Proliferative Lesions of the Eye in Rats

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\section*{INTRODUCTION}

Even though the eyes are routinely examined both microscopically and ophthalmologically in long-term toxicity and carcinogenicity studies, primary ocular tumors are rare in rats. A recent review of the proliferative lesions of the eye in the rat and the diagnostic criteria for these lesions was reported by Mohr (16). Many of the diagnostic criteria presented in this report include the changes reported by Mohr. In a review of the literature by Weisse (29), spontaneous ocular tumors were found to occur at a very low incidence in old rats and were found to be more common in male rats than female rats. Spontaneous neoplastic lesions were reported in the cornea/conjunctiva, uvea, optic nerve, eyelids, Harderian gland, lacrimal glands and periocular tissue (orbit). Of these, adenomas or carcinomas of the Harderian gland and Schwannomas of the optic nerve or orbital tissue were more commonly observed. Tumors of the lacrimal glands and eyelids are rare in the rat. Spontaneous retinoblastomas have not been reported in the rat (29).

Reported spontaneous intraocular tumors have primarily involved the uvea. Of the intraocular tumors reported, melanomas are the most common and have been found in Sprague Dawley, Wistar and Fischer 344 strains. Spontaneous Schwannomas and leiomyomas have also been reported in these three strains. Because of the amelanotic character of melanomas in the albino rat, spindle cell tumors usually require electron microscopy and immunocytochemical staining for the differentiation of uveal melanomas, leiomyomas and Schwannomas. Melanocytic hyperplasia has been reported in the eye and eyelid of pigmented rats (30).

Experimentally induced intraocular tumors, including retinoblastoma, have been reported in Fischer 344 rats by the intraocular injection of nickel subsulfide (1), in Sprague Dawley rats by the inoculation of newborn animals with human adenovirus type 12 or by injecting retinal tumor cells into the vitreous (13, 14), in August hooded rats by subcutaneous administration of urethane or N-nitroxyurethane during the neonatal period (11), and in Wistar rats by the oral administration of ethionine and N-2-fluorenylacetamide (3). Generalized lymphoma or leukemia is probably the most common secondary ocular tumor in the rat and when present usually involves the uvea and Harderian gland (29).

\section*{ANATOMICAL DISTRIBUTION}

For this report the ocular tissues are divided into the ocular and extraocular proliferative lesions. The ocular tissues include the cornea/conjunctiva, uvea (iris, ciliary body, choroid), retina and optic nerve. The extraocular tissues include the eyelids, Harderian gland, lacrimal glands, lacrimal duct and periocular tissue (orbit).
EYE/EYELID

Squamous cell papilloma and carcinomas (Figures 1–4)

Squamous cell papilloma and carcinomas have been reported in the cornea, conjunctiva and eyelids of Fischer 344 rats (8, 22) and the conjunctiva of Sprague Dawley rats (16, 20, 29). Squamous cell papilloma is differentiated from the squamous cell carcinoma by its exophytic growth and the absence of invasion of the corneal stroma by atypical squamous cells. In Fischer 344 rats, squamous cell carcinomas have exhibited papillary growth patterns, dyskeratosis, epithelial pearl formation and a corneal stroma thickened by chronic inflammatory cells and fibrosis (22).

DERMOID

Dermoid of the cornea, a rare lesion in rats, has been observed in the Sprague Dawley rat (17). The dermoid is a congenital growth composed of stratified squamous epithelium overlying hair follicles, sebaceous glands and fibrous connective tissue.

Epithelial (Inclusion) cysts

Epithelial (Inclusion) cysts of the cornea have been seen in Fischer 344 rats. The cyst is lined by a keratinized stratified squamous epithelium which is several layers thick (22). No dermal appendages are found in the wall.

