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## **Pathophysiology of Retinal Disease**

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The retina is a complex tissue composed of numerous cellular and synaptic layers. These layers can be split grossly into outer epithelial (retinal pigment epithelium) and inner sensory (neural retina) layers. The retina, as well as most other ocular structures, is readily examined without the use of invasive procedures although special diagnostic instruments are necessary. As with any other aspect of medicine, one must have a firm understanding of the normal embryology, anatomy, and physiology of the organ or tissue being studied in order to appreciate abnormal findings.

### **EXAMINATION OF THE RETINA**

The two methods by which the retina can be examined in the usual clinical situation are subjective and objective. One should use both types of examination to accurately assess retinal disorders.

A word of caution is in order. Too often many examiners attempt to equate the presence of pupillary responses (to light) with normal retinal function. Although some retinal (and optic nerve) function must be present to produce the pupillary response, there may not be enough viable tissue for vision. Lack of pupillary response is likewise not definitive because other problems (such as iris atrophy, synechiae, or oculomotor nerve damage) may prevent the response without interfering with vision. Thus, lack of pupillary response does not mean blindness and presence of pupillary response does not mean vision.

#### **Subjective Assessment of Vision**

Waving the hand in front of the eye is not an acceptable means of evaluating sight because movement of air causes most animals to blink regardless of degree of sight. To test this menace reflex, one should use

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a clear plastic barrier between the animal's eye and the menacing object to prevent blinking due to nonvisual stimulation.

Tufts or balls of cotton may be dropped some distance in front of the animal (must drop through the visual axis). Very little sound or air disturbance is created, and most sighted animals will briefly follow the cotton, establishing the presence of at least some vision.

A simple obstacle course is quite useful to determine the presence of bilateral blindness although uncooperative patients, particularly cats, may prevent adequate assessment. The course should be run in both daylight (photopic) and dim light (scotopic) to determine differences in cone-mediated (photopic) and rod-mediated (scotopic) vision. The course should be changed slightly with each test because some animals learn quickly where the various obstacles are located. A red light bulb of low wattage is useful for simulating scotopic conditions.

Unilateral blindness can be determined by bandaging one eye before testing the animal's response in an obstacle course. Both eyes should be tested regardless of the response with the first eye because some animals, even though they have vision in the unbandaged eye, will refuse to move with a bandage on.

### **Objective Physical Examination**

Examination of the ocular fundus (including retina) is termed ophthalmoscopy, and this is best performed through a dilated pupil. For routine pupillary dilation 1 per cent tropicamide (Mydracyl) is best because of its short onset (10 to 15 minutes) and short duration (several hours).

Direct ophthalmoscopy provides approximately 15 $\times$  magnification, an erect image, but only a limited view of the fundus. Indirect ophthalmoscopy, although providing only 2 to 4 $\times$  magnification, allows a wide field of view at one time. Other advantages of indirect ophthalmoscopy include stereoscopy, brighter illumination, and facilitation of peripheral fundus examination. One must keep in mind, however, that the image produced by the indirect method is inverted and reversed. Direct and indirect ophthalmoscopy should be considered to be complementary rather than mutually exclusive. The fundus can be surveyed with the indirect method to localize lesions. The direct ophthalmoscope can then be used to study the lesions more closely.

The hand-held direct ophthalmoscope is a standard part of the typical diagnostic kit which also includes the otoscope. The ophthalmoscope is held close to the examiner's eye with the lens selection disc set at 0. From about 30 cm, the pupil of the patient is found and kept in view as the ophthalmoscope (and the examiner's eye) is brought to within a few centimeters of the patient's eye. At this time the structures of the fundus should be visible; the lens selection disc is adjusted to bring these structures into sharp focus.

Indirect ophthalmoscopy is usually performed using a condensing lens along with a light source mounted on a head-band. These units usually cost upwards of \$500, but they provide the best stereoscopic view of the fundus particularly when an aspheric glass condensing lens is used. A reasonable assessment of the fundus can be made by using the principles of indirect ophthalmoscopy but eliminating the expense. Any glass or plastic lens having a power of about 20 diopters and being flat (plano) on one side and convex on the other can be used. (Optical supply houses have seconds that can cost as little as \$2.00.) To be comfortable, the diameter of the lens should be approximately 35 to 40 mm. Of course, a standard aspheric lens can be purchased for around \$25 for plastic or \$90 for glass. The light source can be a penlight or the otoscope part of the standard diagnostic kit.

