOP response was 2.0–2.5 mmHg (0.27–0.33 kPa). When testing various concentrations of pilocarpine from 0.5%–8% in the glaucomatous beagle, all concentrations produced statistically significant decreases in IOP; all concentrations were equally effective, although the higher concentrations had more side effects.[114] Carbachol and *N*-demethylated carbachol both produced similar decreases in IOP as pilocarpine in the glaucomatous beagle and were not concentration-related, indicating that weak solutions were as effective as the higher concentrations.[115,116] The decrease in IOP was associated with an increase in conventional outflow, with the coefficient of outflow increasing from 0.33 μL/min/mmHg to 0.61 μL/min/mmHg in normal beagles, and from 0.15μL/min/mmHg to 0.38 μL/min/mmHg in glaucomatous beagles.[117]

Demecarium bromide and echothiophate iodide produced similar decreases in IOP as pilocarpine in the glaucomatous beagle, but the effect was for 3–4 days; thus, the drugs decreased the opportunity for pressure fluctuations during the day and would presumably increase owner compliance if frequency of application was reduced.[118] The pressure in acute closed-angle glaucoma (most common in the dog) is usually too high for miotics to be of much benefit, and the angle morphology so disrupted that outflow facility would be unlikely to be improved. When treating acute glaucoma, miosis is not observed until the IOP has been decreased.

Intracameral carbachol (0.5 mL of 0.01%) has been used in humans and dogs after cataract surgery. In the dog, carbachol minimized or eliminated the transient postoperative hypertensive episode that occurs in 50% of operated eyes.[119,120]

Glaucoma prophylaxis

Miotics have been advocated for years for prophylactic treatment of the normotensive eye when a unilateral primary glaucoma is diagnosed (see section Prophylaxis, Chapter 12). Until recently, there were no good clinical trials to support this use,[121] but because of the difficulty in treating this disease, clinicians will use anything that might have theoretical value. Because of their convenience, the long-acting preparations are often selected. Based on the studies to date, the type of glaucoma medication used in prophylaxis does not apparently make a significant difference.[121,122]

Displaced lens

Miotics may be used to try to trap a subluxated lens in the posterior chamber to keep it from luxating forward, or to trap an anterior luxated lens in the anterior chamber before surgery. Long-term miotic therapy results in a decrease in miosis; in the author's experience, cholinergic therapy is usually less successful in producing sustained, marked miosis than the prostaglandin (PG) analog latanoprost.[112,113,123]

Hyphema therapy

Miotics may be recommended for the treatment of hyphema because they increase the outflow of red blood cells (RBCs) from the anterior chamber. Miotics also produce vascular dilation and may induce secondary bleeding. Miotic therapy also aggravates traumatic iritis discomfort by inducing ciliary spasm[110] and may encourage pupillary block.

Keratoconjunctivitis sicca (dry eye)

Patients with some residual tear production may respond to stimulation with a parasympathomimetic drug to increase their tear production.[124] The oral use of ophthalmic pilocarpine had been used successfully for years before the advent of topical cyclosporine. Most clinicians preferred to use pilocarpine in food, but in multiple dog households where food is *ad lib*, the topical route has been recommended. The efficacy of the topical route has been discounted by Smith et al.[125] who found no increase in tear production in normal dogs in treated eyes and, paradoxically, a decrease in tear production in the contralateral untreated eye. Oral application of pilocarpine has been shown to be effective in the treatment of neurogenic keratoconjunctivitis sicca.[126]

The stimulation of lacrimation may take several weeks, and thus, a trial of 4 weeks or more is recommended. The use of topical cyclosporine as a lacrimomimetic has almost completely supplanted the use of pilocarpine (see section Therapy, Chapter 9). On rare occasions, a dog may respond to pilocarpine but not to cyclosporine.

Diagnostics

Miotics may be used to define the cause of a dilated pupil(s). Direct acting miotics should constrict the pupil unless there is a problem with the iris sphincter muscle. Indirect-acting miotics require an intact neuron in the iris to function and thus do not cause miosis with peripheral parasympathetic denervation (**Table 2.7**).

Side effects

- Ciliary muscle contraction or spasm may be stimulated. The discomfort is variable with patients, usually lasts 5–10 minutes, and often a tolerance develops within several days.
- Decreased vision may result if an axial lenticular opacity is present.
- Conjunctival congestion and mild flare (due to increased protein) may occur in the anterior chamber. This is a transient phenomenon.
- Systemic absorption from topical application or overdosing with oral medication produces vomiting, salivation, and diarrhea. Dogs with a heart block may be compromised. Systemic toxicity must be considered when intensive treatment is administered, as is frequently recommended for acute glaucoma.
- Long-term topical use may produce drug hypersensitivity, resulting in a severe follicular conjunctivitis.

