Primary Pigmented Intraocular Tumors in Animals

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Intraocular melanomas, among the most common eye tumors in man, have seldom been reported in animals. This is particularly surprising in regard to the dog, a species that usually lives well into the "tumor age" and is affected by diverse neoplasms. In his "Pathology of Tumours" (1953) Willis (48) stated: "I have not read of an intraocular melanoma in an animal." While reported cases are not as rare as this statement might imply, those that we have found do not make an imposing total, attesting to the apparent rarity of intraocular melanomas in animals. In addition to melanomas, this report embraces the tumors arising from the epithelium of the iris and ciliary body.

Reports of intraocular tumors of any kind in animals, whether primary or metastatic, number less than 50. The metastatic tumors (five), leiomyomas (one), hemangiomas (one), and retinoblastomas (seven) have been omitted, but reports of all primary tumors that might come under the heading of this paper are summarized in Table 1. Of the cases listed there, only those reported in adequate detail are discussed in the text that follows.

The study of Case 1 of our series in 1951 was hampered by the lack of any general discussion of intraocular tumors of animals in the literature, and to this day the only sources of information are widely scattered case reports. Since a number of other cases of intraocular tumors have become available for study it is now feasible to compile the information gained from this material and from the literature into a single report. It is hoped that this report will dispel the prevalent opinion that pigmented intraocular tumors do not occur in animals and will stimulate recognition and further study of them.

According to the literature, pigmented tumors in the eye may be melanomas of the uveal tract, medullo-epitheliomas, adenomas, and carcinomas. The last two listed are derived from the mature pigmented or nonpigmented epithelium of the ciliary body and from the pigment epithelium of the iris. In the older literature, both medical and veterinary, the tendency was to combine all pigmented intraocular tumors together as "melanomas." However, medullo-epitheliomas and uveal melanomas are distinct from each other and from adenomas and carcinomas in histogenesis, which makes such combining scientifically untenable. Medullo-epitheliomas are not known to metastasize, whereas carcinomas can and uveal melanomas often do; hence, there are also practical reasons for distinguishing among them.

In classifying human intraocular melanomas for prognostic purposes, Wilder and Paul (47) applied two diagnostic criteria. The first is the histologic type, of which six are recognized: spindle A, spindle B, fascicular, necrotic, mixed, and epithelioid, in order of increasing malignancy. This order was determined through a 10-year follow-up on 585 cases and a 5-year follow-up on an additional 226 cases from a series of 2535.

The second criterion is the argyrophil fiber content as revealed by the Wilder reticulum stain. The reticulum of a tumor may be heavy, medium, light, or absent in order of increasing malignancy, as has been determined by following up the same series of cases. The rationale of this classification as proposed by Wilder and Paul is: "If the tumor is slow-growing, fiber production keeps pace with tumor growth and fibers are able to encompass individual tumor cells, forming a barrier to their escape from the globe and particularly into blood vessels."

MATERIALS AND METHODS

Fifteen cases of intraocular tumor in dogs were available for study, eleven at the Armed Forces Institute of Pathology, and three contributed by Drs. C. P. Zepp, Jr., H. A. Smith, and H. Veenendaal. The eye in Case 1, studied clinically by one of us (L.Z.S.) at Cornell University, was obtained after enucleation. Additional canine material was studied from the cases of Bloom (6), Hopper (26), and Cotchin (12), previously published, and from an unpublished case of Dr. R. M. Mulligan. Material from several human intraocular tumors at the Armed Forces Institute of Pathology was studied for comparison.

The materials were embedded in either paraffin or celloidin, and sections were stained with hema-
SUMMARY OF PREVIOUSLY REPORTED CASES OF POSSIBLE PRIMARY INTRAOCULAR TUMORS IN ANIMALS*

