Neoplasms in Domestic Animals:
A Review of Experimental and Spontaneous Carcinogenesis

BRUCE R. MADEWELL, V.M.D., M.S.

*Section of Clinical Oncology, Department of Veterinary Surgery,
University of California, Davis*

Clues to environmental and host factors in human oncogenesis are derived from clinical or epidemiologic studies; additional evidence is provided by animal experimentation. Induced tumors in animals are useful because of their reproducibility and predictability, allowing detailed study of specific carcinogens or carcinogenic influences. Spontaneously or naturally occurring tumors in domestic animals are of particular interest for comparative studies—these tumors occur in heterogenous outbred populations of animals closely sharing man's environment; their cause is generally unknown; many tumors occur in numbers suitable for detailed investigations; and tumors generally occur in aged animals, thus facilitating study of chronic processes associated with carcinogenesis in nature.

Observations of spontaneous and induced tumors in animals have been useful for determining mechanisms of carcinogenesis. Although the ultimate proof of the importance of an animal model for cancer requires parallelism to a human disease, it must be remembered that it is not yet possible to define precisely those changes that occur in normal cells that allow them to become neoplastic; it would seem, therefore, that all models that are definable and reproducible are worthy of study whether or not there exists an immediately evident counterpart in the human disease spectrum [1].

The purpose of this paper is to review the causes for neoplastic disease in common domesticated animals. Included are those neoplasms that occur "spontaneously" in numbers suitable for additional investigation, and for which some risk factors have been identified which may provide clues as to etiology. Also included are "induced" tumors, those requiring a recognized and defined carcinogen—systems useful because of their predictability. No claim is made as to the importance of these animal models for study of human cancer, but each model is indeed a biological enigma in itself. The models are categorized by body system.

Skin

Neoplasms of the skin and subcutaneous tissues are the most frequently recognized neoplastic disorders in domestic animals [2]. Some of the known causes of skin cancer in man are operative in animals. Prolonged and continuous exposure to sunlight is the best known etiologic factor, and a sunlight-induced-skin cancer (carcinoma) relationship has been established in several domestic species. The

sunlight-associated neoplasms in animals include squamous cell carcinoma of the pinnae and external nares in white cats [3], squamous cell carcinoma of the eye and periocular structures in white-faced cattle, notably of Hereford breed [4], carcinoma of the vulva in sheep and Ayrshire cattle [5], carcinoma of the perineum in goats [6], carcinoma of the ear and other areas poorly covered by wool in sheep [7], carcinoma of the non-pigmented glabrous skin of the ventral abdomen in dogs [8], and possibly horn carcinoma in Indian Zebu cattle [9].

A viral cause for some skin tumors is recognized in domestic animals. Species-specific infectious DNA viruses belonging to the family papovaviridae cause benign papillomas of the skin and mucous membranes in most animals. The progression of viral-induced warts to squamous cell carcinoma has been described most convincingly in rabbits [10], and evidence suggests that squamous cell carcinoma can be a sequel to papillomatosis in goats, cattle, and dogs [11–13].

Other viral-induced neoplasms of the skin and subcutaneous tissues in domestic animals include poxvirus-induced myxomas and fibromas in rabbits [14], papovavirus-induced fibromas in deer, and oncornavirus-induced sarcomas of poultry and cats [15].

Analysis of risk for skin cancer in a specific species or breed may provide insight into etiologic mechanisms. Heavily pigmented (black) dogs such as Scottish terriers are at excess risk for melanoma, but the factor(s) responsible for the increased risk is not known [16]. Similarly, Arabian horses are at excess risk for melanoma; the risk factor is not due to an inborn genetic factor, but probably due to pigment changes that take place as part of the aging process for that breed [17]. Melanosis and melanomas are sometimes recognized in young and newborn pigs, particularly Duroc-Jersey and Sinclair Miniature breeds, suggesting a congenital influence [18–20]. Cats are at low risk for melanoma of any site, but a strain of feline sarcoma virus has been isolated that induces melanomas in inoculated newborn kittens [21].

Boxer and Boston terrier dogs are at increased risk for mast cell tumors. The risk factor is unknown, but both breeds are related ancestrally to the English bulldog and English bull terrier [22]. The Kerry blue terrier is at excess risk for several benign tumors of the skin, most notably papillomas and sebaceous adenomas [16].

Blood and Blood-Forming Organs

Exposure to certain chemicals or ionizing radiation, and complex hereditary factors have been implicated as etiologic factors in the initiation of leukemia-lymphoma in man. The factors contributing to the development of most cases of human leukemia, however, are still unknown.

Studies in animal leukemia clearly implicate viruses in etiopathogenesis: RNA tumor viruses have been frequently isolated from or associated with the leukemic cells of animals as diverse as fish, snakes, birds, rodents, cats, cattle, and non-human primates [23]. One of the best studied of the natural animal neoplasms is feline leukemia, which has been demonstrated convincingly to be caused by the horizontal infection with feline leukemia virus [24,25]. The disease can be induced by virus inoculation and can be prevented by immunization [26]. Another well-studied natural animal neoplasm caused by a retrovirus is bovine leukemia. The disease is contagious. It spreads within a herd of cattle through milk, contacts, and saliva, and from herd to herd mainly by commercial exchanges. It is induced by bovine leukemia virus, a retrovirus exogenous to the bovine species, and the disease can be transmitted by the virus to cattle or sheep [27].

DNA viruses are also found among those causing leukemia-lymphoma in domestic

animals; best studied is Marek's disease, a form of leukemia in poultry involving peripheral nerve tissue, caused by virus of the herpes group [28].

In addition to viruses, hereditary factors appear to influence the risk for certain leukemias in domestic animals. For example, the boxer breed of dog has an increased risk for lymphosarcoma [29]; genetic factors influence the susceptibility of cattle to bovine leukemia virus infection [30]; and a hereditary form of lymphosarcoma controlled by an autosomal recessive gene has been described in a breeding herd of large white pigs in Great Britain [31].

With the exception of the cat, myelogenous leukemias are rarely diagnosed in any domestic animal species. Induction of myelogenous leukemia in animals by ionizing radiation is well established, however, most notably in swine and dogs receiving ^{90}Sr exposure [32,33]. These well-established experimental systems now provide useful models for study of the sequential marrow cellular and structural changes associated with leukemogenesis.

Alimentary

With the possible exception of oral neoplasms in dogs, tumors of the alimentary tract in animals occur less frequently than those in humans. Comparison of etiologic factors associated with neoplasms of the alimentary tract in animals and man is difficult because many of the ethnic, social, and environmental factors that influence risk for digestive tract neoplasms in humans are not operative in animals.

