The Epidemiology of Cancer in Animals

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■ *The principles of epidemiology are applicable to the study of the distribution and determinants of cancer in both human and animal populations. There are many examples of epidemiologic factors (host, environment, agent and time) related to cancer in animals. Certain host characteristics such as age, sex and breed are related to risk of developing cancer. Some environmental influences are illustrated by differences in the geographical distribution of certain types of animal cancer.*

Aggregations of cancer cases have been reported in herds, families and households. However, the usual distribution of cases in a population does not resemble epidemics typical of infectious diseases. Several factors (radiological, chemical, dietary, parasitic, mechanical, genetic and viral) have been identified as influences that affect the development of animal tumors.

Animal species that have been domesticated live longer and consequently malignant disease develops in more of them. Cancer incidence rates now available from data compiled by an animal neoplasm registry in Alameda and Contra Costa counties, California, indicate that some of the frequent sites of cancer in man (skin, breast and the hemic and lymphatic systems) are among the most frequent sites in dogs and cats, man's closest animal associates.

CANCER IS WIDESPREAD in nature, affecting domestic animals, wild mammals, birds and fish. Malignant lesions of similar cellular types to those observed in man are found in lower animals. Although some animals inhabit environments that appear quite different from that of man, many exposures and disease characteristics are common to both man and animals. It is therefore of scientific importance not only to study carcinogenesis in animals in the controlled environment of the laboratory, but also to study cancer as it occurs in natural animal populations.

This report discusses some of the present epidemiologic knowledge about spontaneous neoplasms in various animal species. The traditional epidemiologic factors of host, environment and agent as well as the dimension of time are discussed as they relate to the development of cancer in animals.

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Host

Cancer has been found in most animals, including such remote species as whales.[14] Wild animals such as rats, that have adapted to living in human communities, also have both benign and malignant tumors. In conjunction with studies at the U.S. Public Health Service Plague Laboratory in San Francisco, McCoy[49] found tumors in 103 of approximately 100,000 wild rats examined at necropsy. Curiously, tumors rarely develop in wild house mice, although tumors are common in experimental mice of the same species as wild mice, *Mus musculus*. The literature contains only one article describing a tumor in a wild house mouse—Huebner's study,[35] in which a mammary tumor was found in a house mouse trapped in New York City. Andervont and Dunn[8] observed that wild house mice kept in their laboratory for several generations, however, lived longer and had a wide array of tumors similar to those of laboratory strains of *Mus musculus*.

As most captive wild animals in zoos live longer than their wild counterparts, they provide a rich source of cancers for epidemiologic research. Since 1901, animals that die at the Philadelphia Zoo have been examined at necropsy.[60] Since that time, tumors have been observed in most phylogenetic families of mammals and birds kept there. The class *Aves* was less subject to new growths than the *Mammalia*. Birds had more new growths in the genito-urinary organs and mammals had more in the digestive organs. At the San Diego Zoo, an unusually large number of hepatic and biliary carcinomas developed in bears.[20]

Recent epidemiologic research in the California Cancer Field Research Program[69] of the California State Department of Public Health has concentrated upon quantifying the incidence of tumors in domestic animals. A central animal tumor registry initiated in July 1963,[21] derives cases from approximately one hundred practicing veterinarians in Alameda and Contra Costa counties, California. Pet animals (dogs, cats and pet birds) make up the major proportion of animals seen by veterinarians in this area and consequently contribute the most tumors to the registry.

Preliminary analysis of cases collected in the first three years of the animal registry indicates that the incidence of malignant neoplasms in dogs and cats is high. The annual incidence rates of all cancers (Chart 1) were 381 per 100,000 dogs and 155 per 100,000 cats compared with 272 per 100,000 humans in Alameda County.[18] The comparison of the canine and feline rates to human rates cannot be exact because the human rates excluded skin and *in situ* cancers and were based mainly upon hospital reporting while the animal data included these cancers and were based upon cases reported from veterinarians.

