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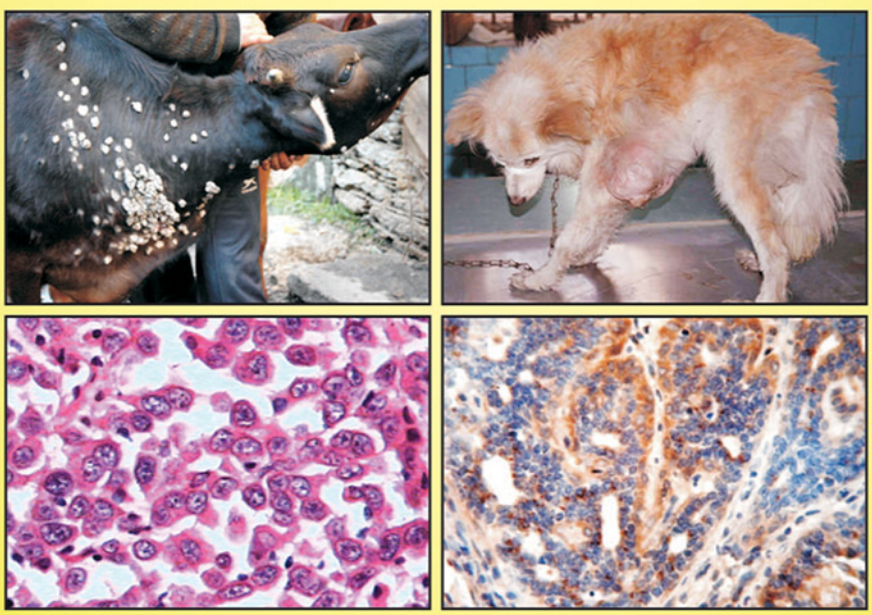
Animal Cancers

Trends in Diagnosis Treatment & Management



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Foreword

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CHAPTER 2

Veterinary Meets Medical Science to Tackle Human Cancer

➢ RVS Pawaiya, Ram Kumar

It appears that time has come for the veterinarians to play a significantly contributory role in treating and controlling human diseases, especially cancers. Veterinary pathologists have consistently suggested since the beginning that occurrence of neoplasms in domestic or pet animals are particularly similar to those occuring in humans with respect to myriad of factors involved in its etiology including environment, food and water, and that the inclusive approach in investigations of medical oncology would be immensely helpful in addressing various human cancers. However, medical fraternity continued to ignore the factual 'essence' underlying the arguments and rather preferred laboratory animals including mice, rats, rabbits, guinea pigs and hamsters as model animals to study various aspects of cancer, carcinogens, carcinogenicity and carcinogenesis. Traditionally, the cancer research including risk assessment to humans has been evaluated through experiments in laboratory animals or epidemiology studies in people. Although laboratory studies have advantage of being controlled experiments, their practical utility as an indicator of human risk is limited by the uncertainties of extrapolating from laboratory animals to human and from high doses to those typically experienced naturally. Similarly, epidemiological studies to evaluate human cancer risks directly at the exposure levels present in residences or environment are limited by their potential for misclassification, biased recall and uncontrolled mix-ups, as long time intervals involved between exposure and diseases have marred accurate recall, resulting in confounding (Woodward and McMichael, 1991). The extensive research in cancer for about half a century has yielded an unprecedented amount of information and understanding of cancer and cancer cells. However, the translation of this knowledge into treating cancer patients and saving lives has been depressingly slow. On cancer therapeutic aspect, several drugs have been discovered which prevented and eliminated experimentally-induced cancers in laboratory animals, but when it came to human application, the much touted compounds have failed miserably and generally consistently. The rodent animal models projected to imitate cancer in human have not measured up to the expectations. This has forced the researchers to look for some alternative approaches to beat the dreaded disease. Intense activities are going on among cancer researchers in western countries to include veterinary oncology and

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study particularly dog cancers as model for understanding tumor biology as well as drug development and trials for ultimate use to treat human cancer.

