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Neoplasia of the Nervous System

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Neoplasia of the nervous system is reported frequently in dogs and cats [1]. In dogs, tumors of the nervous system occur with a frequency and a variety similar to that in people, whereas in cats, tumors are relatively less common, with the majority being meningiomas and lymphomas. The incidence of central nervous system (CNS) neoplasia in dogs is perhaps 1% to 3% of all canine necropsies [2-4]. Primary nervous system tumors originate from neuroectodermal, ectodermal, and/or mesodermal cells normally present in, or associated with brain, spinal cord or peripheral nerves. Secondary tumors affecting the nervous system may originate from surrounding structures such as bone and muscle, or may result from hematogenous metastasis of a primary tumor in another organ. Tumor emboli can lodge and grow anywhere in the brain, meninges, choroid plexus, or spinal cord. Dissemination or metastasis of CNS tumors is rare, but may occur via the cerebrospinal fluid (CSF) pathways, especially if tumors are located close to the subarachnoid space or ventricular cavities (e.g., choroid plexus papilloma, ependymoma, pinealoblastoma, neuroblastoma, or medulloblastoma), or via a hematogenous route, such as the dural sinus, with subsequent development of remote metastasis, usually in the lung. Tumors may also spread to surrounding tissues, especially bone, by direct extension. The osseous tentorium may be used as a reference point for localizing different areas of the brain within the cranial vault: tumors occurring in the brainstem and cerebellum may be called "infratentorial" or "posterior fossa" tumors, whereas those occurring in the cerebral hemispheres are often referred to as "supratentorial" or "anterior fossa" tumors.
Neoplasias have been arbitrarily grouped as follows:

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Classification of Nervous System Tumors

Classification of nervous system tumors in animals has followed the criteria used for human tumors [5]. Classification is primarily based upon the characteristics of the constituent cell type, its pathological behavior, topographic pattern, and

secondary changes seen within and surrounding the tumor. Classification may be facilitated by use of immunocytochemical studies [6] and imaging techniques [7]. In general, primary tumors have a slowly progressive growth pattern, whereas, secondary, highly malignant, metastatic tumors, and bone tumors, frequently have a more acute progression. Although many animal neoplasms have characteristics analogous with corresponding tumors in people, 15 - 20% of neuroectodermal tumors (especially gliomas) remain unclassified [5], many of which have a topographical relationship to the ventricular system and/or to the subependymal cell nests [1].
Immunocytochemical staining of neuroectodermal brain tumors reveals that up to 26% of the tumors are undifferentiated [6]. In general, tumors of the nervous system are more common in mature and older animals, although there are sporadic reports of brain tumors in animals less than a year of age [8]. Brachycephalic breeds are at risk for certain neuroectodermal tumors (see below). No gender predisposition for the various types of nervous system tumors has been clearly defined at this time.

Brain Tumors

Overview

Primary tumors of the nervous system in dogs and cats occur more often in the brain than in the spinal cord or peripheral nerves [1]. Commonly reported primary brain tumors in dogs are meningiomas, gliomas (astrocytomas, oligodendrogliomas), undifferentiated sarcomas, pituitary tumors, and ventricular tumors (choroid plexus papillomas and ependymomas [1,2,9-11]. Primary reticulosis (see granulomatous meningoencephalomyelitis), also described as gliomatosis [12] and microgliomatosis [1], although, perhaps incorrectly [4], is reported sporadically. Other primary brain tumors, such as malformation tumors (see below), tumors of nerve cells (e.g., gangliocytomas, neuroblastomas), pinealomas, craniopharyngiomas (a suprasellar ectodermal tumor that may destroy the pituitary gland), spongioblastoma (or "embryonal glioma", often with a periventricular orientation), and medulloblastomas (usually in the cerebellum), are rare [4]. Dogs over 2 years of age in the brachycephalic breeds with common ancestry, e.g., Boxers, English Bulldogs, and Boston Terriers, have the highest incidence of brain tumors among domestic animals, and of these, the glial tumors (including unclassified gliomas) are the most numerous [1,2,10,11]. Extension of primary nasal cavity tumors into the cranial vault is relatively common. Nasal tumor types include epidermoid carcinoma, adenocarcinoma, anaplastic nasal carinomas or sarcomas, neurofibrosarcoma, neuroendocrine carcinoma, anaplastic chondrosarcoma, squamous cell carcinoma, and esthesioneuroblastoma. In contrast, tumors originating in middle or inner ear structures that extend into the brain are rare (see otitis media-interna).

Hematogenous Metastatic Brain Tumors

Hematogenous metastatic brain tumors originating from extracranial sites are common [1]. Hematogenous metastases in dogs frequently originate from carcinomas of the mammary glands, thyroids, bronchopulmonary epithelium, kidneys, chemoreceptor cells, nasal mucosa, squamous epithelium of the skin, prostate, pancreas, adrenal cortex and salivary glands. Less common intracranial metastases include transmissible veneral tumor in a 5 year old dog [13] and ovarian dysgerminoma in a 2 year old dog [188]. Recently, brain metastasis from a transmissible veneral tumor was reported in a 5 year old male crossbreed dog [13]. Common sarcoma metastases in dogs include hemangiosarcomas, lymphosarcomas, fibrosarcomas, and melanoblastomas. Brain metastases may accompany intramedullary spinal cord metastasis in dogs with hemangiosarcomas and lymphosarcomas [14]. In cats, metastases most frequently originate from mammary carcinomas and lymphosarcomas. Most instances of CNS lymphomas, especially in dogs, are manifestations of multicentric disease with frequent and extensive infiltration of the choroid plexus and leptomeninges [4,15], although a renal T-cell lymphoma with exclusive cerebral metastasis has been reported in a 5 year old Staffordshire bull terrier [182]. Primary CNS T-cell lymphoma has also been reported in a 5 year old Labrador retriever, with infiltration of cranial roots and meninges by neoplastic lymphocytes [210]. Neoplastic angioendotheliomatosis, or intravascular lymphoma (IVL), is a rare angiotropic large-cell lymphoma in which neoplastic lymphocytes proliferate within the lumina of blood vessels in the absence of a primary extravascular mass or leukaemia [16,183,204]. To date, canine IVLs have been derived primarily from T cells and non-T, non-B lymphocytes [183]. In a single case of IVL in a cat, the tumor was of T-cell origin [205]. Extraneural tumors cells sometimes localize in the meninges, e.g., meningeal carcinomatosis, often associated with an intestinal carcinoma or mammary adenocarcinoma [17,18].

Meningiomas

Meningiomas are extra-axial tumors that arise from the arachnoid cap cells of the dura within the cranial and spinal spaces. They are the most commonly reported brain tumors in cats [1,19] and one of the most common intracranial tumors in dogs, with a reported incidence in mature and immature dogs ranging from 30 to 45% [7-10,20,211]. In most reports, meningiomas occur in dogs over 7 years of age and in cats over 9 years of age, although meningiomas have also been observed in young cats (less than 3 years of age) with mucopolysaccharidosis type I [21], and in young dogs less than 6 months of age [8]. These tumors commonly occur in dolicocephalic breeds, especially German Shepherds [1,22].
Meningiomas in dogs and cats are usually benign tumors that tend to grow slowly under the dura mater, although in one canine study, there was direct invasion of the brain in 27% (6/22) of meningiomas [22]. Several molecular features have been examined in an effort to predict patient survival, including the presence of estrogen, progesterone and androgen receptors [23], as well as receptors for vascular epithelial growth factor (VEGF) [212]. The majority of canine and feline

meningiomas express progresterone receptors, but not estrogen receptors [176,213]. Although the presence of greater numbers of progesterone receptors has been associated with a lower cell proliferation rate this has not shown any correlation with survival [214,215]. The presence of high numbers of VEGF receptors may be associated with poor outcome [212]. Meningiomas may be irregular, nodular, globular, ovoid, lobulated, or plaque-like masses ranging in size from a few millimeters to several centimeters in diameter. Meningiomas often are firm, rubbery, and encapsulated, and usually discrete. They can contain granular calcifications known as psammoma bodies. Independently of these bodies, there can be focal or massive calcification of the tumor. A significant number of basal and plaque-like meningiomas involve the floor of the cranial cavity, especially in the optic chiasmal or suprasellar region [24]. They also occur commonly over the convexities of the cerebral hemispheres, less commonly in the cerebello-pontomedullary region, and infrequently in the retrobulbar space arising from the sheath of the optic nerve [1,22). In cats, common locations include tela choroidea of the third ventricle and the supratentorial meninges. There is also a high incidence of multiple meningiomas in cats. Thickening of bone adjacent to meningiomas, termed hyperostosis, may occur, especially in cats [25]. Meningiomas may extend into paranasal regions, rarely metastasize outside the brain [26], and may occur as primary extracranial masses as a result of embryonic displacement of arachnoid cells or meningocytes [27]. These tumors differ from intracranial meningiomas mainly in their more anaplastic/malignant nature and aggressive behavior. In one study using CT scans, meningiomas were distinguished from tumors within the brain parenchyma because they usually were broad-based, peripherally located masses that were enhanced homogeneously with contrast material [7]. Cystic and edematous meningiomas have been detected using CT [28] and MRI [29]. When a "dural tail" (a linear enhancement of thickened dura mater adjacent to an extra-axial mass seen on Gd-DTPA-enhanced T1 weighted images) is seen using MRI, an associated mass is most likely a meningioma [30]. It is uncertain whether the dural tail represents neoplastic infiltration beyond the margins of the meningioma. The histologic types of meningioma in dogs include psammomatous, transitional, meningothelial or syncytial, fibroblastic, anaplastic (malignant) and angioblastic [4,27,179]. Microcystic/myxoid and papillary forms may also be seen [4,31,32]. In most instances, the tumors consist of large meningothelial cells or fusiform cells arranged in whorls, nests, and islands, or in stream-like patterns. Cell boundaries are typically ill-defined. Nuclei contain little chromatin. Canine meningiomas commonly express vimentin intermediate filaments [4]. More variable expression occurs with pancytokeratin, S100, and neuron-specific enolase (NSE), while glial fibrillary acidic protein (GFAP) expression has been observed in an anaplastic meningioma [179]. In this study of 15 meningiomas, synaptophysin was uniformly negative. Regressive changes may include hemorrhage, cavernous vascular formations, hyalinization of connective tissue, and deposits of fat, lipopigments, or cholesterol. Many have evidence of focal necrosis with suppuration [10], which probably accounts for the reported predominance of polymorphonuclear cells in CSF reported in many dogs with meningioma [33]. In cats, the majority of meningiomas are meningotheliomatous or psammomatous, often with cholesterol deposits [4].