Mydriatics

Pharmacology

Mydriatics produce pupillary dilation (mydriasis), and some agents are also cycloplegics (paralyze the ciliary muscles). As with the miotics, there are direct- and indirect-acting mydriatics. The duration of action between drugs and variation between species may be significant. Two groups of drugs are most commonly used for mydriasis, either individually or in combination for maximum effect. By convention, mydriatic solutions have a red cap.

Parasympatholytic agents

Parasympatholytic agents have both mydriatic and cycloplegic actions, and they are direct acting and compete with acetylcholine. The duration and strength of their action varies.[127] The rapidity and degree of mydriasis vary with the age, species, and pigmentation of the iris. Heavily pigmented irises bind many drugs, and the result is a slower onset and a decrease in magnitude of mydriasis, but the duration of action may be prolonged. This may explain why the pupils of some horses remain dilated for weeks after long-term atropinization.[128] Some but not all rabbits produce atropine esterase that inactivates atropine by hydrolysis. Occasionally, a dog may respond, paradoxically, to atropine or tropicamide with miosis. This is usually encountered preoperatively, and subsequent intraocular epinephrine will dilate the pupil. Long-term atropinization in young cats resulted in smaller resting pupils after discontinuation of the drug, and this was thought to be due to a compensatory increase in cholinergic receptors due to deprivation of transmitter.[129] This phenomenon has

Table 2.7 **Pharmacologic lesion localization with a dilated pupil.**

DRUG	NORMAL	CENTRAL PARASYMPATHETIC LESION	PERIPHERAL PARASYMPATHETIC LESION (ADIE'S SYNDROME)	IRIS ATROPHY	GLAUCOMA	ATROPINE BLOCKAGE
1% Pilocarpine	+	+	+ (hypersensitive)	0	0	0
0.01% Phospholine iodide	+	+	0	0	0	0

Note: +: constriction; 0: no response.

been used to explain the previously mentioned paradoxical miosis with mydriatics, but it is lacking in evidence.

While Mughannam et al.[130] were unable to find any change in IOP after atropine instillation in the horse, Herring et al.[131] found an 11% decrease in IOP in 10/11 horses, but one horse had a significant increase in IOP. Stadtbaumer et al. found significant increases in IOP in the cat after 0.5% tropicamide.[132] Unilateral instillation of tropicamide produced bilateral statistically significant increases in IOP of cats, but the mydriatic effect was only unilateral. While the mean increase in IOP was 3 mmHg (0.4 kPa), some individual cats had increases in IOP of 18 mmHg (2.4 kPa), resulting in IOP values of 30–37 mmHg (4.0–4.9 kPa). The phenomenon was age-related, with younger cats responding with higher mean changes in IOP. The mechanism for bilateral response with unilateral treatment is unknown but is thought to be due to a systemic effect. Stadtbaumer et al.[133] repeated the trial later and found a lack of bilateral IOP rise, with the only difference in trials being the lack of a topical anesthetic used for tonometry in the second study. The mydriasis lasted longer than the increase in IOP. The effect of tropicamide on the IOP of dogs is equivocal, with apparently minimal change.[134] Taylor et al.[135] evaluated post-mydriatic IOP in three breeds (Golden retrievers, Siberian huskies, and English Cocker Spaniels) and found that the majority of the dogs had less than a 5 mmHg increase in IOP, but the huskies had the highest IOPs before and after mydriasis.

Examples of parasympatholytics:

- Atropine 0.5%–4% solution: Atropine is the most commonly used mydriatic for therapy. In a normal eye, one administration of atropine may last for 4–5 days, but when used in uveitis therapy, more frequent administration is required (every 6 to 12 hours).
- Homatropine 2%–5% solution: Used in therapy. In a normal dog eye, one administration may last for 2 days.
- Scopolamine 0.25%–0.5% solution: Used in therapy. Duration of action of one administration in a normal eye is 4–5 days.
- Cyclopentolate 1% solution: Potent drug that frequently produces marked chemosis in the dog, so is not routinely used.
- Tropicamide 0.5%–1%: Most common agent used for diagnostic purposes because of its short duration of 6–12 hours.

Adrenergic agents/sympathomimetic agents

Due to the development of new drugs with activity targeted against specific adrenergic receptors, and due to species differences in receptors, not all adrenergic drugs dilate the pupil. For instance, apraclonidine dilates the dog pupil but constricts the cat pupil. Some adrenergic agonists such as nonselective α and β agonists and selective α agonists generally produce mydriasis without cycloplegia. Adrenergic agents may be either indirect (act by stimulating the release of norepinephrine) or direct (act on catecholamine receptors, similar to norepinephrine). Catecholamine receptors are classified as α-1, α-2, β-1, and β-2.