COMPARATIVE PATHOLOGY

The valuable observations in veterinary pathology in the past have helped in learning more about the diseases of man. This gave rise to a new term "comparative pathology", which Leader and Leader (1971) had defined as "that branch of pathology which emphasizes comparisons of disease phenomena between various species, usually with the ultimate objective of learning more about the diseases of man, but at the same time with an intrinsic interest in diseases of anomen (the pleural of anoman, the Leaders' acronym for animals other than man). Obviously, comparative pathology embodies more than veterinary pathology, which is one of its two major non-medical components, the other being experimental pathology.

During early periods of disease understanding, particularly of infectious diseases, comparative methods were recognized as an essential approach to the study of human diseases. In this context, the remarks by Theobald Smith made to the Pathological Society in Philadelphia in 1900 that were quoted by Shope (1959), the discoverer of viral fibroma and papilloma in rabbits, in his address on the occasion of 75th anniversary of the School of Veterinary Medicine in Philadelphia are worth mentioning: 'Man frequently attempts the conquest of problems from the least accessible quarter. This is true of that stage in the development of medical science when the human species was the chief object of study. Within the past two or three decades, medicine has been gradually and almost unconsciously drifting towards animal pathology as the chief, if not the sole, means of clearing up the greater doubts which a broader science inevitably brings with it. We have lately definitely reached this second stage, the study of the more accessible, more varied diseases of animals. The preparations for this stage date well back, and the most conspicuous investigators of human pathology have always had a yearning towards the rich fields of animal pathology.'

Early successes in the field of infectious diseases by using comparative methods were contributed by medical, veterinary and other scientists including the illustrious names of Koch, Salmon and Pasteur. This first flush of success followed by a kind of lull, however, the explorations for animal models of human diseases increased during seventies, particularly in fields of toxicology, hereditary and congenital defects, immunological abnormalities and chronic degenerative diseases.

COMPARATIVE ONCOLOGY

Like comparative pathology, it certainly implies that comparative oncology encompasses more than veterinary oncology. A working definition of comparative oncology could be formulated on the lines of that given for comparative pathology by Leader and Leader (1971). Here, veterinary oncologists use naturally occurring cancers in pet animals (dogs, cats, birds and other household pets) as surrogates of human cancer risk and to better understand and treat cancer in humans.

The first real interest in animals in relation to cancer is reflected in studies (from 1700s) of their possible susceptibility to transplantation of human tumors (Triolo, 1964). Predictably, such attempts failed to produce any results. A transient investigational sparkle came in 1802 in London when the Medical Committee of the Society for Investigating the Nature and Cure of Cancer (1806) formulated their thirteen questions, which show an exceptionally prescient and piercing thought. Notably, one member of the Committee was Dr Everard Home, an examiner at the London Veterinary College. The Committee's tenth question was: 'Are brute creatures subject to any disease resembling cancer in the human body?' An explanatory note attached to this query reads: 'It is not at present known whether brute creatures are subject to cancer, though some of their diseases have a very suspicious appearance. When this question is decided, we may inquire

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what class of animals is chiefly subject to cancer: the wild or the domesticated; the carnivorous or the graminivorous; those which do, or those which do not, chew the cud. This investigation may lead to much philosophical amusement and useful information; particularly it may teach us how far the prevalence or frequency of cancer may depend on the manners and habits of life. As establishments are now formed for the reception of several kinds of animals, and as the treatment of their diseases has at length fallen under the care of scientific men, it is hoped that the information here required may be readily obtained. If animals which live only on herbs, and never drink any liquid other than water, prove to be the least or not at all susceptible to cancer; such proof may, in many cases, become a guide in practice.'