Rarely, focal or diffuse sarcomas involve the meninges in dogs. With the latter, termed **meningeal sarcomatosis**, the meninges are diffusely thickened, often with extensive hemorrhages, and tumors (cell types include lymphoid, plasmacytoid, mature plasma cells, immunoblastic cells, and multinucleate giant cells [4] tend to infiltrate the nervous tissue and run along blood vessels [1]. Also very rare is the occurrence of meningiomas with granule cell component in dogs [34]. In this study, granular cells were oval to polygonal in shape and of various sizes. The cells had abundant, pale, eosinophilic cytoplasm with distinct intracytoplasmic granules, distinct cell margins, and mostly central nuclei, and reacted to the antibody S-100 protein.

Malignant Histiocytosis

Recently, focal and diffuse forms of CNS malignant histiocytosis (some reserve this term for disseminated histiocytic sarcomas) have been reported in dogs [172,173,211]. This seemingly rare condition is characterized by proliferation and/or infiltration of neoplastic histiocytes. In one report in which the condition was described as diffuse leptomeningeal malignant histiocytosis, there was moderate to severe infiltration of pleomorphic histiocytic mononuclear cells bilaterally in the basiarachnoidal and ventricular areas of the brain. The spinal dura mater, arachnoidal space, leptomeninges, and spinal nerve roots were also affected by infiltrative proliferation of these mononuclear cells. The infiltrating cells had the morphologic characteristics of histiocytes but exhibited moderate pleomorphism and numerous mitotic figures. Immunohistochemical studies revealed that most of the infiltrating cells were positive for lysozyme and lectin RCA-1 and negative for glial fibrillary acid protein, suggesting a monocytic/histiocytic-origin. Positive proliferating cell nuclear antigen immunostaining demonstrated that most nuclei of the histiocytic cells were in the S phase of the cell cycle, consistent with a proliferating population of cells. Ultrastructurally, the neoplastic cells have features of histiocytic cells with abundant lysosomes. The pathological features of malignant histiocytosis appear similar to those seen in the neoplastic form of granulomatous meningoencephalomyelitis (neoplastic reticulosis). It has been suggested that canine localized and disseminated histiocytic sarcomas are likely myeloid dendritic cell sarcomas [178].

Astrocytomas

Astrocytomas are probably the most common neuroectodermal brain tumors in dogs. In one study of neuroglial tumors in 215 dogs [10], 118 (55%) were benign or malignant astrocytomas. Eighty were located in the cerebrum, 20 in the brainstem, and 17 in the cerebellum. In one report of an 11 year old entire female German shepherd dog presented with a progressive non-painful exophthalmos, an anaplastic astrocytoma was found in a retrobulbar location, along with

pulmonary metastases [35]. Astrocytomas consist of relatively large, protoplasmic-rich cells, or smaller cells with many processes. In most astrocytomas, there is a tendency for the cells to be arranged around blood vessels. Several variants have been described, e.g., fibrillary, protoplasmic, pilocytic, anaplastic, and gemistocytic, most of which stain positively for glial fibrillary acidic protein (GFAP), the chemical subunit of the intracytoplasmic intermediate filaments of astrocytic cells [6]. Regressive changes include necrosis, mucinoid degeneration, cyst formation, vascular proliferation often in the form of glomeruloid nests, and multinucleated giant cells. Hemorrhage is very uncommon. Malignant astrocyomas are characterized by nuclear polymorphism, presence of mitotic figures, and small cells with dense, hyperchromatic nuclei [4]. An anaplastic astrocytoma involving the left optic nerve, optic chiasm, hypophysis and hypothalamic area was diagnosed in a 3.5 year old Boxer with progressive blindness of the left eye and was termed an "optic chiasmatic-hypothalamic glioma" based on its unusual location and similarity to its human counterpart [175]. In one study using CT, astrocytomas were not distinguished easily from oligodendrogliomas because both tumors had similar features of ring-like and non-uniform enhancement, and poorly-defined tumor margins [7]. Distinguishing oligodendrogliomas from malignant astrocytomas with MRI has also been difficult [29], although MRI was considered superior to CT in defining diffuse leptomeningeal and cerebral low-grade astrocytoma in two dogs [36].
Astrocytomas are usually found in middle-aged or older dogs, but they have been reported in dogs less than 6 months of age [8]. They are common in brachycephalic breeds but can occur in any breed. Astrocytomas are very uncommon in cats [184]. In one report of four cats, the tumors invaded the third and lateral ventricles [37]. A mass with histological characteristics of a subependymal giant cell astrocytoma has been recently reported in a cat in which neoplastic cells were positive for S-100 protein, GFAP, and neuron-specific enolase and negative for neurofilament protein [185].

Glioblastoma Multiforme
Glioblastoma multiforme is a relatively common tumor in dogs and in one study represented 12% of 215 neuroglial tumors [10]. In another study, glioblastomas represented 3% of all primary CNS tumors [211]. These tumors are considered to be "high-grade" gliomas, of diverse origin, including astroglial, oligodendroglial, and ependymal tissue [4]. Most are of considerable size and are most commonly located in the cerebrum. The tumor cells consist of medium sized, round or fusiform cells with isomorphic nuclei. Considerable pleomorphism has been noted in some tumors with small and large mononucleated and multinucleated cells [1,38]. Glioblastomas have an infiltrative, destructive growth. These are well vascularized and often contain necrotic zones. Gliobalstomas may or may not express glial fibrillary acidic protein [6], although in a recent report of glioblastomas in 5 dogs, all tumors were GFAP positive, as well as positive for apoptosis and showed a proliferative index ranging from 12 - 25% [174]. MR characteristics include isointense to hypointense lesions on T1-weighted images that are hyperintense on T2-weighted images with prominent edema and mass effects, and sometimes ring enhancement [174]. The MRI and histological features have similarities to human gliobastomas. These tumors occur most commonly in brachycephalic breeds of dogs.

Oligodendrogliomas
Oligodendrogliomas are also common tumors in dogs (especially brachycephalic breeds), comprising 28% of neuroectodermal tumors (54 oligodendrogliomas were located in the cerebrum, and 6 were found in the brainstem) and 14% of primary CNS tumors overall [10,211]. In another review of 60 oligodendrogliomas, the neoplasm bordered on a ventricle or broke through the ependyma in more than half of the cases [1]. These tumors consist of densely packed, chromatin-rich, round cells with perinuclear halos. Most oligodendrogliomas grow by infiltration and destroy invaded tissue. Capillaries have a tendency to proliferate within these tumors, producing glomerulus-like structures. Regressive changes are similar to those in astrocytomas. Necrosis and extensive calcification are uncommon. These tumors do not stain with glial fibrillary acidic protein (GFAP); but in one study, three of 11 oligodendrogliomas reacted with myelin-associated glycoprotein [6]. None reacted with myelin basic protein. Many canine oligodendrogliomas are mixed tumors with areas of astrocytic, and sometimes ependymal, differentiation [4]. The MRI features are similar to those for high-grade (malignant) astrocytomas [29]. Oligodendrogliomas are rare in cats. In a recent report, oligodendrogliomas in 2 cats (one tumor was well differentiated; the other was an anaplastic subtype) occurred intraventricularly in the midbrain and fourth ventricle with aggressive intraparenchymal infiltration and extension into the basilar subarachnoid space of the midbrain and brain stem in one cat [195]. Immunostaining for several myelin- and oligodendroglia-specific antigens was negative. In both tumors, component cells of the intratumoral vascular proliferations were positive for human von Willebrand factor VIII antigen or smooth muscle actin. In both masses, GFAP staining identified both reactive astrocytes and a subpopulation of minigemistocytes. Prominent desmosomal junctions and paucity of microtubules were noted ultrastructurally.

Primitive Neuroectodermal Tumors (PNETs)
PNETs are a group of highly malignant embryonal tumors, the most common of which is the medulloblastoma. PNETs are uncommon, highly malignant neurectodermal tumors in dogs that are commonly located in the cerebellum but which have also been reported in the olfactory lobe [1,211]. The cell of origin of these tumors is unclear, and in humans they may show divergent differentiation along neuronal, astroytic, ependymal, myogenic and melanocytic lineages [Graham and Lantos Greenfield's Neuropath]. When they occur in the cerebellum, these tumors often replace part of the cerebellar vermis, tend to bulge into the fourth ventricle, and may compress the midbrain rostrally and the brainstem ventrally. They may metastasize within the CSF pathways, cause obstructive hydrocephalus, and infiltrate the meninges. Microscopically, the

tumor is characterized by sheets of densely packed cells with pale cytoplasm and oval or carrot-shaped nuclei that have coarse granulated chromatin. Mitotic figures are common. Regressive changes include pyknosis and karyorrhexis. In a recent survey, PNETs comprised 3% of all primary CNS tumors seen in dogs [211]. While most cases involve young dogs, there is a recent report of a cerebellar medulloblastoma with multiple differentiation in a 4 year old Border Collie dog [39].

Ependymomas

Ependymomas are rare neuroglial tumors derived from the lining epithelium of the ventricles and central canal of the spinal cord and have been reported more frequently in brachycephalic breeds [1]. In one study, ependymomas represented only 2% of 215 neuroglial tumors, and three of the four ependymomas were noted in the third ventricle [10]. They are soft, gray to reddish, lobular masses with a propensity to invade the ventricular system and the meninges. Obstructive hydrocephalus may be a complication [216]. Ependymomas of the fourth ventricle may grow out to girdle the brainstem. Metastases within the CSF system have been commonly observed [1]. Epithelial and fibrillary varieties have been described. Cells are isomorphic with pale or invisible cytoplasm and have round chromatin-rich nuclei. A characteristic feature is presence of nucleus-free zones around vessels. Some ependymomas appear hemorrhagic, and may show mucinoid degenerative changes and cyst formation. Malignant or anaplastic ependymomas show a moderate degree of pleomorphism and necrosis and may merge into glioblastoma multiforme [4]. In one study, only one of nine ependymomas was positive for glial fibrillary acidic protein [6]. In a computed tomographic study of brain tumors, there were no definitive distinguishing features identified with ependymomas [7].