Inverted mucopidermoid papilloma (Figures 5–6)

Inverted mucopidermoid papilloma of the palpebral conjunctiva has been reported in the Fischer rat. The inverted papilloma is an endophytic growth of proliferative conjunctival epithelium with lobular arrangement into the subepithelial fibrous stroma. The lobules with luminal formation consists primarily of well differentiated squamous cells, which are intermixed with single or small groups of goblet cells and surrounded by clear or basophilic cuboidal cells (28).

Mucopidermoid carcinoma (Mucous cell) (Figures 7-8)

Mucopidermoid carcinoma of the palpebral conjunctiva has been reported in the Fischer rat. This tumor is located in the subepithelial fibrous stroma and consists of pale or eosinophilic, plump to spindle epithelial cells arranged in a lobular or cord-like pattern. The tumor cells often have an eccentrically situated nucleus compressed by an intracytoplasmic, eosinophilic or hyaline globoid body. The mucous cells are recognized only when their cytoplasm is positively stained by PAS after digestion. Ultrastructurally, the tumor cells are composed of three different cell populations: mucus-secreting cells, filament containing cells and intermediate cells. The mucus-secreting cells usually contain numerous electron-lucent, small mucous vesicles or infrequently several large mucous granules as seen in normal goblet cells. The filament containing cells contain abundant, intracytoplasmic, unbound intermediate filaments which sometimes form globular filamentous bodies (28).

EYE

Melanoma, malignant (Uveal) (Figures 9–13)

Spontaneous uveal melanomas in rats are usually unilateral and in the region of the ciliary body while chemically induced tumors have been found to originate from all parts of the uveal tract including the iris, ciliary body and choroid (7, 19). Spontaneous melanomas of the iris, ciliary body or choroid have been reported in Fischer 344, Sprague Dawley and Wistar strains of rats (2, 10, 11, 15, 16, 20, 29). Uveal melanomas have been induced in rats by the intravitreal instillation of nickel subsulfide in Fischer 344 rats and nickel sulfide in ACI rats. Melanomas have been induced by subcutaneous administration of Urethan and N-hydroxy-urethan in August rats and by the oral administration of ethionine and N-2-Fluo-renylacetamide in Wistar rats (7).

In the Fischer 344 rat, amelanotic melanomas of the eye may arise in the iris, ciliary body and/or choroid. These neoplasms usually have spindle cells arranged in parallel and forming curving bundles or whorls, sometimes having a perivascular orientation. The spindle cells have poorly defined cell boundaries, scant to moderate cytoplasm, fusiform nuclei and indistinct nucleoli. The neoplastic cells are often positive when stained for S-100 protein and vimentin intermediate filaments. Ultrastructurally the cytoplasm of the neoplastic cells contain variable numbers of microtubules including filamentous or membranous structures. Chemically induced melanomas have been found to contain premelanosomes and melanosomes which may stain positive with the Fontana stain (23). Melanocytic hyperplasia has been reported in the eye of a Brown Norway rat and in the eyelid of a F1 BNF (Brown Norway x Fischer 344 cross) rat (30). These changes were described as small aggregates of pigment filled polygonal melanocytes with minimal atypia and very little displacement of normal structures.

Some areas may be composed of a loosely arranged mixture of epithelioid and spindle-shaped cells with foci of necrosis. Epithelioid cells have ill-defined cell borders, pale-staining cytoplasm, and large oval nuclei with or without nucleoli. Large epithelioid cells with large bizarre nuclei with nucleoli may occur, but are rare. Mitotic figures may be numerous and argyrophilic fibers may be present along with a few cells containing yellow-brown pigment.

Leiomyoma, Uveal (Figures 14 - 15)

Leiomyoma of the iris has been reported in the Sprague
Dawley rat (18) and in the Wistar rat (29). The leiomyoma of the iris in the Sprague Dawley rat was mainly composed of spindle-shaped cells with ill defined eosinophilic granular cytoplasm and elongated oval nuclei. Mallory's phosphotungstic acid hematoxylin stain demonstrated myofibers emanating from bundles of smooth muscle cells in the tumor. The neoplastic cells may stain positive for desmin. The tumor was well vascularized with palisading of neoplastic cells around blood vessels.