The cause for most oral-pharyngeal tumors in domestic animals is unknown. In cattle, carcinoma of the pharynx and upper alimentary tract has been reported from regions of the world where bracken fern (*Pteridium aquilinum*) grows plentifully. It is suspected that environmental carcinogens may influence the transformation of viral papillomas to carcinomas [13]. For dogs, a significant urban association has been reported for tonsillar carcinoma, suggesting that environmental carcinogens might be implicated in etiopathogenesis [34]. The simultaneous occurrence of squamous cell carcinomas of the esophagus of humans and chickens living in certain northern provinces of China has been described; food processing perhaps leading to nitrosamine formation or their precursors has been implicated as contributing to high cancer incidence [35].

Intrinsic (host) factors influence risk for oral-pharyngeal neoplasms in the dog. For squamous cell carcinoma, melanoma, and fibrosarcoma, breeds with high risk include German short-haired pointers, weimeraners, golden retrievers, boxers, and cocker spaniels, whereas breeds with low risk are beagles and dachshunds. For melanoma and fibrosarcoma, males have higher risk than females [36]. The causes(s) for breed and sex predilections has not been determined.

An unusual neoplasm develops in the esophagus of dogs in regions of the world where *Spirocerca lupi*, the esophageal worm, is enzootic. A reactive granuloma develops around the parasite, and neoplastic transformation of the inflammatory tissue occurs in some cases forming osteosarcomas and fibrosarcomas—some of which ultimately metastasize [37]. Whether the tumor develops as a result of chronic irritation, or whether the parasite elaborates a carcinogenic substance or carries an oncogenic virus has not been determined.

Stomach neoplasms are uncommon in all domestic animal species. The rarity of gastric carcinomas in animals compared to the high frequency of this tumor in man suggests that animals avoid the necessary prolonged contacts with gastric carcinogens, most likely consumed in food, or that they are inherently resistant to the carcinogenic effects of such contacts [38]. Gastric adenocarcinomas can be induced

experimentally in the dog, however, by the intragastric adminstration of nitrosamine, or by the intragastric formation of N-nitroso compounds from nitrites and amines; tumors induced are locally invasive and eventually metastasize to regional lymph nodes and distant organs [39,40].

Carcinomas involving small or large bowel are uncommon in domestic animals. A seemingly high number of intestinal carcinomas have been reported in sheep from Australia and New Zealand [41,42]. The tumors may be related to environmental factors such as aromatic amines used in orally administered vermicides, intragastric formation of N-nitroso compounds from forage, or undefined factors association with "fat-lamb" farming [43]. Intestinal carcinomas in sheep arise from the lower jejunum and ileum; the predominant sites in the dog are duodenum and colon, while in the cat, the ileum is the most common site. The causes(s) for these site predilections has not been determined.

Although the role of hereditary or pre-existing intestinal disorders as risk factors for intestinal neoplasms are well established in man, such risk factors have not been clearly defined in animals. Only one case of intestinal carcinoma arising in a colorectal polyp has been described in the dog [44].

Pancreatic neoplasms have been described in most domestic animal species. These tumors are uncommon and few risk factors have been identified. In dogs, ductular and acinar carcinomas occur more frequently in females than in males, are strongly associated with increasing age, and may be found excessively in the Airedale terrier breed [45]. For tumors of the pancreas derived from islet cells, excess numbers have been reported in the standard poodle breed [46].

The cause of most liver tumors in domestic animals is unknown. Hepatoblastoma, similar to the fetal type in man, occurs in domestic animals, particularly in lambs, but the cause of the tumor is unknown [47]. Aflatoxin, produced in food material contaminated by some strains of *Aspergillus flavus*, is a potent liver carcinogen in fish, birds, and some mammals [48], and may play a role in hepatic carcinogenesis in domestic herbivorous animals. An association between parasites and liver cancer in animals is supported by reports of bile duct carcinoma in the dog associated with clonorchiasis, and hepatocellular carcinoma in cattle associated with liver fluke infection [49,50].

The high incidence of hepatocellular carcinoma in human patients with cirrhosis and hemochromatosis is well known. The occurrence of hepatic carcinoma in association with biliary cirrhosis has also been described in cattle in which damage was caused by *Fasciola hepatica*, but no relationship could be found between cirrhosis and liver cancer in a canine study [51].

The environmental carcinogen N-nitrosodiethylamine has been found to be carcinogenic in at least 18 animal species [52]. Following experimental oral adminstration, the chemical has been used to induce hepatocellular carcinomas, cholangiomas, and squamous cell papillomas of the esophagus in the cat; hemangioendotheliomas, leiomyosarcomas, and fibrosarcomas of the liver in dogs; and several benign and malignant hepatic tumors in pigs [52]. The liver is the main target organ for carcinogenicity of this nitrosamine. Other chemicals shown to be hepatocarcinogenic for dogs by experimental studies include o-aminozotoluene, p-dimethylaminoazobenzene [53], 2-acetylaminofluorene [54], and the insecticide Aramite (2-(p-tert-butylphenoxy) isopropyl-2-chloroethyl [55]. Neoplasms of the gall bladder and bile ducts have also been induced in dogs by implantation of methylcholanthrene pellets into the gall bladder [56].

Respiratory

Host and environmental factors contribute to risk for respiratory tract neoplasms in domestic animals.

Intranasal tumors (papillary adenoma or adenocarcinomas) of the ethmoid olfactory mucosa in sheep have been observed in Europe, the United States, Africa, and Japan [57,58]. These tumors have occurred enzootically and seem to be contagious. Viral particles resembling visna-maedi virus have been detected in tumor tissue in some cases, although the role of virus in tumorigenesis is not well established [59]. Ethmoidal carcinomas have also been recognized in cattle, and enzootics have been reported from Hong Kong, Portugal, Brazil, and the Dominican Republic [60]; the cause for these enzootics has not been determined although virus is suspected.

Intranasal tumors (sarcomas and carcinomas) occur more frequently in the dog than in other domestic animal species, and account for 1–2 percent of all canine neoplasms [61]. The risk for intranasal tumors increases with age, but other risk factors have not been established [61,62]. Nasal carcinomas can be induced in the dog by inhalational exposure to soluble forms of single beta-emitting radionuclides, particularly $^{91}YCl_3$ and $^{144}CeCl_3$, and it is suspected that nasal cavity epithelium is a major target tissue for these radionuclides [63].

Annual incidence rates for naturally occurring pulmonary neoplasms in domestic animals are unknown but are probably low [64]. Risk increases with age for dog, cat, cow, and horse, and the boxer breed of dog may be at excess risk [65,66]. In sheep, pulmonary carcinoma (Jaagzietke) is an infectious disease caused by a virus and transmitted by aerosol. The early stage of disease is characterized by adenopapillo-matous transformation of the alveolar septae. Later, adenocarcinoma resembling bronchiolar-alveolar cell adenocarcinoma of man involves lungs and visceral (meta-static) sites. Type-A and type-C virus particles are consistently demonstrated in tumor tissue in advanced stages of disease [67].