Choroid Plexus Papillomas

Choroid plexus papillomas are common tumors in dogs with a reported frequency similar to that of glioblastomas (about 12% of neuroglial tumors). Approximately half of the 25 choroid plexus papillomas reported in one study [10] were located in the fourth ventricle, four were in the third ventricle, four were in lateral and third ventricles, and three were in the lateral ventricles. In another report of 16 tumors in dogs [40], their ventricular distribution was lateral and third ventricle (6 dogs each) and fourth ventricle (4 dogs). The choroid plexus epithelium originates from a differentiation of the primitive medullary epithelium and is related embryologically to the ependymal cells [40]. These tumors are reddish, papillary growths that have a tendency to bleed. Microscopically, choroid plexus papillomas are well defined, grow by expansion, and have a granular papillary appearance [1]. Tumor papillae consist of vascular stroma lined by one layer of cuboidal or cylindrical epithelium. These tumors have been classified as:

a. choroid plexus papilloma (resembling normal choroid plexus and with low mitotic index),
b. choroid plexus papilloma with atypical features (including increased cellular density, nuclear atypia, and 2 to 4 mitoses per 40x microscopic field, necrosis, and infiltration of the brain parenchyma, ventricular cavities/subarachnoid space, and/or leptomeninges, and
c. choroid plexus carcinoma (characterized by marked nuclear atypia, poorly formed papillae, > 4 mitoses per 40x microscopic field, abnormal mitotic figures, and/or extraneural metastasis) [40,177].

In immunocytochemical studies of choroid plexus tumors in dogs [6,40], it was concluded that these tumors express epithelial but not glial differentiation, based on absence of staining with glial fibrillary acidic protein. Some tumors express keratin (pankeratin, cytokeratin AE1/AE3), and have positive vimentin immunoractivity, occasional positivity for carcinoembryonic antigen, but are negative for epithelial membrane antigen, Ber EP4 and S-100 [40,177]. Exfoliation of choroid plexus papillomas (benign and malignant variants) may occur with subsequent dissemination to other areas of the brain or spinal cord via the CSF pathways. Obstructive hydrocephalus may be a complication. Extensive spread of the tumor in the subarachnoid space may lead to meningeal carcinomatosis [4,41]. When studied by CT, choroid plexus tumors were seen as well-defined, hyperdense masses that had marked, uniform contrast enhancement [7]. Strong enhancement is also seen with MRI, sometimes with hemorrhage and mineralization [29]. In one dog with choroid plexus carcinoma and meningeal carcinomatosis, multiple cyst-like structures were found in the parenchyma of the cerebrum, cerebellum and brainstem using MRI [42]. Choroid plexus papillomas have no apparent predilection for brachycephalic breeds. They are rare in cats.

Gangliocytomas

Gangliocytomas are rare intracranial tumors that have been described in mature dogs of several breeds [1]. Microscopic features often include mature, neuronal-like cells with multiple processes, a central nucleus and a nucleolus. Neuroblastlike immature cells may also be seen, and occasionally, newly formed myelin sheaths. These tumors appear to have a predilection for the cerebellum. Pure gangliocytomas have no glial elements and do not express glial fibrillary acidic protein [43]. Mineralization and extensive necrotic areas accompanied by edema and variable capillary proliferation have been observed in some cases.

Pituitary Tumors

Pituitary tumors are common in dogs but infrequently seen in cats. In one review, approximately 50% of the canine pituitary adenomas occurred in brachycephalic breeds [1]. They may be non-functional or functional. Although it is

uncommon, tumors of either type are capable of causing hypopituitarism by mechanical or functional impairment of remaining pituitary tissue. Nonfunctional pituitary tumors occur often in dogs and are usually chromophobe adenomas, although non-functional pituitary adenocarcinomas have been reported [44]. Functional pituitary tumors associated with the adenohypophysis are typically characterized by pituitary-dependent hyperadrenocorticism (PDH). Eighty percent or more of cases of pituitary Cushing's disease are reportedly associated with a pituitary tumor [45]. In dogs, these tumors may stem from the pars distalis (80%) or the pars intermedia (20%) since both regions contain cells that are capable of producing adrenocorticotropic hormone (ACTH). The tumors are usually chromophobic microadenomas (< 1 cm in diameter) that do not produce neurological signs. Results of MRI suggest that up to 60% of PDH dogs without neurological signs have pituitary tumors 4 to 12 mm in diameter (at greatest vertical height). It has also been stated that up to 50% of dogs with PDH have large chromophobic macroadenomas (> 1 cm in diameter) and some of these dogs do not manifest clinical signs of an intracranial mass [46,47]. It has been estimated that at least 15 to 20% of all dogs with PDH will develop clinical problems due to a growing pituitary tumor during the first 2 or 3 years after diagnosis [48,49]. In one study, seven of eight dogs with pituitary gland neoplasms (2x malignant pituitary adenocarcinomas and 5x pituitary adenomas) that had been treated for PDH for varying periods of time (from 1 to 2 years), developed neurological signs, including behavior abnormalities (such as pacing, lethargy, wandering, hiding, tight circling, head pressing, and trembling), seizures, and positional nystagmus [50]. As most pituitary tumors, especially those derived from the pars distalis (chromophobe tumors in dogs from the pars intermedia are smaller and less destructive [4]), tend to grow dorsocaudally because of an incomplete diaphragma sella [1], dorsal extension of pituitary tumors may lead to compression and obliteration of the infundibulum, ventral aspects of the third ventricle, hypothalamus and thalamus, and eventually impinge on internal capsules and optic tracts [4]. Involvement of the hypothalamus and median eminence may result in central diabetes insipidus [51], particularly in middle-aged and older dogs with neurological signs as well as polyuria, polydipsia, and isosthenuria or hyposthenuria [136].

Disturbance of water balance is the result of interference with the synthesis of antidiuretic hormone in the supraoptic nucleus or release of the hormone into capillaries of the pars nervosa [45]. While visual impairment is reportedly infrequent with pituitary tumors, acute blindness and dilated non-responsive pupils have been observed in seven dogs and one cat with pituitary masses that caused optic chiasmal compression [44]. According to Feldman [49], approximately 80% of cats in his practice diagnosed with Cushing's disease had PDH, and tumors included pituitary microadenomas, macroadenomas, and adenocarcinomas. Pituitary acidophil adenomas, especially the large variety, have been associated with acromegaly and nervous system signs (such as circling and seizures) in cats, accompanied by insulin-resistant diabetes mellitus and high serum growth hormone concentrations [52]. In pituitary tumors, polygonal, round, and cylindrical cells are arranged in close contact to blood vessels or form islands of cells divided into compartments by connective tissue [1]. The cell pattern may be monotonous and resemble normal pituitary gland tissue. Many pituitary tumors contain both chromophobe and chromophil cells. Regressive changes include necrosis, cyst formation, and hemorrhage. Chromophobe carcinomas are infrequent and usually separated from adenomas on the basis of invasion along the base of the brain into the sphenoid bone, since nuclear pleomorphism and mitotic index may be similar to those seen in adenomas [4]. MRI is an extremely useful aid for visualizing the presence of microtumors (3 to 10 mm in diameter) and macrotumors (up to 24 mm) in dogs with PDH, with or without neurological signs [46,48], especially when it is considered that there is no significant difference in endocrine test results when comparing dogs with a visible pituitary mass to dogs without [53]. Tumors are better visualized with contrast enhancement [48]. MRI and CT scans of pituitary tumors have revealed minimal peritumoral edema, uniform contrast enhancement, and well-defined margins [7,29]. Pituitary tumors less than 3 mm in diameter may not be visible with MRI or CT [47]. Note that pituitary and adrenal tumors can coexist in dogs with hyperadrenocorticism, resulting in a confusing mixture of test results that may complicate diagnosis and treatment of hyperadrenocorticism [54].

Suprasellar Germ Cell Tumors

Suprasellar germ cell tumors, located at the base of the brain above the sella turcica, are rare developmental tumors that are often intimately associated with the pituitary gland that may be trapped within or replaced by the germ cell tumor [55-57]. These tumors are thought to result from extensive migration of germ cells during embryogenesis. Neurological signs may be acute in onset and include lethargy or depression, bradycardia, dilated non-responsive pupils, ptosis, and visual deficits or blindness. Germ cell tumors can be quite large, extending from the olfactory peduncles to the pons and pyriform lobes [4], and can envelope other cranial nerves (e.g., III through VII). Microscopically, the tumors usually contain a mixture of primitive germs cells, cords resembling hepatocytes, and acini and tubules of tall columnar epithelial cells. They may stain positively for alpha-fetoprotein. Affected animals are usually 3 to 5 years of age and Doberman Pinschers may be at risk. The tumor has been reported in a 5 year-old Rottweiler [55]. Some germ cell tumors have been misdiagnosed as pituitary tumors and craniopharyngiomas [4].

Malformation Tumors

Malformation tumors, such as epidermoid and dermoid cysts, teratomas, and teratoids, are rare neoplasms in dogs that originate from heterotopic tissue. These tumors usually lie close to embryonal lines of closure.

Epidermoid and Dermoid Cysts

Result from inclusion of epithelial components of embryonal tissue at the time of closure of the neural tube. Those that

have been reported have a predilection for young dogs (e.g., from 3 months to 2 years of age), although cysts have been seen in older dogs, and typically involve the cerebello-pontine angle, fourth ventricle, or both [1,58,59]. Cysts within the fourth ventricle may produce secondary compression of the medulla oblongata and the cerebellum. A cerebellar epidermoid cyst has been reported in a 7 year-old Pitbull with signs of progressive disequilibrium [60]. Cerebellar and medullary dermoid cysts have been recently reported in 7 year-old dogs. In one dog, a 1.6 x 0.8 x 1.5 cm, thinly encapsulated mass was found on the left cerebellar peduncle. It had caused dorsal displacement of the left portion of the cerebellum and ventral compression of the fourth ventricle [59]. In the other dog, MRI revealed the medullary cyst and secondary hydrocephalus. There was little edema associated with this lesion and no enhancement with gadolinium [61]. Some epidermoid cysts are found as incidental findings at necropsy [58,62]. Epidermoid cysts may have a multilocular structure and are typically lined by stratified squamous epithelium and contain keratinaceous debris, desqualmated epithelial cells, and occasional inflammatory cells; whereas, dermoid cysts contain adnexal structures such as hair follicles, sebaceous glands, and sweat glands. Cysts may measure up to 2.5 cm in diameter. Because of their location, dogs may show signs of a pontomedullary syndrome (including trigeminal, facial, cerebellar, and/or vestibular dysfunction).

