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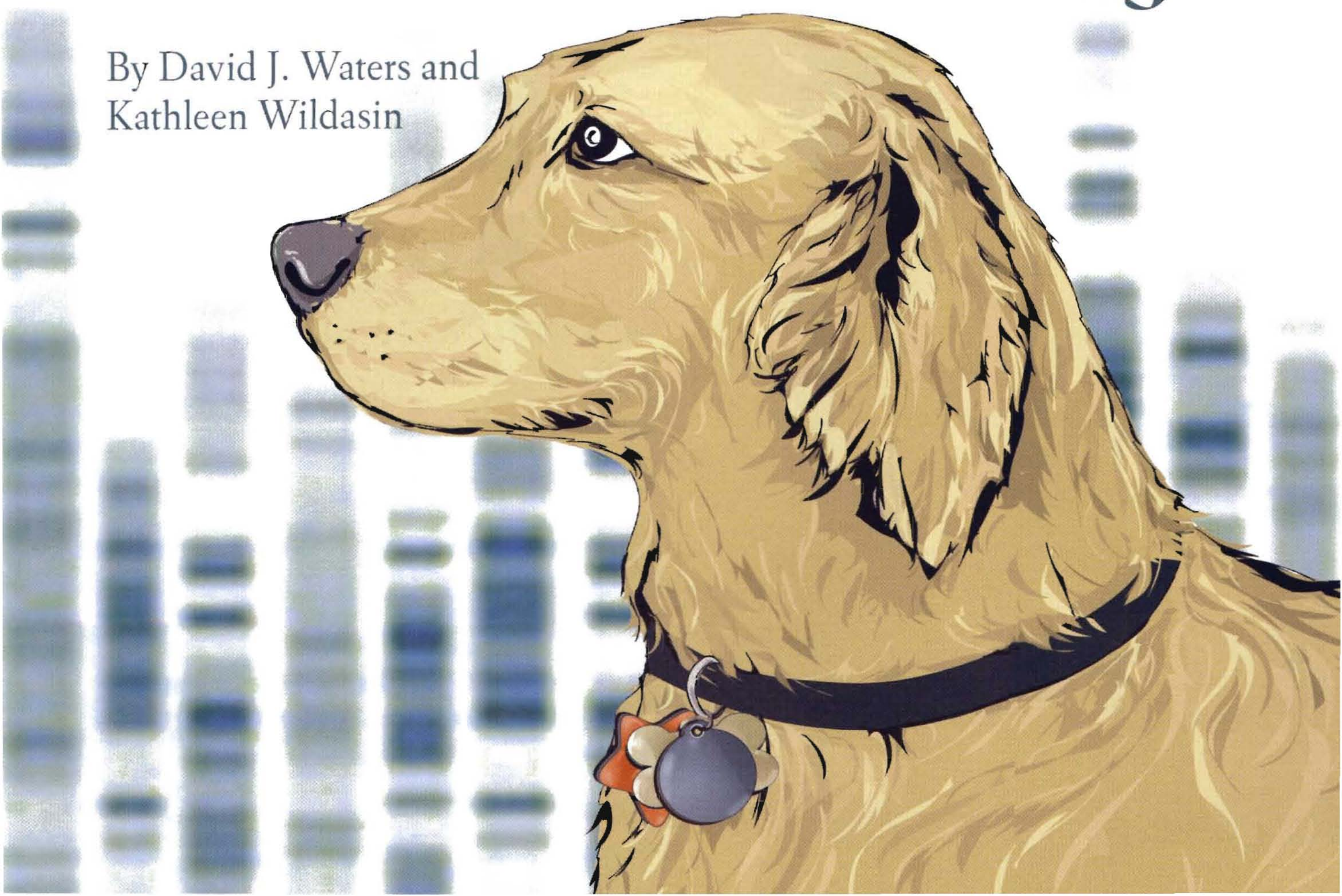
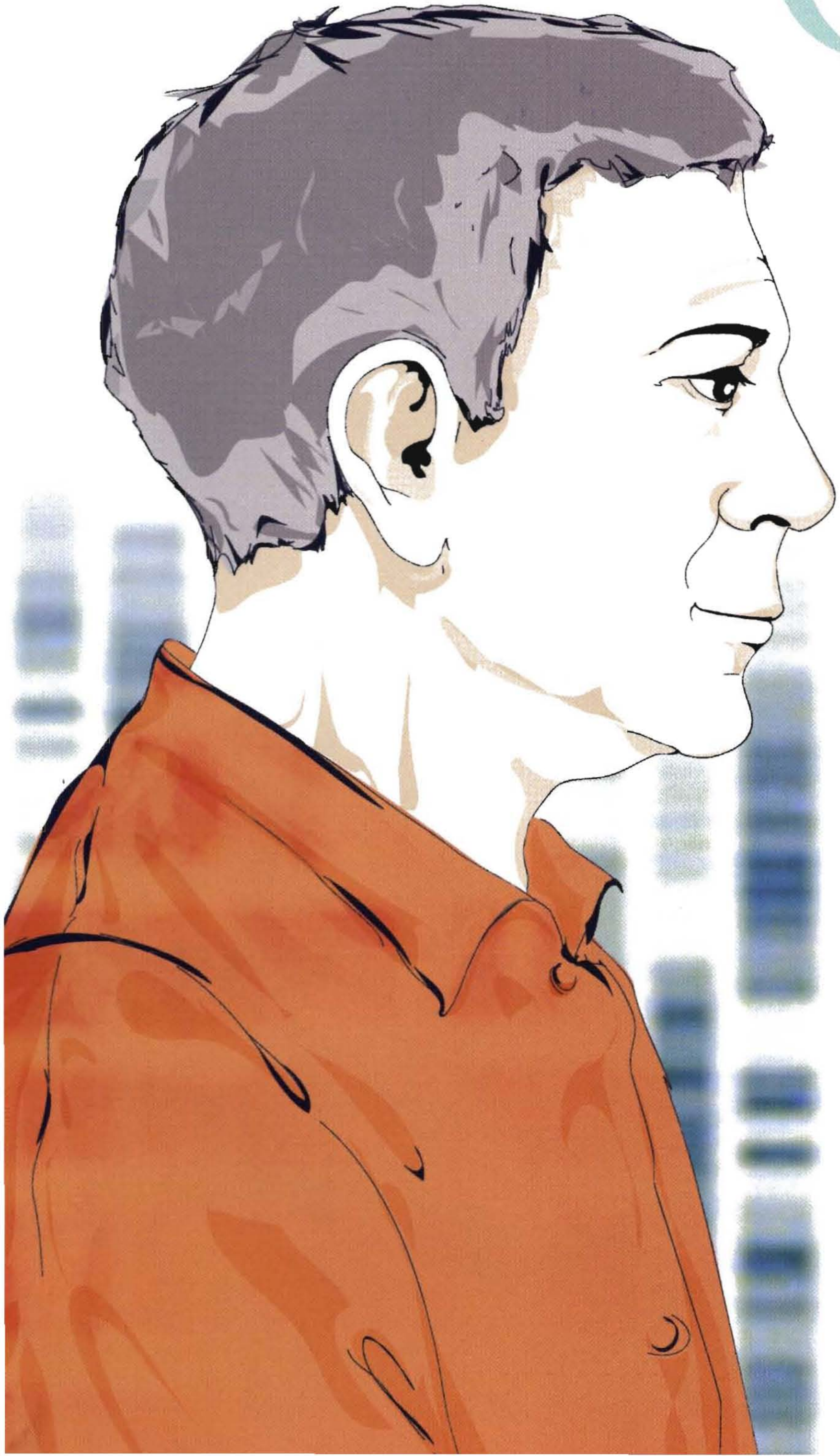
CANCER Clues from PET DOGS