Sympathomimetic agents may be used to augment mydriasis, in glaucoma therapy to increase aqueous humor outflow and decrease aqueous humor production, and in diagnostics to localize sympathetic lesions involving the pupil (**Table 2.8**). Examples are:

- Epinephrine 0.1%–2%: Direct action, used for therapy and diagnostics. It is a nonselective α and β agonist and is used for glaucoma therapy, to dilate the pupil intraoperatively, and for vasoconstriction and hemostatic control in surgery.
- Dipivalyl epinephrine (Propine®): A prodrug of epinephrine. It is the esterified form of epinephrine and penetrates the cornea much better (9–17×) than epinephrine and can thus be used in lower concentrations. Once in the anterior chamber and

Table 2.8 **Pharmacologic lesion localization in Horner's syndrome.**

		LESION		
DRUG	**NORMAL**	**CENTRAL**	**PREGANGLIONIC**	**POSTGANGLIONIC**
1% Hydroxamphetamine[a]	+	+	+	0
1% Phenylephrine	0	0	0	+
10% Phenylephrine	–	+60 min	+30–45 min	+10–20 min
0.001% Epinephrine	0	0	mild+	+

Note: +: dilates; 0: no response.
[a] No longer available.

in the uvea, it is hydrolyzed to epinephrine, which is direct acting.[136]

- Paradrine® (hydroxyamphetamine) 1%: Indirect action, has been used for diagnostics for localizing the sympathetic lesion in Horner's syndrome.[137,138] It is no longer available as a commercial product.
- Phenylephrine 2%–10% solution: A direct-acting α agonist, used in diagnostics and therapy. Phenylephrine is not effective as a mydriatic in the cat, the cow, and the horse.[139–141] It has been used to localize sympathetic lesions in Horner's syndrome.[142]
- Cocaine: Indirect sympathomimetic, which dilates the pupil, causes vasoconstriction, and is a potent long-acting topical anesthetic. It is rarely used now because it is a Class IV controlled drug. It blocks the uptake of epinephrine by nerve endings, allowing a prolonged action of epinephrine and norepinephrine.[143] It can be used to try to break synechiae or adhesions of the pupil.
- Apraclonidine: α-2 agonist that is used in humans to treat postoperative IOP spikes and augment maximum medical therapy in glaucoma treatment. The selective α-2 agonists have been developed for glaucoma therapy to overcome the side effects that topical epinephrine produces in many patients. Apraclonidine 1% decreases aqueous humor formation by decreasing cyclic AMP, increases uveoscleral outflow in the treated as well as the untreated eye, and produces mydriasis.[143] Tachyphylaxis limits the duration of effectiveness of the drug for many patients.

In normal dogs, 0.5% apraclonidine decreases IOP and produces mydriasis.[144] In normal cats, apraclonidine lowers IOP and produces miosis, bradycardia, and vomiting. The side effects in cats preclude using commercially available 0.5% apraclonidine.[145]

Brimonidine is a selective α-2 agonist that is more selective than apraclonidine. It lowers the IOP by decreasing aqueous humor production as well as increasing uveoscleral outflow. Gelatt et al. tested 0.2% and 0.5% brimonidine in glaucomatous beagles and did not find a statistically significant decrease in IOP, although the pupil dilated.[146] Tachyphylaxis results in a decreased effectiveness over time.

The adrenergic agonists have not become an important group of drugs for glaucoma therapy because of their minimal effectiveness combined with significant side effects.

Indications for use

Diagnostics

Mydriatics are used for examination of the lens and in ophthalmoscopy. A long-acting agent is undesirable, and tropicamide is the agent of choice.[127,139] Very young animals do not respond as well or as long, and the addition of a sympathomimetic agent may be necessary to achieve good dilation. The use of sympathomimetic drugs for lesion localization in Horner's syndrome (sympathetic denervation to the eye and adnexa) is based on denervation hypersensitivity and the ability, or lack thereof, to stimulate intact sympathetic fibers in the iris. Direct-acting sympathomimetics are used to determine whether the iris is stimulated by dilute concentrations of epinephrine, or similar acting drugs, that are not effective in the normal eye. Hypersensitivity indicates that the lesion is peripheral or in the third neuron and that the nerve endings in the iris have degenerated. Boydell[142] utilized the speed of pupil dilation to topical 10% phenylephrine to distinguish between first-, second-, and third-order neuron involvement in Horner's syndrome in the dog. Dogs with first-order neuron disease responded to 10% phenylephrine in 50–60 minutes, second-order neuron disease in 30–45 minutes, and third-order neuron disease in 10–20 minutes. Similarly, drugs such as Paradrine (hydroxyamphetamine) act by stimulating intact nerve endings to release norepinephrine, and thus a positive response indicates an intact third neuron (**Table 2.8**). The results from these tests are highly variable, and interpretation is based on speed of onset and degree of reaction. Ideally, the opposite eye (if normal) should be used as a control.