Dogs have been used for experimental radiation and chemical pulmonary car-cinogenesis studies. Limited success was obtained by exposure of normal dogs to cigarette smoke or carcinogens derived from smoke; tumorigenesis was inconsistent, and induced tumors were often multicentric and randomly located [68]. Several studies, however, have shown increased numbers of lung tumors in dogs exposed to cigarette smoke when compared to controls, using either intratracheal instillation of carcinogens or inhalation methods of exposure [69–72]. In most cases, latent periods of at least two years occurred following inhalation exposure to induction of lung cancer. Inflammatory, hyperplastic, metaplastic and atypical lesions of the dog respiratory tract could be induced rapidly (five to six months), however, using moderate smoke-exposure systems (i.e., 12 cigarettes/day). The similarity of lesions observed in dogs to those observed in man suggests that the dog is a useful model for bioassay procedures for comparing the health effects of different cigarettes and cigarette-smoke compositions for long-term studies aimed at evaluating chronic lung disease and cancer [73].

Optimization of pulmonary carcinogenesis has recently been reported in dogs using sustained release implantation techniques of either chemical (3-methyl-cholanthrene) or radiation ($^{91}YCl_3$) carcinogens. Squamous cell cancers were induced at specific preselected sites, and tumors were preceded by well-defined pre-malignant changes [74].

Plutonium ($^{239}PuO_2$) is also a potent pulmonary carcinogen in dogs. Following

inhalation of average plutonium doses ranging from 100–1,500 times the maximal permissible level for man, the incidence of pulmonary neoplasia in one large beagle study was nearly 100 percent. Most of the tumors were bronchiolar-alveolar carcinomas of peripheral origin, and many developed distant metastases [75].

Another chemical pulmonary carcinogen for cats is 2-acetylaminofluorene, shown experimentally to cause lung sarcomas [76].

Skeleton

Several factors contributing to bone cancer have been recognized in different animal species. Risk factors include ionizing radiation, chemical carcinogens, viruses, pre-existing bone defects and skeletal abnormalities, and other host factors. Of domestic animal species, bone cancer occurs most frequently in the dog. The increased risk for osteogenic sarcoma of the appendicular skeleton with increasing age in large and giant breeds of dogs is well known, although the cause for this increased risk has not been determined. It has been estimated that the risk for primary bone cancer in large and giant breeds is 60 to 185 times the risk for small dogs [77]. For primary chondrosarcoma of bone large (i.e., boxer, German shepherd), but not giant breeds are at increased risk [78]; for primary hemangiosarcoma of bone, excess numbers have been reported in boxer, German shepherd, and Great Dane breeds [79].

A tendency for familial aggregation of osteogenic sarcoma in Saint Bernard dogs has been described. Analysis of pedigrees of affected dogs suggested that the presence of specific genes within family lines influences susceptibility to osteogenic sarcoma [80].

Ionizing radiation is the only external agent known to produce a diverse array of bone tumors including osteogenic sarcoma, chondrosarcoma, fibrosarcoma, and hemangiosarcoma; nearly all radionuclides that localize in bone can produce bone cancer in laboratory animals, and all mammals tested with appropriate doses of either internal or external radiation have developed bone cancer [81].

The beagle dog has been used frequently in skeletal radiation oncogenesis studies [82–84]. Tumor-inducing radionuclides include ^{226}Ra, ^{239}Pu, ^{228}Th, ^{228}Ra, ^{90}Sr, ^{224}Ra; bone surface seeking radionuclides (^{239}Pu, ^{228}Th) produce a higher proportion of osteosarcomas in trabecular regions than do bone volume seeking radionuclides (^{226}Ra, ^{228}Ra). A long latent period is necessary for the development of bone tumors in dogs after exposure to radiation.

Hemangiosarcoma involving bone (and extraskeletal sites such as lung, liver, heart) was the most comon tumor induced in beagle dogs after inhalational exposure to $^{90}SrCl_2$, $^{144}CeCl_3$, and relatively insoluble ^{90}Sr and ^{144}Ce in fused alumino-silicate particles [85].

The role of oncogenic viruses in naturally occurring or radiation-induced skeletal neoplasms in domestic animals is unknown. Type-C particles resembling those of feline leukemia or sarcoma viruses have been identified in several exostotic osteochondromatous growths in several cats, but the role of virus in disease pathogenesis is unknown [86]. Similarly, other than the induction of osteosarcoma in rabbits using beryllium oxide, little is known regarding chemical induction of bone tumors in domestic animals [81].

Certain syndromes of skeletal maldevelopment or disease have been identified in association with primary bone tumors in animals. The transformation of osteochrondroma to osteo- or chondrosarcoma has been reported in the dog and cat [87]; bone sarcomas associated with bone infarctions have been described in the dog [88]; and

osteosarcoma associated with long-standing nutritional osteodystrophy has been described in three cats [89].

An association between foreign bodies such as metallic implants, bullets, shrapnel, and bone sarcoma has been recognized [90]. Similarly, an association between metallic implant devices and osteogenic sarcoma has been described in the dog; many of the tumors were diaphyseal in origin, an unusual site for primary bone cancer in the dog, and all implant devices had been in place for six months to 11 years before neoplasia was recognized [91,92].

Endocrine

Mechanisms for etiopathogenesis of endocrine gland neoplasms may be studied in animals using naturally occurring or induced tumors.

Radiation exposure of the thyroid increases the frequency of neoplasms in experimental animals and man, but ionizing radiation has not been implicated as a cause of naturally occurring thyroid tumors in domestic animals [93,94]. Prolonged thyroid stimulating hormone (TSH) stimulation of the thyroid can produce malignancies; this has been demonstrated in animals given goitrogenic drugs and in experimental animals subjected to prolonged iodine deficiency [95]. Several reports from regions of the world where goiter is endemic have suggested that thyroid hyperplasia is a precursor of canine thyroid neoplasms [96,97], but convincing experimental induction of thyroid neoplasms in iodine-deficient dogs is lacking [98].

The role of thyroiditis in the origin of thyroid cancer, suggested by the association of thyroid tumors in human patients with Hashimoto's thyroiditis and Graves' disease is unknown. Long-term follow-up of colonies of experimental beagles with high incidence rates of spontaneous thyroiditis may clarify this relationship [93,99].

The simultaneous occurrence of thyroid neoplasms with other primary tumors of endocrine glands has been recognized in animals and man; in one retrospective study of 144 thyroid neoplasms in dogs, 45 had other primary tumors [93]. Other studies show the association of thyroid (medullary) carcinoma in bulls with pheochromocytoma, and thyroid carcinoma in dogs with chemodectoma [93,100,101].

In dogs, the risk for thyroid cancer rises sharply with age; no sex predilection has been reported, but boxer, beagle, and golden retriever breeds are reported to have increased risk [93]. Thyroid C-cell adenomas derived from the ultimobranchial body occur frequently in cattle; approximately 30 percent of aged bulls are reported to have ultimobranchial thyroid tumors, many of which are biologically active [102,103].