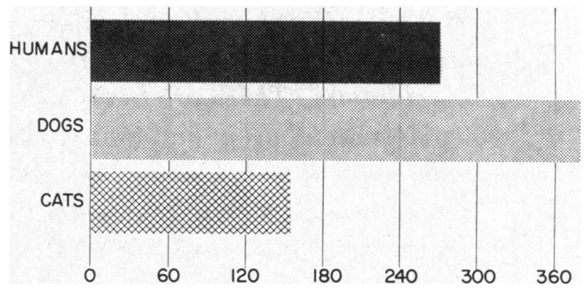

Chart 1.—Comparison of annual cancer incidence rates per 100,000 humans,* dogs† and cats† in Alameda County.

Sources:

*State of California, Department of Public Health, Alameda County Cancer Registry, unpublished data for 1960-1964, excludes skin and *in situ* cancers.

†California State Department of Public Health, Animal Neoplasm Registry, Alameda County, unpublished data for July 1963 - June 1964.

Data on the most common sites in the dog and cat reported to the animal registry and on the most common sites in humans in the "Ten City Study,"[24] which included skin and *in situ* cancers (Table 1),

TABLE 1.—*Rank Order of Major Cancer Sites, in Humans,* Dogs† and Cats†*

Rank	*Humans*	*Dogs*	*Cats*
1	Skin	Skin	Skin
2	Breast	Mammary gland	Leukemia and lymphoma
3	Stomach	Leukemia and lymphoma	Mouth and pharynx
4	Large intestine	Mouth and pharynx	Stomach and intestine
5	Cervix uteri	Testis	Mammary gland
6	Rectum	Bone	
7	Lung		
8	Leukemia and lymphoma		

*Dorn, H. F. and Cutler, S. J.: Morbidity *from* Cancer in the United States. Public Health Service Monograph No. 56. U.S. Government Printing Office, Washington, 1959.

†Dorn, C. R.: An animal neoplasm registry as a source of morbidity information. Proceedings of the 70th annual meeting of the U.S. Livestock Sanitary Association, October 10 to 14, 1966, Buffalo, New York.

showed a higher frequency of gastrointestinal and cervical cancers in humans and a higher frequency of leukemia and lymphoma in dogs and cats.

The leukemia and lymphoma cases reported to the animal registry during the first two and a half years of operation have been examined in greater detail.[23] As shown in Chart 2, the annual canine

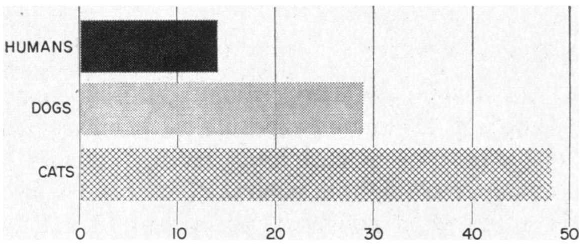

Chart 2.—Comparison of annual leukemia-lymphoma incidence rates per 100,000 humans,* dogs† and cats† in Alameda County.

Sources:
*State of California, Department of Public Health, Alameda County Cancer Registry, unpublished data for 1960-1964, excludes Hodgkin's disease and myeloma.
†Dorn, C. R., Taylor, D. O. N., and Hibbard, H. H.: Epizootiologic characteristics of canine and feline leukemia and lymphoma, Amer. J. Vet. Res. 28:993-1001, 1967.

incidence rate for leukemia and lymphoma is approximately twice as large as the combined leukemia-lymphoma rate (excluding Hodgkin's disease and myeloma) for man, and the annual feline incidence rate is over two and a half times as large as the human incidence rate.

Environment

Some of the relationships between environment and cancer may be shown by examining the geographical distribution of cancer cases. While cancer is global in occurrence, differences in its distribution in various areas of the world have been observed.

Horn core cancer of cattle in India is a carcinoma which develops at the base of the horn in native cattle.[42] These carcinomas are found in cattle of some other eastern countries, but not in other parts of the world.