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Sex</th>
<th>Age</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petit: 1919</td>
<td>F</td>
<td>6 years</td>
<td>Melanotic sarcoma of the choroid which penetrated the cornea at the limbus of the right eye.</td>
</tr>
<tr>
<td>Leone: 1926</td>
<td>M</td>
<td></td>
<td>Pigmented sarcoma of left eye resulting in increased intraocular tension. Euthanasia, followed by necropsy; no visceral metastases found, opposite eye normal. Tumor involved iris and ciliary body but not the choroid. Histologically, the cells were in alveolar and glandlike formations.</td>
</tr>
<tr>
<td>Chailous and Robin: 1930</td>
<td>F</td>
<td>8 years</td>
<td>“Melanotic sarcoma” in anterior chamber. Tumor, primary in ciliary body, pierced the upper half of the iris and extended into cornea. Tonometry indicated intraocular pressure was increased. Enucleation of eyeball. No extension to the orbit.</td>
</tr>
<tr>
<td>Buckler: 1933</td>
<td></td>
<td></td>
<td>Bilateral pigmented tumor of the iris, histologically a &quot;round-celled sarcoma.&quot;</td>
</tr>
<tr>
<td>Darraspen: 1939</td>
<td></td>
<td>18 months</td>
<td>Tumor of the choroid, no details.</td>
</tr>
<tr>
<td>McClelland: 1941†</td>
<td>M</td>
<td>10 years</td>
<td>Melanoma of choroid, causing blindness, increased intraocular tension, and pain. Eye enucleated, dog alive and well 1 year later.</td>
</tr>
<tr>
<td>Bloom: 1942</td>
<td>M</td>
<td>1½ years</td>
<td>Similar symptoms, euthanasia decided upon. No metastases found at necropsy. Epitheloid type of melanoma in choroid.</td>
</tr>
<tr>
<td>Fedrigo: 1942</td>
<td>M</td>
<td>14 years</td>
<td>Left eye involved by pannus for 1 year and buphthalmus for 5 months. Enucleation. Round-celled melanoma of choroid invading the retina, sclera, and cornea, without penetrating the globe.</td>
</tr>
<tr>
<td>Nordmann and Hoerner: 1946</td>
<td>M</td>
<td></td>
<td>Neuroepithelioma of the ciliary body.</td>
</tr>
<tr>
<td>Michael: 1947</td>
<td>F</td>
<td>5 years</td>
<td>Eye enucleated because of inflammation, exophthalmos, and pain; healing uneventful. Posterior chamber contained a thick black mass. Death 6 months later; melanotic tumors found in kidneys, ovaries, and uterus. No histologic examination of growths in eye or other organs.</td>
</tr>
<tr>
<td>Cotchin: 1954</td>
<td></td>
<td>11 years</td>
<td>Intraocular epithelial tumor of unknown type.</td>
</tr>
<tr>
<td>Leger: 1951</td>
<td>M</td>
<td>8 years</td>
<td>Adenoma of ciliary body.</td>
</tr>
<tr>
<td>Veenendaal: 1954</td>
<td></td>
<td>Aged</td>
<td>Intraocular melanoma, no recurrence or metastasis 3 years after enucleation.</td>
</tr>
<tr>
<td>Smythe: 1956</td>
<td></td>
<td>15 years</td>
<td>Intraocular melanoma.</td>
</tr>
<tr>
<td>Petisca: 1947</td>
<td>M</td>
<td></td>
<td>Tumor arising from the pars ciliaris retinae. Melanotic sarcoma of choroid with extension along optic nerve to thalamus.</td>
</tr>
<tr>
<td>Cotchin: 1957</td>
<td>M</td>
<td>7 years</td>
<td>Carcinoma of the ciliary body.</td>
</tr>
<tr>
<td>Born: 1876</td>
<td>M</td>
<td>18 years</td>
<td>Intraocular sarcoma invading choroid, retina, and optic nerve with metastases to orbit and submaxillary nodes. Whole eye included in a tumorous mass. No histologic details, but referred to as a sarcoma.</td>
</tr>
<tr>
<td>Konhäuser: 1884</td>
<td></td>
<td></td>
<td>Melanoma of choroid, 3 years' duration. Swelling and protrusion of the bulb. Terminally, abnormally high gait (&quot;goose step&quot;) and ataxia. Euthanasia because of nervous symptoms. Tumor had pierced the cornea and also invaded the brain.</td>
</tr>
<tr>
<td>Kitt: 1895</td>
<td></td>
<td></td>
<td>Sarcoma of the iris; no details except illustration.</td>
</tr>
<tr>
<td>Eberlein: 1902</td>
<td></td>
<td></td>
<td>Melanoma of the iris, listed in statistical compilation of clinic cases, no details.</td>
</tr>
<tr>
<td>Houdemer and Guyonnet: 1907</td>
<td></td>
<td>8 years</td>
<td>Spindle-cell sarcoma with many pigmented cells, primary in the ciliary body.</td>
</tr>
<tr>
<td>Hartog and Loran: 1924</td>
<td>F</td>
<td>8 years</td>
<td>Adenosarcoma of cylindrical and polygonal cell type, with tendency to rosette formation in posterior chamber, optic nerve, and orbit. &quot;Melanosarcoma&quot; of choroid, eye enucleated, no details.</td>
</tr>
</tbody>
</table>

* Note: Where the sex and age are not given after the authors, this information was omitted in the original description. † Material from these cases and some additional information were subsequently submitted to the Armed Forces Institute of Pathology. The cases are reported in detail herein as cases six and fourteen, respectively.
TABLE 1—Continued

<table>
<thead>
<tr>
<th>AUTHOR AND YEAR</th>
<th>SEX</th>
<th>AGE</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hess: 1884</td>
<td>F</td>
<td>1 year</td>
<td>Sarcoma of the iris which impinged on the cornea and lens. Eye enucleated, healing uneventful.</td>
</tr>
<tr>
<td>Richter: 1907</td>
<td>F</td>
<td>5-6 years</td>
<td>Round-celled sarcoma of right eye following a horn injury by another cow. Exenteration of orbit. No further details.</td>
</tr>
<tr>
<td>Ball and Zaessinger: 1929</td>
<td></td>
<td></td>
<td>Epithelioma of the nonpigmented cells of the ciliary body which grew through the the iris causing keratoconus, staphyloma, and rupture of the cornea. Eye enucleated. Histologically, the tumor cells had a glandular arrangement resembling thyroid.</td>
</tr>
<tr>
<td>Craig and Davies: 1937</td>
<td>F</td>
<td>11 years</td>
<td>Tumor of iris and ciliary body of right eye; enucleated. Cow became emaciated after surgery and was killed 8 months later. Necropsy revealed similar tumor in left eye and in the parotid lymph nodes, lungs, liver, and kidneys.</td>
</tr>
<tr>
<td>Brown and Pearce: 1926</td>
<td>M</td>
<td>18 months</td>
<td>Melanoma arising from either the iris or the ciliary body. No extension present at necropsy to the orbit or to other organs.</td>
</tr>
<tr>
<td>Ball: 1946</td>
<td>F</td>
<td>2 years</td>
<td>Melanoma of iris, loss of pupillary reflexes. Preceded by small dark bleblike patches on the iris. No lesions elsewhere in the body.</td>
</tr>
<tr>
<td>Levine and Gordon: 1946</td>
<td></td>
<td></td>
<td>Malignant melanoma of the choroid, bilateral, conditioned by a genetic factor.</td>
</tr>
</tbody>
</table>