Spontaneous focal hyperplastic and neoplastic changes of secretory (ACTH/MSH) cells occur frequently in both the pars distalis and pars intermedia (pituitary) of old dogs of different breeds; boxer and Boston terrier dogs are at high risk for development of tumors of the pars distalis, while tumors of the pars intermedia appear in all breeds of dogs with equal frequency [104]. The cause for these tumors is unknown; many are functionally active and contribute to endocrine diseases including Cushing's disease, anovulation, disturbances of thyroid function, and possibly mammary tumors [105].

Other than increasing age in dogs, cattle, sheep, and goats, few risk factors associated with neoplasms of the adrenal cortex have been identified in domestic animals, The simultaneous occurrence of adrenal medullary tumors (pheochromocytomas) with ultimobranchial tumors of the thyroid has been mentioned. Also an association between neurofibromatosis and cortical and medullary tumors of the adrenal has been described in cattle [106,107]. Another tumor derived from para-

ganglia, the chemodectoma, occurs most commonly in brachycephalic breeds of dogs over six years of age [108]; an association between hypoxia and enlargement of the carotid body has been described in animals, but its relationship to neoplasia is unknown [109].

Urogenital

Few risk factors associated with renal neoplasms have been described in animals. For dogs, excess risk has been identified for males with increasing age; familial (breed) predisposition has not been recognized, suggesting that genetic determinants (if any) are not conspicuous [110]. An unusually high number of embryonal nephromas have been reported from necropsy and abbatoir surveys of swine. In some areas of the United States, this is the most common tumor of swine, although the causes(s) has not been determined [111].

Bracken fern (*Pteridium aquilinum*) has been shown to be carcinogenic in several species including cattle, mice, rats, guinea pigs, and quail [112]. An association between grazing of cattle on forage in regions of the world where bracken fern grows plentifully, a syndrome known as chronic enzootic hematuria, and cancer of the urinary bladder has been described; tumors reported included an array of benign and malignant epithelial and mesenchymal tumors, although transitional cell carcinomas, hemangiomas, and papillomas predominated [113–115]. No virus has consistently been isolated from the field cases of bladder neoplasms in cattle, although bovine papillomavirus has occasionally been recognized in association with bladder tumors, and fibroma-like lesions can be induced with bovine papillomavirus when injected into submucosa of the urinary bladder of cows [116,117].

In dogs, bladder neoplasms occur more commonly in females than males, and Scottish terriers, Shetland sheepdogs, beagles, and collies are reported to be at excess risk [118]. Other risk factors for naturally occurring bladder tumors in dogs are unknown, although an association between cyclophosphamide-induced hemorrhagic cystitis and transitional cell carcinoma has been described [119].

The dog has served as a model for bladder chemical carcinogenesis studies, particularly using aromatic amines [120]. Early studies in dogs with 2-naphthylamine showed that feeding this compound produced bladder tumors, that bladder cancer would not appear if the urine was diverted, but instead renal pelvic and ureteral tumors would develop [121]. Similar studies have shown that 4-aminobiphenyl, its derivatives, para-aminobiphenyl, and para-nitrobiphenyl are bladder carcinogens for dogs [122,123].

The abdominal or partially descended ectopic testis has an increased risk for cancer in the dog, particularly sertoli cell tumors and seminomas, and dogs with testicular tumors associated with cryptorchidism are younger than those with tumors in descended testes. Dogs with an inguinal hernia also have a higher risk for testicular cancer than normal dogs [124]. Several breeds of dogs have been identified with high risk for different tumor cell types; the multiplicity of breeds suggests that other factors, in addition to heredity, play a role in etiology [124–126].

Ovarian tumors have been described in most domestic animal species, but most often in the dog. For dogs, a striking increase in risk by age for the occurrence of epithelial tumors in contrast to granulosa-theca cell tumors was reported. Breeds of dogs with excess risk include the pointer for epithelial ovarian tumors and the English bulldog for granulosa-theca cell tumors [127]. A relatively high proportion of ovarian tumors of the granulosa-theca cell type are also described in horses [16]; most of the tumors are functional but their cause is unknown [128].

An unusual neoplasm of the external genitalia occurs in dogs; the transmissible venereal tumor is a naturally occurring neoplastic disease characterized by a high rate of spontaneous remission. The tumor affects both sexes and is transmitted by coitus. Experimentally, the transmissible venereal tumor can be transmitted by the transplantation of living cells and is probably a naturally occurring allograft; the tumor is antigenic in the dog and tumor regression is followed by transplantation immunity [129]. The concept of the tumor as a neoplastic allograft is supported by demonstration of the absence of host cell isoantigens on the tumor cells, by its peculiar karyotype, and by the failure of early attempts to transmit the tumor as a cell-free filtrate [130].

Spontaneous and induced tumors of the mammary glands in dogs and cats occur in sufficient numbers to provide useful models for etiological studies. At least 12 breeds of dogs were reported in one study to have significantly high risk for all mammary tumor types and the hunting breeds were disproportionately represented in the high risk breeds [131]. The risk for benign and malignant canine mammary tumors increased with age until 10 years. Neutered bitches had only one-third the risk observed in non-neutered bitches [131]. The importance of reproductive endocrinology in mammary neoplasia has been studied in the dog and cat; bitches neutered before any estrous cycles had significantly lower risk than intact bitches, and this sparing effect was operative if neutering occurred before 2.5 years of age [132]. A similar sparing effect on mammary cancer risk was associated with early ovariectomy in the cat [2].

Specific hormones such as estrogen and prolactin have been incriminated in the genesis of mammary cancer in the bitch, but experimental proof of their role is lacking [105]. In one study, canine mammary tumorigenesis was associated with increased secretory activity of pituitary growth hormone cells, and depressed secretory activity of follicle-stimulating hormone-, luteinizing hormone-, and thyrotrophin-producing cells. Signs of inhibition of ovulation and thyroid function were also observed, and there were concomitant hyperplastic and neoplastic changes of the thyroid and adrenal cortex. These findings suggest that endocrine imbalance mainly of pituitary origin may be involved in spontaneous canine mammary neoplasia [105].

Progesterone and several synthetic progestagens have been used experimentally to induce mammary hyperplasia and tumor development in experimental beagle dogs [133–135]; their effect may be related to the high rate of mammary proliferation induced by these compounds, or to their effects on pituitary hormone secretion [105].

In addition to neoplasms, many hyperplastic, dysplastic, and inflammatory lesions have been recognized in canine mammary glands as naturally occurring lesions, or resulting from administration of progestational agents [136,137]. The biological significance of the non-neoplastic lesions is unknown, but it is tempting to speculate that some of these lesions are pre-neoplastic.

Mammary adenocarcinomas have also been induced in cats using progestagens [138]. A viral cause for feline mammary cancer has been suspected but not confirmed; type-C virus particles resembling feline leukemia virus and type-A particles similar to those found in some mouse mammary tumors have been identified in tumor tissue by immunofluorescence and electron microscopy. The etiological role of these viruses has not been confirmed by transmission studies [139].