By David J. Waters and Kathleen Wildasin

CANCER Clues *from*



Studies of pet dogs with cancer can offer unique help in the fight against human malignancies while also improving care for man's best friend

Imagine a 60-year-old man recuperating at home after prostate cancer surgery, drawing comfort from the aged golden retriever beside him. This man might know that a few years ago the director of the National Cancer Institute issued a challenge to cancer researchers, urging them to find ways to "eliminate the suffering and death caused by cancer by 2015." What he probably does not realize, though, is that the pet at his side could be an important player in that effort.

Reaching the ambitious Cancer 2015 goal will require the application of everything in investigators' tool kits, including an openness to new ideas. Despite an unprecedented surge in researchers' understanding of what cancer cells can do, the translation of this knowledge into saving lives has been unacceptably slow. Investigators have discovered many drugs that cure artificially induced cancers in rodents, but when the substances move into human trials, they usually have rough sledding. The rodent models called on to mimic human cancers are just not

PET DOGS

By David J. Waters and Kathleen Wildasin

DOGS AND HUMANS often fall ill with the same kinds of cancers. Scientists contend that the similarities between these tumors, including genetic resemblances, can be instructive. (The background represents the DNA sequence from a tissue sample.)

measuring up. If we are going to beat cancer, we need a new path to progress.