Therapy of corneal ulcers

Intraocular pain may be decreased by producing cycloplegia to stop the pain from ciliary muscle spasms. Ciliary muscle spasms may occur with stimulation of the cranial nerve V endings in the cornea. The spasms are thought to arise from antidromic impulses that travel down the sensory nerve to the muscles. Atropine is usually the agent of choice and is administered every 8–12 hours. While some horses appear sensitive to topical atropine-induced colic at moderate doses every 6–12 hours, intensive therapy is more likely to induce colic from systemic absorption. Williams et al. induced colic with topical atropine administered hourly in 4/6 horses.[147] Occasionally, a pupil may remain dilated for weeks after multiple atropine applications, and this is probably due to depletion of atropine esterase or binding of atropine by uveal pigment and subsequent prolonged release.[128]

Therapy of anterior uveitis

Mydriatics, specifically atropine, are used in uveitis therapy to dilate the pupil, minimize adhesions or

complications from complete adhesions, and decrease ciliary muscle pain. Atropine is also used after surgically induced uveitis.

> Unless severe uveitis is present, intensive use of postoperative atropine in cataract surgery has been discontinued by many surgeons in favor of no mydriatics or tropicamide.

Nonsurgical therapy for axial cataracts

Vision can be improved in patients with axial cataracts and a clear periphery by dilating the pupil. Mydriasis allows the patient to see around the central opacity.

Medical therapy of equine glaucoma

The horse has a significant amount of aqueous humor outflow via the uveoscleral route, and it has been hypothesized that atropine may be beneficial in treating glaucoma in this species. Normal horses had an 11% decrease in IOP when treated with atropine compared to the control eye.[148]

Side effects

- Parasympatholytics decrease tear production and may produce transient keratoconjunctivitis sicca (KCS). Atropine administered to one eye decreases the Schirmer tear test (STT) in both eyes and may persist for 5 weeks or more after cessation of therapy. This is commonly observed in postoperative cataract patients.[149]
- Parasympatholytics may produce atony of the gut. While atropine may be used in most horses as often as every 2–4 hours without problems, the gut motility should be monitored.[147,150] Some horses are more sensitive than others to atropine-induced colic.
- Atropine may produce prolonged mydriasis and photophobia.
- Sympathomimetics often sting and may cause self-mutilation or rubbing. This tendency is most critical after intraocular surgery.
- Phenylephrine is toxic to the corneal endothelium and may produce corneal edema when used intensively in 10% concentration or if the absorption is enhanced by breaks in the epithelium.
- Frequent therapy with atropine may result in disorientation and incontinence. This usually occurs in very old or small dogs.
- Topical 10% phenylephrine may induce significant systemic hypertension through systemic absorption.[151]
- Acute, transient enlargement of the salivary glands may occur in cats after administration of tropicamide and atropine. The condition resolves in about 30 minutes.[152]

β-adrenergic blockers

Pharmacology

Topical β-adrenergic blockers decrease the production of aqueous humor by as much as 50% in humans.[153] The mode of action on the inhibition of aqueous humor production is unknown, although β-adrenergic blockers are known to be potent inhibitors of cyclic adenosine monophosphate (AMP) in the ciliary body. The major receptor in the anterior segment is the β-2 receptor; thus, drugs such as βxolol, which are β-1 blockers, are less effective than nonselective blockers, but they have fewer systemic side effects.[154] β-blockers do not affect carbonic anhydrase or the aqueous humor outflow.[153] The effect of β-blockers is variable in different species, due in part to concentration differences necessary to elicit a response.[153,155] In the normal cat and dog, higher concentrations of drug appear to be necessary to produce a reduction in IOP than in humans, and this may explain the early reports that β-blockers were ineffective in the dog.[156] Two studies reported that timolol (Timoptic®), which is a nonselective β-1 and β-2 blocker, was effective in both the dog and the cat and in the normal and glaucomatous beagle.[157–159]