Neurological

Breed and species predilections for spontaneous tumors of the nervous system in

domestic animals offer few clues as to etiology. Cats appear to be predisposed to meningiomas and cattle to nerve sheath tumors. Gliomas are more common among brachycephalic breeds of dogs, especially boxers, English bulldogs, and Boston terriers [140]. Naturally occurring neoplasms of the nervous system affect middle-to-old-age animals in all species.

Several types of viruses have been used experimentally to induce tumors of the central nervous system in domestic animals. These viral carcinogenesis studies are reviewed in detail elsewhere [141–144]. Perhaps best studied is the avian sarcoma virus, which has been shown experimentally to be neuro-oncogenic for dogs, cats, and pigs. A variety of tumors have been induced with avian sarcoma virus, including astrocytomas, spongioblastomas, ependymomas, meningiomas, and sarcomas [141,142]. The bovine papillomavirus, a DNA containing virus, has also been used experimentally to induce intra-cranial fibromas and fibrosarcomas, and meningeal fibromas in calves [145].

SUMMARY

Clues to environmental or host factors in human oncogenesis are derived from clinical or epidemiologic studies; additional evidence has been provided by animal experimentation. There are advantages and limitations to study of cancer in domestic animals. Spontaneous tumors arise in heterogenous outbred animals, and their cause is generally unknown; study of these tumors provides some clues to environmental and host factors in oncogenesis, such as interactions between physical agents and specific genetic abnormalities. Induced tumors in animals are useful because of their reproducibility and predictability, allowing detailed study of specific carcinogens or carcinogenic influences.

Physical carcinogens in domestic animals include ultraviolet and ionizing radiation. Ultraviolet radiation is a cause for skin cancer in several species, and more deeply penetrating ionizing radiation produces a variety of skeletal, lung, and hematopoietic neoplasms, most notably in the dog. Chemical carcinogens affect the urinary bladder, respiratory, and alimentary tracts. Viral oncogenesis has been studied in detail in cats and cattle with retrovirus infections, and bovine papilloma virus infection in heterospecies allows study of viral-induced solid tumors.

Host factors place individual species or breeds of animals at very high or low risk for certain neoplasms. For example, the boxer breed of dog is at high risk for skin, thyroid, and lymphatic neoplasms, although the specific factor(s) influencing risk in this breed is unknown. The influence of gene or chromosomal aberrations or immunodeficiency on cancer risk may be further elucidated by study of specific breed predilections.

The use of large (domestic) animals for carcinogenesis studies is fostered by their size and temperament, allowing relatively easy handling and procurement of large samples of blood or tissue for study. In addition, many pet animals (dogs, cats, horses) have long life spans, and tumors occurring in aged animals may accurately reflect those chronic processes associated with carcinogenesis in nature.

REFERENCES

1. Huseby RA: Utility and failure of models in oncology. Fed Proc 28:211–215, 1969
2. Dorn CR, Taylor DON, Schneider R, et al: Survey of animal neoplasms in Alameda and Contra Costa Counties, California II. Cancer morbidity in dogs and cats from Alameda County. J Natl Cancer Inst 40:307–318, 1968
3. Dorn CR, Taylor DON, Schneider R: Sunlight exposure and the risk of developing cutaneous and oral squamous cell carcinomas in white cats. J Natl Cancer Inst 46:1073–1078, 1971
4. Anderson DE, Lush JL, Chambers D: Studies on bovine ocular squamous carcinoma ("Cancer eye")

II. Relationship between eyelid pigmentation and occurrence of cancer eye lesions. J Anim Sci 16:739–746, 1957

5. Burdin ML: Squamous cell carcinoma of the vulva of cattle in Kenya. Res Vet Sci 5:497–505, 1964

6. Ramadan RO: Squamous cell carcinoma of the perineum of the goat. Br Vet J 131:347–350, 1975

7. Ladds PW, Entwistle KW: Observations of squamous cell carcinomas of sheep in Queensland, Australia. Br J Cancer 35:110–114, 1977

8. Hargis AM, Thomassen RW, Phemister RD: Chronic dermatosis and cutaneous squamous cell carcinoma in the beagle dog. Vet Pathol 14:218–228, 1977

9. Naik SN, Balakrishnan CR, Randelia HP: Epidemiology of horn cancer in Indian Zebu cattle: Breed incidence. Br Vet J 125:222–230, 1969

10. Shope RE, Hurst EW: Infectious papillomatosis of rabbits. J Exp Med 58:607–624, 1933

11. Moulton JE: Cutaneous papillomas on the udders of milk goats. North Am Vet 35:29–33, 1954

12. Watrach AM, Small E, Case MT: Canine papilloma: Progression of oral papilloma to carcinoma. J Natl Cancer Inst 45:915–920, 1970

13. Jarrett WFH: High incidence of alimentary carcinoma in cattle associated with an environmental carcinogen and viral papillomas. In Antiviral Mechanisms in the Control of Neoplasia. Edited by P Chandra. New York, Plenum Press, 1978, pp 39–45

14. Fenner F, Ratcliffe FN: Myxomatosis. Cambridge, Cambridge University Press, 1965

15. Gross L: Oncogenic Viruses. Second Edition. Oxford, Pergamon Press, 1970

16. Priester WA: Epidemiology. In Veterinary Cancer Medicine, Edited by GH Theilen, BR Madewell. Philadelphia, Lea and Febiger, 1979

17. Lerner AB, Cage GW: Melanomas in horses. Yale J Biol Med 46:646–649; 1973

18. Manning PJ, Millikan LE, Cox VS, et al: Congenital cutaneous and visceral melanomas of Sinclair Miniature Swine: three case reports. J Natl Cancer Inst 52:1559–1563, 1974

19. Hjerpe CA, Theilen GH: Malignant melanomas in porcine littermates. J Am Vet Med Assoc 144:1129–1131, 1964

20. Millikan ME, Hook RR, Manning PJ: Gross and ultrastructural studies in a new melanoma model: The Sinclair Swine. Yale J Biol Med 46:631–645, 1973

21. McCullough B, Schaller J, Shadduck JA, et al: Induction of malignant melanomas associated with fibrosarcoma in gnotobiotic cats inoculated with Gardner-feline fibrosarcoma. J Natl Cancer Inst 48:1393–1398, 1972

22. Peters JA: Canine mastocytoma: Excess risk as related to ancestry. J Natl Cancer Inst 42:435–443, 1969

23. Gallo RC, Meyskens FL: Advances in the viral etiology of leukemia and lymphoma. Semin Hematol 15:379–398, 1978

24. Jarrett WFH, Martin WB, Crighton GW, et al: Leukaemia in the cat. Transmission experiments with leukaemia (lymphosarcoma). Nature 202:566–567, 1964

25. Hardy WD, Old JL, Hess PW, et al: Horizontal transmission of feline leukaemia virus. Nature (London) 244:266–269, 1973