Now consider these facts. More than a third of American households include dogs, and scientists estimate that some four million of these animals will be diagnosed with cancer this year. Pet dogs and humans are the only two species that naturally develop lethal prostate cancers. The type of breast cancer that affects pet dogs spreads preferentially to bones—just as it does in women. And the most frequent bone cancer of pet dogs, osteosarcoma, is the same cancer that strikes teenagers.

Researchers in the emerging field of comparative oncology believe such similarities offer a novel approach for combating the cancer problem. These investigators compare naturally occurring cancers in animals and people—exploring their striking resemblances as well as their notable differences.

Right now comparative oncologists are enlisting pet dogs to tackle the very obstacles that stand in the way of achieving the Cancer 2015 goal. Among the issues on their minds are finding better treatments, deciding which doses of medicines will work best, identifying environmental factors that trigger cancer development, understanding why some individuals are resistant to malignancies and figuring out how to prevent cancer. As the Cancer 2015 clock keeps ticking, comparative oncologists ask, Why not transform the cancer toll in pet dogs from something that is only a sorrow today into a national resource, both for helping other pets and for aiding people?

Why Rover?

FOR DECADES, scientists have tested the toxicity of new cancer agents on laboratory beagles before studying the compounds in humans. Comparative oncologists have good reason to think that pet dogs with naturally occurring cancers can likewise become good models for testing the antitumor punch delivered by promising treatments.

One reason has to do with the way human trials are conducted. Because of the need to ensure that the potential benefits of an experimental therapy outweigh the risks, researchers end up evaluating drugs with the deck stacked against success; they attempt to thrash bulky, advanced cancers that have failed previous treatment with other agents. In contrast, comparative oncologists can test new treatment ideas against early-stage cancers—delivering the drugs just as they would ultimately be used in people. When experimental drugs prove helpful in pets, researchers gain a leg up on knowing which therapies are most likely to aid human patients. So comparative oncologists are optimistic that their findings in dogs will be more predictive than rodent studies have been and will help expeditiously identify those agents that should (and should not) be tested in large-scale human trials.

Pet dogs can reveal much about human cancers in part because of the animals' tendency to become afflicted with the same types of malignancies that affect people. Examples abound. The most frequently diagnosed form of lymphoma affecting dogs mimics the medium- and high-grade B cell non-Hodgkin's lymphomas in people. Osteosarcoma, the most common bone cancer of large- and giant-breed dogs, closely resembles the osteosarcoma in teenagers in its skeletal location and aggressiveness. Under a microscope, cancer cells from a teenager with osteosarcoma are indistinguishable from a golden retriever's bone cancer cells. Bladder cancer, melanoma and mouth cancer are other examples plaguing both dog and master. In a different kind of similarity, female dogs spayed before puberty are less prone to breast cancer than are their nonspayed counterparts, much as women who have their ovaries removed, who begin to menstruate late or who go into menopause early have a reduced risk for breast cancer.

Canine cancers also mimic those of humans in another attribute—metastasis, the often life-threatening spread of cancer cells to distant sites throughout the body. Solving the mystery of how tumor cells metastasize to particular organs is a top research priority. When certain types of cancers spread to distant organs, they tend to go preferentially to some tissues over others, for reasons that are not entirely clear. Because metastasis is what accounts for most deaths from cancer, researchers would very much like to gain a better understanding of its controls. Studies in pet dogs with prostate or breast cancer might prove particularly useful in this effort, because such tumors frequently spread in dogs as they do in humans—to the skeleton. Indeed, research in pet dogs is already attempting to work out the interactions between tumor cells and bone that make the skeleton such a favorite site for colonization.

Scientists also have deeper theoretical grounds for thinking that pet dogs are reasonable models for human cancer. Evolutionary biologists note that dogs and humans are built like Indy race cars, with successful reproduction as the finish line. We are designed to win the race, but afterward it does

Overview/*Canine Cancer*

- **Millions of pet dogs will have cancer diagnosed this year. In many of those animals, the malignancy will look and behave much as it would in humans, such as spreading to the same organs.**
- **Investigation of these cancers can help researchers to better understand the biology of the human forms. Also, studies of experimental treatments in the animals can indicate which therapies most deserve further testing in dogs and humans and can offer guidance on the best doses and methods of delivery.**
- **Such studies should improve cancer prevention and therapy for both humans and their canine companions.**