Schwannoma, Malignant, (Intraocular) (Figures 16–17)

Schwannomas have been reported in the iris and choroid of Wistar rats (29). A malignant Schwannoma involving the iris has been reported in the Fischer 344 rat (24). This neoplasm consisted of plump spindle cells arranged in a perivascular pattern (uncommon in Schwannomas of rats). The plump spindle cells had an abundant eosinophilic cytoplasm associated with marked cytoplasmic vacuolation. The cells of this neoplasm were arranged in parallel rows forming palisades around vessels. Areas of "pseudo" rosette formations were present and the cells had a positive immunoreactivity for S-100 protein (16).

Differential Diagnosis of Uveal Neoplasms

Morphologically the uveal spindle cell neoplasms (Schwannoma, melanoma and leiomyoma) may have very similar patterns. Electron microscopic examination and immunocytochemistry are very useful tools to distinguish uveal spindle cell neoplasms. All three types of neoplasms may be composed of spindle cells. Malignant Schwannomas are composed of spindle shaped cells which may be arranged in a perivascular fascicular pattern (not a whorled pattern). Leiomyomas and melanomas may be composed of spindle-shaped cells and may form perivascular whorls.

Ultrastructurally Schwannomas have partial to complete pericytoplasmic basal lamina, attenuated cellular processes and desmosomes. Leiomyoma cells have cytoplasmic myofibrils, focal cytoplasmic densities and surface-connected vesicles. Melanoma cells may have ellipsoid premelanosomes (stage II melano-somes) or melanosomes or both (16).

Immunocytochemically Schwann cells are negative for desmin and positive for S-100 protein. Leiomoma cells are generally positive for desmin and are negative for S-100 protein. Melanomas are negative for desmin, cytokinin and glial fibrillary acid protein (GFAP) and positive for S-100 protein and vimentin intermediate filaments (16).

Retinoblastoma

Spontaneous retinoblastomas have not been reported in the rat. Such tumors have been induced in the Fischer 344 rats by intraocular injections of nickel compounds and in the Sprague Dawley rat by intraocular injections of human adenovirus type 12 (1, 12, 13, 16). In the Fischer 344 rat the neoplasms are characterized by undifferentiated cells having large round nuclei and a scant amount of cytoplasm. Neuroepithelial rosettes may be seen. Ultrastructurally these tumors may have triple-membrane structures involving the nuclear envelope and attachments by zonula adherens and macular occludens. In the Sprague Dawley rat these tumors were primarily composed of small hyperchromatic undifferentiated cells forming perivascular wreaths or rosettes (22).

OPTIC NERVE

Spontaneous tumors of the optic nerve are rare in rats. Glioma, ganglieneuroma and Schwannoma of the optic nerve have been reported in Sprague Dawley, Copenhagen and Wistar rats, respectively (29). Meningiomas and Malignant Schwannomas of the optic nerve have been found in Fischer 344 rats (22).

Meningiomas involving the optic nerve in the Fischer 344 rat may have an epithelioid pattern, which is rare in the cranial cavity. The epithelioid tumor may also have pleomorphic spindle cells arranged in a whorl pattern, often with a perivascular orientation or forming concentric whorls, resembling the Hassall's corpuscles of the thymus. Some of these neoplasms may demonstrate a positive reaction for S-100 protein. Ultrastructurally, the cells of these neoplasms have interdigiting cellular processes and an abundance of desmosomes (25).

Malignant Schwannoma involving the optic nerve (and orbit) has been reported in the Fischer 344 rat and the morphology was similar to the Schwannomas arising from other cranial and peripheral nerves. These neoplasms may have a typical Antoni type A pattern of closely packed spindle cells or more often show the type B arrangement of loosely arranged small cells with cystic areas (24).

Neoplasms resembling astrocytomas were induced in Fischer rats with nickel compounds (22).