A dermoid cyst and an intracranial teratoma, both approximately 1 cm in diameter, were found in a 4 month old kitten [135] located in the ventral forebrain protruding into the lateral ventricle. The teratoma was grossly mottled tan-gray and multilobulated with small cysts and markedly compressed the 3rd ventricle. It was located close to the thalamus and hypothalamus, adjacent to the pituitary stalk. Microscopically the mass was composed of myriad structures including collagenous stroma, striated muscle cells, melanocytes, adipose tissue, dilated tubules lined by cuboidal-columnar-pseudostratified epithelium containing goblet cells, and exocrine pancreatic cells forming acini. Teratomas represent well-differentiated germ cell tumors (see above) arising from several embryonic germ cell layers.

Intracranial intra-arachnoid Cysts

Have also been described in dogs [63,202,203]. These rare malformation tumors (see also spinal arachnoid cysts) appear to have a predilection for the quadrigeminal cistern. The cysts are often found in small breed dogs of either sex, and occur in both immature and adult dogs. Other developmental anomalies (e.g., abnormal corpus callosum and block vertebrae) may be detected. The cysts, on MRI and CT scans, are extra-axial and have sharply defined margins, and contain fluid usually iso- or hypointense to CSF (in T2-weighted images). In some instances, intracystic hemorrhage has been demonstrated [203]. Ultrasonographic images are characterized by well-defined, oval to triangular-shaped anechoic area between the caudal aspect of the occipital lobes, dorsal to the midbrain, and rostral to the cerebellum [202].

Hamartomas

Are focal malformations that resemble neoplasms and are formed by disorderly overgrowth of tissue elements normally present at that site [4]. Hypothalamic hamartomas have been reported only rarely in dogs and usually as subclinical entities [64]. However, a 10 month old Wire-haired Pointing Griffon dog had a hamartoma of the hypothalamus and manifested episodes of sudden flaccid collapse that increased in frequency and duration for 7 months [65]. Cerebrospinal fluid pressure was normal. A flat, pedunculated mass, 2.5 X 3.0 X 1 cm, covered the brain stem between the pituitary gland and pons. Its 1.2 cm diameter connection to the hypothalamus obliterated the mammillary bodies and extended to the tuber cinereum, distorting the hypothalamus and displacing the third ventricle, which also divided the rostral part of the mass. The tissue of the hamartoma resembled gray matter with bullous cytoplasmic vacuolation of many neurons, spongiform change, gemistocytosis and microscopic foci of calcification. Vascular malformations are also uncommon in dogs and cats and are considered developmental lesions rather than true neoplasms [4]. Fankhauser and colleagues reported the occurrence of vascular malformations (telangiectatic hamartomas and cavernous hemangiomas) in 11 dogs aged from 6 to 17 years [66]. Locations were the cingular gyrus (3 dogs), piriform-hippocampal area of the temporal lobe (3 dogs), basal ganglia (2 dogs), septum pellucidum and fornix (1 dog), occipital lobe (1 dog) and cerebellum (1 dog). The hamartomatous structures consisted of accumulations of vessels (arteries, veins, and capillaries, either alone or in combination). The anomalous vessels tended to be dilated and had a sinusoidal shape, and were often accompanied by hemorrhages. These authors also observed a large cavernous angioma in the cerebral hemisphere of a cat. A large vascular hamartoma (possibly a cavernous angioma), located in the septal area and thalamus, has been noted in a 13 year-old Poodle [4]. In a recent report, vascular hamartomas from the brains of five dogs were characterized using histochemistry and immunohistochemistry [67]. All five hamartomas were located in the telencephalon, three in the pyriform lobe, without any predilection for the left or right side. Each hamartoma consisted of a proliferation of thin-walled vessels that varied in caliber. These vessels were elastin-negative, with varying amounts of collagen and no muscular component. In four of the five hamartomas, lining cells were actin- and factor VIII-positive. All five hamartomas contained glial fibrillary acid protein (GFAP)-positive parenchyma at moderate to high frequency, and four contained neurofilament-positive axons between component vessels.
Meningioangiomatosis, a rare benign malformation of the vasculature of the central nervous system, characterized by the proliferation of blood vessels and spindle-shaped, perivascular meningothelial cells has been described in the cerebral cortex and brainstem of immature and mature dogs [4]. The meningothelial cells stain positively for vimentin [68,69], which, together with presence of collagen and mucopolysaccharides among proliferating cells, suggests a mesenchymal and fibroblastic origin of these cells [69]. A hematoma located in the parietal portion of the right cerebral hemisphere surrounded by numerous thin-walled veins, considered to be a venous malformation, has been reported in a 14 year-old dog

[70].

Primary Skeletal Tumors

Primary skeletal tumors infrequently result in neurological signs. Multilobular osteochondroma occurs as a firm, fixed mass originating from the flat bones of the skull, usually in older medium-to large-breed dogs [71,193]. The tumor can erode the cranium and compress, rather than infiltrate, underlying brain tissues. Radiographically, the tumor contains nodular or stippled mineralized densities resulting in a characteristic 'popcorn ball' appearance. Microscopically, the tumor is characterized by multiple lobules of osseous and chondroid tissue. Local tumor recurrence and metastasis are common. The spinal cord counterpart is the vertebral osteochondroma (see osteochondromatosis). An extremely rare primary intracranial malignant plasma cell tumor has been reported in a 5 year old female spayed Spitz dog with a 5-week history of right head tilt, seizures, and progressive quadriplegia [72]. Analysis of cerebrospinal fluid revealed 27,600 white blood cells per ul with 63% mononuclear phagocytes, 27% lymphocytes, 6% neutrophils, 3% plasmacytoid cells, and 1% eosinophils, and over 2000 mg/dl protein. On contrast-enhanced magnetic resonance images, a focal 1 cm oval lesion was identified in the right ventral brainstem. There was also marked contrast enhancement of the meninges in the following areas: surrounding the brainstem, outlining cerebellar folia, along the ventral floor of the brain and extending to the falx cerebri, and partially outlining the left frontal lobe. At necropsy, the areas of contrast enhancement corresponded to the presence of compact cellular sheets of pleomorphic, anisocytotic, oval to polygonal neoplastic cells with plasmacytoid differentiation. The smaller of these plasmacytoid cells stained predominantly for cytoplasmic immunoglobulin A using immunoperoxidase methodology. Ultrastructurally, the neoplastic cells had morphologic features typical of plasma cells, with large amounts of predominantly rough endoplasmic reticulum with variably prominent Golgi formation.

Clinical Signs of Brain Tumors

Some of the clinical signs/syndromes associated with specific intracranial CNS tumors have already been mentioned. According to tumor location, one might anticipate cerebral, hypothalamic/diencephalic, midbrain, cerebellar, pontomedullary, and vestibular syndromes associated with focal discrete intracranial masses. In many cases, accurate anatomic diagnosis (localization) is possible, especially in the early stages of tumor growth. However, in some intracranial tumors, accurate clinicopathological correlations are frequently impossible [73]. This is because the actual location of a tumor may be masked by secondary changes such as cerebral edema, hemorrhage, obstructive hydrocephalus, brain herniations, tissue necrosis, and tumor spread within the brain [4], all of which may result in clinical manifestations in their own right.

Usually as a consequence of increased intracranial pressure and/or shifts in parts of the brain as a result of the mass lesion, herniation of portions of the brain may ensue. Several types of herniation have been described in dogs [4,74]:

a. The cingulate gyrus herniates under the falx cerebri toward the unaffected hemisphere, leading to compression of the opposite cingulate gyrus. Interestingly, clinical signs attributable to this form of herniation were not identified in one report [74].
b. The occipital or temporal lobe (mainly the parahippocampal gyrus) herniates under the tentorium cerebelli (caudal transtentorial herniation). This often causes dorsoventral and lateral compression of the midbrain at the rostral colliculi and partial occlusion of the mesencephalic aqueduct. There may also be caudal displacement of the diencephalon and midbrain. Clinical signs include pupillary constriction (initially) often followed by mydriasis, tetraplegia and coma.
c. The rostral cerebellar vermis herniates under the tentorium cerebelli (rostral transtentorial herniation) which may lead to flattening of the rostral cerebellum, compression of the temporal cortex, and marked compression and rostral displacement of the brainstem. Despite the gross pathology occurring with this form of herniation, clinical deficits may not be seen [74].
d. The cerebellum (especially the caudal lobe of the cerebellar vermis) herniates through the foramen magnum. The herniated portion is flattened and may be malacic and hemorrhagic, and compresses the underlying medulla oblongata. Clinical signs may include apnea, hypoxia-induced coma, and tetraplegia. Concurrent foramen magnum and caudal transtentorial herniation has been reported leading to signs of both midbrain and medulla oblongata dysfunction [74].

Herniation is more likely to occur with large masses, especially if they are located either rostrally or dorsally [217]. Clinical signs most commonly seen with herniation include changes in mentation (dullness, depression, stupor or coma), proprioceptive deficits (usually contralateral to the side of the mass) and menace response or PLR deficits. However, up to 40% of dogs with herniation do not show any clinical signs [217]. Herniation combined with attenuation of the ventricular system, especially at the level of the mesencephalic aqueduct, can lead to obstructive hydrocephalus and elevated intracranial pressure, and ischemic necrosis of the herniated tissue can result [75]. An additional clinicopathological caveat is that as many as 50% of cats with meningiomas do not manifest clinical signs [21,76].