ALISON KENDALL (*illustration*); PASIEKA *Photo Researchers, Inc.* (*autoradiogram*) (*preceding pages*); JANA BRENNING (*this page*)

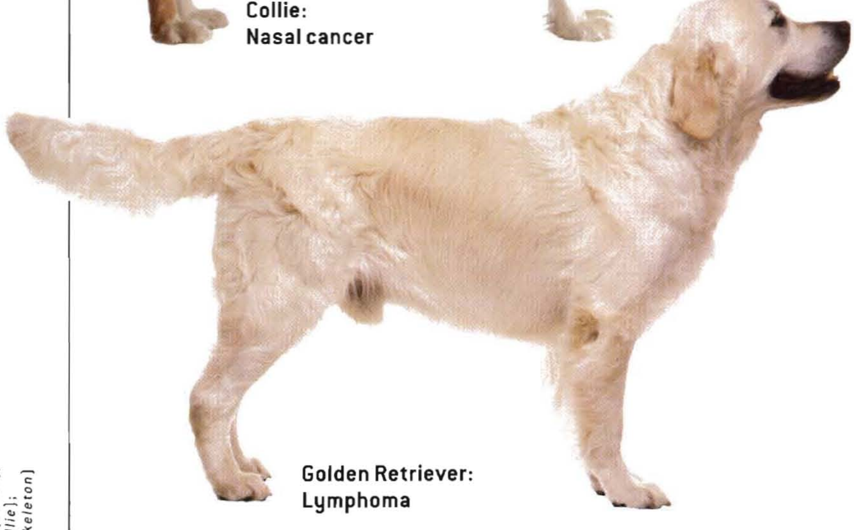
BREEDS AT RISK

The breeds represented by the dogs shown here are particularly susceptible to cancers that also afflict humans. These malignancies look like the human forms under a microscope and act similarly as well. Such resemblances mean that canine responses to experimental drugs should offer a good indication of how the compounds will work in humans. In addition, research into the genes that increase susceptibility of specific breeds to particular cancers is expected to help pinpoint susceptibility genes in humans.

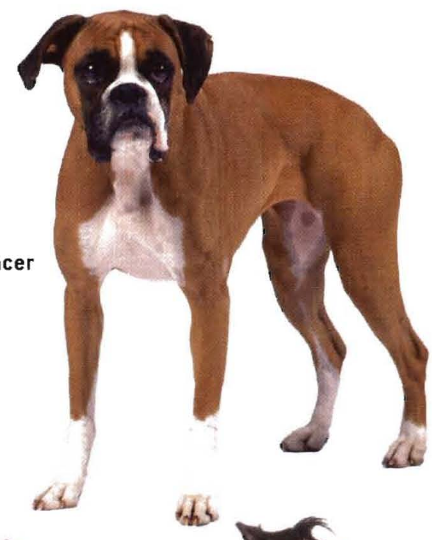
Rottweiler: Bone cancer

Collie: Nasal cancer

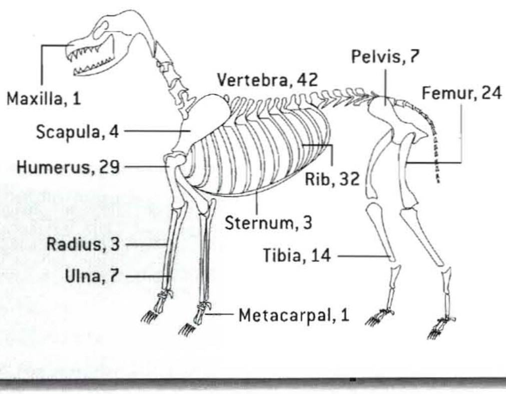
Chow Chow: Stomach cancer



Golden Retriever: Lymphoma



Boxer: Brain cancer



SKELETAL DISTRIBUTION of metastases is another aspect of cancer similar in dogs and humans. In dogs, the lesions display the same "above the elbow, above the knee" pattern seen in people. Insights into why that pattern occurs in dogs could help explain the distribution in humans and perhaps suggest new ideas for intervening. (The numerals indicate the number of metastases found at each site in one study.)