The lens is held in one hand with the convex side facing the examiner. A finger of the same hand is placed on the patient's face to provide support and keep the lens a constant distance of several centimeters from the patient's eye. The light source is held in the other hand such that the path of the light is as parallel with and close to the viewing axis as possible. Generally, penlights are held against the side of the examiner's head. The magnifying lens of the otoscope can be swung out of the way and the examination performed through the opening created.

The examiner should be at arm's length from the patient. Ideally the pupil should be dilated, but this system can be used on undilated eyes if a darkened room is employed. One disadvantage to this method is the necessity of a second person for holding the patient. Also, although the tapetal area and nonpigmented fundi are easily viewed, a relatively strong light source is necessary for heavily pigmented nontapetal areas. Nevertheless, this system provides a relatively inexpensive method of indirect ophthalmoscopy that can augment direct ophthalmoscopy. The main point to remember is that a certain amount of practice is necessary to master the technique.

### **Special Procedures**

There are several, more complicated methods of assessing retinal structure and function. One of the most useful laboratory methods for assessing retinal function is electroretinography. The electroretinogram is especially valuable in the presence of an opaque cornea or lens or when the fundus appears normal but vision is disturbed. The electroretinogram is not a measure of vision but rather a measure of the functional integrity of the entire outer portion of the retina. The electroretinogram indicates nothing about the integrity of the pathways leading from the ganglion cell layer of the retina to and including the occipital cortex. The technical aspects of electroretinography are described elsewhere in this symposium.

Another procedure that is helpful in examining the retina is fluorescein angiography. A 10 to 25 per cent solution of sodium fluorescein is injected intravenously, and its path through the retinal and choroidal vessels is observed using various filters to facilitate fluorescence. A series of rapid black and white fundus photographs of the passage are taken and studied rather than the passage itself since that occurs within a few seconds. The observer is interested in determining if the passage time is normal and if there are filling defects or leaks. The major problem with fluorescein angiography in veterinary medicine is that it is usually utilized after clinical signs are seen and by then, ophthalmoscopy is usually sufficient for diagnosis.

### CENTRAL PROGRESSIVE RETINAL ATROPHY

Central progressive retinal atrophy is a specific retinal epithelial dystrophy that begins in the central (posterior) retina and progresses peripherally with secondary sensory retinal degeneration. The retinal epithelial cells accumulate a light-brown pigment and become hypertrophied to form individual giant cells or multicellular clumps of pigmented cells (Fig. 1). The sensory retina is normal early in the disease, but soon the photoreceptor outer segments overlying the abnormal epithelial cells degenerate, followed by further degeneration of all retinal layers late in the disease.

The pigment clumps are first visible in the tapetal area temporal to

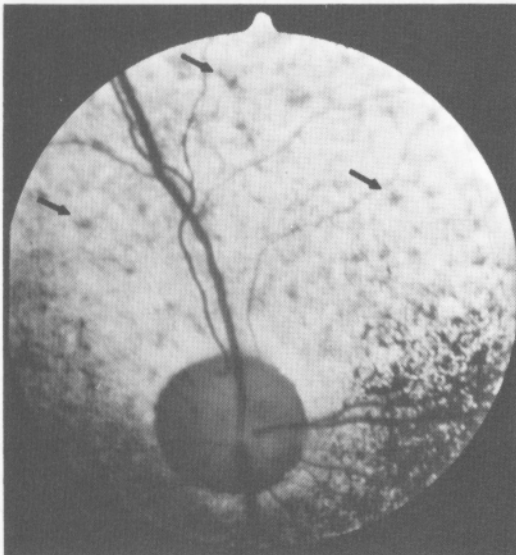


Figure 1. Ophthalmoscopic view of the eye of a dog affected with central progressive retinal atrophy. Note pigment clumps in tapetal area (*arrows*). (Courtesy of Dr. Seymour Roberts.)

and above the level of the optic disk (area centralis). This may begin from two to five years of age. Initially both day and night vision are normal. Central vision is first affected and, as it becomes worse, only moving objects are seen since the peripheral field of vision is normal and responds to movement. At this time a deficit in daytime vision may be apparent since the pupil is smaller in bright light and allows illumination of primarily the abnormal central retina. Ophthalmoscopically there is now diffuse distribution of pigment clumps in the tapetal area with some tapetal hyperreflectivity in between.