Initial abnormalities associated with tumors involving the rostral cerebrum (e.g., olfactory and frontal lobes) may be restricted to seizures and behavioral changes [77]. Lesions in frontal and prefrontal lobes of the brain may be clinically silent [9]. Acute blindness may be the initial presenting clinical sign in animals with tumors in the region of the optic chiasma, e.g., pituitary tumors, paranasal sinus carcinoma, polycentric lymphosarcoma, and suprasellar germ cell tumors

[44,57]. Presence of papilledema (often bilateral) has been reported in dogs with brain tumors and is considered to arise from generalized increase in intracranial pressure [73]. Clinical signs of a multifocal syndrome may occur in animals from a variety of causes. This syndrome may result from multiple small metastatic masses from extracranial tumors, especially with malignant melanoma and hemangiosarcoma [4,78]. Other tumors, such as carcinomas (pulmonary, mammary) tend to produce fewer, larger metastases [4]. Some hematogenous metastases appear to have a propensity for gray matter, commonly in the cerebrum, hippocampus, and cerebellar cortex [4,78]. Extraneural tumors cells sometimes localize in the meninges, e.g., meningeal carcinomatosis associated with an intestinal carcinoma or mammary adenocarcinoma [17,18]. Metastases to the meninges and/or choroid plexuses often occur in dogs and cats with multicentric lymphoma [4,15,79]. A multifocal syndrome may also occur with primary CNS tumors having multiple sites (meningiomas in cats are often multiple [1]), from spread of the original tumor to another site by extension (e.g., astrocytoma, glioblastoma) or through metastases via the CSF pathways (e.g., medulloblastoma, choroid plexus papilloma, and ependymoma) [73]. Because of their ventricular orientation, ependymomas and choroid plexus papillomas have a tendency to obstruct cerebrospinal pathways, particularly when they arise in the fourth ventricle. Accordingly, neurological signs associated with ventricular tumors will reflect tumor localization and varying degrees of ventricular dilatation resulting from obstructive hydrocephalus. With either of these tumors, clinical signs are often insidious and the clinical course is usually protracted, ranging from months to years. Extraneural immunoproliferative diseases in dogs and cats [80,81], such as macroglobulinemia-associated lymphocytic leukemia and multiple myeloma, can also produce a spectrum of intermittent cranial neurological abnormalities (including disorientation, ataxia, intention tremor of the head, possible visual impairment, occasional circling, and staggering/falling) as a result of serum hyperviscosity - the transient signs probably result from impaired blood flow in the vascular beds of affected areas due to increased intravascular erythrocyte aggregation [81].

Various endocrine signs can be associated with pituitary tumors, including polydypsia, polyuria, obesity, gonadal atrophy, abnormal hair coat, and acromegaly. A condition similar to pituitary apoplexy in humans has been described in a 7 year-old German Shorthaired Pointer with a pituitary adenoma. Extensive hemorrhages from within the tumor had extended dorsally through the hypothalamus into the ventricular system [82]. Signs included polydypsia, polyuria, acute vomiting and collapse followed by development of convulsions and hyperthermia, and a shift from bilateral pupillary miosis to mydriasis. The dog also had evidence of hypernatremia and abnormal thermal regulation. A rare condition termed "diencephalic syndrome" was described in a 3 year-old Doberman Pinscher associated with an astrocytoma located in the rostral hypothalamus [83]. The dominant clinical sign was chronic weight loss, followed by hypothermia with lack of a shiver response, lack of thirst despite negative water balance, and persistently low-normal heart rate. The only neurological abnormality noted was circling.

Extension of primary nasal cavity tumors into the cranial vault may lead to seizures, behavior changes, paresis, circling, and visual deficits [9,84]. Respiratory signs such as sneezing, nasal discharge, epistaxis, stertor, dyspnea, and mouth breathing may develop after neurological signs, or may not be seen at all.

Spinal Cord Tumors

Overview

Spinal cord tumors are relatively common in dogs and cats and are usually classified according to their position with respect to the spinal cord and meninges as either extradural, intradural-extramedullary, or intramedullary tumors [85]. According to tumor location, any of the four spinal cord syndromes can be anticipated (see cervical syndrome, cervicothoracic syndrome, thoracolumbar syndrome, and lumbosacral syndrome). Most dogs with spinal tumors, regardless of type, have a mean age around 6 years of age [86-88]. Cats with lymphosarcoma tend to be younger, having a mean age of approximately 3.5 years [89], possibly related to the infectious etiology of most cases (i.e. feline leukemia virus). However, age alone does not preclude a diagnosis of spinal tumor. In one study of spinal tumors in dogs, 8 of 29 animals (30%) were 3 years of age or less [90]. In that study, approximately 90% of the spinal tumors occurred in medium and larger canine breeds. The clinical course is still not clearly defined for tumor types and their location. In one study, the rate of progression was fastest with intramedullary tumors (1.7 weeks), followed by extradural tumors (3.4 weeks), and intradural-extramedullary tumors (5.7 weeks) [90].

Extradural Tumors

Extradural tumors are located outside the dura mater and result in spinal cord compression. Extradural tumors are the most common spinal tumors in dogs and cats. The most frequently occurring types of canine spinal cord tumors are primary, malignant bone tumors (osteochondromas or multiple cartilaginous exostoses, osteosarcoma, chondrosarcoma, fibrosarcoma, hemangiosarcoma, hemangioendothelioma, and multiple myeloma), and tumors metastatic to bone and soft tissue [1,86,91,92]. Secondary tumors of the vertebrae of the dog that have been reported include mammary carcinoma, prostatic carcinoma, anaplastic tumors, transitional cell carcinoma, osteosarcoma, thyroid carcinoma, perianal gland carcinoma, chemodectoma, ganglioneuroma, fibrosarcoma, bronchogenic carcinoma, tonsilar carcinoma, hemangiosarcoma, Sertoli cell carcinoma, lymphosarcoma, rhabdomyosarcoma, pancreatic adenocarcinoma, malignant melanoma, squamous cell carcinoma, and aortic body tumors [1]. An extradural ganglioneuroma and its undifferentiated

counterpart, ganglioblastoma, have been reported in dogs [93,94]. Primary vertebral tumors are rare in the cat, with osteosarcoma being most commonly reported [209] followed by fiborsarcoma, undifferentiated sarcoma, and plasma cell tumors. Metastatic extradural tumors affecting the spinal cord are unusual in dogs, e.g., uveal melanoma [208]; however, extradural lymphosarcomas are the most common feline spinal tumors [19,89]. In most instances, these tumors are secondary to lymphosarcoma elsewhere in the body, although primary spinal cord lymphosarcoma has been reported sporadically in dogs [15,95]. In a study of spinal lymphosarcoma in 23 cats, the absence of detectable extraneural involvement was noted in approximately 50% of cats [89]. The tumors were solitary in 22 of the cats and there was an apparent predilection for the thoracic and lumbar vertebral canal; however, they may occur in any spinal region [19]. Three of the tumors involved the cervical roots of the brachial plexus (see peripheral nerve tumors). Spinal lymphomas in cats may extend over multiple vertebral bodies, and there may be more than 1 level of spinal cord involvement [96]. In one study of necropsy specimens, approximately half of the 20 cat spinal cords examined had lesions and half had extradural lesions [209]. In contrast with intracranial lymphoma, leptomeningeal spinal cord involvement is not common in cats 4. At least some of these tumors are large granular lymphocyte lymphomas [181]. Recently, an extradural spinal liposarcoma was described in an 8 year old female Doberman Pinscher [97]. It was not determined if this was a primary tumor. A tumor termed myxoma-myxosarcoma has been described for the first time in 4 dogs [98]. These malignant tumors resemble soft tissue myxomas in that the cells were polygonally shaped with gray and vacuolated cytoplasm and stained positive for S-100 protein antibody. The masses were reported as being extradural in 3 cases and intradural-extramedullary in the fourth dog. A primary extracutaneous mast cell tumor compressing the spinal cord at the level of the sixth cervical to first thoracic (C6 - T1) vertebrae was reported in a 6 year old Rottweiler [192].

Intradural-extramedullary Tumors

Intradural-extramedullary tumors are located in the subarachnoid space. Intradural-extramedullary tumors are usually represented by meningiomas and nerve sheath tumors (e.g., neurofibromas, neurilemomas, and schwannomas) that grow into the vertebral canal and compress the spinal cord [86,90,94]. It has been estimated that intradural-extramedullary tumors represent approximately 35% of all spinal cord tumors [85,86]. About 14% of CNS meningiomas reportedly involve the spinal cord in dogs [10] (27% in the cervical spinal cord, 47% in the thoracic cord, and 27% in the lumbar cord), whereas in cats, only 4% of all CNS meningiomas reportedly occur in the spinal cord [99]. In another study of spinal meningiomas in 13 dogs, 10 were located in the cervical region and three were found in the lumbar area [100]. Four of these meningiomas invaded the spinal cord. In a report of spinal cord tumors in 29 dogs, nerve sheath tumors were the second most common tumor (vertebral tumors were the most common) [86]. In another review of spinal tumors in dogs, 39 of 60 nerve sheath tumors involved the spinal cord [10]. Nerve sheath tumors are commonly associated with the brachial plexus (see peripheral nerve tumors). An unusual intradural-extramedullary lipoma has been reported in a 4 year-old, female mixed-breed dog that was presented for chronic, persistent lumbar pain, episodic urinary incontinence, fecal incontinence, and weak anal sphincter tone [101]. Due to congenital absence of a tail, the presence of eight lumbar vertebrae, and a dimpled area in the lumbosacral region, the lipoma was suspected to have a developmental origin. Summers and colleagues consider these tumors to be malformative or hamartomatous [4] (see hamartoma).

A primary intradural-extramedullary tumor that has a predilection for T10 to L2 spinal cord segments in young dogs, especially German Shepherds and Retrievers, has been variously diagnosed as ependymoma, medulloepithelioma, neuroepithelioma, and **nephroblastoma** [86,90,102]. The origin of this tumor is presently unknown; immunocytochemical studies have not supported a neuroectodermal origin as staining for neurectodermal antigens (e.g., GFAP, neurofilament, and neuron-specific enolase) is negative; however, monoclonal antibody studies support the nephroblastoma claim [4]. Most affected dogs are between 5 and 36 months of age. There is no gender predilection. Clinical signs are characterized by a thoracolumbar syndrome. Analysis of CSF is usually normal, although an elevated protein level has been documented in one dog. The extramedullary masses are tan to grayish-white in color and may measure from 1 to 3 cm in length. The masses are usually located dorsal and lateral to the spinal cord and may entrap the spinal roots. Some have areas of hemorrhage. The spinal cord may be severely compressed. Microscopic findings include solid sheets of ovoid to fusiform cells interspersed with areas of acinar and tubular differentiation, focal squamous metaplasia, and rudimentary glomeruli [4,102]. Recently, multifocal or possible intraspinal metastasis of a canine spinal cord nephroblastoma was reported in a 2 year old Basset Hound [137].