Bladder tumors are frequently observed in cattle in Turkey around the Black Sea.[55] These tumors have also been found in cattle of Yugoslavia, Bulgaria, Panama and Brazil. They were once common in cattle located in the northwest coastal area of North America, but now are rarely seen in the United States.[9] They are benign and malignant tumors of both epithelial and mesenchymal origin. Only certain breeds of cattle are afflicted; the disease develops in as high as 10 to 15 per cent of cattle in endemic areas. These tumors are often found in association with another disease, enzootic hematuria, common in areas of acidic soil. The bracken fern grows in acidic soil and has been associated with chronic enzootic hematuria. Therefore, this plant has been suspected as a possible cause of bladder tumors.[55]

Leukosis or lymphosarcoma of cattle is another example of varying geographical distribution. Bendixen[8] reviewed the distribution of bovine leukosis in Europe. Before World War II, leukosis was rare in districts west of the River Elbe in Germany. Since that time, the disease has increased in western parts of Germany. This apparent spread from east to west followed the usual trade route of cattle.[80] If an infectious agent is responsible for this disease, it was perhaps spread with the movement of breeding cattle. Another possible means of spread, as suggested in Sweden,[33] was a viral agent present as a contaminant in piroplasmosis vaccine. Bovine lymphosarcoma has been found in many areas outside of Europe, including California.[70]

The transmissible venereal tumor of dogs has been found in several countries and some areas of the United States; however, it apparently does not occur spontaneously in some populations. Only four cases were reported to the animal neoplasm registry[21] in Alameda and Contra Costa counties, California, from July 1963 to June 1966. In all cases the dogs had been brought into California shortly before the condition was reported to the registry. The four dogs had come from Texas, Louisiana, Costa Rica and Vietnam.

Burkitt's lymphoma of man has a nonrandom geographical distribution, and histopathologically similar conditions have been described in dogs[48] and cats.[67] In man, this tumor usually affects the jaw of children and was first reported in southeastern and central Africa.[12] In Africa, this disease appeared to be altitude-dependent because it may be temperature-dependent. For this reason the mosquito was thought to be a vector of a viral agent responsible for this disease. Epstein and coworkers[28] successfully transplanted this tumor into African green monkeys. Dalldorf and Bergamini[18] reported the isolation of a cytopathogenic agent from lymphoma cases in Africa. Several isolations of reoviruses and herpes-like viruses have been made.[7,27,68] The etiological significance of these agents has not been determined.

Time

Neoplasms have been observed as far back as recorded history. Evidence from fossils indicates that neoplasms occurred even earlier. An osteoma of a dinosaur bone that dates back to the paleozoic period has been found.[53] Within more recent times, there have been secular trends in the incidence of cancer. Best known are the increase in the incidence of lung cancer and the decrease in the incidence of stomach cancer in man.

Epidemics resembling those of infectious diseases are not typical of most types of cancer. A possible exception is myxomatosis of rabbits which is usually considered to be neoplastic and which does occur in epidemics. The decided increase of lung cancer in man over the last 30 years is often referred to as an epidemic.

The term *microepidemic* has been used to describe a very small increase in incidence or several cases occurring in a relatively small geographical area in a limited period. The most notable example is the cluster of leukemia in children living in Niles, Illinois.[32] Aggregations of bovine lymphosarcoma were reported in cattle herds,[17] and a household cluster of feline malignant lymphoma has been observed.[64] A number of studies have shown familial aggregations of human cancer. Pinkel and coworkers reported that childhood leukemia and solid tumor cases located within a one-eighth mile radius in Buffalo, New York, also were clustered in time.[57] Application of methods developed by Ederer and coworkers to cases of poliomyelitis and hepatitis in Connecticut showed significant clustering, but cases of leukemia were not significantly clustered.[26] Other studies have demonstrated significant clustering in time and space for childhood leukemia in Northumberland and Durham, England,[41] and in Portland, Oregon.[50]

Factors in Carcinogenesis

The various agents or factors involved in carcinogenesis may be broadly grouped into the following categories: radiological, chemical, dietary, parasitic, mechanical, genetic and viral.

Radiation

Ultraviolet rays of the sun have been associated with the development of squamous cell carcinomas or "cancer eye" of cattle.[2] Ultraviolet radiation has also been identified as a possible cause of squamous cell carcinoma of the ears of sheep in Australia.[45]

During atomic testing in the Southwest, there was inadvertent exposure of a herd of cattle to radioactive fallout, and in cattle from this herd squamous cell carcinomas of the skin have developed.[10] Radioactive fallout also resulted in *beta* burns in these cattle.

