OCULAR TUMORS IN ANIMALS AND HUMANS
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DEDICATION

To Kathleen, to Wendy, to the children
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The subspecialty of ocular oncology has attracted the interest of a number of specialists in ophthalmology and veterinary medicine in recent years. A few ophthalmology departments have individuals who specialize almost exclusively in ophthalmic oncology. This centralization of a unique subspecialty has greatly improved methods of diagnosis and management of patients with tumors of the eyelids, conjunctiva, intraocular structures, and orbit.

There are several recent textbooks that cover well the subject of ocular tumors in humans. Bob Peiffer and Ken Simons, who have extensive experience in the pathology of tumors in all species, have conceptualized and completed an authoritative textbook on the unusual and fascinating subject of tumors in animals as well as humans. The concept of combining animal and human ocular oncology into one text represents an unusual approach. In addition to their own exhaustive contributions to this magnificent treatise, Bob Peiffer and Ken Simons have solicited the contributions of a number of other well-known experts in veterinary medicine, clinical ophthalmology, and ophthalmic pathology.

The result is Ocular Tumors in Animals and Humans, a comprehensive work that includes clinical and histopathologic characteristics of virtually all important ophthalmic tumors and pseudotumors in a wide variety of species. The book is well organized, being divided into anatomic sites in the ocular region, which are further divided into lesions that arise from specific ocular and adnexal tissues. The clinical illustrations and photomicrographs are bountiful and excellent. Each chapter has a thorough bibliography that includes almost all pertinent references.

All ophthalmologists and veterinary medicine specialists who have an interest in tumors in and around the eye will find it a useful source of reference and fascinating reading. Ocular Tumors in Animals and Humans is a highly informative book that will be a standard reference source for many years.

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As I struggled to create an introduction that would provide the reader with insight into the purpose and scope of this text, as well as to justify its creation, it occurred to me that perhaps the most meaningful background that I could provide would be to relate this text to the events of my career and my evolution as a comparative ophthalmic pathologist.

I was attracted to ophthalmology as a specialty for four reasons. First, it encompassed both medical and surgical aspects of disease management. Second, there was an alluring mystique surrounding the specialty associated with the uniqueness and sensitivity of the eye as well as the sophistication of the instrumentation that ophthalmologists utilized. Thirdly, seeds of interest had been planted and nurtured by Dr. Don Carter at Iowa State University, where I interned, and Drs. Andy Lavignette and Bill Carlton at Purdue University, during the first year of a surgical residency. Dr. Carlton provided me with my introduction to ophthalmic pathology when he allowed me to attend the course that he offered to his graduate students. Lastly, I was fortunate to be awarded an NIH postdoctoral fellowship in comparative ophthalmology at the University of Minnesota, my alma mater. These events unraveled by happenstance and circumstance as much as decision making on my part.

As there was no structured program in place to train a veterinary ophthalmologist, I was compelled to design my own and was fortunate enough to come into contact with Dr. John Harris, Chairman of the Department of Ophthalmology in the School of Medicine at the University of Minnesota. He was broad-minded enough to offer all of the resources that were available through his nationally recognized department to his own residents to this young veterinarian. I suspect that his motivations were based on a combination of generosity of spirit as well as curiosity.

These were busy times as I recollect trying to acquire the skills necessary to be a competent clinical veterinary ophthalmologist and do justice to my thesis research, which involved inherited glaucoma in beagles (no doubt the passage of time has somewhat romanticized these early years). These events were superimposed, of course, on the social and political context of the seventies, and I suspect that I am not alone in my generation in looking upon the somewhat Bohemian experiences as a graduate student as perhaps the most interesting years of my life.

The story of this book really begins as I began to prepare and organize material from my clinical cases to submit to the American College of Veterinary Ophthalmologists, a requisite to achieve the highly esteemed membership in this organization. Although the pathology department in the College of Veterinary Medicine was nationally recognized for its excellence, there was no individual who had developed an interest in ophthalmic pathology and no technicians who were experienced in the preparation of ophthalmic tissues. Slides that came back from enucleated globes portrayed the organ in every possible geometric configuration but spherical, and tissue relationships (indeed, if some tissues could be identified at all) were significantly distorted. Because of the prominent pigmentation found in the canine uvea, “melanoma” was a frequent diagnosis, even though clinical observations supported alternative diagnoses. I had just begun to participate in the weekly pathology rounds at the medical school, where Drs. Charlotte Hill and Hugh Monahan had developed an outstanding
program for both service and resident education. I asked Charlotte if she would be kind enough to allow me to process my animal globes through her laboratory, and her agreement to do so was a key event in the evolution of this text.