Intramedullary Tumors

Intramedullary tumors are the least common of the three categories of spinal cord tumors - a frequency of 15 to 24% has been reported [85,90,103]. This group is largely represented by primary glial tumors (e.g., astrocytoma, oligodendroglioma, undifferentiated sarcoma, ependymoma, and choroid plexus papilloma). In a review of 205 cats with spinal cord disease, intramedullary tumors constituted 3% of all cases with half of these identified as primitive neuroectodermal tumors and half as glial tumors [209]. In one report of an anaplastic astrocytoma in a 9 year old cat, areas of the lumbar spinal cord were flattened and contained a dorsal cleft [186]. Intramedullary spinal cord metastasis (ISCM) is an uncommon complication of systemic malignancy. This condition has been described in dogs [14,85]. There is no evidence of tumor metastasis in the epidural space or in vertebral bone. Intramedullary involvement may consist of large space-occupying masses or micrometastases in the absence of gross tumor. In dogs, hemangiosarcoma and lymphosarcoma have a propensity for intramedullary spinal cord involvement, but mammary gland adenocarcinoma, malignant melanoma, and

bronchoalveolar carcinoma are also occasionally observed [14,104]. Neurological signs in animals with ISCM may be the first clinical manifestation of systemic malignancy. The mean age of affected dogs is around 6 years, and any area of the spinal cord may be affected. Brain metastasis may accompany ISCM. Spinal cord malignancy associated with granulomatous meningoencephalomyelitis is reported sporadically.
Malformation tumors affecting the spinal cord are rare. An intramedullary epidermoid cyst has been reported in a 2 year-old, female Rottweiler presented with a thoracolumbar syndrome [105]. A gray to pearl-colored intramedullary cyst approximately 2 cm long and 1 cm in diameter extended from T13 to L1 spinal cord segments. The empty lumen was lined by simple stratified squamous epithelium or, less frequently, by desqualmating keratinized epithelium, containing keratohyaline granules. The spinal cord was severely compressed. These cysts may arise from growth of primordial epithelial cells entrapped during closure of the neural tube (see also arachnoid cysts).A caudal lumbar intramedullary chordoma has been reported in a 4 year old Labrador Retriever [196]. Histologically there were variable sized cells that were stellate in appearance with vacuolated cytoplasm (physaliferous cells) and mucinous background. Chordomas originate from remnants of the embryonal notochord. An intramedullary spinal cord hamartoma was recently identified in a 9 year old Golden Retriever [201].

Peripheral Nerve Tumors
Tumors of cranial and spinal nerves and nerve roots are common in dogs [10]. In one study, peripheral nerve tumors represented approximately 27% of canine nervous system tumors [106]. The terminology given to these tumors has been confusing because of differing opinion regarding their cell of origin. Although "schwannoma", "neurilemmoma", and "neurofibroma" are accepted and used interchangeably, the designation "malignant peripheral nerve sheath tumors" (MPNST) is recommended [4], especially since many of these tumors are malignant (based on cytological criteria such as anaplasia, high mitotic index and necrosis, or invasive biological tendencies, including spinal cord invasion) and determining the cell of origin (e.g., Schwann cell, perineurial cell, fibroblast, etc) is usually impossible [4]. Microscopic findings of MPNSTs often include dense fascicles of Schwann cells and/or fibroblasts with elongated nuclei, as well as cells with anaplastic features, imbedded in dense connective tissue. There may be evidence of myelinated axons. Schwannomas may be characterized by spindle-shaped cells exhibiting band-like herringbone or pallisading patterns (Antoni A tissue) and spindle or oval cells arranged randomly within a loose matrix, often with extensive regressive changes (Antoni B tissue) [10]. Varying patterns of differentiation, such as cartilage, bone, squamous epithelium with keratinization, epithelial/glandular components, and rhabdomyoblastic features have been reported [4,107,200]. Rare variants, as malignant melanotic schwannomas have been seen in dogs [108]. Immunohistchemical studies have shown that tumor cells in schwannomas (neurinomas) were positive for S-100 antigen, while neurofibroma cells were negative [107]. A recent report suggests that expression of a point mutation of the neu oncogene could be a useful diagnostic genetic marker in MPNSTs [198].

MPNSTs most commonly involve mid to low cervical and/or rostral thoracic nerve roots, especially ventral roots [86,109], or more peripherally-located single nerves in which the tumor may advance distally or proximally. Dorsal root involvement has also been noted and may be associated with ill-defined cervical pain [110]. MPNSTs less commonly affect thoracolumbar and lumbosacral roots [88,111,200]. Tumors frequently involve nerves of the brachial plexus, often appearing as bulbous or fusiform thickenings of one or more nerves [4], and are capable of spreading to other nerves once they advance to the area of the common brachial plexus bundle [85,86,88]. The tumors typically result in slow, progressive unilateral thoracic limb lameness and muscle atrophy, often involving the infraspinatus and supraspinatus muscles. Affected animals may have a unilateral Horner's syndrome, there may be pain on leg movement or axillary pain on palpation, a palpable axillary mass may be found, and the animal may be licking or chewing at the foot or carpus of the affected limb [87,88,109]. It should be noted that dogs might present with acute onset of signs associated with spinal cord compression without showing any forelimb signs [87]. Tumors at the level of the spinal nerve roots are usually those involved with intradural-extramedullary spinal cord compression, although the more peripherally-located tumors can also sometimes invade the vertebral canal from without [88]. Wright reported that all 9 brachial plexus tumors in her study involved the spinal cord [86], while other have observed a lower incidence [109]. Bradley and colleagues reported 10 of 15 cases were myelographically positive for an intramedullary-extramedullary lesion [88]. In one study, pelvic limb signs were not seen in 50% of dogs with cervical MPNSTs with evidence of intradural extramedullary involvement, suggesting slow rate of growth and spinal cord compensation [88]. In contrast, in the same study, MPNSTs found in the thoracolumbar region were always intradural and all produced cord compression and or invasion of the cord parenchyma [88]. Of the cranial nerves, MPNSTs commonly involve the trigeminal nerve producing signs of unilateral trigeminal nerve dysfunction (e.g., unilateral temporalis and masseter muscle atrophy) [112]. Brain stem compression from a neurofibroma thought to be of cranial nerve origin, and from a trigeminal neurofibrosarcoma/schwannoma, has been reported in dogs [113,180]. An intrathoracic MPNST believed to originate from ventral nerve roots has been identified in a dog [187]. A large MPNST was detected in the ventral cervical region of an eight year old Bernese mountain dog, originating from the right vagosympathetic trunk [197]. Clinical findings included Horner's syndrome, ipsilateral laryngeal hemiplegia, coughing, gagging, respiratory distress and vomiting. Note that local vertebral erosion is occasionally reported in dogs with MPNSTs [86].
Peripheral nerve sheath tumors are rare in cats but there have been reports of tumors producing spinal cord compression at

T4 and T12-L1 vertebral levels [4,19]. Vertebral body erosion occurred in one report [4]. In a recent report, a soft tissue MPNST that invaded the occipital and temporal bones of the skull was reported in a 9 year old cat. The tumor was diffusely positive for S-100 protein and scattered cells stained intensely for GFAP.

Other tumor types may also involve peripheral nerves. A giant cell sarcoma was reported in one dog with a suspected cervical MPNST, along with local vertebral erosion [86]. Two sarcomas and a malignant tumor of the apocrine sweat glands extending into the brachial plexus were reported in dogs [109]. Peripheral tumors of neuronal origin, such as ganglioneuromas and their more undifferentiated counterparts, ganglioneuroblastomas, resulting in neurological signs, appear to be extremely rare, but extradural spinal cord compression has been reported in dogs [93,94]. In one report of a ganglioneuroma extending into the nerve root sheaths, the tumor consisted of a diffuse population of neuronal cells with distinctive Nissl substance, round vesicular nuclei and prominent nucleoli, distributed in a background of nerve fibers and fibrous connective tissue [93]. Ganglioneuromas are thought to be derived from sympathetic ganglia [4]. Lymphosarcoma occasionally involves cranial and spinal nerves and nerve roots in dogs and cats, and may extend intracranially [19,89,114,138]. Myelomonocytic neoplasia of the trigeminal nerves and ganglia, resulting in dropped mandible and symmetrical atrophy of masticatory muscles, has been reported in dogs [115,116]. In these cases, neoplastic blast cells also infiltrated multiple cranial and spinal nerves. Other signs may include Horner's syndrome, loss of corneal sensation, diminished palpebral reflex, decreased sensation of the nasal mucosa, tongue paralysis, and hind limb weakness/paralysis. Various tumors of the ear canal, such as squamous cell carcinoma, ceruminous adenocarcinoma, and fibrosarcoma, as well as osteosarcoma of the skull, may involve the facial nerve or one of its branches. Neurofibromas involving the vestibulocochlear nerve are very rare. Cranial nerves may be attenuated by compression from meningiomas lying on the calvarial floor. The vagosympathetic trunk can be compressed by aortic body tumors.

Diagnosis of Tumors of the Nervous System

Diagnosis of a tumor of the nervous system is usually made using diagnostic aids which include plain-film radiography, contrast radiography (e.g., myelography), or specialized radiographic techniques, such as radionuclide imaging (scintigraphy), computerized tomography (CT), and magnetic resonance imaging (MRI). Plain-film radiography will detect evidence of bone neoplasia. Various references have been made to the use of specialized imaging, such as CT and MRI, for evaluating brain tumors (see individual tumors above). These techniques can provide important diagnostic information regarding axial origin, (e.g., extra-axial tumors: meningiomas, pituitary tumors, and intracranially invading nasal tumors; versus intra-axial tumors: including the various glial tumors, ependymoma, choroid plexus papilloma, medulloblastoma, etc.), anatomic location, shape, pattern of growth, signal intensity, edema, and enhancement characteristics of various brain tumors [7,29,117]. These criteria can be important factors in determining prognosis, outcome and therapy. MRI is considered the better method for detecting and characterizing intracranial tumors because of its superior depiction of soft tissues and relative lack of degrading artifacts [118]. While definitive diagnosis of intracranial tumors requires histopathological tissue biopsy evaluation, some indices of malignancy have been defined using MRI scans, for example, presence of edema, poor margin definition, invasion of tissues, and extension of growth across the midline [29]. Smear preparations of intracranial lesions, obtained either by computed tomography-guided stereobiopsy or from a craniotomy provide rapid and accurate intraoperative diagnosis of many primary nervous system tumors [120,121,199].