Eventually, over a course of as long as eight years, the peripheral retina becomes involved, the retinal vasculature becomes attenuated (but usually not to the degree seen in generalized progressive retinal atrophy), and the pigment clumps seen initially seem to disappear. The retina appears diffusely atrophic, and the animal may have little to no vision.

Central progressive retinal atrophy is relatively uncommon and appears to be limited to dogs among domesticated animals. Primarily working breeds are affected and include the Labrador Retriever, Shetland Sheepdog and Border Collie as well as others. Although central progressive retinal atrophy is considered to be hereditary, the exact mode is unknown. In the Labrador Retriever, a dominant mode of inheritance with variable penetrance is suspected.

Diagnosis is based on the characteristic ophthalmoscopic changes. The owner's history may indicate that the animal chases moving objects but loses them when motion ceases. By rolling objects in front of the animal, one may be able to detect this visual deficit. There is no treatment for central progressive retinal atrophy although pharmacologic dilatation of the pupils may provide some increase in vision early in the disease by facilitating peripheral retinal stimulation.

The pigment in the retinal epithelial cells is a lipopigment that is normal but is in excessive amounts in the cytoplasm. Intracellular accumulation of lipopigment (lipofuscin, specifically) occurs normally with age. Rod and cone cells shed portions of their membranous outer segments as part of their normal metabolism. This shed material, rich in lipid, is phagocytized and metabolized by the retinal epithelial cells. As aging occurs the digestive mechanisms apparently become less efficient so that lipopigment accumulates in the retinal epithelial cells but does not pose a problem. It is conceivable that in central progressive retinal atrophy the degradation of the ingested and modified membranous material may be defective, resulting in an overload of lipid compounds, particularly lipofuscin. Dogs that are made vitamin E-deficient accumulate lipofuscin in their retinal epithelial cells. Perhaps dogs with central progressive retinal atrophy have a local (retinal) biochemical defect whereby they cannot utilize vitamin E. Research in this area may eventually result in effective therapeutic regimens.

At the moment, only selective breeding can be recommended for control of central progressive retinal atrophy.

### RETINAL SEPARATION (DETACHMENT)

The clinical condition termed retinal "detachment" is usually a retinal separation. Sensory (from photoreceptors inward) and epithelial retina are derived from the same tissue embryologically and are considered to be one tissue as a whole. The term separation is preferable because the actual site of discontinuity is usually between the retinal epithelial cells and the photoreceptor outer segments. If the retinal epithelium were to lose continuity with the choriocapillaris (an unusual occurrence), this would be a true detachment.

Various types of separation may be seen. If the area of separation is small and the sensory retina remains relatively close to the epithelium, it is called a flat separation (Fig. 2A). When there is a cystic elevation the term bullous is descriptive. Complete separation, leaving only the attachments at the optic disc and ora ciliaris retinae intact, is described as having a funnel or "morning glory" shape (Fig. 2B). A breakdown of the attachments at the optic disc or ora ciliaris retinae is termed a dialysis. Rhegmatogenous separations refer to those associated with breaks, tears, or holes in the sensory retina (Fig. 2C).

Retinal separation is usually secondary to intraocular inflammatory disease, especially choroidal. It may be associated with renal disease or systemic hypertension, or may occur alone (idiopathic). Ocular maldevelopment syndromes such as the Collie eye anomaly sometimes are associated with separations.

Clinical signs produced by retinal separation depend on bilaterality and degree. If the separation is bilateral and complete, the animal will be blind although pupillary responses, though abnormal, may be retained. If the condition is unilateral or incomplete, the animal will compensate with the good eye or fundus zones so that there may be no presenting problem. Sensory retina in apposition to the lens will create a leukocoria which may be a presenting complaint.

Indirect ophthalmoscopy through a dilated pupil is the easiest method of diagnosis of retinal separation. Incomplete separations (flat, bullous) appear as out-of-focus areas; retinal vessels coursing through the affected zone will appear to be elevated. If the sensory retina is floating in the vitreous adjacent to the posterior lens, special diagnostic instruments may not be necessary (see Fig. 2B).