Case reports

**Case 1.**—A 12-year-old male cocker spaniel was admitted to the small animal clinic at Cornell University with symptoms of glaucoma in the right eye. The intraocular tension was increased over that of the left eye, and the dog evinced pain on palpation of the right eyeball. A light gray growth with a smooth surface could be seen on the anterior surface of the right iris, involving about one-fourth of its circumference (Fig. 1). It had first been noted by the owner 1 month previously. The base of the growth was at the periphery of the iris, where it had grown into the cornea. Its apex extended somewhat beyond the pupillary margin. The pupil was fixed in dilation, and no pupillary reflex could be elicited. The refracting media were clear, and cupping of the optic disc was not seen ophthalmoscopically. The right eye appeared normal; its pupillary reflexes were present.

The growth had obliterated the filtration angle on the temporal side, the glaucoma being secondary to impaired drainage of intraocular fluid. Enucleation was performed, since the tumor did not meet Duke-Elder’s criteria for iridectomy. Neoplastic tissue was not found in the orbit. Two years later the dog was reported to be alive and well.

**Toxicity and eosin, Masson’s trichrome stain, Wilder’s reticulum stain, toluidine blue for mucin, and melanin bleach followed by hematoxylin and eosin.**

Upon dissection of the eye, the tumor was found to be adherent to the internal periphery of the cornea over a segment of about 60° of its circumference in the lower outer quadrant. In addition, a round nodule of tumor tissue about 1 mm. in diameter was found on the anterior surface of the iris at a point opposite the large tumor.

Histologically, the tumor consisted of cuboidal epithelial cells with scanty cytoplasm and large, round or ovoid nuclei. Only a few mitotic figures were seen. Many of the cells were arranged in the form of alveoli (Fig. 2), but in some areas they were packed solidly enough to obliterate the alveolar architecture. Homogenous eosinophilic material in some of these closely packed areas did not stain as mucin with toluidine blue nor as collagen with Masson’s trichrome stain.

The tumor seemed to arise from the root of the iris and did not involve the ciliary body. The filtration angle was obliterated by tumor cells which had grown forward from the iris to the cornea and then extended along, but did not invade, Descemet’s membrane. The melanin content of the tumor was slight; a few melanin-containing cells were scattered through it or appeared in a clump near the pupillary margin of the iris. In bleached sections, these appeared as plump, rounded cells (2–3 times the size of those forming the bulk of the tumor) with round nuclei; mitosis was not seen in them. The histologic appearance of the isolated iris nodule was similar to that of the larger tumor. Both were classified as adenoma of the iris originating from its pigment epithelium.
Case 2.—An 8-year-old female cocker spaniel was brought to the veterinary clinic at Iowa State College for euthanasia, because it had bitten a man. At necropsy (by Dr. H. A. Smith) it was noted that the refractive media of the left eye were not as transparent as the right. The eye was removed and incised, revealing a mass of white tissue with black borders, 1.5 cm. in diameter and 0.5 cm. thick in the region of the ciliary body on the medial side. The lens was rotated and displaced laterally. A lesion was not found elsewhere in the body.

Histologically, the tumor extended anterolaterally from the root of the iris on the medial side to involve approximately four-fifths of the cornea. The sclera at the root of the iris was deeply infiltrated and thickened by tumor cells which had almost, but not quite, penetrated it (Fig. 3). The tumor was in close apposition to the posterior surface of Descemet’s membrane and invaded the corneal substantia propria along its anterior surface. The anterior lens capsule was adherent to a portion of the tumor and to that portion of the cornea not covered by tumor.

The tumor was composed of large, round and cuboidal cells with pale cytoplasm and dark, round to ovoid nuclei. These cells were devoid of pigment, and mitoses were rare. The cells were packed in solid masses in most areas, but in a few their arrangement simulated alveolar formation. In parts of the tumor a heavy stroma had formed, and in some of the stroma and at the edges of the tumor large plump, melanin-containing cells with round nuclei were seen. The reticular content of the tumor was fairly heavy.

The retina had lost its layer organization and appeared as a thin sclerotic membrane adherent to the choroid. Both structures were infiltrated with plump, melanin-containing cells; similar cells were present in the sclera, ciliary body, iris, and cornea.

The tumor apparently arose from the epithelium of the iris or ciliary body. In spite of a heavy reticular fiber content, it was evident that the neoplastic cells would shortly have penetrated the sclera and spread to the orbit. Therefore, the tumor was interpreted as an adenocarcinoma of the iris or ciliary body. The retinal degeneration was of the type usually seen in canine glaucoma, which had probably resulted from blocking of the filtration angle by the tumor.

Case 3.—An aged cocker spaniel dog was destroyed because of a metastatic seminoma. In an...
Case 5. A 14-year-old male mongrel terrier was brought to Dr. C. P. Zepp, Jr., because of swelling of the left eye and corneal opacity of unspecified duration. Profuse hemorrhage in the eye prompted the owner to seek veterinary advice. He reported the dog in good health, its appetite and activity normal, and no evidence of pain until the day before, when hemorrhage occurred. The terrier was senile but lively and alert and in good condition. The left eye was greatly enlarged, and the cornea had ruptured, but the globe had not collapsed and was abnormally firm. Shreds of black tissue were seen at the margins of the ruptured cornea.