HARDERIAN GLAND

Hyperplasia (Figures 18–19)

Hyperplasia of the Harderian gland may occur as a regenerative response to degeneration and inflammation or as a primary proliferative lesion. Hyperplasia without evidence of degeneration is uncommon in the Fischer 344 rat (22). Hyperplasia is characterized by an increase of alveolar cells, retention of the normal alveolar architecture and generally without compression of the adjacent parenchyma. The increase in alveolar cells may cause a pseudostratified or folded appearance of the epithelium.
Hyperplastic cells are usually large, variable in staining, with normal nuclei and rare mitotic figures. Areas of distortion of the normal alveolar pattern and papillary projections may be present (16).

**Adenoma (Figures 20–21)**

Harderian gland neoplasms are rare in the Fischer 344 rat, and most of those observed have been malignant (22). Spontaneous adenomas have been reported in Fischer 344 and Wistar rats (5, 6, 8, 21, 29). Harderian gland neoplasms have been observed in MRC rats injected repeatedly with 10% urethane and in rats fed a low fat diet containing 0.03% 2-acetylamino-fluorene (4). Adenoma is characterized as an expansive enlarging lesion with obvious compression of surrounding tissues. The neoplastic cells and/or the nuclei are enlarged. Alteration of the normal alveolar architecture and cellular atypia may be present but minimal. Adenomas may have a papillary growth pattern and the alveolar epithelium may appear pseudostratified or stratified.

**Adenocarcinoma (Figures 22–23)**

Adenocarcinomas have been reported in Fischer 344 and Osborne-Mendel rats (6, 8, 9, 21, 29). Adenocarcinoma is characterized as an expansive enlarging lesion with compression, distortion and invasion of surrounding tissues. The normal lobular pattern is obscured or distorted. Cellular pleomorphism (variation in cell and nuclear size and shape) and atypia are usually more pronounced. Well differentiated adenocarcinomas consist of cuboidal to columnar epithelial cells arranged in tubular or gland like structures. Less well-differentiated or anaplastic neoplasms exhibit stratification of the epithelium or solid sheets of cells. Foci of necrosis and fibrosis may be present (16). The presence of a scirrhouss reaction is indicative of malignancy (22).

**Schwannoma**

Schwannoma has been observed in the Harderian gland of the Wistar rat (29).

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**LACRIMAL GLANDS (EXORBITAL)**

**Hyperplasia**

Hyperplasia of the lacrimal glands is usually secondary to degenerative or inflammatory lesions. Spontaneous or chemically induced hyperplasia of the lacrimal gland has not been reported in the Fischer 344 rat (22).

**Adenoma**

Adenomas have been reported in the Fischer 344 rat (22). Adenomas are expansive lesions that compress or displace the surrounding parenchyma. The lobular mass is composed of tubular and acinar structures lined by uniform cuboidal cells with uniform rounded nuclei. The acinar arrangement within the mass is distorted and/or irregular, but the acinar cells are well differentiated. Intercalated ducts are not usually observed. Mitoses may be seen but generally are not frequent.

**Adenocarcinoma (Figures 24–25)**

Adenocarcinoma has been reported in the Fischer 344 rat (22). Adenocarcinoma is characterized as an expansive enlarging lesion with compression, distortion and invasion of adjacent tissues. The normal lobular pattern is obscured or distorted. Acinar cells are moderately well to poorly differentiated but contain secretory (serous) vacuoles. Cellular pleomorphism and atypia are observed to varying extents (16).

**Eyelids /Lacrimal Duct/ Periorbital tissue (Figures 26–28)**

Spontaneous neoplasms of the eyelid of rats are rare. Neoplasms of the skin of the eyelids when found in rats are morphologically similar to skin and subcutaneous tumors found in other locations. Rarely, malignant neoplasms of neural crest origin with similarities to amelanotic melanomas and melanotic Schwannomas may occur in the eyelids of rats (26). Pigmented melanomas have been reported in the eyelid of BN/Bi rats. A granular cell tumor, basal cell tumor and sebaceous cell adenoma also have been reported in the Fischer 344 rat (27).