When a diagnosis of retinal separation is made, the cause must be found before treatment is initiated. If the separation is associated with ocular maldevelopment, treatment is not feasible. If it is associated with

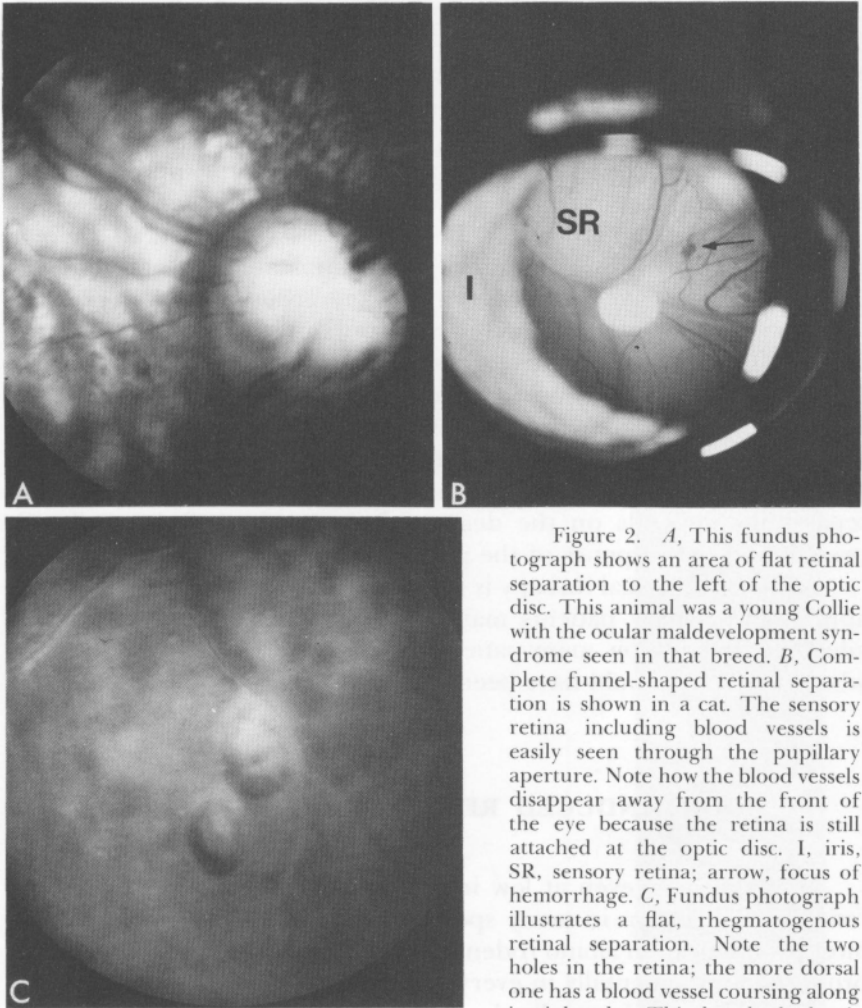


Figure 2. *A*, This fundus photograph shows an area of flat retinal separation to the left of the optic disc. This animal was a young Collie with the ocular maldevelopment syndrome seen in that breed. *B*, Complete funnel-shaped retinal separation is shown in a cat. The sensory retina including blood vessels is easily seen through the pupillary aperture. Note how the blood vessels disappear away from the front of the eye because the retina is still attached at the optic disc. I, iris, SR, sensory retina; arrow, focus of hemorrhage. *C*, Fundus photograph illustrates a flat, rhegmatogenous retinal separation. Note the two holes in the retina; the more dorsal one has a blood vessel coursing along its right edge. This dog also had retinal atrophy (note the thin retinal vessels and mottled fundus background).

uveitis or another inflammatory disease of the eye, treatment must be aimed at the causative agent rather than specifically at the separation. Traumatic separations are usually associated with severe head injury, which is more urgent than the immediate ocular problem.

For simple effusive separations, symptomatic treatment should include systemic corticosteroids and diuretics in addition to definitive treatment of any primary disease (such as renal or vascular). Corticosteroids are given at anti-inflammatory levels for an extended period, sometimes as long as six weeks, before being considered to be ineffec-



tive. Prednisolone (orally at 1.0 mg per kg or higher daily, tapering to 0.5 to 1.0 mg per kg range after 10 to 14 days) or dexamethasone (0.25 to 2.0 mg daily, orally) are commonly used. Furosemide is the diuretic often used (2 to 4 mg per kg orally once or twice daily). If the patient is hypertensive, oral methyl dopa may be helpful (5 mg per kg twice daily) in addition to a tranquilizer such as promazine (orally at approximately 2 mg per kg twice daily).