Chemical Factors

While there are many examples of occupational cancers of man due to exposure to chemicals, few examples exist of chemically induced tumors in animals resulting from natural exposures. Hueper, in a review of chemical carcinogens, noted the lack of examples of chemically induced tumors in animal populations.[37]

A report based on a U.S.S.R. investigation indicated that the incidence of lung cancer is higher in dogs kept in cities than in those living in rural areas.[44] Existing data are insufficient to make a similar comparison of urban to rural canine lung cancer rates in the United States.

Observations of tumors in fish have suggested possible association with water pollutants. Carcinomas and papillomas of the lips have been found in white croakers, fish which feed off the bottom of the Pacific coastal areas.[62] These croakers were found in waters that were contaminated by wastes from oil refineries. Papillomas have also been found in eels in the Baltic Sea and it has been suggested that the lesions may result from carcinogenic substances from industrial wastes.[29]

Hueper,[36] in his book *Occupational Tumors,* cited four reports of tumors developing in animals exposed to smelter dust and fumes. Paris,[56] in 1822, observed the loss of hoofs in horses and cows kept near copper smelters and tin-burning houses in Cornwall. The contaminant was thought to be arsenic. Prell,[59] describing the Freiberg smelter in Saxony, related that precancerous warts developed in domestic animals and one deer. Nieberle,[54] also reporting about the Freiberg smelter, described adenocarcinomas of the nasal sinus of sheep in a flock that was within the dust and fume zone of the smelters.

Lead has also been incriminated as a cause of cancer in animal populations. Kilham and coworkers[40] reported a high frequency of kidney tumors in wild rats trapped at a refuse dump in New Hampshire. Five per cent of these rats had carcinoma of the kidney. Intranuclear inclusions in the kidneys were found in nearly all of the rats. It was hypothesized that inhalation of lead in smoke from the smoldering dump fires produced the tumors. Intranuclear inclusions were reproduced by experimental feeding of lead acetate to laboratory rats. The exact relationship of the exposure to lead and the intranuclear inclusions which are sometimes indicative of viral disease is unknown.

Diet

Dietary components and contaminants have been associated with tumors of mammals and fish. In 1960, an outbreak of liver hepatomas developed in hatchery-reared rainbow trout in California and other states. Wolf and Jackson[71] showed that trout fed on diets containing cottonseed meal had more hepatomas than trout fed on control diets that excluded cottonseed meal. It was later shown that hepatomas could be induced in trout by feeding aflatoxin, a metabolic product of *Aspergillus flavus,* which is a common contaminant of cottonseed meal.[81] As was previously noted, bracken fern has been investigated as a bladder carcinogen in cattle.[55]

Parasites

A favored hypothesis some years ago was that parasites caused cancer. More recent evidence has disproved some of the reported parasite-induced tumors. However, some animals' parasites have been established as the cause of certain tumors. For example, the cysticercus form of *Taenia taeniaformis,* the cat tapeworm, was found with liver tumors of wild rats.[6] The rat serves as an intermediate host in the life cycle of this tapeworm. Liver tumors have been induced experimentally by infecting rats with tapeworm ova.[11] In addition, an active factor in washed, ground *Taenia* larvae induced sarcomas in rats by intraperitoneal injection.

A nematode of dogs, *Spirocerca lupi,* has been found in physical association with esophageal sarcomas. These sarcomas are common among dogs living in the southern part of the United States where *Spirocerca lupi* infection is more prevalent. Two hundred and sixty-four of 3,148 dogs examined at necropsy at the School of Veterinary Medicine, Auburn University, Georgia, were found to be infected.[4] In the same group of dogs, 39 esophageal sarcomas were found; *Spirocerca lupi* infection was observed in 38 of these cases. Esophageal sarcomas were observed to be of significantly higher prevalence in hounds than in other types of dogs.