The following is a review of the myelographic characteristics associated with extradural, intradural-extramedullary, and intramedullary locations [85]: extradural lesions are located outside the dura mater and result in attenuation of the dural tube and spinal cord. Confirmation of an extradural lesion is made when the dye column is deflected away from the vertebral canal resulting in a widened epidural space. Intradural-extramedullary lesions are located in the subarachnoid space. A mass in this location acts as a wedge displacing the dura mater to the bony vertebral canal and the spinal cord to the contralateral vertebral canal. A characteristic cup or golf tee appearance is seen as the contrast material abuts the cranial and caudal margins of the tumor. In contrast, intramedullary tumors displace spinal cord substance from within, resulting in a circumferential enlargement of the spinal cord and accompanying attenuation of contrast material in the subarachnoid space around the tumor.

An evaluation of radiographic, myelographic and CT images has been reported in 16 dogs with histologically diagnosed vertebral or spinal cord neoplasia [119]. Radiographs were compared with CT images to evaluate vertebral bone changes (bone production, lysis or both), and myelographic and CT images were evaluated to classify lesions into extradural, intradural-extramedullary or intramedullary sites. Histologically, 7 lesions were vertebral tumors and were classified as extradural lesions; 10 lesions were spinal cord tumors of which 8 were classified as intradural-extramedullary and 2 as intramedullary. This study suggested that when evaluating extradural lesions, the amount of bone change was better visualized using CT than survey radiographs, and that myelography was better than CT for classifying spinal cord lesions. In another imaging study, twenty-one dogs with confirmed tumors of the spinal cord or paraspinal tissues were evaluated with MRI scans [94]. Bone infiltration was correctly assessed in all but one dog, and the anatomical locations (especially using sagittal T2-weighted images) were accurately determined in all dogs; however, localization of tumors in the intradural-extramedullary compartment was not always possible (in 3 of 9 dogs, the tumors were thought to be intramedullary). Transverse T1-weighted images pre and post Gd-DTPA administration were considered helpful for

additional localization and definition of tumor extension. The marked, uniform contrast enhancement helped distinguish the intradural component of MPNSTs from the spinal cord. Myelographic interpretation of intramedullary spinal cord metastasis may be difficult and intramedullary tumors must be differentiated from spinal cord edema or hemorrhage [14]. Classically, with intramedullary masses, there is widening of the spinal cord shadow and tapering and attenuation of the contrast columns in both lateral and ventrodorsal views.
Diagnosis of peripheral nerve tumors can be facilitated using electrodiagnostic techniques (electromyography, nerve conduction velocity determinations) in conjunction with myelography and imaging techniques, including CT, MRI, and ultrasonography. Myelographic studies are reportedly often negative with cervical MPNSTs [88], in which case, exploration of the brachial plexus can be useful to examine the color, size and texture of the nerve trunks, in conjunction with fascicular or nerve trunk biopsy. In a report of MPNST in 10 dogs involving the trigeminal nerve [112], CT imaging revealed an enlarged foramen and distorted rostral petrous temporal bone in one case, while MRI scans identified the lesion accurately in seven cases. Ultrasonographically and CT studies were used to define and facilitate percutaneous biopsy of a lumbosacral plexus nerve sheath tumor in a 10 year old dog [194].

Analysis of CSF from 77 dogs with primary brain tumors (including astrocytomas, choroid plexus papillomas, ependymomas, meningiomas, and oligodendrogliomas), revealed a moderately increased total protein content (e.g., 30 to 70 mg/dl), a moderate increase in total white cell count (usually mononuclear pleocytosis and typically < 50 cells/ul), and an elevated CSF pressure (e.g., from 180 to 250 mm of CSF) [33]. In this study, the CSF associated with meningiomas was unique in having a WBC count greater than 50 cells/ul and a WBC differential count greater than 50% polymorphonuclear (PMN) cells, which correlated with necrosis or PMN cell infiltration of the tumors. CSF protein was highest in dogs with choroid plexus papilloma (e.g., approximately 150 mg/dl) and CSF pressure was highest in dogs with ependymomas and choroid plexus papillomas (e.g., approximately 250 mm of CSF). While this and other studies [90] point to the low frequency of tumor cells in CSF from animals with brain or spinal cord neoplasia, malignant cells have been reported in dogs and cats with intracranial and spinal cord (extradural and intramedullary) lymphosarcomas [14,15,79,89] and in cats with oligodendrogliomas [195]. An intense mixed pleocytosis with numerous epithelial-like round, neoplastic cells were noted in a dog with meningeal carinomatosis [18]. A CSF study of spinal lymphosarcoma in 23 cats revealed a nonspecific mixed pleocytosis (mean of 140 cells/ul) with elevated protein content (mean of 140 mg/dl). Interestingly, several cats had an increased neutrophilic population in association with hemorrhage and necrosis of the infiltrating tumor and adjacent spinal cord. An increase in CSF protein has been found in animals with intravascular lymphoma (malignant angioendotheliomatosis).

Prognosis and Treatment

In general, prognosis of animals with tumors of the nervous system is guarded to poor, but will depend on tumor location, surgical accessibility, rate of tumor growth, and degree of damage to the nervous tissue. Based on more accurate localization and identification of brain tumors using sophisticated imaging techniques, such as CT and MRI, management of brain tumors has tended to evolve around surgical resection, radiation therapy, and chemotherapy. Identification and characterization of tumors from tissue biopsies using stereotactic-guided biopsy devices should prove to be very beneficial in establishing therapeutic modalities [120,121,199], since at present, many dogs with brain tumors are irradiated without histopathological diagnosis or cytoreductive surgery prior to irradiation [122]. While comprehensive data on survival following definitive treatment for many tumor types and locations are lacking at this time, it has been stated that cerebral tumors (including meningiomas and ependymomas) without brainstem signs carry the best prognosis, especially for cats [123,139]. Factors that have been shown to improve prognosis include a solitary site of involvement, mild-to-moderate neurologic signs and normal CSF findings or albuminocytologic dissociation [20].

Several studies have shown that radiation therapy appears to significantly extend survival for a variety of intracranial tumors [122,124-126,191,218,219], and if surgery is performed, postoperative radiation therapy appears to further extend survival times in dogs with brain masses. Radiation therapy is particularly useful for inoperable tumors, and may be preferable to surgical resection in dogs if the mass appears infiltrative [122]. Protocols have been described using both hyperfractionated and hypofractionated doses, generally with a maximum total dose approaching 50 Gy [125,126,218]. Median survival times for dogs treated with radiotherapy alone ranges between 11 and 23 months, and although some studies have suggested a slight difference in survival time between those dogs with intraaxial vs extraaxial tumors, others have not [,218,220-222]. For meningiomas, there is some evidence that surgery and radiation therapy combined provide longer median survival times than radiation therapy alone. In one study of 31 dogs with meningiomas treated either with radiation therapy alone or radiation therapy following surgical resection, those dogs treated with radiation therapy alone survived a median of 7 months, as opposed to a median of 16.5 months for dogs treated with surgery followed by radiation therapy. However, the same findings have not been shown with gliomas. One study involving 30 dogs showed no significant difference between dogs treated with radiation therapy alone or radiation therapy following surgical excision, with median survival times of 8.5 and 10 months respectively for the two groups. Pituitary tumors have also been shown to respond well to radiation therapy alone, with median survival times of 743 days reported in one study of 6 dogs [223].

Surgery is considered the primary therapeutic modality for meningioma in dogs [126,128,129]. In a report of meningiomas

in dogs and cats treated by surgery alone, mean survival times were 198 and 485 days, respectively, with 1 year survival rates of 30% for dogs and 50% for cats [129]. Longer survival times can be anticipated with addition of irradiation [28,130] and/or cytotoxic drugs. Surgical fenestration and hematoma removal were effective in treating intracranial intra-arachnoid cysts and intracystic hemorrhage in 2 adult dogs, although the cyst persisted in 1 dog [203]. Gene therapy may become an important future treatment modality [131]. Endocrine therapy may have a role in the treatment of unresectable or recurrent meningiomas in dogs and cats [176].

Long-term control of brain tumors using cytotoxic chemotherapy alone is poor [126,127], and symptomatic medical therapy, such as use of antiinflammatory doses of corticosteroids and/or anticonvulsants, is palliative at best. Corticosteroids may ameliorate signs by reducing edema around the tumor and may produce temporary regression of lymphoid and reticulohistiocytic tumors.

Most extradural spinal tumors are either primary bone tumors (removal of which often results in decreased spinal stability, subluxation, or pathological fractures) or metastatic tumors, with possible sites elsewhere. Post-surgical survival times were low in one study of malignant extradural tumors in dogs (including osteosarcoma, plasma cell tumor, and metastatic endocrine cell tumor) [98]. A recent study of vertebral tumors (primary or metastatic osteosarcoma or fibrosarcoma) in 20 dogs supports the overall guarded prognosis for dogs with vertebral neoplasia [132]. These dogs were treated with combinations of surgery, radiation, and chemotherapy. All dogs died due to their disease, 15 died due to local failure, and five died due to nonvertebral metastasis. Overall median survival time was 135 days, with a range of 15 to 600 days. Postoperative neurological status was the only factor that had a significant influence on outcome. It was stated that better combinations of surgery, chemotherapy, and radiation therapy remain to be defined for these tumors. Note that tumor induction can be a rare late effect of radiation therapy of spinal tumors. In one report, lumbar vertebral osteosarcoma was identified more than 5 years following cytoreductive surgery and Cobalt 60 teletherapy in a Rottweiler diagnosed with an intradural extramedullary spinal cord tumor [207]. Modalities recommended for treating cats with spinal lymphosarcoma include surgical cytoreduction, focal radiotherapy (see radiation therapy), and systemic chemotherapy, including L-asparaginase, vincristine, and prednisone [89]. Long-term results were poor. In another study of spinal lymphoma in 21 cats [96], the majority of those necropsied having multicentric lymphoma, 9 cats were treated with chemotherapy alone. The complete remission rate was 50% in 6 cats given cyclophosphamide, vincristine, and prednisone. The median duration of complete remission was 14 weeks. Complete remissions were not observed in 3 cats given only corticosteroids. A single cat treated by laminectomy and postoperative chemotherapy had a prolonged remission (62 weeks). In another study, survival times for dogs with spinal lymphomas and myxomas-myxosarcomas ranged from 560 to 1080 days after surgical excision, although some dogs received post-surgical radiotherapy and chemotherapy [98]. An extradural ganglioneuroma was successfully treated with laminecetomy and surgical resection, although tumor recurrence occurred after 12 months [93].