Therapy, particularly with the diuretics, is empirical. If there is sufficient distance between retinal epithelium and sensory retina to preclude proper metabolism by the photoreceptor cells, irreversible degenerative changes may occur in these cells after ten days. If these two layers reunite prior to this time, return of function may occur. Generally the prognosis is poor. Idiopathic cases generally have a better prognosis simply because there are no (obvious) contributing pathologic processes. Rhegmatogenous separations or those in which there is dialysis usually do not respond to any type of therapy. The prognosis in inflammatory separations depends on the degree of destruction of tissue already present and the response of the process to treatment.

Although surgical therapy is widely used in humans, it is difficult to apply to veterinary patients mainly because surgical exposure is not adequate. In addition, many patients are presented long after the period when correction would have been feasible.

## LIGHT-INDUCED RETINAL DEGENERATION

Ambient light even at low intensities can cause irreversible outer retinal degeneration in many species of animals. This susceptibility is most pronounced in albino rodents such as the laboratory rat but can be produced experimentally in every species studied to date.

Generally, moderate levels of light that is cyclic (approximately equal time on and off) will not cause damage. However, as little as 24 hours of continuous light will cause some damage in most albino laboratory animals. Several weeks of continuous light results in complete outer retinal degeneration in these albino animals.

Animals that have melanin in their retinal epithelial cells are protected from this effect of continuous light if the intensity remains moderate. Increasing the intensity of the light and/or focusing the light on a specific area will nevertheless produce degeneration in a wide variety of animals including birds, pigs, and primates. I have studied the effects of indirect ophthalmoscopic light on the canine retina. The susceptibility of the tapetal retina was compared with the pigmented, nontapetal retina. Retinal melanin seemed to afford the retina protec-

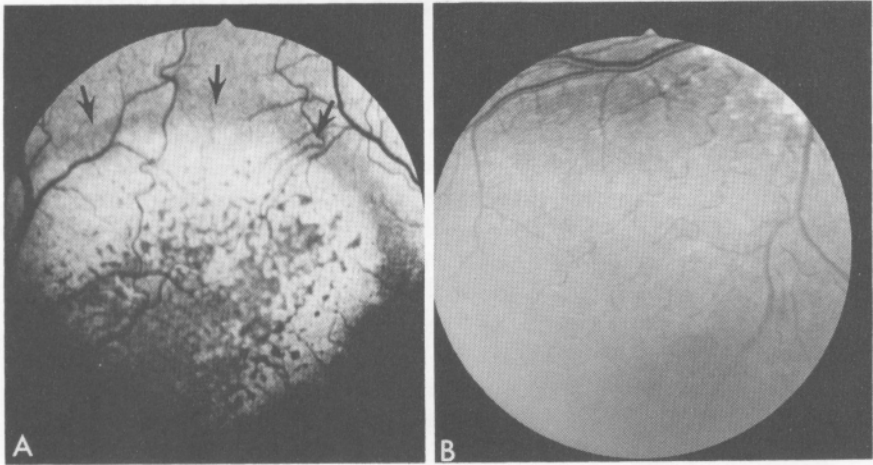


Figure 3. *A*, Fundus photograph of a dog's eye shows a circular area of retinal degeneration (arrows) produced in the tapetal zone eight days after this area was exposed to the light of the indirect ophthalmoscope for one hour. *B*, Fundus photograph of the fellow eye of the dog in *A*. The nontapetal area shown in the photograph had been exposed for one hour to the light of the indirect ophthalmoscope. No lesions are apparent 28 days after the exposure.

tion, whereas partial to complete retinal degeneration occurred in the tapetal area (Fig. 3). A complete report of the study is forthcoming.

The pathogenesis of light-induced retinal degeneration is poorly understood. It is known that free radicals produced when oxygen is used by cells are detrimental to these cells. These free radicals are normally converted to inactive or harmless substances by various protective biochemical processes within the cells. If the protective mechanisms fail or are overloaded in some way, free radicals build up in the cells leading to potentially serious damage. Visible light as well as numerous other sources of energy can produce free radicals. Current thought is that this may be a mechanism by which light-induced retinal damage may occur.

The importance of light-induced degeneration is particularly evident in the evaluation of drugs in toxicity trials or any experiment in which deleterious effects on the eyes are possible or are being determined. If one is not aware that this phenomenon may occur, erroneous evaluations may result. In these situations lighting conditions must be satisfactory for the species involved. It is possible that some progressive retinal atrophies in domesticated animals are influenced by this adverse effect of light; that is, light may speed up the naturally occurring degenerative process. Future research may reveal that certain types of progressive retinal atrophies may benefit from providing reduced lighting conditions, although to date this has not been proved.