Hounds may be more genetically susceptible than other breeds, but the report concludes that hounds were at a greater risk because they have a greater opportunity to become infected. The life cycle of *Spirocerca lupi* explains why the hounds were more often infected. The eggs of the worm are picked up by a dung beetle. The intermediate host can be many different free-living animals, including chickens and game birds. The infective stage is the third stage larva encysted in the walls of the intestinal tract of the intermediate host. The infective third stage larvae in the intestinal wall are ingested by the definitive host, in this case, the dog. The larvae excyst in the dog's stomach and then burrow into the stomach wall. They then migrate through the gastric artery and the aorta to the esophagus, where the adult worms develop. Other circuitous routes are possible. Most dogs are infected while eating the entrails of dressed chickens or wild game. Hounds are more likely than other breeds to be fed the remains of birds and therefore are more often infected. There is need to determine what part of the parasite is carcinogenic and the mechanism by which it causes malignant transformation of cells.

Mechanical Factors.

Another hypothesis in cancer etiology is the mechanical induction of tumors; but, again, few of the examples have stood up to thorough investigation. The horn core cancer of cattle in India remains a possible example of a mechanically induced tumor.[43] These carcinomas of the horn develop after dehorning or traumatic injury to the horn by the yoke. Horn core cancer has an interesting sex distribution in that it is most frequent in steers; a few cases are found in cows, and none in bulls.

Genetic Factors

For the purpose of this discussion, the examples of genetic factors in neoplastic disease are divided into congenital influences and hereditary influences. Congenital tumors of animals include embryonal nephromas of pigs, mesotheliomas of the ox, and rhabdomyomas, rare heart tumors. A report from England[16] described a very large abdominal fibrosarcoma which was present in a calf at the time of birth. The tumor weighed 32 pounds, while the total weight of the calf was only 108 pounds.

Carcinoma or epithelioma of the eye in cattle provides an example of hereditary influences. Anderson[1] showed that the susceptibility to this disease was related to the degree of pigmentation of the conjunctiva. The variability between breeds was correlated with variability in conjunctival pigmentation. Hereford cattle, which characteristically have a white face and usually lack pigmentation of the conjunctiva, had a higher incidence of this disease than other breeds. A high occurrence of melanoma has been shown in offspring of red Duroc boars with melanomas.[34] Melanomas were far more common in gray horses than in horses of other colors.[52]

Studies of dogs in Alameda and Contra Costa counties have shown that the prevalence of neoplasms is higher in purebred than in crossbred dogs.[22] This observation suggests that a genetic influence associated with dog breeding practices, such as inbreeding, may affect cancer risk in dogs.

Viruses

The study of oncogenic viruses is of great current interest in cancer research. It is not the purpose of this section to discuss the mechanism of viral carcinogenesis; only brief descriptions of established viral-induced tumors in other than experimental animals are presented.

In wild animals, the Shope papilloma virus has been identified as the cause of papillomas in cottontail rabbits.[65] The original isolation was made by Dr. Shope from tumors procured from wild rabbits in Iowa. These tumors sometimes became malignant, and the virus provided a good laboratory model for studying transition from benign to malignant neoplasms.

The Shope fibroma virus, another virus of cottontail rabbits, has been classified as a pox virus while all the papilloma viruses are included in the papova group.[51] The Shope fibroma virus is transmitted from rabbit to rabbit by fleas and mosquitoes.

Rabbit myxoma virus, also classified as a pox virus, causes myxomatous lesions in the European rabbit *(Oryctolagus cuniculus)* but does not produce the acute systemic disease in the American rabbit *(Sylvilagus spp.)*. It has also been shown to be an arthropod-borne disease in which the mosquito is a mechanical rather than a biological vector. Sanarelli[63] first described the infectious nature of this disease in 1898.

Another oncogenic animal virus, the fibroma virus of squirrels, was isolated by Kilham.[39] This pox virus was shown to be related to the Shope fibroma virus by cross-neutralization tests. The mosquito was also found to be a vector of the fibroma virus.

A virus isolation was made from wild mice near Brisbane, Australia; it was found to be related to the Friend mouse leukemia virus.[58] However, no neoplasms were found in these mice. Wild mice were found to be infected with polyoma virus, but they did not develop the disease because they do not live long enough or they receive passive immunity from their mothers which protects them during the first few days of life during which they must be infected in order for tumorigenesis to occur.[61]

The fibroma of deer has also been shown by Shope[66] to be a virus disease. Using cell-free filtrates, he was able to reproduce the disease in deer. The fibromas which provided his material were from deer in New Jersey. Fibromas have been diagnosed by the California Cancer Field Research Program[69] in deer from California's north coastal area and Yosemite National Park.