Virginia Havener was the ophthalmic histotechnologist in Charlotte's lab, and Virginia took me under her wing to teach me both the basics and subtleties of how one gets from a tissue in a bottle to a diagnosis that will contribute to optimal patient management. My experiences led to an increasing fascination, even infatuation, for ophthalmic pathology and I suspect that I spent more time in the ocular pathology laboratory, located in the bowels of the hospital at the University of Minnesota at that time, than anywhere else during my postdoctoral period.

Charlotte was kind enough to invite me to attend and present a case report at the Georgiana Dvork Theobold Midwestern Society of Ophthalmic Pathology, and I remember the trek across the plains to attend my first meeting in Omaha, hosted by Drs. Jerry Christiansen and Harold Gifford. My associations with the ocular pathologists that I have come into contact with through this organization over the years have served as a stimulus for personal growth; Dr. Harry Brown is one of these individuals who has contributed to this text. Dr. Jerry Shields, who has been a pioneer of human ophthalmic oncology, provided both inspiration and insight during these periodic contacts. Space does not allow acknowledgment of all of the valued colleagues that the Theobald and later the Hogan Societies introduced me to.

As my experience with tissues from my patients, as well as with the human tissues that came through the laboratory at the University of Minnesota, grew, I was struck by both similarities and differences in the way that the eye responded to disease when one began to cross species lines. I was particularly interested in the comparative aspects of ocular neoplasia, and frustrated by the lack of information regarding ocular tumors in animals. Our knowledge at that time consisted predominantly of case reports and small series; there was a tendency for investigators to assume that animal ocular tumors were inherently identical to human tumors, both in terms of morphology and biologic behavior. This early work by such individuals as Leon Saunders and Charles Barron was the foundation of our current understanding. Closer scrutiny revealed interesting similarities but striking differences.

In 1978, Dr. David Eifrig, who I had met and interacted with as a post doc while he was on the faculty as a retinologist at the University of Minnesota, invited me to Chapel Hill to oversee the ocular pathology laboratories and the resident ophthalmic pathology training in his fledgling department at the University of North Carolina (UNC). I had recently accepted my first academic position in the College of Veterinary Medicine at the University of Florida in Gainesville, but the challenge and opportunity of this offer made the decision to move not extremely difficult. David packed me off for a summer at the Armed Forces Institute of Pathology, where my exposure to their materials, other young ocular pathologists in training, and the teaching of Drs. Zimmerman, McLean, and Hidayat provided me with both additional substance and the courage to beat the path I had chosen. Dr. Marilyn Kincaid was one of the young pathologists with whom I crossed paths just north of Washington.

At UNC, I was fortunate to inherit Mrs. Doris Brown, a wonderful and delightful lady as well as an ocular histotechnologist par excellence whose role in the development of the program was invaluable. In addition to providing diagnostic services and training the residents, we developed a comparative ophthalmic pathology laboratory and, bolstered by the support of submissions of practicing veterinary ophthalmologists throughout the country and indeed the world, were able to develop an archive of animal ocular tissues that has been utilized to train young veterinary ocular pathologists and ophthalmologists as well as for retrospective research that hopefully has strengthened the foundations of our understanding of animal ocular oncology. I have been privileged along the way to work with valued human pathologist colleagues, initially Dr. Stanley Lipper and currently Dr. Tom Bouldin.

In this light, I would be sorely remiss not to mention my veterinary pathologist friend and colleague, Dr. Brian Wilcock. While at the University of Guelph, Brian's interest in ocular pathology paralleled my own, and our collaborations have enhanced the numbers and validity of our observations.
Ophthalmic pathology has changed over my years of involvement; what was once a department-supported ophthalmic pathology laboratory has, because of fiscal realities, become incorporated into the Department of Pathology. In the early years, there were few pathologists with inclinations toward the eye, and ocular pathology was largely within the realm of clinical ophthalmologists who had received additional training in ocular pathology; now pathologists are claiming this turf, and the trends are to train individuals who are formally exposed to both pathology and ophthalmology. However, the importance of providing students, be they in veterinary or human medicine, or pre- or postdoctoral degree programs, with training in the pathology of the eye has remained constant and will, I hope, continue to be so. I do not try to train my students to become ophthalmic pathologists; rather, I try to provide them with an appreciation of disease at a cellular and subcellular level. Occasionally, you will come across a student who heeds the siren's song: Dr. Ken Simons is such an individual. We were scheduled to have brunch with Ken, a resident in our program, on a lovely summer Sunday morning in 1982, but we had to cancel abruptly because of the birth of our first child. Ken went on to do an ocular pathology fellowship under Dr. Bob Foos at UCLA and then to the Medical College of Wisconsin, where I suspect unfortunately his duties as an administrator limit the time that he spends at his microscope. Ken is responsible not only for parts of the text that he himself has written but for organizing and overseeing the contributions of the human sections of this text.