26. Wold WSM, Green M: Historic milestones in cancer virology. Semin Oncol 6:461–478, 1979

27. Burny A, Bex F, Bruck C, et al: Biochemical studies on enzootic and sporadic types of bovine leukemia. In Antiviral Mechanisms in the Control of Neoplasia. Edited by P Chandra. New York, Plenum, 1979

28. Gross LK: The development of the concept of viral etiology of leukemia and related neoplastic diseases. Present status and prospects for the future. In Advances in Comparative Leukemia Research. Edited by P Bentvelzen, J Hilgers, DS Yohn. Amsterdam, North Holland Biomedical Press, 1978

29. Priester WA: Canine lymphoma: Relative risk in the boxer breed. J Natl Cancer Inst 39:833–845, 1967

30. Burridge MJ, Wilcox CJ, Hennemann JM: Influence of genetic factors on the susceptibility of cattle to bovine leukemia virus infection. Europ J Cancer 15:1395–1400, 1979

31. McTaggart HS, Head KW, Laing AH: Evidence for a genetic factor in the transmission of spontaneous lymphosarcoma (leukaemia) of young pigs. Nature (London) 232:557–558, 1971

32. Dougherty JH, Taylor GN: Incidence of myelogenous and lymphatic tumors of irradiated and non-irradiated beagles. Proc Amer Assoc Cancer Res 8:14, 1967

33. Howard EB, Ushijima RN, Hackett PL, et al: Corollary studies of ^{90}Sr-induced leukemogenesis in swine. In Myeloproliferative Disorders of Animals and Man. Edited by WJ Clark, EB Howard, PL Hackett. Proc Eighth Annual Hanford Biology Symposium, Washington, 1968

34. Reif JS, Cohen D: The environmental distribution of canine respiratory tract neoplasms. Arch Environ Hlth 22:136–140, 1971

35. Yang CS: Research on esophageal cancer in China: A review. Cancer Res 40:2633–2644, 1980

36. Dorn CR, Priester WA: Epidemiologic analysis of oral and pharyngeal cancer in dogs, cats, horses, and cattle. J Am Vet Med Assoc 169:1202-1206, 1976

37. Bailey WS: Parasites and cancer: Sarcoma in dogs associated with *Spirocerca lupi*. Ann NY Acad Sci 108:890-923, 1963

38. Lingeman CH, Garner FM, Taylor DON: Spontaneous gastric adenocarcinomas of dogs: A review. J Natl Cancer Inst 47:137-153, 1971

39. Kurihara M, Shirakabe H, Murakami T, et al: A new method for producing adenocarcinomas in the stomach of dogs with N-ethyl-N¹-nitro-N-nitrosoquanidine. Gann 65:163-177, 1974

40. Sugimura T, Tanaka N, Kawachi T, et al: Production of stomach cancer in dogs by N-methyl-N¹-nitro-N-nitrosoquanidine. Gann 62:67, 1971

41. McDonald JW, Leaver DD: Adenocarcinoma of the small intestine of Merino sheep. Aust Vet J 41:269-271, 1965

42. Ross AD: Small intestinal carcinoma in sheep. Aust Vet J 56:25-28, 1980

43. Simpson BH: An epidemiological study of carcinoma of the small intestine in New Zealand sheep. N Z Vet J 20:91-97, 1972

44. Silverberg SG: Carcinoma arising in adenomatous polyps of the rectum in a dog. Dis Colon Rectum 14:191-194, 1971

45. Priester WA: Data from 11 United States and Canadian Colleges of veterinary medicine on pancreatic carcinoma in domestic animals. Cancer Res 34:1372-1375, 1974

46. Priester WA: Pancreatic islet cell tumors in domestic animals. Data from 11 Colleges of Veterinary Medicine in the United States and Canada. J Natl Cancer Inst 53:227-229, 1974

47. Ponomarkov V, Mackey LJ: Tumours of the liver and biliary system. Bull Wld Hlth Organ 53:187-194, 1976

48. Newberne PM, Butler WH: Acute and chronic effects of aflatoxin on the liver of domestic and laboratory animals: A review. Cancer Res 29:236-250, 1969

49. Hou PC: Hepatic clonorchiasis and carcinoma of the bile duct in a dog. J Pathol Bacteriol 89:365-367, 1965

50. Vitovek J: Hepatozellulare Karzinome beim Rind und ihre Beziehung zur biliären Zirrhose fasziolaren Ursprungs. Vet Pathol 11:548-557, 1974

51. Rooney JR: Liver carcinoma in the dog. Acta Pathol Microbiol Scand 45:321-330, 1959

52. Schmähl D, Habs M, Ivankovic S: Carcinogenesis of N-nitrosodiethylamine (DENA) in chickens and domestic cats. Int J Cancer 22:552-557, 1978

53. Nelson AA, Woodard G: Tumors of the urinary bladder, gall bladder, and liver in dogs fed o-aminoazotoluene or p-dimethylaminoazobenzene. J Natl Cancer Inst 13:1497-1509, 1953

54. Allison JB, Wase AW, Leathem JH, et al: Some effects of 2-acetylaminofluorene on the dog. Cancer Res 10:267-271, 1950

55. Sternberg SS, Popper H, Oser BL, et al: Gall bladder and bile duct adenocarcinomas in dogs after long term feeding of Aramite. Cancer 13:780-789, 1960

56. Fortner JG, Leffall LD: Carcinoma of the gall bladder in dogs. Cancer 14:1127-1130, 1961

57. Duncan JR, Tyler DE, van der Maaten MJ, et al: Enzootic nasal adenocarcinoma in sheep. J Am Vet Med Assoc 151:732-734, 1967

58. Njoku CO, Shannon D, Chineme CN, et al: Ovine nasal adenopapilloma: Incidence and clinico-pathologic studies. Am J Vet Res 39:1850-1852, 1978

59. Yonemichi H, Ohgi T, Fujimoto Y, et al: Intranasal tumor of the ethmoid olfactory mucosa in sheep. Am J Vet Res 39:1599-1606, 1978

60. Pospischil A, Haenichen T, Shaeffler H: Histologic and electron microscopic studies of endemic ethmoidal carcinomas in cattle. Vet Pathol 16:180-190, 1979

61. Madewell BR, Priester WA, Gillette EL, et al: Neoplasms of the nasal passages and paranasal sinuses in domesticated animals as reported by 13 Veterinary Colleges. Am J Vet Res 37:851-856, 1976

62. Ablashi DV, Easton JM, Glaser R: Animal models for nasopharyngeal carcinoma. In Nasopharyngeal Carcinoma: Etiology and Control. Edited by G de-Thé, Y Ito. Lyon, International Agency for Research on Cancer, 1978, pp 85-94

63. Benjamin SA, Boecker BB, Cuddihy RG, et al: Nasal carcinomas in beagles after inhalation of relatively soluble forms of beta-emitting radionuclides. J Natl Cancer Inst 63:133-139, 1979