It is wonderful to look foreshadowed here, what has come to be the conspicuous fact about the occurrence of tumors in different species of animals, species-wise variability in occurrence, even allowing for the fact that many are killed young for food and also the hint that epidemiology is likely to be one of the most rewarding disciplines for the approach to comparative oncological studies.

Notwithstanding, animal cancers were given least attention during the nineteenth century, although some tumors that are still present, such as mammary tumors of bitch, were well known then. A Russian veterinarian Nowinsky in 1876 drew the attention towards the transmissible venereal tumor of the dog, which passes through coitus from male to female and vice versa and behaves like transplant derived from a single clone of cells. The tumor shows an abnormal but specific karyotype, typically of 59 chromosomes, of which 17 are metacentric and 42 are acrocentric, as compared with the 78 of normal dog kidney cells, all of which are acrocentric except two sex chromosomes. In a recent study, Murgia et al. (2006) analyzed blood samples from 16 cancer-ridden unrelated dogs from five different continents through forensic DNA analysis and showed that all the venereal tumor cells were originated from a common ancestor cell which was not from the dogs themselves. Comparing tumor cell DNA with dog DNA from reference samples held by US Kennel Club and Crufts, the authors deduced that it most likely originated from a cancer in a single wolf or an "old" East Asian dog breed closely related to a wolf such as husky or Shih Tzu which lived between 200 and 2500 years ago. The transmissible venereal tumor spread like wildfire thereafter from dog to dog through coitus, licking, or biting, the cancer cells themselves acting "parasitically" on each infected animal. Also, heavily disrupted chromosomes on tumor cells seem to have ceased further fragmentation and became "stable". The tumor can be readily transplanted subcutaneously into dogs, even by single cell suspension. Both as a spontaneous and a transplanted tumor, it tends to regress spontaneously after a while, particularly when transplanted into healthy adult dogs. However, it could be metastasized when transplanted into pups, and may provide a useful experimental subject for therapeutic trials. The tumor is known to be markedly radiosensitive.

Discoveries of viral neoplasms avian leucosis by Ellerman and Bang in 1908 (Bang being a veterinarian) and Rous sarcoma in 1910, resulted into intense activity in virus cancer research that we have seen in the form of revolutionary discoveries of several cancer causing oncogenes for which J. Michael Bishop and Harold E. Varmus won 1989 Nobel Prize. However, many investigators questioned the truly neoplastic nature of the Rous sarcoma.

The ever growing interest of veterinary pathologists in the tumors of animals for about last four decades is evident by the great increase in published papers. The reasons being the expansion of number and size of Veterinary Colleges, state of the art Veterinary Hospitals and Pet Clinics, increase in veterinary pathological investigations in general and increased interest and concern of animal owners leading to a call for greater use of and accuracy in histopathological and other methods of diagnosis. Again, dogs and cats which are major source of animal tumors, being a pet in many countries are allowed to live out their full life span under quality veterinary care and vaccination. Closer involvement of veterinary clinicians in diagnosing and treating animal tumors has compelled veterinary pathologists

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to make closer studies of these tumors to improve diagnosis. The study of spontaneous tumors in animals is fully justified for its own sake. The significance of such comparative studies was recognized, albeit slowly, by cancer research workers as evident from WHO histological classification of animal tumors that runs almost parallel to that of human tumors, a tangible outcome of WHO mediated meetings of medical and veterinary investigators (WHO, 1974). The World Health Organization's Series on Tumors of Domestic Animals provide a sound basis for comparative oncology and to advance veterinary pathology by providing a widely accepted standard nomenclature of tumors of domestic animals and currently its second edition (2007) is available.

Noting high frequency of mammary cancers in canines, Mulligan in 1975 suggested that the incidence of mammary tumours in dogs should be investigated in countries with high (USA) or low (Japan) risk of human breast cancer. The importance of comparative oncology was emphasized, apparently for the first time, by renowned veterinary pathologist, Professor E. Cotchin of Royal Veterinary College, Hertfordshire, UK in his presidential address to the meeting of Royal Society of Medicine on 10 March, 1976, where, alongside certain constraints, he had brilliantly outlined the merits of studying spontaneous tumors in animals and their utilization for epidemiological, therapeutic studies and as environmental and dietetic risk assessment monitors for human populations (Cotchin, 1976).