Topical 0.5% timolol applied unilaterally in the normal cat eye reduced IOP by 22% in the treated eye and by 16% in the untreated eye. In addition, the pupil in the treated eye constricted by 38% for over 12 hours but not in the nontreated eye.[158,159] In one study in the normal dog, 0.5% timolol produced a significant mean reduction of 16% (2.5 mmHg [0.33 kPa]) in IOP, a 34% reduction in pupil size in the treated eye, and a 14% decrease in pupil size in the untreated eye, whereas other studies were unable to demonstrate a significant difference in IOP at this concentration.[156,158,159] The beagle with open-angle glaucoma did respond, with a significant drop in IOP using 0.5% timolol, but the decrease was only 4–5 mmHg (0.53–0.7 kPa). In the glaucomatous beagle, concentrations of timolol of 4%, 6%, and 8% did produce a significant drop in IOP of 8–14 mmHg (1.0–1.9 kPa) in the treated eye and a less extensive decrease in the untreated eye. This study did not detect any changes in the pupil size but did note a significant decrease in the heart rate at all concentrations.[157]

Available β-blockers may be either nonselective, blocking both β-1 and β-2 receptors, or selective. Timolol and levobunolol are nonselective β-blockers and are available as 0.25% and 0.5% solutions; as previously indicated, these drugs are minimally effective in the dog and the cat at this concentration. Betaxolol 0.5% is a selective β-1

blocker. While not studied as extensively as nonselective β-blockers, in the dog, it is also questionably effective at this concentration. Therapy is usually administered every 12 hours with both agents.

β-blockers can be additive in their effect when used with carbonic anhydrase inhibitors (61% decrease in IOP), parasympathomimetics, and even with epinephrine (50% decrease in IOP) when treating glaucoma.[160,161] The additive effect with epinephrine is confusing, considering that epinephrine is an adrenergic α and β-1 and β-2 agonist.

Indications for use

β-blockers are used in glaucoma therapy and prophylactic treatment of eyes thought to be susceptible to glaucoma (**Table 2.9**).

Side effects

Systemic absorption of β-2 blockers may produce or exacerbate pulmonary signs of bronchoconstriction and spasms and cardiovascular signs of bradycardia and heart blocks.[162] Decreased exercise tolerance may be noted, and, therefore, these drugs should be avoided in athletic dogs. Corneal erosions may occur and may be related to a decrease in tear production.[163]

DIURETICS

Two specific forms of diuretics are routinely used in ophthalmology, osmotic and carbonic anhydrase inhibitors.

Osmotic diuretics

Osmotic diuretics are used to draw fluid from the eye (aqueous humor and vitreous), and they are of dramatic benefit in the emergency therapy of acute glaucoma.[164] They produce systemic dehydration, so they are limited as to their frequency of use. Since they expand the blood volume, the presence of a weak cardiovascular system should be considered and care taken in the speed of administration.

The preparations usually used are:

- Mannitol: Recommended dose is 1–2 g/kg IV via slow push (over 5 minutes) or 1 mL/kg/min.[165] The author routinely uses 0.5–1.0 g/kg mannitol and obtains the expected results with glaucoma patients. Mannitol may crystallize out of solution if not kept in a fluid warmer. Mannitol tends to remain in the vascular system and exits via the kidneys, thus producing less rebound of fluids into the interstitial spaces. This is not absolute, particularly with inflammation, and with repeated administration, it becomes less effective until a minimal response is achieved after the third or fourth dose. Lowered IOP is evident by 20–30 minutes and may last for 6–72 hours.
- Glycerol or glycerine: Administered orally at 1–2 g/kg. Glycerol is irritating to the stomach and frequently results in vomition unless diluted. Glycerol is less expensive than mannitol and is an alternative in the horse.
- Isosorbide: Administered orally as a 50% solution at a dose of 1.5 g/kg.

Indications for use

- Glaucoma: Mannitol is used in emergency glaucoma therapy until surgery can be performed or until medical therapy becomes effective. Mannitol may also be used to treat transient postcataract surgery ocular hypertensive episodes if the IOP becomes very elevated.

  Topical latanoprost often produces dramatic decreases in IOP in acute glaucoma and may be used instead of mannitol in emergency therapy. If latanoprost does not realize the desired reduction in IOP within 30 minutes, mannitol is then administered.
- Preoperatively, intraoperatively, and postoperatively to reduce the vitreous size and so minimize vitreous prolapse through the pupil.