64. Nielsen SW: Spontaneous canine pulmonary tumors. In Lung Tumors in Animals. Edited by L Severi. Perugia, Italy, University of Perugia, 1965, pp 151-164

65. Monlux WS: Primary pulmonary neoplasms in domestic animals. Southwest Vet 6: 131-133, 1953

66. Brodey RS, Braig PH: Primary pulmonary neoplasms in the dog: A review of 29 cases. J. Am Vet Med Assoc 147:1628-1643, 1965

67. Perk K, Michalides R, Spielman S, et al: Biochemical and morphological evidence for the presence of

RNA tumor virus in pulmonary carcinoma of sheep (jaagsietke). J Natl Cancer Inst 53:131–135, 1974

68. Mohr U, Reznik G: Tobacco carcinogenesis. In Pathogenesis and Therapy of Lung Cancer. Edited by CC Harris. New York, Marcel Dekker, 1978, pp 263–367

69. Auerbach O, Hammond EC, Kirman D, et al: Effects of cigarette smoking on dogs. II. Pulmonary neoplasms. Arch Env Hlth 21:754–768, 1970

70. Hammond EC, Auerbach O, Kirman D, et al: Effects of cigarette smoking on dogs. I. Design of experiment, mortality, and findings in lung parenchyma. II. Pulmonary neoplasms. Am Cancer Soc, NY 21:78–94, 1971

71. Rockey EE, Speer FD: The ill effects of cigarette smoking by dogs. Int Surg 46:520–530, 1966

72. Staub EW, Eisenstein R, Hess G, et al: Bronchogenic carcinoma produced experimentally in the normal dog. J Thorac Cardiovasc Surg 49:364–372, 1965

73. Zwicker GM, Filipy RE, Park JF, et al: Clinical and pathological effects of cigarette smoke exposure in beagle dogs. Arch Pathol Lab Med 102:623–628, 1978

74. Paladugu RR, Shors, EC, Cohen AH, et al: Induction of lung cancers in preselected, localized sites in the dog. J Natl Cancer Inst 65:921–927, 1980

75. Park JF, Bair WJ, Busch RH: Progress in beagle dog studies with transuranium elements at Batelle-Northwest. Hlth Phys 22:803–810, 1972

76. Skoryna SC, Rudis LA, Webster DR: Pathogenesis of feline lung tumors produced by 2-acetylaminofluorene. Cancer Res 11:280, 1951

77. Tjalma RA: Canine bone sarcoma: Estimation of relative risk as a function of body size. J Natl Cancer Inst 36:1137–1150, 1966

78. Brodey RS, Misdorp W, Riser WH, et al: Canine skeletal chondrosarcoma: A clinicopathologic study of 35 cases. J Am Vet Med Assoc 165:68–78, 1974

79. Bingel SA, Brodey RS, Allen HL, et al: Hemangiosarcoma of bone in the dog. J Sm Anim Pract 15:303–322, 1974

80. Bech-Nielsen S, Haskins ME, Reif JS, et al: Frequency of osteosarcoma among first degree relatives of Saint Bernard dogs. J Natl Cancer Inst 60:349–353, 1978

81. Pritchard DF, Finkel MP, Reilly CA: The etiology of osteosarcoma. Clin Orthop 111:14–22, 1975

82. Thurman GB, Mays CW, Taylor GN, et al: Growth dynamics of beagle osteosarcomas. Growth 35:119–125, 1971

83. Thurman GB, Mays CW, Taylor GN, et al: Skeletal location of radiation induced and naturally occurring osteosarcomas in man and dog. Cancer Res 33:1604–1607, 1973

84. Wronski TJ, Smith JM, Jee WSS: The microdistribution and retention of injected ^{239}Pu on trabecular bone surfaces of the beagle: Implications for the induction of osteosarcoma. Rad Res 83:74–89, 1980

85. Benjamin SA, Hahn FF, Chifelle TL, et al: Occurrence of hemangiosarcomas in beagles with internally deposited radionuclides. Cancer Res 35:1745–1755, 1975

86. Pool RR, Harris JM: Feline osteochondromatosis. Feline Pract 5:24–30, 1975

87. Pool RR: Tumors of bone and cartilage. In Tumors in Domestic Animals, second edition. Edited by JE Moulton. Berkeley, University of California Press, 1978, pp 88–149

88. Riser WH, Brodey RS, Biery DN: Bone infarctions associated with malignant bone tumors in dogs. J Am Vet Med Assoc 160:411–421, 1972

89. Riser WH, Brodey RS, Shirer JF: Osteodystrophy in mature cats: A nutritional disease. J Am Vet Radio Soc 9:37–46, 1968

90. Brand KG: Foreign body induced sarcomas. In Cancer: A Comprehensive Treatise, Vol 1. Etiology: Chemical and Physical Carcinogenesis. Edited by FF Becker. New York, Plenum Press, 1975

91. Knecht CD, Priester WA: Osteosarcoma in dogs: A study of previous trauma, fracture, and fracture fixation. J Am Anim Hosp Assoc 14:83–84, 1978

92. Sinibaldi K, Rosen H, Liu S, et al: Tumors associated with metallic implants in animals. Clin Orthop 118:257–266, 1976

93. Hayes HM, Fraumeni JF: Canine thyroid neoplasms: Epidemiologic features. J Natl Cancer Inst 55:931–934, 1975

94. Lu ST, Michaelson SM, Quinlan WJ: Sequential pathophysiologic effects of ionizing radiation on the beagle thyroid gland. J Natl Cancer Inst 51:419–441, 1973

95. Schaller RT, Stevenson JD: Development of carcinoma of the thyroid in iodine deficient mice. Cancer 19:1063–1080, 1966

96. Cotchin E: Neoplasms of the domesticated mammals: Review series Number 4 of the Commonwealth Bureau of Animal Health; the Commonwealth Agricultural Bureau. Bucks, England, Farnham Royal, 1956

97. Zarrin K, Hänichen T: Comparative histopathological study of the canine thyroid gland in London

and Munich. J Small Anim Pract 15:329–342, 1974

98. Leav I, Schiller AL, Rijnberk A, et al: Adenomas and carcinomas of the canine and feline thyroid. Am J Pathol 83:61–93, 1976

99. Gosselin S, Capen CC, Martin SL: Lymphocytic thyroiditis in the dog. Am J Pathol 90:285–288, 1978

100. Black HE, Capen CC, Young DM: Ultimobranchial thyroid neoplasms in bulls. Cancer 32:865–878, 1973

101. Wilkie BN, Krook L: Ultimobranchial tumor of the thyroid and pheochromocytoma in the bull. Pathol Vet 7:126–134, 1970

102. Von Sandersleben J, Hänichen T: III. Tumors of the thyroid gland. Bull Wld Hlth Organ 50:35–42, 1974

103. Young DM, Capen CC, Black HE: Calcitonin activity in ultimobranchial neoplasms from bulls. Vet Pathol 18:19–27, 1971