Squamous cell hyperplasia is frequently observed in the lacrimal duct, often associated with inflammation. Spontaneous squamous cell papillomas or carcinomas of the lacrimal duct are rare in the rat but have been found in the nasolacrimal duct of rats exposed to vapors of certain carcinogens (22). Malignant fibrous histiocytoma, sarcoma, and sarcoma not otherwise specified have been reported in Sprague Dawley, Copenhagen and Wistar rats, respectively (29). The morphology of these neoplasms is similar to the morphology of these neoplasms found in other areas.

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**NOMENCLATURE AND DIAGNOSTIC CRITERIA**

**EYE /EYELID**

**PAPILLOMA, SQUAMOUS CELL**

1. Growth is exophytic.
2. Multiple branched fronds lined by keratinized squamous epithelium and containing a vascular connective tissue core.
3. Cells are retained by basement membrane and there is no invasion into the underlying tissues.
4. No cellular dysplasia present and mitotic activity is none to slight.

**CARCINOMA, SQUAMOUS CELL**
1. Composed of cords and nests of neoplastic squamous cells with variable amounts of keratinization.
2. Large cells with an abundant eosinophilic cytoplasm.
3. Cells have round to oval vesicular nuclei and prominent nucleoli.
4. Cells penetrate the basement membrane and invade the underlying corneal stroma and adjacent tissues.
5. Neoplastic cells may form areas of dyskeratosis and keratin 'pearls.'
6. Malignant characteristics include lack of cellular differentiation, numerous mitotic figures, loss of intercellular bridges, and metastasis.

**DERMOID, OCULAR**
1. Localized lesion on cornea or conjunctiva.
2. Stratified squamous epithelium overlying hair follicles, sebaceous glands and fibrous connective tissue.

**INVERTED MUCOEPIDEMODID PAPILLOMA**
1. Growth is endophytic.
2. Characterized by lobular arrangements with luminal formation.
3. Lobules consist of squamous cells which are intermixed with goblet cells and surrounded by clear or basophilic cells.

**MUCOEPIDEMODID CARCINOMA (MUCOUS CELL CARCINOMA)**
1. Located in the subepithelial fibrous stroma and composed of pale or eosinophilic, plump to spindle-shaped cells.
2. Tumor cells are sometimes stained by PAS or often contain an eosinophilic or hyaline globoid body in the cytoplasm.

**EPITHELIAL (INCLUSION) CYSTS**
1. Cyst lined by a keratinized stratified squamous epithelium which is several layers thick.
2. No dermal appendages found in wall.

**EYE**

**MELANOCYTE HYPERPLASIA**
1. Aggregates of polygonal melanocytes filled with pigment.
2. Minimal or no cellular atypia.
3. Minimal displacement of normal structures.

**MELANOMA, MALIGNANT, UVEAL**
1. Composed of bundles and whorls of spindle-shaped cells with perivascular orientation. Spindle-shaped cells have indistinct cell borders and slender fusiform nuclei having indistinct nucleoli.
2. Some areas may be composed of a loosely arranged mixture of epithelioid and spindle-shaped cells with foci of necrosis.
3. Epithelioid cells have ill-defined cell borders, pale-staining cytoplasm, and large oval nuclei with or without nucleoli.
4. Large epithelioid cells with large bizarre nuclei with nucleoli may occur, but are rare.
5. Mitotic figures may be numerous and argyrophilic fibers may be present along with a few cells containing yellow-brown pigment.

**LEIOMYOMA, UVEAL**
1. Composed of closely packed interlacing bundles and whorls of spindle-shaped cells.
2. Cells have eosinophilic granular cytoplasm with poorly defined cytoplasmic borders.
3. Nuclei are elongated with rounded ends and a finely stippled chromatin.
4. May be well vascularized with palisading of neoplastic cells around blood vessels.