The eye was enucleated; evidence of extension to the orbit was not seen at operation. A transverse section through the eyeball revealed that both chambers were filled with firm, dense, black tissue (Fig. 5). The lens was displaced posteriorly, shrunken, and dark brown. Impression smears of the tumor showed it to be a melanoma. There was no evidence of perforation of the sclera.

Six months later the owner requested euthanasia for the dog because of complete anorexia, a harsh paroxysmal cough, moderate dyspnea, and a circling gait. At necropsy, the carcass was found to be obese. Discrete pigmented tumors, from several millimeters to several centimeters in diameter, were seen on the parietal pleura and pericardium, in the bronchial lymph nodes, in all lobes of the lungs, and in the liver. The pituitary gland was massive destruction of the ventricular floor.

Histologically, the intraocular tumor consisted of polyhedral cells with large round nuclei and lightly pigmented cytoplasm (Fig. 7). Mitotic figures were fairly numerous. The globe was almost filled with neoplastic tissue which also invaded the sclera and cornea. Several areas of necrosis were present deep in the tumor. Tumor cells were seen in the scleral blood vessels. The epithelium of the cornea was hyperkeratotic. The histologic structure of the metastatic tumors was similar to that of the ocular one, and the reticular fiber content was light in all. The tumor was classified as a malignant melanoma, epithelioid type, of the uvea. Because of extensive involvement of the eye, it was impossible to determine the portion of the uveal tract in which the tumor had arisen. The symptoms of circling may have been due to metastatic invasion of the brain, also a sequel in Hopper's case. The obesity and genital atrophy were probably related to destruction of the hypothalamus; the adiposogenital syndrome had been seen in several other dogs with hypothalamic lesions (48).

Case 6. A 10-year-old male Boston terrier with a history of blindness and pain in the right eye of 2 months' duration was presented for treatment. The intraocular pressure was increased. The eye was enucleated. A black raised area was present under the bulbar conjunctiva. Further gross description of the specimen was not available.

Histologically, the choroid was diffusely but not uniformly thickened by round cells containing heavy melanin deposits. In bleached sections the tumor cells were of fairly uniform size and shape, corresponding to the epithelioid type. Most of the sclera was infiltrated, and invasion of the cornea had begun. The argyrophil fiber content was heavy. The tumor had apparently penetrated the sclera to the conjunctiva, as seen at enucleation, but this area was not included in the sections. It was classified as a malignant melanoma, epithelioid type, of the choroid. The dog was reported to be alive and well 1 year later.

Case 7. The owner of an 8-month-old female German shepherd dog had noted a progressively enlarging growth in the eye for a month prior to the examination. Clinically, a blackish, discoid protuberance approximately 0.5 cm. in diameter was seen in the lower border of the left iris. In gross section of the eye, the iris appeared locally thickened.

Histologically, the filtration angle was being invaded by tumor cells from a nodule at the periphery of the iris. It was made up of large polygonal pigment-laden cells with round or ovoid nuclei (Fig. 8). The reticular fiber content was light. The tumor was classified as a malignant melanoma, epithelioid type, of the iris. Follow-up was not available.

This case is of interest, because neoplasia is not common in immature dogs. However, among the cases of iridal tumor in Table 1 are two others in which young animals were affected. In Bloom's (6) case the dog was 9 months old when the iridal growth was first seen. In Buckler's (9) case the dog

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*AFIP acc. 766650.*

6 This is a detailed description of McClelland's Case 1 (35). AFIP acc. 177080.

7 AFIP acc. 300892.
was 15 months old when presented for examination, but it is evident from his report that the growth was already well established at that time.

Case 8.---The specimen from an 8-year-old female Boston terrier dog was not accompanied by a clinical history. A pigmented mass was present in the region of the ciliary body, subjacent to the scleral bulge, and also involved the whole of the ciliary body and formed a small mass on the opposite side (Fig. 9).

Histologically, a large tumor in the ciliary body and root of the iris filled the anterior chamber at the filtration angle. The overlying sclera was elevated and thin. The neoplasm was closely adherent to the corneal endothelium but did not penetrate the cornea. The iris and ciliary body on the opposite side were also infiltrated with tumor cells. The neoplastic cells varied somewhat in size and shape; the majority were large and round, with ballooned cytoplasm distended with melanin granules. The small hyperchromatic nuclei were usually obscured by the melanin and could be seen only in bleached sections. In several places, the tumor cells tended to be spindle-shaped. The central portions of the tumor were necrotic. Numerous cells laden with melanin were present in the anterior and posterior chambers. Because of the presence of epithelioid and spindle cells, the tumor was classified as a malignant melanoma, mixed type, of the iris and ciliary body.

Case 9.---A 7-year-old male shepherd dog was presented with one eye completely destroyed by a tumor. There was no history of neurologic involvement, and the mass was movable, so that surgical removal was attempted, but could not be completed. The pigmented tumor tissue that was visible was curedt until the orbit appeared free of it. The wound healed readily; however, the dog had convulsions and died 6 weeks later. A post mortem examination could not be obtained.

A description of the gross specimen was not available. Histologically, the tumor was composed of oval to spindle-shaped cells which were usually compact and arranged as irregular whorls in a connective tissue stroma (Fig. 10). The nuclei of the tumor cells were large and vesicular with a prominent nucleolus. Mitotic figures were infrequent, and only a few nuclei were hyperchromatic. The cytoplasm of a few cells contained brown pigment, and there were scattered deposits of this pigment in areas of necrosis. Plasma cells and neutrophils were scattered in the conjunctival tissue. Neoplastic cells had infiltrated the optic nerve.