104. El Etreby MF, Müller-Peddinghaus R, Bhargava AS, et al: Functional morphology of spontaneous hyperplastic and neoplastic lesions in the canine pituitary gland. Vet Pathol 17:109–122, 1980

105. El Etreby MF, Müller-Peddinghaus R, Bhargava AS, et al: The role of the pituitary gland in spontaneous canine mammary tumorigenesis. Vet Pathol 17:2–16, 1980

106. Luginbühl H, Frankhauser R, McGrath JT: Spontaneous neoplasms of the nervous system in animals. Prog Neurol Surg 2:85–164, 1968

107. Wright BJ, Conner GH: Adrenal neoplasms in slaughtered cattle. Cancer Res 28:251–263, 1968

108. Patnaik AK, Liu SK, Hurvitz AI, et al: Canine chemodectoma (extra-adrenal paragangliomas)—a comparative study. J Small Anim Pract 16:785–801, 1975

109. Edwards C, Heath D, Harris P, et al: The carotid body in animals at high altitude. J Pathol 104:231–238, 1971

110. Hayes HM, Fraumeni JF: Epidemiological features of canine renal neoplasms. Cancer Res 37:2553–2556, 1977

111. Migaki G, Nelson LW, Todd GC: Prevalence of embryonal nephroma in slaughtered swine. J Am Vet Med Assoc 159:441–442, 1971

112. Jarrett WFH, McNeil PE, Grimshaw WTR, et al: High incidence area of cattle cancer with a possible interaction between an environmental carcinogen and a papilloma virus. Nature 274:215–217, 1978

113. Datta S: Chronic bovine haematuria. I. History of the disease. Ind Vet J 29:187–209, 1952

114. Pamukcu AM, Goskog SK, Price JM: Urinary bladder neoplasms induced by feeding bracken fern (Pteris aquilina) to cows. Cancer Res 27:917–924, 1967

115. Price JM, Pamukcu AM: The incidence of neoplasms of the urinary bladder of the cow and the small intestine of the rat by feeding bracken fern (*Pteris aquilina*). Cancer Res 28:2247–2251, 1968

116. Olson C, Pamukcu AM, Brobst DF: A urinary bladder tumor induced by a bovine cutaneous papilloma agent. Cancer Res 19:779–782, 1959

117. Olson C, Gordon DE, Robl MG, et al: Oncogenicity of bovine papilloma virus. Arch Environ Hlth 19:827–837, 1969

118. Hayes HM: Canine bladder cancer: Epidemiology features. Am J Epidemiol 104:673–677, 1976

119. Weller RE, Wolf AM, Ojejide A: Transitional cell carcinoma of the bladder associated with cyclophosphamide therapy in a dog. J Amer Anim Hosp Assoc 15:733–736, 1979

120. Radomski JL: The primary aromatic amines: Their biological properties and structure-activity relationships. Ann Rev Pharmacol Toxicol 19:129–157, 1979

121. Prout GR: Bladder carcinoma. New Engl J Med 287:86–90, 1972

122. Coplan MM: Report of carcinogenic action of certain agents on urinary bladder of dogs. J Amer Med Assoc 172:1611–1618, 1960

123. Marchold J, Matrka M, Hub M, et al: The possible complicity of diphenyline in the origin of tumours in the manufacture of benzidine. Neoplasma 15:3–10, 1968

124. Hayes HM, Pendergrass TW: Canine testicular tumors: Epidemiologic features of 410 dogs. Int J Cancer 18:482–487, 1976

125. Reif JS, Brodey RS: The relationship between cryptorchidism and canine testicular neoplasia. J Am Vet Med Assoc 155:2005–2010, 1969

126. Pendergrass TW, Hayes HM Jr: Cryptorchidism and related defects in dogs: Epidemiologic comparisons with man. Teratology 12:51–55, 1975

127. Hayes HM, Young JL: Epidemiologic features of canine ovarian neoplasms. Gynecol Oncol 6:348–353, 1978

128. Stabenfeldt GH, Hughes JP, Kennedy PC, et al: Clinical findings, pathological changes, and endocrinological secretory patterns in mares with ovarian tumors. J Repro Fert Suppl 27:277–285, 1979

129. Cohen D: In vitro cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity to the transmissible venereal tumor of the dog. J Natl Cancer Inst 64:317–321, 1980

130. Yang TJ, Jones JB: Canine transmissible venereal sarcoma: Transplantation studies in neonatal and adult dogs. J Natl Cancer Inst 51:1915–1918, 1973

131. Priester WA: Occurrence of mammary neoplasms in bitches in relation to breed, age tumour type, and geographic region from which reported. J Small Anim Pract 20:1–11, 1979

132. Schneider R, Dorn CR, Taylor DON: Factors influencing canine mammary cancer development and postsurgical survival. J Natl Cancer Inst 43:1249–1261, 1969

133. Geil RG, Camar JK: FDA studies of estrogen, progestagens, and estrogen-progestagen combinations in the dog and monkey. J Toxic Environ Hlth 3:179–193, 1977

134. Nelson LW, Carlton WW, Weikel JH: Canine mammary neoplasms and progestagens. J Am Med Assoc 219:1601–1606, 1973

135. Owen LN, Briggs MH: Contraceptive steroid toxicity in the beagle dog and its reference to human carcinogenicity. Curr Med Res Opin 4:309–329, 1976

136. Cameron AM, Faulkin LJ: Hyperplastic and inflammatory nodules in the canine mammary gland. J Natl Cancer Inst 47:1277–1287, 1971

137. Warner MR: Age incidence and site distribution of mammary dysplasias in young beagle bitches. J Natl Cancer Inst 57:57–61, 1976

138. Hernandez FJ, Fernandez BB, Chertach M: Feline mammary carcinoma and progestogens. Feline Pract 5:45–48, 1975

139. Misdorp W, Weijer K: Animal Model: Feline mammary carcinoma. Am J Pathol 98:573–576, 1980

140. Hayes HM, Priester WA, Pendergrass TW: Occurrence of nervous-tissue tumors in cattle, horses, cats, and dogs. Int J Cancer 15:39–47, 1975

141. Bigner DD, Swenberg JA: Experimental Tumors of the Central Nervous System. Kalamazoo, Michigan, The Upjohn Co, 1977

142. Johnson RT, Narayan O: Experimental neurological diseases of animals caused by viruses. In Models of Human Neurological Diseases. Edited by HG Klawans. Amsterdam, Excerpta Medica, 1974

143. Rabotti GF: Experimental intracranial tumors of viral etiology. In The Experimental Biology of Brain Tumors. Edited by WM Kirsch, E Grossi-Paoletti, P Paoletti. Springfield, Illinois, Charles C Thomas, 1972

144. Yohn DS; Oncogenic viruses: Expectations and applications in neuro-pathology. Prog Exp Tumor Res 17:74–92, 1972

145. Gordon DE, Olson C: Meningiomas and fibroblastic neoplasia in calves induced with bovine papilloma virus. Cancer Res 28:2423–2431, 1968