RECENT DEVELOPMENTS

Pet dogs can reveal much about human cancers, not only because of animals' tendency to get afflicted with the same type of malignancies that affect people, but also mimic metastasis of cancer just as in human cancers. Spontaneous cancers in dogs are an underused group of naturally occurring malignancies that share many features with human cancers such as mammary carcinoma, osteosarcoma, prostate carcinoma, lung carcinoma, non-Hodgkin's lymphoma, melanoma, soft tissue sarcoma, head and neck carcinoma, mouth cancer, bladder cancer and virally induced lymphomas. Many of these cancers have strong similarities to human cancers including histological appearance, tumor genetics, biological behavior and response to conventional therapies. Several histological types of canine mammary tumors resemble those that occur in human breast cancer with similar metastatic and prognostic behavior. Like in humans, mammary and prostate cancers in dogs frequently metastasize to the skeleton, facilitating a golden opportunity to study these cancers in dogs to understand the interactions between cancer cells and bone tissue favoring metastatic colonization. Canine mixed mammary tumor could be a better morphological model for the human mixed salivary tumor and its great content of proliferating myoepithelium could have interesting significance. Osteosarcoma of dog which affect the limbs of larger dogs, upper humerus, lower radius and lower femur, almost ditto mimic those occur in youngster humans. There was time when diagnosis of osteosarcoma in a teenager meant amputation of the affected limb or else death. One can witness beautiful limbs of young teenager boys and girls that were amputated due to this killer cancer and preserved in the Cancer Institute, Adyar, Chennai. Today, limb amputation can be avoided by chiseling out the cancer affected bone tissue and replacing it with a bone graft or metal implant, a process initially tried and perfected in dogs by veterinary oncologists at American university. The credit goes to them that a significantly higher percentage of osteosarcoma affected teenagers can be cured today. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs), which in general shows remarkable anticancer activity against several canine tumors, especially canine bladder cancer, is now being used for clinical trials in human bladder cancer. The compressed course of cancer progression seen in dogs allows timely assessment of new cancer therapies. Companion animals could serve as sentinels or "watchdogs" to identify lowly carcinogenic substances in our homes and surroundings as the disease will appear first in pets due to their compressed life spans, well before it will in people, thus assisting in

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preventing human cancers by allowing ample time to take corrective or remedial measures.

Realizing the importance of comparative oncology, developed countries have begun, though belatedly, establishing pet tumor registries. The first comprehensive pet tumor registry was begun in California in the late 1960s, but the project was not emulated and idea languished. More recently, Cornell College of Veterinary Medicine and the Animal Cancer Foundation started a pilot program to monitor cancers in cats and dogs. There are about 70 million pet dogs in USA of which about 10% are diagnosed with naturally occurring tumors. Majority of these dogs are seen by veterinary oncologists in private practices or at teaching hospitals, using therapies similar to those for humans such as surgery, chemotherapy, radiation therapy and biotherapy. The inclusion of this large number of dogs suffering from cancer in the study of human cancer is the 'essence' of comparative oncology. This pivotal field is bringing together the work of veterinary oncologists with medical oncologists, the pharmaceutical industry and academic cancer research centers with the vibrant hope of improving our understanding of the biology of cancer and lead to improved cancer treatment options for both dogs and humans.