This then is an encapsulated sequence of the events and cast of characters that have led to this book. As our knowledge of ocular tumors and animals has expanded (although still lacking), the similarities and differences become evermore compelling. There are obvious advantages of enhanced understanding of ocular tumors in terms of patient management for both M.D. ophthalmologists and veterinary ophthalmologists; the need for this understanding increases as our clinical diagnostics and treatment modalities become increasingly sophisticated and technology evolves. Similarities and differences across species lines are not only intellectually fascinating but practical in the sense of model systems and investigations into the validity of interspecies applications. My personal experiences have shown to me the excitement that can be generated and the progress that can be made when you bring together individuals and ideas from seemingly diverse arenas of the biologic sciences. From this perspective, we hope that this text will be of value to all those with an interest in ocular tumors.

Robert L. Peiffer, Jr.
Chapel Hill, NC
May 2001
ACKNOWLEDGMENTS

The editors would like to acknowledge all those whose endeavors have made this text possible. To our contributing authors—we are indebted for the quality of their work and their patience over several years of preparation. To our colleagues—we recognize that without the submission of tissues the pathologist is lost indeed. For our families who have shown tolerance as we try to achieve balance between our personal and professional lives—we are blessed.

The vision of Iowa State University Press in undertaking the production of the first truly comparative ophthalmology text has been inspirational and the competency and professionalism of their staff has made the effort enjoyable.
OCULAR TUMORS IN ANIMALS AND HUMANS
ANIMALS

Historical Perspectives. Definitive knowledge of orbital tumors in animals is somewhat limited for a variety of reasons related to low incidence and the limitations of clinical diagnosis and management. Refinement and application of contemporary diagnostic techniques—notably ultrasound and imaging by computer-assisted tomography and magnetic resonance imaging, as well as enhanced practitioner awareness—have recently contributed to early diagnosis and more effective management.

Terminology. In general, although the anatomy of the bony orbital rim and walls will vary among species, orbital anatomy and contents are quite consistent, the notable exception being the hard-erian gland found in lagomorphs and rodents. Proliferative diseases may arise from the bony walls; the connective tissue that lines the orbit, muscles, globe, and other structures; the orbital fat; the extraocular muscles; the vessels and nerves that course through this space; the lacrimal gland; the gland of the third eyelid; or the zygomatic salivary gland. Tumors of the optic nerve and secondary orbital tumors are discussed in separate chapters.

Noninfectious inflammatory disease is uncommon in animals as compared with humans; dysthyroid ophthalmopathy has been described in a monkey as an isolated example. Young dogs—notably golden retrievers—are subject to an immune-mediated extraocular myositis. Cranio-mandibular osteopathy and eosinophilic myositis can indirectly involve the orbit. Immune-mediated posterior scleritis may mimic orbital proliferative processes. Otherwise, such conditions as orbital pseudotumor and the granulomatous proliferative diseases encountered in humans have not been well documented in animals; case reports of a pseudotumor in a bush baby (a prosimian), eosinophilic orbital cellulitis in a cat, and bilateral fibrosing pseudotumor in a cat are found in the literature. Infectious inflammatory disease—oral cellulitis or abscessation—may occur as an extension of processes involving the molars, the adjacent sinuses, or the periorbital glands, and foreign bodies may occasionally be encountered. Clinical and histopathologic distinction from neoplasms is usually not difficult.

Cystic orbital disease is infrequent and most frequently includes zygomatic salivary gland mucoceles or lacrimal cysts. A case of hydrops, apparently from lacrimal and/or conjunctival secretions, following alleged enucleation has been described, and air can gain access to the orbit either from the adjacent sinuses or via the nasolacrimal system after enucleation. Vascular malformations can result in a pulsating exophthalmos.