This tumor was classified as a malignant melanoma, fascicular type, of the uvea.

The neoplastic tissue filled the globe to an extent that obliterated its individual structures. It was thus impossible to determine the portion of the uveal tract from which the tumor had arisen. Its reticular fiber content was medium, and this, along with the necrosis, would indicate a poor prognosis. In the absence of a necropsy, the cause of the convulsions and death of the dog cannot be determined. The symptoms suggest the possibility that the tumor metastasized to the brain, as occurred in Case 5, and in two published cases (3, 26).

Case 10.---An 8-year-old female St. Charles-cocker spaniel cross-bred dog was presented for euthanasia. She had been ill for a week and, when examined, was too weak to stand. The cervical lymph nodes were enlarged.

Post mortem findings consisted of a pigmented subretinal mass in one eye, a mass on the buccal mucosa, nodules from 1.5 to 2 cm. in diameter in the lungs, bronchial nodes, pancreas, and kidneys, and enlargement of the right adrenal.

Histologically, a highly cellular neoplastic mass was present near the ciliary body (Fig. 14). It contained considerable melanin pigment and several areas of necrosis. The cells were spindle-shaped, with large elongate nuclei, prominent nucleoli, and scanty cytoplasm. Mitotic figures were numerous. The stroma was scanty, and reticular fibers were almost lacking. Tumor cells were present in the scleral veins (Fig. 13), but not in the retinal or choroidal arteries. Neoplastic masses similar in cellular structure to the ocular tumor were seen in the lungs, kidney, ovary, pancreas, right adrenal, and buccal mucosa; melanin, however, was present only in the buccal nodules. A diagnosis of malignant melanoma, spindle-type B, of the ciliary body with metastasis was considered.

The buccal mucosa of the dog is frequently pigmented; hence, it can and often does give rise to melanotic tumors. Since in this case a malignant tumor (possibly a melanoma, though lightly pigmented) was also present in the buccal mucosa, one cannot state with certainty that the visceral metastases came from the intraocular tumor. Against this possibility is the propensity of ocular melanomas to metastasize first to the liver, yet no metastasis was seen in the liver sections, while numerous other organs were infiltrated. In support of a primary uveal origin with metastasis are the facts that (a) tumor cells were present in the scleral veins, (b) the tumor was necrotic, and (c) it
had almost no reticular fibers. The two latter features place it among the most malignant of intraocular melanomas in the Callender-Wilder classification. With the concurrent buccal tumor the relationship of the ocular melanoma to the growths elsewhere in the body cannot be determined, nor should the possibility of multicentric origin be overlooked. In our opinion the least likely possibility is that the intraocular tumor was metastatic from an extraocular primary site; an opinion bolstered by the absence of tumor cells in the arteries of the choroid and retina.

Case 11.—The owner noted an abnormal appearance of the left eye in an 8-year-old male cocker spaniel dog shortly before presenting him for examination. A growth on the left iris extended from 6 to 10 o’clock. It extended posteriorly to the ciliary body, and anteriorly to the cornea. The eye was enucleated. Upon incision, two-thirds of the ciliary body, and anteriorly to the cornea. The eye was enucleated. Upon incision, two-thirds of the iris was found to be infiltrated by a white mass measuring 18 × 5 × 2 mm.; it occluded the filtration angle on one side (Fig. 12).

Histologically, the growth involved the iris and ciliary body, which were extensively infiltrated and thickened. In addition, it extended forward and came in contact with the limbus. The tumor consisted of large anaplastic cells with fused cytoplasm and round or ovoid nuclei showing varying degrees of hyperchromatism. There were numerous mitotic figures throughout the growth, and some of the cells contained melanin pigment. The reticular content varied; in some areas it could be classified as medium to heavy, but in adjacent ones there was no reticulum at all. Deposits of melanin but no neoplastic cells were seen in some of the scleral veins. The tumor was classified as a malignant melanoma, epithelioid type, of the iris, and because of the active mitosis and the presence of areas devoid of reticulum it was considered to be highly malignant.

On follow-up it was learned that the dog was returned to the surgeon 4 months after enucleation with a tumorous enlargement of the upper gum externally. A month later the dog was destroyed because of the rapidly growing gingival tumor and noisy respirations, the latter of 4 days’ duration. The left orbital region was grossly free of tumor. A black, firm, oval growth, 3 mm. in diameter, was present on the right lower eyelid. The gingival tumor extended inward through the nasal cavity to destroy the sinuses and turbinates. The medulla of both adrenals was involved by similar grayish to black tumor tissue. The gingival and adrenal tumors were reported on histologic study to be malignant melanomas by the examining pathologist, but we have not studied them personally. Whether they are similar morphologically to the intraocular tumor has not been established. Thus it cannot be stated with certainty that the intraocular tumor metastasized.

Case 12.—A 3-year-old male Irish terrier had sustained an injury to the right eye 4 months before he was examined. The veterinarian suspected a neoplasm, and the eye was enucleated. Grossly, the specimen was a dark, irregular mass, approximately 5 × 3 × 3.5 cm., without distinguishing features; its anatomic position in relation to the ocular structures could not be established. Upon incision of the specimen it was seen that a mass of dark tissue surrounded the sclera throughout the greater portion of its circumference and had invaded it posteriorly and extended to the adjacent extraocular muscles.