After about three years of groundwork and planning, National Cancer Institute (NCI) of America has recently launched the Comparative Oncology Program headed by Dr. Chand Khanna, a veterinary oncologist. The $ 1.2 million program at NCI's Center for Cancer Research incorporates an integrated approach to drug discovery and development by using the knowledge of the recently sequenced complete dog genome (Lindblad-Toh et al. 2005) as well as many newly established centers for dog trials in an effort to achieve three pronged aims: The first is to develop a set of reagents, including oligonucleotide microarrays and proteomic assays, to help predict drug toxicity, efficacy, and mechanism of action in dogs. It relies on the pronounced genetic similarities between man and dog, which should result in a highly predictive model for human application. Second, like human clinical trials cooperative groups, NCI has established a multicenter Comparative Oncology Trials Consortium. The scientific and clinical leaders from human and veterinary oncology have come together to form a multidisciplinary consortium, the Canine Comparative Oncology and Genomics Consortium (CCOGC) to initiate and facilitate collaborative efforts and exploit the opportunities provided by the dog in cancer research. The multicenter Consortium involving top-tier veterinary oncology institutes will collaborate using standardized protocols to take following actions: (i) Develop a robust and well-annotated biospecimen repository of canine cancers and tissues, as funding of a large, accessible biospecimen repository is difficult using existing resources. (ii) Improve opportunities to link the efforts of veterinary and comparative oncologists with the work of basic cancer researchers and clinicians. (iii) Initiate non-clinical trials using pet dogs with cancers that are integrated into the development path of new cancer drugs. Mechanism development for review of these non-clinical trials in such a way that information from these studies, where appropriate, may help to focus the scope of early human clinical trials. Until now, non-clinical studies in dogs with cancer under program have answered questions that would have been difficult or impossible to answer in either mice or humans. This will also provide opportunity for the early evaluation of new therapies for dogs suffering with cancer. Third and finally, it is essential to increase awareness of the suitable use of 'naturally occurring cancer models in pet dogs' within the cancer research community.

Until recently, a significant weakness in the study of cancer biology in canine cancer models has been the availability of reagents. With the realization of the need for more useful animal models in human cancer, the completion of the canine genome sequence, the increasing availability of dog-specific biological reagents and investigative methodologies, (e.g. antibodies specific for dog proteins or dog-specific oligonucleotide arrays) and the interest of the animal health biotech and drug industry, there is no doubt that this program with new approach throws opportunities for veterinary pathologists and oncologists to fully exploit the many advantages of the dog in cancer and drug development research.

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WHERE INDIA STANDS

It appears that veterinary oncology is least developed in India. The education in Veterinary Colleges as well as animal health research program and policies of the country prioritize and emphasize only on the economically important diseases of domestic animals. The work on non-infectious diseases-like tumors is always viewed with skewed mindset and more often than not weighed against the economic viability of the animals.

The scenario of cancer incidences in India is unclear as there has not been any systematic study at national level to find out specific pattern of cancer occurrence in animals. However, appearance of increased Indian publications on animal cancers, albeit isolated and sporadically, points to the increased frequency of tumor occurrence. A twenty year survey study in Madras State (1945-1964) reported 4.9% (82% male and 18% female) lymphoid neoplasms in dogs, whereas a study by Mukhopadhyay and Som (1992) on 136 canine tumor cases from Calcutta revealed highest incidence of skin tumors (42.6% followed by tumors of genital organs (23.5%), mammary gland (20.6%) and other organs (13.2%). Shekar (2001) in Bangalore recorded 59 malignant tumors out of total 72 canine mammary tumors. In Mumbai, Adak (2005) found 33.14% mammary tumors out of 347 canine tumor cases, and studies on canine neoplasms at IVRI, Izatnagar, Bareilly revealed highest incidence of mammary tumors (41.6-60%) followed by skin (14.8 to 40%), venereal (18.1%), vaginal (14.5%) and testicular (6.2%) tumors (Pawaiya, 2005; Nair et al. 2007; Reddy, 2007). It is evident from these data that such increased and precise diagnosis of tumor cases, particularly in dogs preceded by the fact of increasing urbanization, awareness and living status of people with consequent increase in the interest in pet animals and demand for better veterinary services. Dogs were never included in the country's national livestock census until 1982 when their population stood at 18.54 million that had increased to 29 million in 2003, with 16.7 million (57.59%) being domestic (licensed) dogs and 12.3 million (42.41%) others (Basic Animal Husbandry Statistics, 2006).