**SCHWANNOMA, MALIGNANT, INTRAOCULAR**
1. Composed of spindle-shaped cells arranged in a perivascular fascicular pattern (not a whorled pattern).
2. Plump spindle-shaped cells with abundant eosinophilic vacuolated cytoplasm.
3. Cells are often arranged in parallel rows palisading around vessels. Areas of “pseudo” rosette formations may be present.
4. Nuclei are normochromatic, oval to short elongate and some cells may have a small eosinophilic nucleolus.
5. Mitotic figures may be numerous and areas of necrosis may be present.

**RETINALBLASTOMA**
1. Composed of small uniform hyperchromatic, undifferentiated cells that form perivascular wreaths, or are arranged in uniform tubular alignments or in columnar patterns.
2. Cells have irregularly shaped, round or slightly elongated hyperchromatic nuclei and a scant amount of cytoplasm with indistinct borders.
3. Pseudorosettes (Homer Wright type) and mitotic figures are numerous.
4. Hemorrhages and foci of necrosis may be present.
HARDERIAN GLAND

HYPERPLASIA
1. Normal alveolar pattern. Nodules or papillary formations may be present but compression of the adjacent parenchyma is generally absent.
2. Increase in number of cells lining acini. The increase in cells may cause a pseudostratified or folded appearance.
3. Hyperplastic cells are usually large and may be variable in staining when compared to normal cells.
4. Nuclei are normal and mitotic figures are rare.

ADENOMA
1. Adenoma is usually well demarcated with compression of surrounding tissues and are rarely encapsulated.
2. Neoplastic cells and/or the nuclei are enlarged. Cells may stain less intensely. Nuclei are uniform and mitotic activity is rare.
3. May have a papillary growth pattern. Epithelium may appear pseudostratified or stratified.

ADENOCARCINOMA
1. Adenocarcinoma is characterized as an expansive enlarging lesion with compression, distortion and invasion of surrounding tissues.
2. Lobular pattern is obscured or distorted. Cellular pleomorphism and atypia are present.
3. Well-differentiated adenocarcinomas consist of cuboidal to columnar epithelial cells arranged in tubular or gland like structures.
4. Less well-differentiated or anaplastic neoplasms exhibit stratification of the epithelium or solid sheets of cells.
5. Metastasis, foci of necrosis and fibrosis may be present.

LACRIMAL GLANDS (EXORBITAL)

HYPERPLASIA
1. Normal alveolar pattern. Nodules or papillary formations may be present but compression of the adjacent parenchyma is generally absent.
2. Increase in number of cells lining acini. The increase in cells may cause a pseudostratified or folded appearance.
3. Hyperplastic cells are usually large, may be variable in staining when compared to normal cells.
4. Nuclei are normal and mitotic figures are rare.

ADENOMA
1. Adenomas are expansive lesions that compress or displace the surrounding parenchyma.
2. Composed of tubular and acinar structures lined by uniform cuboidal cells with uniform rounded nuclei.
3. Acinar arrangement within the mass may be distorted and/or irregular, but the acinar cells are well differentiated.
4. Intercalated ducts are not usually observed.
5. Mitoses may be seen but generally are not frequent.

ADENOCARCINOMA
1. Expansive enlarging lesion with compression, distortion and invasion of adjacent tissues.
2. Lobular pattern is obscured or distorted. Acinar cells are moderately well to poorly differentiated and may contain secretory (serous) vacuoles.
3. Cellular pleomorphism and atypia are observed to varying extents.
4. Irregular acinar structures are lined by stratified epithelium and much of the neoplasm may be replaced by solid sheets of epithelial cells with round to ovoid variably sized nuclei.

EYELID

In addition to those mentioned above (Eye/Eyelid), tumors similar to other skin and subcutaneous tumors may be found in the eyelid of the rat.
REFERENCES


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**Fig. 1** - Squamous Cell Papilloma: Eyelid. Exophytic growth. (Hematoxalin & Eosin, 6.6x).