Histologically, the mass was composed of neoplastic tissue which had apparently originated in the choroid and extended extraocularly by penetrating the posterior sclera. Some remnants of atrophic ciliary processes were recognized, but lens, iris, retina, or choroidal tissue could not be distinguished. The tumor was vascular and contained several necrotic areas. It was composed of both spindle-shaped and polyhedral cells, with the former predominating. The nuclei of the spindle-shaped cells were hyperchromatic, vesicular, and usually elongated; the nucleoli were prominent. Numerous mitotic figures were present. Most of the cells contained melanin that often obscured all internal detail. The reticular content varied from light in most areas to none in a few. It was diagnosed as a malignant melanoma, spindle-type B, of the uvea.

Because of the extensive destruction of intraocular structures, the portion of the uvea from which the tumor arose could not be determined; it is presumed that it arose from the choroid. This is the only tumor in the series that exhibited posterior or extraocular extension. The subsequent course is unknown, but, because of the extensive extraocular involvement, recurrence and metastasis were predicted.

Case 13.—A 9-year-old male English setter dog was presented for treatment of an inflammation of one eye which had been noted 2 weeks previously. The eye was enucleated and submitted for histologic study without additional clinical data. A mass of tissue about 11 mm. thick was present outside the globe, extending from the limbus along the

11 AFIP acc. 659908.
12 AFIP acc. 480817.
13 AFIP acc. 263491.
sclera for about one-fifth its circumference. The retina was detached.

Histologically, the corneal tunic propria on the involved side was infiltrated by tumor cells. The iris and ciliary body on this side had been largely destroyed by the neoplasm, which infiltrated and involved the adjacent sclera to reach the extracocular muscles (Fig. 13). Neoplastic tissue extended anteriorly and posteriorly to the lens. Tumor cells infiltrated the iris, ciliary body, and retina of the side opposite the main tumor and were also found in an eosinophilic exudate in the anterior chamber, vitreous humor, and subretinal space. The retina may have been loosened by the subretinal infiltration of tumor cells, but its detachment was considered to be an artefact, since the degenerative changes usual in detached retinas were not seen. Excavation of the optic disc was deeper (Fig. 13) than the cupping normal in some canine discs. It was interpreted as a glaucomatous change occasioned by partial blocking of the filtration angle by the tumor.

The neoplasm was composed of polyhedral epithelioid cells with an abundant cytoplasm and large, usually oval, vesicular, hyperchromatic nuclei. Mitotic figures were numerous. The size of the cells varied, and, in addition, numerous multinucleated giant cells were observed (Fig. 14). The tumor grew in diffuse sheets and infiltrated the adjacent tissues extensively. Pigment cells were scattered through the neoplasm, probably as a result of dispersal of such cells normally present in the eye. The reticular fiber content was light in most areas of the tumor and absent in some. The tumor was diagnosed as a malignant melanoma, epithelioid type, of the iris and ciliary body. The extension to the orbit correlated well with its histologic appearance and light reticular content, suggesting eventual metastasis. Follow-up was not available.

Case 14—A 15-year-old spayed female Boston terrier dog was presented for treatment with a history of blindness of the left eye of several years' duration. The intraocular pressure was increased. She was destroyed because of a painful bulging of the left eye. Grossly, soft gray masses were attached peripherally to the sclera beneath the bulbar conjunctiva. Both chambers contained black, friable material. The lens was opaque. A yellow necrotic mass 2.5 cm. in diameter was present in the right lung. The patient reportedly had "fibropapillomas" all over the skin. The material submitted to the Armed Forces Institute of Pathology consisted of a paraffin block of the ocular tumor and of one of the pulmonary lesion.

Histologically, the intraocular structures were largely destroyed by neoplastic tissue which occupied most of the globe. Recognizable lens and corneal tissue were not present in the sections, and only the root of the iris could be identified. Several ciliary processes were infiltrated by neoplastic cells which had destroyed adjacent processes and most of the iris. The posterior choroid was free of neoplasm, but the peripheral portions were invaded. The retina was not invaded by the tumor, but was in close apposition to it and showed changes attributed to pressure atrophy, viz., thinning, complete loss of layer organization, sclerosis, and only a few remaining cells from one of the nuclear layers. The tumor had penetrated the sclera over a wide area and had raised but not penetrated the bulbar conjunctiva.

The tumor consisted of densely packed polyhedral cells of different sizes, with ovoid nuclei and scanty cytoplasm; a few areas consisted predominantly of spindle-shaped cells. Hyperchromatic nuclei were few in epithelioid cells but more numerous in spindle cells. Mitoses, although relatively few in number, were seen in all parts of the tumor. The pigment content of the tumor cells was light, many of them containing a few pigment granules, others none. The bulk of the pigment was concentrated in phagocytic cells which were seen in the vicinity of necrotic areas. The diagnosis was malignant melanoma, mixed type, of the ciliary body and iris, although spindle cells were not numerous.

Two tumor nodules were found in the lung sections. The larger was an adenocarcinoma, and was presumed to be primary in the lung. The other was a tiny metastatic melanoma, morphologically similar to the intraocular tumor.

Case 15—A 12-year-old female German shepherd guide dog was presented for examination 2 weeks after a growth was noticed in her left eye. The clinician found a tumor that involved the lateral half of the iris and extended forward to the cornea, occluding half of the pupillary area. Small "metastases" were evident from 9 to 11 and 6 to 9 o'clock. Some iridal pigment was observed in the nonoccluded pupillary area. The growth was about the same color as the iris. Several weeks later the eye was enucleated because of pain from increased intraocular pressure.