## FELINE NUTRITIONAL RETINAL DEGENERATION

Feline central retinal degeneration was originally believed to be a specific disease of unknown etiology that was characteristically only moderately progressive or nonprogressive. Animals with feline nutritional retinal degeneration usually show no visual deficits but do have ophthalmoscopic abnormalities. The ophthalmoscopic lesion may vary from a small, circular area of retinal degeneration in the area centralis (Fig. 4A) to a larger elliptical lesion with prominent nasal extensions or satellites, and rarely to a large, band-shaped atrophy of the central retina. These lesions appear variably as hyperreflective or dark, depending on the angle of incident light. The electroretinogram in these animals demonstrates a generalized cone abnormality.

In cats fed a diet consisting of dog food only, or a diet in which the only protein is casein, a disease similar (ophthalmoscopically) to feline central retinal degeneration develops. However, in these animals, continuing the abnormal diet results in progression of the central lesion eventually to complete retinal atrophy (Fig. 4B). Electroretinographically these animals show both rod and cone abnormalities. The specific problem in these animals appears to be one of taurine deficiency.

Taurine is an aminosulfonic acid that is necessary for normal retinal function and structure. Cats appear not to be able to adequately produce taurine from precursors. A taurine-deficient diet does not suddenly produce changes because natural stores of taurine in the liver take time

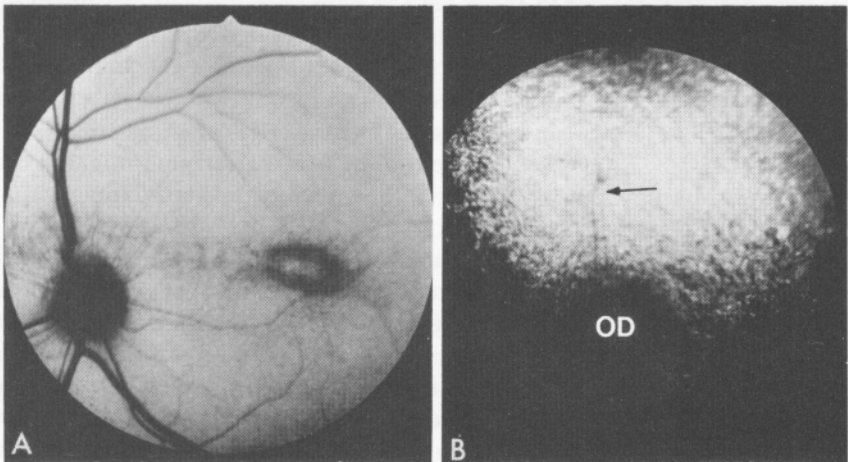


Figure 4. *A*, Fundus photograph of a cat's eye depicts a small, central retinal lesion typical of feline central retinal degeneration or early taurine deficiency. *B*, Fundus photograph of a cat's eye shows diffuse retinal atrophy. This animal had been fed dog food only for several years. Because of the tapetal hyperreflectivity, the strobe on the camera was set as low as possible; this precluded good detail of the nontapetal area. OD, optic disk; arrow, attenuated retinal blood vessels.

to be depleted. After the liver taurine is exhausted, retinal changes occur and progress if the diet remains inadequate. Taurine is almost absent in vegetables but is rich in flesh and milk. Dog foods are deficient in taurine but are being used by many cat owners apparently because of the rising costs of pet foods. This is unfortunate because many cats fed in this manner have become blind from retinal degeneration. The disease will not develop in every cat being fed dog food, but this may depend on their husbandry. Some of these animals have access to the outdoors and may be supplementing their diet with various wild animals or other sources of flesh so that taurine levels remain adequate.

Clinical signs of visual loss are not apparent in taurine-deficient animals until the retina is almost totally degenerated. At this stage, the pupils will be widely dilated but may respond somewhat to light. The ophthalmoscopic appearance is one of diffuse retinal atrophy (see Fig. 4B). Routine ophthalmoscopic examination of all feline patients as well as questioning their nutritional intake will identify the early lesions so that corrective dietary measures may be taken. Although the progression of retinal degeneration in a deficient cat can be stopped by reversion to a proper diet, degeneration already present is irreversible.

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