While a number of intradural-extramedullary tumors (e.g., meningiomas and lipomas) may be successfully removed at surgery and with long post-surgery survival [98], prognosis for animals with MPNSTs is generally poor since only a small percentage of the tumors in this location are completely resectable and their rate of recurrence is high [87,88,101]. Another complication is metastasis, often to the lungs. Intradural-extramedullary tumors that involve spinal cord segments of an intumescence or are ventrally located or invade adjacent neural parenchyma also have a poor prognosis [100]. Early diagnosis of MPNSTs may result in a greater degree of success. Mean survival of 180 days was reported in one study following MPNST surgical resection [98].

Intramedullary masses are generally not surgically resectable. However, successful removal of a thoracolumbar intramedullary ependymoma, and a tumor with characteristics of a nephroblastoma, by exploratory laminectomy followed by durotomy and myelotomy, has been reported [133]. Excision also resulted in a favorable outcome in a 9 year old dog with an intramedullary spinal cord hamartoma [201]. Prognosis for dogs with intramedullary spinal cord metastasis (most frequently associated with hemangiosarcoma and lymphosarcoma) is poor due to the frequent presence of disseminated disease, although temporary response to corticosteroid therapy may be achieved [14].

Peripheral nerve and nerve root tumors can be resected successfully [85,134,200], but it is sometimes necessary to remove the affected nerve and nerve root. Resection, with anastomosis of the nerve, is possible if the tumor is not too large. Recurrences are common following resection of peripherally-located tumors, and in one report, the average time to recurrence was 5 months [88]. Complete amputation of the limb may be required if more than one root is involved, as is commonly found, or if atrophy of all muscle groups is extreme (as may occur with a tumor involving multiple nerves of the brachial plexus) [87,88,101]. In one report of dogs with MPNST involving the trigeminal nerve, surgery was performed for biopsy and lesion removal in three cases [112]. Cases not treated had a progressive course eventually resulting in euthanasia or death (with survival times ranging from five to 21 months). Of the cases treated surgically, one case had no disease progression 27 months after surgery.

Skeletal Muscle Tumors

Skeletal muscle tumors are infrequently reported in dogs or cats. Those involving the limbs may result in focal swellings and lameness. Primary tumors such as rhabdomyomas or rhabdomyosarcomas appear to be rarely seen [190,206], while primary skeletal muscle lymphomas and vascular hamartomas are reported only sporadically [140,141]. Skeletal muscle rhabdomyosarcomas can be highly malignant tumors with a propensity for aggressive local invasiveness and metastasis and carry a very guarded prognosis [207]. Microscopic findings include non-cohesive, round/oval cells with hyperchromatic nuclei and strongly eosinophilic cytoplasm, and considerable mitotic activity. Interestingly, the majority of these tumors occur in tissues other than skeletal muscle. An invasive intracranial juvenile parameningeal rhabdomyosarcoma was reported in a 23 month old dog causing unilateral denervation atrophy of masticatory muscles [189]. There have been several reports of tumors metastasizing to skeletal muscles in dogs and cats, including malignant histiocytosis, epitheliotropic T-cell lymphosarcoma, and acute myelomonocytic leukemia [142-145]. In my experience, metastatic lymphosarcoma in canine skeletal muscle is relatively common. In some instances, there may be spread of tumors into muscle from surrounding tissues, such as periosteal sarcomas [146]. Imaging techniques (e.g., sonography) may suggest a diagnosis of skeletal muscle neoplasia [147], and confirmation may be made using cytopathology from surgical biopsy . Focal masses may be surgically resected and removed. Prognosis is guarded, even with chemotherapy and/or radiation therapy.

Paraneoplastic Disorders

Paraneoplastic syndromes of the nervous system represent nonmetastatic complications of cancer. These "remote" effects are unrelated to metabolic or nutritional disorders, infection, stroke, or complications of therapy (e.g., chemotherapy), and are believed to be immunologically mediated [148-150]. The syndromes appear to be the result of molecular mimicry in which an immune repsonse against a tumor antigen cross-reacts with a similar antigen expressed by neural tissues (usually neurons), although the exact pathogenesis remains unclear [151]. Several of these syndromes are characterized by presence of tumor-specific autoantibodies (termed anti-Yo, Hu, Ri) in CSF and serum [151] (the autoantibodies, which are predominantly IgG, are believed to be produced in the CNS [149]). For example, high titers of anti-Hu antibody occur in patients with paraneoplastic encephalomyelitis and subacute sensory neuropathy (in association with small cell lung cancers, neuroblastomas, and medulloblastomas); anti-Yo antibodies occur in patients with paraneoplastic cerebellar degeneration (in association with ovarian cancer, breast cancer, small cell lung cancer, and Hodgkin's disease); and anti-Ri antibodies are seen in patients with paraneoplastic opsoclonus-myoclonus (in association with neuroblastoma, and cancers of breast, gynocologic, or small cell lung origin). In people, these syndromes may precede tumor diagnosis by weeks, months, or even years and many are good diagnostic and prognostic indicators.

Paraneoplastic syndromes affecting the nervous system in people include those involving the brain and cranial nerves, the spinal cord and dorsal root ganglia, the peripheral nerves, and the neuromuscular junction and muscle. While paraneoplastic disorders have become increasingly common in people with malignancies as therapy becomes more effective and the patients live longer [153], their overall incidence remains low, ranging from 1 to 7% of cancer patients [154,155]. However, the incidence varies with tumor type, e.g., it may be 4 to 5% in patients with breast cancer and up to 16% of patients with small cell lung cancer [156]. CNS paraneoplastic syndromes recognized in people are rarely documented in animals with malignancies, although the veterinary literature probably does not reflect the real incidence of this paraneoplastic disorder. A paraneoplastic syndrome involving the spinal cord has been described in an 8 year old, male German Shepherd dog [157]. The dog had a history of acute pelvic limb paralysis. Over a 10-day period, there was progressive loss of motor function, conscious proprioceptive deficits, and loss of superficial and deep pain sensation over the trunk and pelvic limbs. Schiff-Sherrington-like hyperextension developed as a late sign in the thoracic limbs. Necropsy revealed a hepatocellular carcinoma with metastasis to the lungs, liver, spleen, and lymph nodes. A severe necrotizing myelopathy was present throughout the thoracic spinal cord affecting gray and white matter - changes included spongy degeneration, gliosis, demyelination, axonal swelling and degeneration, and neuronal necrosis. In another report, a spectrum of neurological abnormalities in a 17 month old male Poodle was attributed to hyperviscosity syndrome secondary to macroglobulinemia-associated lymphocytic leukemia [158].

Paraneoplastic disorders of the neuromuscular junction in people are most commonly associated with Lambert-Eaton myasthenic syndrome (LEMS) in which autoantibodies act against neuronal voltage-gated calcium channels and subsequent decrease in acetylcholine release at neuromuscular junctions and autonomic nerve synapses [159]. Approximately 60% of patients with LEMS have small cell lung cancer [155]. To my knowledge, LEMS has not been reported in dogs or cats. Paraneoplastic myasthenia gravis (MG), a postsynaptic neuromuscular disorder caused by antibodies against the nicotinic acetylcholine receptor is found in approximately 50% of human patients with thymomas [160-162]. Patients with thymoma-associated MG may also produce autoantibodies to a variety of neuromuscular antigens, including the muscle protein titin, skeletal muscle calcium release channel (ryanodine receptor, RyR), and voltage-gated potassium channels [162]. Acquired MG also occurs in dogs with thymoma. In one review, the average age of animals with thymoma was 8.7 years, German shepherd dogs accounted for 28% of the cases, and there was no sex predominance [163]. Approximately 47% of these dogs had MG, 33% had non-thymic cancer (including mammary adenocarcinoma, pheochromocytoma, and pulmonary adenocarcinoma), and 20% had signs of a polymyositis. Recently, titin and RyR antibodies were identified in dogs with MG and thymoma [164].

With respect to paraneoplastic syndromes and muscle, the association between myositis (e.g., dermatomyositis and polymyositis) and malignant neoplasms has been well established in people, and the reported clinical frequency ranges from 7 to 30% [165,166]. Some forms of myositis, such as dermatomyositis, can be especially significant markers of occult malignancy in people, including ovarian and breast cancer in women, and lung and gastrointestinal cancer in men [155]. A paraneoplastic necrotizing myopathy, with little inflammation, may occur in humans in association with a variety of tumors, including gastrointestinal adenocarcinoma, transitional cell carcinoma, prostatic carcinoma, and non-small cell lung carcinoma [167]. Weight loss and muscle weakness may be other independent prognostic factors in human patients with underlying malignancies, with more than 50% of human cancer patients suffering from cachexia [168]. Cytokines, produced by tumors or by the immune system, may mediate this cachectic process [169]. While necrosis and low-grade myositis is seen sporadically in dogs with malignant tumors, such as bronchogenic carcinoma, myeloid leukemia, and tonsilar carcinoma [170,171], the frequency of this suspected paraneoplastic association is presently unknown. Dogs and cats with histopathologically confirmed myositis/necrotizing myopathy who fail to respond to therapy, or who relapse, may merit similar malignancy evaluation as accorded people, including chest radiography, sonography, computed tomography and magnetic resonance imaging. This vigilance may detect tumors at a more treatable stage.
Paraneoplastic changes also occur in peripheral nerves of people and are believed to occur in nerves of animals (paraneoplastic neuropathy).

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