Carbonic anhydrase inhibitors (CAIs)

CAIs reversibly interfere with the hydration of carbon dioxide to form carbonic acid. CAIs are sulfonamides and are relatively ineffective diuretics, but they decrease aqueous humor production by about 30%–40%.[166,167] CAIs affect only the aqueous humor and not the vitreous. The exact mechanism of CAIs is still unknown, but they are thought to act on the active secretory component of

Table 2.9 **Topical ophthalmic β-blockers and their action.**

DRUG	CONCENTRATION/FORMS	ACTION
Timolol	0.25%, 0.5% solutions	Nonselective β-1, β-2 blocker
Levobunolol	0.25%, 0.5% solutions	Nonselective β-1, β-2 blocker
Carteolol	2% solution	Nonselective β-1, β-2 blocker
Metipranolol	0.3% solution	Nonselective β-1, β-2 blocker
Betaxolol	0.25% ointment, 0.5% solution	Selective β-1 blocker
Levoβxolol	0.5% ointment	Selective β-1 blocker

aqueous humor production, and this is independent of the kidney.[167]

Four isoenzymes of carbonic anhydrase have been described. Carbonic anhydrase II is the predominant form present in the eye and is involved with aqueous humor production.[168] It is also present in the corneal endothelium, iris, and retina. In general, CAIs must be given systemically to have an effect as >99% of the enzyme must be inhibited.[169,170] As carbonic anhydrase is ubiquitous in the body, nonselective inhibitors are likely to produce side effects other than the desired decrease in IOP. Systemic CAIs have historically been the backbone of medical maintenance therapy in canine glaucoma therapy.

Enhancing the corneal penetration by increasing the liphophilia of the compounds has allowed topical preparations of CAIs to produce modest decreases in IOP.[171–173] The quest for an effective topical CAI was pursued because of the frequent side effects noted with systemic CAI therapy and consequent poor patient compliance. Dorzolamide was the first commercially available topical CAI. It is not as effective as systemic CAIs but does not have the usual side effects of systemic therapy. It is available as a 2% solution, and every-8-hour therapy is recommended. In humans, dorzolamide decreases the IOP by 17%–20% and is only slightly less effective than timolol.[174,175] Dorzolamide can be given with β-blockers, and the effect is additive. Intraocular penetration of the drug is probably through the limbus and the sclera rather than the cornea. The hypotensive effect is greater in lighter pigmented irises than in the darker irises found more commonly in animals. This is presumably due to drug binding by melanin.

Corneal decompensation or edema might be expected with CAIs as carbonic anhydrase is present in the endothelium and postulated to be responsible for pumping water out of the stroma. To date, corneal decompensation is a rare event.[174] Statistically significant decreases in IOP have been found in the horse, the dog, and the cat after treating with dorzolamide, and the decrease is larger when combined with a β-blocker such as timolol.[176–178] While not as effective as systemic CAIs, the lack of systemic side effects and cost for equine patients has made topical CAIs popular in veterinary ophthalmology.

Brinzolamide 1% is the newest topical CAI. It is equally effective in suppressing aqueous humor secretion as dorzolamide but with less ocular irritation.[179–181]

Systemic preparations

- Acetazolamide: Is available as a tablet, spansule, and IV preparation. It is the most widely available CAI, but at a dose of 10–20 mg/kg every 8–12 hours, many dogs have side effects.
- Dichlorphenamide: Has fewer side effects. It has recently been discontinued by the manufacturer and must be compounded. It was available only as a tablet (50 mg) and administered at 2–5 mg/kg every 8–12 hours.
- Ethoxzolamide: 5 mg/kg every 8–12 hours.
- Methazolamide: 5 mg/kg every 8–12 hours.

Side effects

Side effects are common with systemic CAIs, in particular with acetazolamide at the recommended dose. Systemic acidosis, vomiting, diarrhea, anorexia, panting, poorer temperament, and paresthesia manifesting as lameness are possible. Ataxia is common in cats. In humans, kidney stones and fatal blood dyscrasias have been recorded.[182,183] An individual patient may be sensitive to all or only one of the preparations. Potassium supplementation has been recommended with long-term therapy. Besides ocular irritation, in humans, corneal edema, sterile mucopurulent conjunctivitis, and nephrolithiasis have been rare complications of topical CAIs.[184–186]

Other diuretics

Ethacrynic acid in cell cultures of trabecular cells produced reversible changes in cell shape. In enucleated canine eyes, ethacrynic acid increased the outflow facility and decreased IOP when injected intracamerally in monkeys and humans.[187,188] Pilot studies in dogs with a 2% solution were very disappointing. No changes in IOP were noted, marked ocular irritation was produced, and it was difficult to prepare a stable solution.[189]

ARTIFICIAL TEARS

Artificial tear solutions are used as vehicles for ophthalmic solutions, replace tears if deficient, protect eyes from exposure, and act as a filling substance between the cornea and a diagnostic lens (gonioscopy). They are generally over-the-counter products that do not require a prescription. Their main goal is to lubricate the surface of the eye, and many agents or combinations of agents are capable of this goal to varying degrees. The usual variables between the products are tonicity (isotonic versus hypotonic), presence of preservatives, and type and viscosity of lubricating agent used.