Scottish Terrier: Bladder cancer

DK LTD. *Corbis* (*retriever*); CORBIS (*rottweiler*); CORBIS (*boxer*); YANN ARTHUS-BERTRAND *Corbis* (*chow chow, terrier, collie*); DANIELA NAOMI MOLNAR, SOURCE: DAVID WATERS (*dog skeleton*)

not matter how rapidly we fall apart. This design makes us ill equipped to resist or repair the genetic damage that accumulates in our bodies. Eventually this damage can derange cells enough to result in cancer. In the distant past, our human ancestors did not routinely live long enough to become afflicted with age-related cancers. But modern sanitation and medicine have rendered both longevity and cancer in old age common. Much the same is true for our pets. Pet dogs, whom we carefully protect from predation and disease, live longer than their wild ancestors did and so become prone to cancer in their later years. Thus, when it comes to a high lifetime risk for cancer, pets and people are very much in the same boat.

Aside from acquiring cancers that resemble those in people, pet dogs are valuable informants for other reasons. Compared with humans, they have compressed life spans, so scientists can more quickly determine whether a new prevention strategy or therapy has a good chance of improving human survival rates. Finally, although veterinarians today are far better equipped to treat cancer than they used to be, the standard treatments for many canine tumors remain ineffective. Because most pet cancer diagnoses end in death, dog owners are often eager to enroll their animals in clinical trials that could save their pet's life—and possibly provide the necessary evidence to move a promising therapy to human clinical trials.

The Ideal Animal Model: An Invalid Concept

RODENTS are a favorite model of cancer researchers, but therapies that work beautifully in rats and mice often fail in humans.

Some experts contend that progress toward finding cancer cures has been frustratingly slow because of the inadequacy of available animal models of human cancer. But perhaps the problem is not in the animals themselves but in the way they are used and what we are forcing them to tell us.

The dictionary defines a model as "an imitation." By definition, therefore, an animal model of cancer is not the same as a person who acquires cancer. Rodent models are often produced by making "instant cancers"—that is, by injecting the animals with tumor cells or bombarding them with carcinogen doses that are higher than any human will ever encounter. It is doubtful that cancers produced in that way will accurately recapitulate a complex process that often requires more than 20 to 30 years to develop in people. Naturally occurring animal tumors, such as those affecting pet dogs, provide the opportunity to study this complexity in a less artificial way.

But no one animal model is capable of answering all the important questions related to the prevention or treatment of a particular type of human cancer. Researchers would be best served by turning their attention toward carefully crafting specific questions and letting the questions drive the selection of the model system. For some questions, cell culture or rodent studies will be appropriate. To answer others, researchers will have to resort to studying humans. In that sense, a human clinical trial is a form of animal model research—a specific collection of people is being used to represent the overall human population. *—D.J.W.*

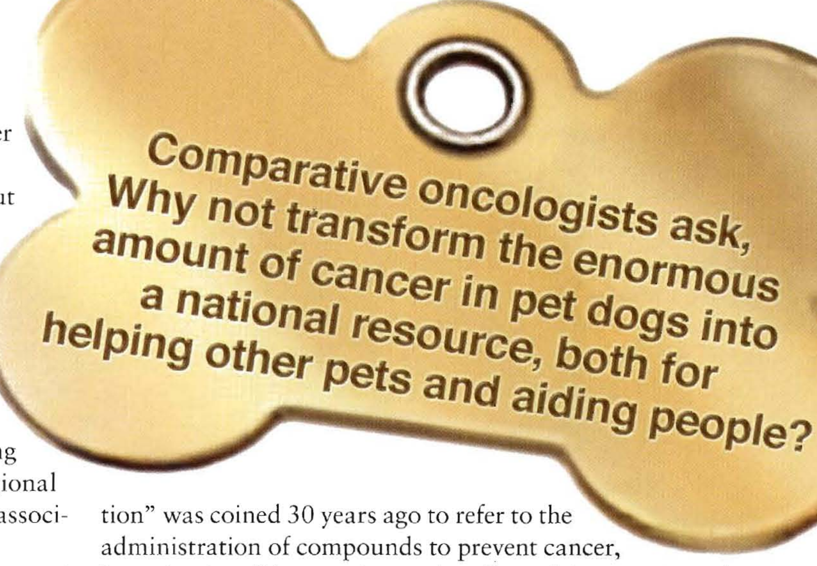
Advancing Cancer Therapy

VARIOUS CANCER TREATMENT studies featuring pet dogs have now been carried out or begun. Some of the earliest work focused on saving the limbs of teenagers with bone cancer. Twenty-five years ago a diagnosis of osteosarcoma in a youngster meant amputation of the affected limb, ineffective or no chemotherapy (drugs administered into the bloodstream to attack tumors anywhere in the body), and almost certain death. Today limb amputation can be avoided by chiseling out the diseased bone tissue and replacing it with a bone graft and metal implant—a process partially perfected in pet dogs by Stephen Withrow and his colleagues at Colorado State University. Withrow's team pioneered technical advances that reduced the likelihood of complications, such as placing bone cement in the marrow space of the bone graft. The researchers also showed that preoperative chemotherapy delivered directly into an artery could convert an inoperable tumor into an operable one. The group's work is credited with significantly increasing the percentage of teenagers who today can be cured of osteosarcoma.