Lucke[47] has shown the infectious nature of kidney carcinomas of frogs. Two to three per cent of frogs sampled from the Mississippi Valley and the Midwest had kidney carcinomas.

In domestic animals and wild birds, chicken leukemia is an outstanding example of virus-induced tumors. There are four types of the disease: lymphomatosis, erythroblastosis, myeloblastosis and osteopetrosis. It has not been clearly established if one or several viruses is responsible for these conditions.

The bovine papilloma agent is included in the papova group of viruses.[51] Papillomas are common in cattle, and it is possible to induce papillomas of horses with the bovine virus. Spontaneous equine cutaneous papillomas are also induced by a virus, as shown by Cook and Olson,[15] using cell-free filtrates. The equine papilloma virus, however, will not induce tumors experimentally in cattle.

The viral nature of canine oral papillomatosis was reported by DeMonbreun and Goodpasture[19] in 1932. The mastocytoma or mast cell tumor of dogs was transmitted by Lombard and coworkers,[46] using cell-free filtrates, but an agent has not been fully characterized.

There have been several reports of viral activity in isolates from bovine lymphosarcoma, but none of these showed a cytopathogenic effect; however, one agent has been shown to form syncitia in tissue culture.[25] Jarrett,[88] using supernatant fluid from centrifuged cell suspensions, reported transmission of leukemia in cats.

The Yaba virus was isolated from an outbreak of histiocytomas in monkeys.[5] Presently, this is the only known naturally occurring virus-induced tumor of primates. The simian virus 40, another primate virus, is oncogenic for hamsters, but has not been shown to produce tumors in the natural host.

Discussion

To support the hypothesis of a viral cause of human cancer, reference is often made to the many examples of virus-induced tumors in animals. However, if one examines more closely the animals that have virus-induced tumors, it becomes evident that very few are domestic animals. Almost all of the tumors induced by viruses that have been characterized are either of wild or laboratory animals. There are no malignancies of domestic animals which have been conclusively established as virus-induced except leukosis in chickens. If papillomas are eliminated, there are no established virus-induced tumors, either benign or malignant, in domestic *mammals*. While there is evidence of viral etiology of canine mastocytoma[46] and feline lymphoma[88] based upon transmission studies, no specific agents have yet been identified. More intensive virological studies should be pursued to further elucidate the role that viruses play in these cancers and the relationships that may exist with the human disease counterparts.

Hence, human studies are not unique in their lack of success to date in demonstrating conclusively a causal relationship between viruses and tumors other than papillomas. This is interesting in that man and the domestic animals, more than wild and laboratory animals, share the same environment and presumably some of the same exposures to carcinogens.

For epidemiologic studies of cancer in domestic animals, one of the fundamental resources is a systematic collection of cases occurring in defined populations. The many sometimes remote field observations have greater value if they can be evaluated quantitatively to determine if they could or could not be expected by chance alone. Because of the infrequency of cancer cases of specific sites and the long periods of time needed for study, it is difficult to adequately study the distribution in time of cancer occurrence in most animal species. Some observations of varying geographical distribution of neoplastic disease based upon presence or absence of the disease are readily apparent. In order to look with greater detail at subtle differences, however, it is necessary to have complete records such as afforded by a central tumor registry.

The animal neoplasm registry in Alameda and Contra Costa counties is an initial step in providing adequate animal cancer morbidity information. Its operation, described elsewhere,[21] parallels that of human cancer registries and provides for the first time an opportunity to compare animal and human morbidity data in the same geographic area.

It would also be of interest to compare cancer incidence in different zoos. As the occurrence of cancer in zoo populations may extend over long periods of time, zoo tumor registries that encompass complete clinical and necropsy records and detailed population information would facilitate such comparison.

New virological, chemical, and statistical tools are needed to permit more probing etiologic studies of cancer. As scientific methods are developed to study a specific type of cancer in one species, applications to other forms of neoplasia and other animal species, including man, should be explored.

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