**Fig. 2** - Squamous Cell Papilloma: Eyelid. Vascular connective tissue core and retention of basement membrane. (H&E, 25x).

**Fig. 3** - Squamous Cell Carcinoma: Third Eyelid. Cords and nests of neoplastic squamous cells. (H&E, 15x).

**Fig. 4** - Squamous Cell Carcinoma: Conjunctiva. Cords of neoplastic cells and keratin 'pearls'. (H&E, 50x).
**Fig. 5 - Mucoepidermoid Papilloma; Eyelid.** Lobular arrangements with luminal formation. (H&E, 16x).

**Fig. 6 - Mucoepidermoid Papilloma; Eyelid.** Lobules of squamous cells surrounded by clear and basophilic cells. Higher magnification of Fig. 5. (H&E, 100x).

**Fig. 7 - Mucoepidermoid Carcinoma; Eyelid.** Subepithelial growth. (H&E, 5x).

**Fig. 8 - Mucoepidermoid Carcinoma; Eyelid.** Lobules of pale plump to spindle cells. (H&E, 100x).
Fig. 9 - Melanoma; Choroid. (H&E).

Fig. 10 - Melanoma; Choroid. Higher power view of Figure 9. Whorled pattern of neoplastic cells (H&E, 40x).

Fig. 11 - Melanoma; Choroid. Higher power view of Figure 9. Epitheloid pattern of neoplastic cells (H&E, 40x).

Fig. 12 - Melanoma; Iris. Whorled pattern of neoplastic cells (H&E, 50x).
**Fig. 13 - Melanoma: Eyelid. Epithelioid pattern of neoplastic cells (H&E, 50x)**

**Fig. 14 - Leiomyoma: Iris/Ciliary Body. (H&E, 13.5x).**

**Fig. 15 - Leiomyoma: Iris/Ciliary Body. Higher power view of Figure 14. Interlacing bundles of whorls and spindle-shaped cells. (H&E, 66x).**

**Fig. 16 - Schwannoma: Eye. Spindle-shaped cell arranged in a perivascular fascicular pattern. (H&E, 50x).**
Fig. 17 - Schwannoma; Eye. Plump spindle-shaped cells with vacuolated cytoplasm. (H&E, 50x).

Fig. 18 - Hyperplasia; Harderian gland. Normal alveolar pattern. Little or no compression of adjacent parenchyma. (H&E, 20x).

Fig. 19 - Hyperplasia; Harderian gland. Increase in number of cells lining acini resulting in pseudostratified and folded appearance. (H&E, 50x).

Fig. 20 - Adenoma; Harderian gland. Well demarcated with compression of adjacent parenchyma. (H&E, 20x).
Fig. 21 - Adenoma; Harderian gland. Increased number of cells lining acini causing pseudostratified appearance. Neoplastic cells and nuclei are enlarged. (H&E, 50x).

Fig. 22 - Adenocarcinoma; Harderian gland. Highly cellular, expansive mass with compression, distortion and invasion of surrounding tissues. (H&E, 33x).

Fig. 23 - Adenocarcinoma; Harderian gland. Solid sheet of anaplastic neoplastic cells. (H&E, 80x).

Fig. 24 - Adenocarcinoma; Exorbital lacrimal gland. Highly cellular, expansive mass with distortion and invasion of surrounding tissues. (H&E, 30x).
Fig. 25 - Adenocarcinoma: Exorbital lacrimal gland. Irregular acinar structures lined by neoplastic cells. (H&E, 55x).

Fig. 26 - Sebaceous gland Adenoma: Eyelid. (H&E, 8x).

Fig. 27 - Fibrous histiocytoma: Eyelid. (H&E, 50x).

Fig. 28 - Rhabdomyosarcoma: Orbit. (H&E, 100x).