The enucleated eye could not be transilluminated, although a few flecks of light came through half of the cornea, which was pigmented at the
limbus, opaque, and streaked with white areas of denser opacity. A horizontal section through the globe revealed a black mass $6.5 \times 4.0 \times 14.0$ mm. attached to the iris. It protruded anteriorly and was in contact with the corneal endothelium at the lateral corneal margin. The lens was in place.

Histologically, a cellular pigmented neoplasm diffusely infiltrated and expanded the bulk of the iris, replacing pre-existing elements and extending to its periphery and into the filtration angle over a considerable area. It consisted predominantly of large polyhedral cells with abundant eosinophilic cytoplasm containing golden-brown melanin granules that were so abundant in some as to obscure cytoplasmic features. The large, round to oval, vesicular nuclei had prominent nuclear membranes and large nucleoli. Mitoses were not recognized. Occasional areas were made up of cells that were similar but spindle-shaped. Very large cells, densely packed with melanin granules, were dispersed irregularly through the tumor. The reticular fiber content was medium. The tumor was interpreted as a malignant melanoma, mixed type, of the iris. It was considered capable of recurring and metastasizing, but because of the cell type and reticular fiber content was believed to be less malignant than melanomas of the epithelioid type with less reticulum. The absence of evident scleral invasion and extraocular extension, coupled with predominant limitation to the iris, were regarded as indicative of a less grave prognosis. The dog was reported alive and well without recurrence or metastasis 21 months after enucleation.

**DISCUSSION**

Fifteen canine cases of pigmented intraocular tumors form the basis of this study. Four cases were tumors of epithelium of iris or ciliary body and eleven were malignant melanomas. The adenomatous epithelial tumors were in three aged cocker spaniels and in one mature fox terrier. A histologic diagnosis of adenocarcinoma was made in one case, but metastasis was not demonstrated.

The size of the series is inadequate to establish breed trends for intraocular malignant melanomas, although three of eleven cases were Boston terriers and two were German shepherds. A difference in incidence as to sex is not indicated. Twelve of the dogs were 7 years old or older, the other three were 44 years, 8 years, and 8 months old.

With respect to site, three of the melanomas in the present series involved the iris, one the ciliary body, and two the choroid. Three involved both the ciliary body and iris to an extent that precluded detection of the primary site, and two filled the globe completely and could only be classified as uveal in origin. Considering the three tumors which involved the iris alone and the three that involved the ciliary body in addition to the iris, this is a very high proportion of iridal tumors—six out of eleven. Reese's series of 421 human uveal melanomas contained only 23 iridal tumors, approximately 5 per cent. The frequent occurrence of tumors of the iris in canine material other than ours and in other species of animals is shown in Table 1. This apparent frequency may be real or merely a function of the greater ease of clinical detection of iridal tumors in animals.

The representation of the various cell types was as follows: five epithelioid, three mixed, one fascicular, and two spindle-type B. In five cases in which a follow-up was available, the correlation between the histologic classification and expected prognosis was good. In four (Cases 11–14) out of the six cases with extraocular extension, the reticular fiber structure was absent in part or all of the tumor. In Case 5, the epithelioid cells, necrosis, and paucity of reticular fibers were all indicative of a poor prognosis; fatal metastases developed within 6 months of enucleation. In Case 6, the marked reticular fiber content indicated a favorable prognosis, and the dog was alive and well 1 year later. In Case 11, the epithelioid type and almost absent reticular content suggested a poor prognosis. On follow-up it was learned that the dog was sacrificed 5 months following enucleation with a rapidly growing gingival tumor that extended to involve the nasal cavity and paranasal sinuses. Bilateral adrenal metastases were found at necropsy. The gingival and adrenal tumors were identified as malignant melanomas. Whether they were metastases from the intraocular melanoma was not established. In Case 14, the slight reticular fiber content suggested a poor prognosis, which was borne out by the pulmonary metastasis. The 21-month post-enucleation in Case 15 without evidence of recurrence or metastasis does not appear unexpected in view of the mixed type, medium reticular content, and predominant iridal confinement. It is likely that the Callender-Wilder classification will also prove useful in the prognosis of intraocular melanomas in dogs, but this will have to be determined in a much larger series of cases. Although some of the cases in the literature cited herein have good descriptions of cellular components, none has any mention of reticular fiber content, so that they cannot be studied from this standpoint of the Callender-Wilder classification.

In five of the cases (Nos. 1, 5, 6, 14, and 15) there
was clinical evidence of glaucoma, secondary to blocking of the filtration angle by neoplastic growth, and in two additional instances (Cases 2 and 18) with inadequate histories we found histologic evidence of glaucoma.

In several instances, the cases reported in the literature appeared to be epithelial tumors. Ball and Zaessinger (2) reported a carcinoma of the nonpigmented epithelium of the ciliary body in a cow, and Darraspen et al. (16) an epithelioma of the pigment epithelium of the iris in a cat. Neither of these reports was illustrated. In Bloom's (6) case, the glandular structure and epithelial appearance were well illustrated and described and are consistent with a diagnosis of medullo-epithelioma. The youth of this patient (8 months) suggests that this was a medullo-epithelioma of the embryonal type which occurs in children, the so-called diktyoma.

The tumor described by Leone (33) as a pigmented sarcoma in the eye of a dog is probably also epithelial in nature. He noted that the growth involved the iris and ciliary body, but not the choroid. His illustrations are good but depict an epithelial tumor rather than a sarcoma, and many of the cells are arranged in distinct alveolar formations. We believe the tumor he described was an adenoma; his descriptions and illustrations are inconsistent with a diagnosis of sarcoma or a present-day diagnosis of malignant melanoma.