Agents

- Methylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose: Preparations with different viscosity are available.
- Polyvinyl alcohol: 1.4%–3%.
- Polyvinylpyrrolidone: Artificial mucus-like agent (mucomimetic).

- Hyaluronic acid: Human studies have indicated no particular advantage, and such viscoelastic agents are expensive. The prolonged contact time, however, imparts better corneal protection and lubrication than other artificial tears. Hyaluronic acid is available commercially in various forms and preparations. Multiuse vials without preservatives, (0.3% i-Drop Vet) are available. Other preparations are Remend 0.4%, Hyasent-S, OptiMend 0.2%, and Opti-Vet.
- Various ointment bases are used as ocular lubricants with tear deficiencies and to protect the cornea from exposure (anesthesia, exophthalmos, cranial nerve VII deficiency). They usually contain some combination of white petrolatum, mineral oil, and lanolin.
- Carbomer (polyacrylic acid) gels have become very popular tear substitutes.[190]

DYES

Most dyes are used for diagnostic purposes. The main dyes used are fluorescein and rose bengal.

Sodium fluorescein

Sodium fluorescein is available as a 1%–2% solution or on sterile strips. The solution is a good culture medium because preservatives are not used as they are inactivated by the dye. Multiple-use vials were found to be a potential culture medium for *Pseudomonas* spp.[191] Single-use strips or small-volume bottles and care in application are recommended to minimize iatrogenic infection.

Indications for use

- To detect corneal epithelial loss and follow the progression of healing. Water-soluble fluorescein does not normally penetrate the intact epithelium, but if breaks in the epithelium exist, it diffuses into the stroma where it is seen as a bright green color. Small breaks can be detected by using a blue light to excite fluorescence.
- To determine the patency of the nasolacrimal duct. Fluorescein applied to the eye usually appears at the nostril within 30–60 seconds. False negatives are possible, so a negative result should be followed by nasolacrimal flushing.
- Fluorescein IV is used to study the fundus vasculature. Fluorescein is a small molecule, and approximately 80% is protein bound. The nonprotein-bound portion is readily diffusible but is retained by tight intercellular junctions. Thus, it is valuable in detecting alterations in vascular permeability and epithelial intercellular barriers.[192]

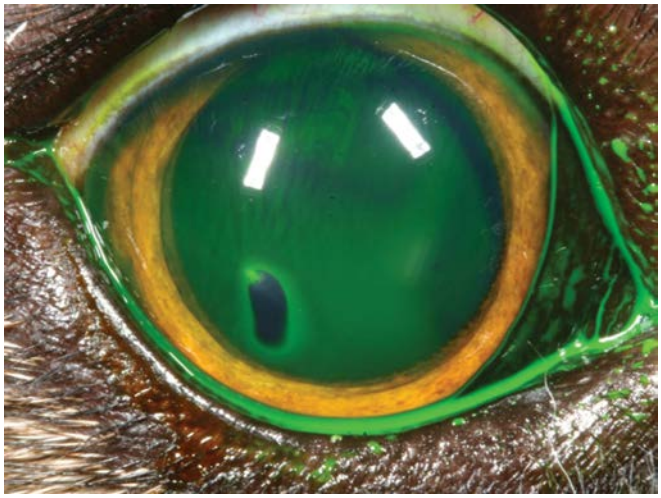

Figure 2.5 Positive Seidel test: Leaking aqueous humor from a small perforation is leaving a dark rivulet in the green tearfilm.

- To detect an aqueous humor leak from a perforating corneal injury (Seidel test).[193] The orange fluorescein applied to the suspicious area develops a dark rivulet in the green tear film where the aqueous humor trickles out of the wound (**Figure 2.5**).

Rose bengal

Rose bengal has been traditionally called a supravital stain that stains devitalized cells. The staining mechanism has been questioned in that it stains healthy cultured cells. Recent evidence suggests that healthy corneal cells are protected from staining by tear components such as albumin and mucin that block the stain uptake.[194] When rose bengal is applied to the cornea and the conjunctiva, it stains unprotected epithelial cells a rose color.

It is used mainly in diagnosing KCS (dry eye), and it is supposed to be more sensitive than the STT tear film deficiencies.[195] Rose bengal is virucidal and should not be used before culturing. It is also photodynamic and intrinsically toxic to cells. Rose bengal is often irritating when applied as a solution; this can be decreased by using a topical anesthetic prior to use or the use of impregnated strips of rose bengal.