Incidence and Epidemiology. Orbital tumors are in general uncommon; in a study of cats from Auburn University, of 16,655 admitted over a 16-year period, 530 (3.1%) had a diagnosis of neoplasia; of these, 21 involved the orbit and only 3 of these were primary.

Although statistical data are limited, incidence in dogs is likely somewhat higher. From 1968 to 1979 at the University of Pennsylvania, 25 cases of canine orbital tumors were diagnosed; one was an inflammatory pseudotumor and the remainder were neoplastic processes, of which 3 were benign and 21 malignant. Of the malignant neoplasms, 56% were primary and, of the secondary tumors, the most commonly encountered was four cases of nasal carcinomas with extension to the orbit. There was no breed...
or sex predisposition; ages ranged from 1.5 to 15 years, with a mean of 8.5 years. Twenty-three cases were retrieved from the 1975-89 files at Cornell, ranging from 2 to 14 years, with a mean of 8 years. No breed or laterality predisposition was noted, with 15 females represented. Seventeen tumors were classified as primary, and 21 of the 23 were malignancies. Diversity characterizes the nature of these orbital tumors. In the Pennsylvania series, mesenchymal tumors were slightly more commonly encountered than epithelial tumors; extension of nasal or sinus carcinomas was most commonly encountered, with three multilobular osteochondromas and two each of fibrosarcomas and anaplastic sarcomas, with all other diagnoses represented solitarily. The Cornell series included six osteosarcomas, four mast cell sarcomas, four reticulum cell sarcomas, and two fibrosarcomas. Lymphosarcoma is a relatively common secondary orbital neoplasm, involving three of the 21 cases in the aforementioned feline series; in cats, extension of oral, nasal, and adnexal squamous carcinoma is likewise encountered.

Clinical Signs. Usually, space-occupying orbital lesions are present as exophthalmos with resistance to retropulsion; rarely, sclerosing neoplasms and inflammatory processes can result in enophthalmos. Depending on location and extent, the globe may be deviated, the third eyelid protruded, ocular motility impaired, and, if the optic nerve is compressed or stretched, an afferent pupillary defect and/or visual impairment may be present with or without optic disc changes upon ophthalmoscopy. Anterior extension may be present as orbital rim or subconjunctival masses. Tumors in the posterior orbit are likely to result in exophthalmos without deviation; tumors elsewhere result in deviation away from the mass. As might be expected, benign tumors are slow growing; malignant tumors may grow quite rapidly, can be associated with signs related to involvement of the adjacent sinuses, and may be visible extending into the oral cavity just posterior to the last upper molar. In contrast to inflammatory disease, orbital neoplasms are generally painless. Diagnostic workup should include skull radiographs, ultrasound, and computer-assisted tomography or magnetic resonance imaging to define location and extent of involvement. Biopsy is generally required to establish definitive diagnosis and may take the form of tissue sampling of oral or anterior orbital and subconjunctival masses; fine-needle aspiration biopsy of deeper orbital tumors; or exploratory orbitotomy.

Gross Light-Microscopic and Histochemical Features. Described primary orbital neoplasms and their histologic features are described in Table 1.1; the multitude of primary and secondary neoplasms that might be encountered makes inclusive discussion impossible, and readers are directed to more general references in this regard.

Immunohistochemistry and Ultrastructure. Because of the diversity of types of orbital neoplasms, a comprehensive discussion of this topic would involve a lengthy discussion of immunohistochemistry and ultrastructural morphology of both solid and lymphoid tumors, topics elegantly presented by others to whom readers are referred, and only essential general principles that are discussed below.