With the advent of comparative oncology that focuses on the striking anatomical, genetic and biological similarities between canine and human cancers, and allows results obtained in clinical trials in dogs, designed to extend life or cure or prevent disease by identifying carcinogens, to become the foundation of human studies, it has become imperative to initiate such research program in our country for the ultimate benefit of both owners and dogs. The need of the hour is to initiate and streamline the establishment of Pet Tumor Registries on the line of National Cancer Registry Program of Indian Council of Medical Research initiated in December, 1981 for collection of authentic data on human cancer, which currently have eight urban, two rural, four urban-cum-rural and five hospital based registries (Anon, 2006-07). Presently, the only Registry of Veterinary Pathology and Oncology (initiated in 1985 with the aim to establish repository of pathological alterations, their proper documentation with illustrative material of different animal diseases including tumors) of the country is functioning at the Indian Veterinary Research Institute, Izatnagar, Bareilly, UP. Although carrying out its objectives to the best possible level, lack of adequate funds, resources and infrastructure have severely constrained the lonely Registry to perform to the expected level and potential. Even so, it offers a good start point to move ahead and transform into an exemplary comparative oncology centre in the quest of cancer research as well as to keep abreast with the contemporary cancer research development.

CONCLUSION

Research in veterinary and animal sciences has always been the backbone to yield information for understanding the biology and disease processes in the humans. The research in cancer using laboratory animals has so far generated voluminous information and understanding of cancer, however, its application in treating and preventing the human cancer has been utterly unsatisfactory. Complete sequencing of dog genome recently has revealed startling evolutionary similarities with humans, bringing

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a turning point in the way of cancer research. Comparative oncology is the talk of the day, wherein spontaneously occurring dog cancers, most of which are similar to those of humans, will be studied to understand biology and cancer drug development and trials for quick usage in humans suffering from cancer.

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Animal Cancers

Trends in Diagnosis, Treatment & Management

Cancer is an abnormal growth of cells which tend to proliferate in an uncontrolled way and serving no useful function. Cancer is not one disease but it is a group of several different and distinctive fatal diseases which occurs in man and animals. Amongst animals, canines, poultry, bovines, equines and laboratory animals are the most frequently affected species. In cows and buffaloes, ethmoid carcinoma, horn cancer, eye cancer, lymphosarcoma, urinary bladder cancer (of enzootic bovine hematuria), etc. are common malignancies. Cutaneous warts are benign conditions. Similarly amongst dogs, mammary tumors, venereal tumors and skin tumors are major problems. In recent years, investigations have been conducted in canine mammary tumors using immunohistochemistry and molecular tools. Poultry viral neoplasms include, Marek's disease, avian leukosis complex, Rous sarcoma, etc. Cancers are also threat to wildlife and laboratory animals. Numerous sporadic case reports are available in literature on these ailments. Mycotoxins-like aflatoxin B_1 are affecting wide variety of species of animals and birds and causing hepatic cancers.

Statistical data is not available on animal cancers in India owing to lack of importance as compared to economically important infectious diseases. Animal cancer study is mostly limited to case description and reporting. Compared to human medicine, veterinary medicine is lagging behind in early diagnosis and the therapeutic aspects of cancers. Some of these cancers are covered in 24 chapters of the present book by leading national experts. Since no such book is available on the topic in veterinary medicine, therefore, present title *Animal Cancers: Trends in Diagnosis, Treatment and Management* is unique and timely covering the deadly malady on cancers in animals focusing on recent trends in diagnosis, treatment and management. This book will not only be useful to veterinarians but also to scholars and academicians of various life science Institutes, Universities and Toxicology Industries.



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