Indocyanine green

A 0.5% solution of indocyanine green has been used intracamerally to visualize the capsule while performing curvilinear capsulorrhexis. Visualizing the capsule against a mature white cataract is difficult, and staining aids in identification for grasping with capsular forceps.[196,197] In humans, indocyanine green has also been injected intravenously and used for retinal angiography. Combined

with diode laser, it has been used to obliterate retinal neovascularization.

Trypan blue

Trypan blue has been used as a supravital stain to determine the viability of corneal endothelial cells in donor corneas for transplantation. It is also used to stain the capsule to facilitate capsulorrhexis during cataract surgery. Trypan blue is introduced into the anterior chamber under a large air bubble to keep the stain away from the corneal endothelium and against the lens capsule. It is rinsed out after 30 seconds to 2 minutes, leaving a mildly blue-stained lens capsule that is easier to see against the background of a white, mature cataract.

TOPICAL ANESTHETICS

Topical anesthetics are used extensively and exclusively for diagnostic and manipulative procedures of the eye but not for medical therapeutics. They are rapid in their onset, taking effect within 15–30 seconds and lasting about 15 minutes. Herring et al. found that by applying two drops at 1-minute intervals the length of maximal analgesia was extended to 25 minutes.[198] For the most profound analgesia, the author frequently supplements drops with a cotton tip applicator saturated with the anesthetic and placed specifically on the location to be manipulated. As a group, topical anesthetics are readily absorbed from mucosal surfaces but not from the skin. They are very toxic to the epithelium and retard healing of the cornea by inhibiting both mitosis and cellular migration.[199] Repeated usage creates tolerance, which begets increased frequency. It has been demonstrated that a reduced concentration can be used without toxic effects, but the disadvantage of short duration of action still remains.[200] Repeated topical application of anesthetics to diseased epithelium, such as in corneal edema, may result in epithelial erosions.[201] The topical anesthetics are also bactericidal, so conjunctival or corneal cultures should be taken prior to application.

Topical proparacaine has helped to maintain mydriasis or prevent miosis and decrease the breakdown of the blood–aqueous humor barrier as much as topical NSAIDs; therefore, it is being used preoperatively with intraocular surgery.[202]

Do not use topical anesthetics for the treatment of corneal ulcers.

Agents

- Proparacaine 0.5% is the most commonly utilized topical anesthetic.
- Tetracaine 0.5%–2%
- Oxybuprocaine 0.4%
- Piperocaine
- Dibucaine
- Benoxinate 0.4%
- Cocaine 0.5%–4%: The original topical anesthetic, but it is the most toxic to the epithelium. Cocaine is a controlled drug, so is rarely used now for this purpose.

MATRIX METALLOPROTEINASE INHIBITORS

The matrix metalloproteinases (MMPs) are categorized into subgroups according to their structure and matrix specificity, that is collagenases, gelatinases, and stromelysins. The MMPs are a family of zinc-dependent endopeptidases that are present in low levels in normal tissue and upregulated during normal and pathologic remodeling of tissue, such as in embryonic development, inflammation, neoplasia, and angiogenesis. They cleave collagen molecules and are secreted in a latent form. The catalytic domain for proteolytic activity contains a Zn^{2+} binding site that is stabilized by Ca^{2+}[154]. Examples of MMPs are collagenases (MMP-1, MMP-8, MMP-13), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10), elastase, and the serine proteases of plasmin and tissue plasminogen activator.[203–205] These enzymes are present in various cells such as migrating neutrophils, phagocytes, corneal cells, and in infectious agents such as *Pseudomonas* spp.[206,207]

The original ophthalmic interest in MMPs was in their role in corneal ulceration. The regenerating corneal epithelium interacts with the stroma to liberate the enzyme collagenase (MMP-1).[208] Collagenase is liberated in a latent form by corneal cells, is activated by plasmin, and is calcium dependent.[209,210] If present in excessive amounts, collagenase cleaves the stromal collagen and creates a progressive ulcer in both depth and diameter. Once initiated, progression of a superficial ulcer to a perforated ulcer can be a matter of hours.

Strubbe et al.[211] isolated MMP-2, MMP-9, and neutrophil elastase in higher levels from the tear film of horses with corneal ulcerations than from normal aged-matched controls. Levels of MMPs were elevated whether the ulcer was sterile or was associated with bacteria or fungi; MMPs were present in both eyes even with a unilateral ulcer.

Four natural inhibitors of MMPs (tissue inhibitors of MMPs [TIMPs]) have been identified.[212] Various drugs cause collagenase inhibition, and most of these work as chelating agents against calcium and zinc. Clinically, results are often disappointing. A verifiably effective protocol for treating progressive corneal ulcers has yet to be described; however, due to the potential devastating outcome of rapidly progressive corneal ulceration, clinicians utilize empirical treatment with a variety of products.