Nordmann and Hoerner (37) reported a neuro-epithelioma from the ciliary body of a dog, but without histologic details or illustrations. It is assumed that they chose their term to distinguish the tumor from a melanoma.

Cotchin (12) reported two intraocular tumors in dogs, an adenoma of the ciliary body and an intraocular epithelial tumor of unknown type. The tumors were not described in detail, but were distinguished from two other intraocular tumors which were classified as malignant melanomas. It would thus appear that epithelial tumors of the iris and ciliary body are not uncommon in dogs, since four of the fifteen cases in this series were so classified and five possible cases were found in the literature. In addition, two cases were reported in cats (14, 16) and one in a cow (9). Such tumors appear to be somewhat rare among human intraocular neoplasms.

Of the cases recorded in Table 1 there were eighteen with sufficient details to permit a diagnosis of uveal melanoma. Of these, seven cases (Bland-Sutton, Bayer, Bürgi, Freese, McClelland, Pedrigo, and Hopper) were melanomas of the choroid. Ten melanomas arose either in the iris or in the ciliary body, the cases of Hess, Kitt, Houdemer and Guyonnet, Brown and Pearce, Chaillous and Robin, Buckler, Craig and Davies, Ball, and Cotchin. On the basis of tissues available for our study, we interpret Case 2 of McClelland (our Case 14) to be primary in the iris or ciliary body and not the choroid. With so few available cases, both in our own series and in the literature, there is as yet no basis on which to determine the relative frequency of involvement of the three uveal sites.

Although four of the uveal melanomas reported in the literature were in horses, this is a rather small number in view of the great frequency with which this species is affected by cutaneous melanomas. Bland-Sutton (5) commented on this in 1922, when after many years of interest in both melanomas and comparative oncology he was unable to cite a single cases of intraocular melanoma in a horse. Cutaneous melanomas occur almost invariably in grey horses, those with other coat colors being much less frequently affected. Although these tumors usually metastasize widely to the thoracic and abdominal viscera, there is only one case on record where intraocular metastasis may have occurred. Darraspen and associates (16) reported a sarcoma melanique which was primary in the left eye of a nine-year-old grey mare. Metastasis was present in the submaxillary lymph nodes and in the perineum. The latter region is a rather unlikely site for metastasis from an intraocular tumor—on the other hand, it is the region where a large proportion of melanomas in grey horses first appear. We consider it more likely that the tumor they reported metastasized to the globe from the perineum than the reverse.

The iris of the horse normally bears some small dorsal projections into the pupil, the corpora nigra, and these occasionally undergo hyperplasia. Several cases of such hyperplasia are in the literature (17, 18, 21) but there is no unequivocal record of the hyperplasia's ever assuming a neoplastic character. Hyperplasia of the retinal pigment epithelium in a cow has been reported (45), but we have not found any report of a neoplasm arising from these cells.

Most of the authors of the reports cited here, including the recent ones, believed that the tumors they were reporting were very rare, or indeed had not previously been reported. By bringing the various reports together in one place (Table 1), we have shown that pigmented intraocular tumors do occur in animals, even though the published reports, like our own data, are as yet too few for their true incidence to be disclosed.
SUMMARY

Primary pigmented intraocular tumors, which may be diktyomas, adenomas, adenocarcinomas, or uveal melanomas, have been reported for horses, cattle, sheep, cats, dogs, fish, a rabbit, and a hen. We have studied a series of fifteen intraocular tumors from dogs, of which three were adenomas, one an adenocarcinoma of the iris and ciliary body, and eleven were malignant melanomas of the uveal tract. Histologically, the melanomas resembled those of man. The biologic behavior was also comparable, inasmuch as some of the melanomas in the dogs extended to the orbit, to the cranial cavity, or metastasized to distant organs. The prognostic criteria of Callender and Wilder, viz., histologic type and reticular fiber content, were applied to our cases. In two instances of metastasis in which a necropsy was available, and in six cases with invasion of the sclera (arrow). Case 2. H & E, X2.5.

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REFERENCES

Fig. 5.—Cross section of eye completely filled with dark neoplastic tissue. The central depression contained the lens. Case 5.

Fig. 6.—Coronal sections of brain showing invasion of basal region by dark neoplastic tissue. Case 5.

Fig. 7.—Histologic details of intraocular malignant melanoma. Case 5. H & E, ×350.

Fig. 8.—Malignant melanoma, epithelioid type, of iris. Case 7. H & E, ×495.
Fig. 9.—Section through entire eye with a malignant melanoma of the ciliary body and iris. Case 8. H & E, X\(\times 2\).

Fig. 10.—Malignant melanoma of uvea showing fascicular arrangement of cells. Case 9. H & E, X168.

Fig. 11.—Malignant melanoma of ciliary body showing areas of necrosis. The arrow points to a scleral vein packed with neoplastic cells. Case 10. H & E, X12.
FIG. 12.—Malignant melanoma diffusely infiltrating the iris and ciliary body. Case 11.

FIG. 13.—Malignant melanoma of iris and ciliary body showing infiltration and penetration of the adjacent sclera to reach the extraocular muscles, and glaucomatous excavation of the optic disc. Case 13. H & E, ×24.

FIG. 14.—Malignant melanoma of iris and ciliary body, epithelioid type, showing multinucleated giant cells. Case 13. H & E, ×200.
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