This is not at all to distract from the usefulness of these techniques to a pathologist's quest of a definitive diagnosis of an orbital tumor. Not uncommonly, the neoplasms will have few distinguishing light-microscopic characteristics and are thus labeled undifferentiated. Determining cell of origin, whether a primary or metastatic lesion, and probable site of origin of a metastatic lesion are important factors in management and can be enhanced by these ancillary techniques. Immunohistochemistry can be performed on formalin-fixed paraffin-embedded tissues; fresh (less than 2 weeks) 10% formaldehyde will ensure optimal reactivity. Immunohistochemical detection of the presence or absence of intermediate filaments (cytokeratin, actin, vimentin, desmin, and glial fibrillary acidic protein, hematopoietic markers, S-100 protein, and HMB-45, among others) can be useful in clarifying diagnostic confusion that may accompany small round cell neoplasms; spindle cell carcinomas, melanomas, and sarcomas; epithelial neoplasms; and pleomorphic neoplasms. Histiocytic tumors
<table>
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<tr>
<th>Neoplasm</th>
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<th>Gross</th>
<th>Histologic Features</th>
<th>Immunohistochemical Features</th>
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<tbody>
<tr>
<td>Osteoma</td>
<td>Dog/cat</td>
<td>Firm, white</td>
<td>Bone production (Fig. 1.1, a-e)</td>
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<tr>
<td>Osteosarcoma</td>
<td>Dog/cat</td>
<td>Firm, white</td>
<td>Spindles or trabeculae of osteoid bone and cartilage; fibular stroma; pleomorphic spindle mesenchymal cells (Fig. 1.2)</td>
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<tr>
<td>Parosteal osteoma/</td>
<td>Dog/cat</td>
<td>Granular, friable, gritty</td>
<td>Island and cords of chondroid tissues with calcified ossified centers surrounded by a zone of plump spindle cells (Fig. 1.3)</td>
<td></td>
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<tr>
<td>Osteosarcoma</td>
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<tr>
<td>Chondrosarcoma</td>
<td>Dog</td>
<td>Translucent, grayish white</td>
<td>Cartilage with a fibrillary matrix and undifferentiated mesenchymal cells (Fig. 1.4)</td>
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<tr>
<td>Hemangiosarcoma</td>
<td>Dog/cat</td>
<td>Red</td>
<td>Pleomorphic vascular endothelial cells with small vascular channels (Fig. 1.5)</td>
<td>Actin and myosin fibers</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Dog</td>
<td>Nodular gray-pink +/-</td>
<td>Pleomorphic mesenchymal cells with variable ribbon or strap-like cells and multinucleated giant cells. The mesenchymal cells are positive with Masion's trichrome. Cross striations enhanced by Heidenhain's iron, hematoxylin, or phosphotungstic acid hematoxylin</td>
<td></td>
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<tr>
<td>Neurofibrosarcoma</td>
<td>Dog</td>
<td>Pink, lobulated</td>
<td>Whorls of spindle cells about nerves</td>
<td>Cords and sheets of epithelial cells (Fig. 1.7)</td>
</tr>
<tr>
<td>Lacrimal gland adenoma/</td>
<td>Dog</td>
<td>Pink, lobulated (Fig. 1.6)</td>
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<tr>
<td>Adenocarcinoma</td>
<td>Dog</td>
<td>Pink, lobulated</td>
<td></td>
<td></td>
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<tr>
<td>Zygomatic salivary gland</td>
<td>Dog</td>
<td>Sheets of epithelial cells</td>
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<tr>
<td>adenoma/Adenocarcinoma</td>
<td>Dog</td>
<td>Pink, lobulated</td>
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<tr>
<td>Third eyelid gland</td>
<td>Dog</td>
<td>Sheets of epithelial cells</td>
<td></td>
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<td>Adenocarcinoma</td>
<td>Mice</td>
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<td>Harderian gland adenoma</td>
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<td>Granulay cell myoblastoma</td>
<td>Dog</td>
<td>Firm</td>
<td></td>
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<tr>
<td>Fibrosarcoma</td>
<td>Dog</td>
<td>Firm, white to gray</td>
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FIG. 1.1—Osteoma in a young Doberman pinscher. The dog had a history of a slowly progressive right exophthalmos with prominent protrusion of the third eyelid (A). A lateral to medial A scan defined a mass with high reflective spikes (B). (continued)
FIG. 1.1 (continued)—Radiographs showed a circumscribed bony lesion of the medial orbital wall (C and D), which was excised via lateral orbitotomy. The tumor was composed of sheets of cancellous bone within a connective tissue matrix (E). Hematoxylin-eosin, ×100.
FIG. 1.2—Orbital osteosarcoma composed of spicules of osteoid produced by undifferentiated mesenchymal cells. Hematoxylin-eosin, ×300. (Courtesy of Dr. W. Carlton.)

FIG. 1.3—Paraosteal osteoma. Foci of chondroid tissue with mineralized centers are found surrounded by spindle mesenchymal cells. Hematoxylin-eosin, ×88. (Courtesy of Dr. W. Carlton.)