Although a tumor's local effects are often controllable using surgery or radiation, metastasis is much harder to combat. For that, drug therapy is required. New compounds under development aim to disrupt key cellular events that regulate the survival and proliferation of metastatic tumor deposits as well as their sensitivity to cancer-fighting drugs. One experimental agent, ATN-161, which inhibits the formation of new blood vessels that foster tumor growth and metastasis, is currently being evaluated in large-breed dogs with bone cancers that have spread to the lungs. The ability of ATN-161 to enhance the effects of conventional chemotherapies is also under study. If these trials succeed, they could smooth the way toward clinical trials in humans.

Cancer researchers are also turning their attention to more familiar kinds of pharmaceuticals, including nonsteroidal anti-inflammatory drugs (NSAIDs), the class of compounds that includes ibuprofen. Certain NSAIDs have exhibited significant antitumor activity against a variety of canine tumors. In studies of pet dogs with bladder cancer, for example, the NSAID piroxicam showed such impressive antitumor activity that the drug is now in human clinical trials to see if this treat-

PASCAL GOETGHELUCK *Photo Researchers, Inc.*



ment can derail the progression of precancerous bladder lesions to life-threatening cancer.

Developing new cancer therapies is not just about finding novel drugs. It is about optimizing drug delivery to the patient. In your vein or up your nose? That is the kind of information scientists testing new agents against lung cancer need to know. If the right amount of drug does not make it to the tumor, then even substances with impressive credentials for killing tumor cells in a petri dish will not stand a chance of working in human patients. Moreover, delivering pharmaceuticals directly to the target—so-called regional therapy—has the added benefit of avoiding the toxicity associated with systemic therapy.

Investigators have used pet dogs to study the intranasal delivery of a cytokine, a small immune system molecule, called interleukin-2 (IL-2) to treat naturally occurring lung cancers. Positive results from these experiments led to feasibility trials of inhaled IL-2 in human patients with lung metastases, further leading to trials with another cytokine, granulocyte colony stimulating factor. Pet dogs can also aid researchers in optimizing the dosing and delivery protocols for drugs that have already made their way into human trials.

Another challenge that pet dogs are helping to overcome is determining the extent of tumor spread, called clinical staging. Accurate staging is critical for devising therapeutic game plans that will maximally benefit the patient while minimizing exposure to harsh treatments that are unlikely to help at a given disease stage. For example, the odds that a teenager will survive osteosarcoma are increased by accurate identification (and subsequent surgical removal) of lung metastases.

Doctors typically determine the presence and extent of such metastases with noninvasive imaging techniques, such as computed tomography (CT). To assess how accurate such scanning is, one of us (Waters), along with investigators from Indiana University School of Medicine, collected CT images of the lungs from pet dogs with metastatic bone cancer and then examined the tissue at autopsy to verify that what was interpreted as a "tumor" on the scan really was a tumor and not a mistake. Results showed that state-of-the-art imaging with CT—the same type used in clinical staging of bone cancer in teenagers—significantly underestimates the number of cancer deposits within the lung. By revealing the limited accuracy of existing and experimental techniques, pet dogs are helping optimize the next generation of technologies for improved cancer detection.

Taking Aim at Cancer Prevention

BUT CANCER RESEARCHERS are shooting for more than improved detection and better treatment; they also want to prevent the disease. Surprisingly, prevention is a relatively new concept within the cancer research community. What cardiologists have known for a long time—that millions of lives can be saved through the prevention of heart disease—is just now gaining traction in the cancer field. The term "chemoprevention" was coined 30 years ago to refer to the administration of compounds to prevent cancer, but scientists did not gather nationally to debate cutting-edge knowledge of cancer prevention until October 2002.

Today the pace is quickening as investigators are examining a diverse armamentarium of potential cancer-protective agents. But finding the proper dose of promising agents has always been challenging. Indeed, failure to do so proved disastrous for some early human trials of preventives. For example, in two large lung cancer prevention trials, people receiving high doses of the antioxidant nutrient beta-carotene had an unexpected *increase* in lung cancer incidence compared with placebo-treated control subjects.

Can dogs accelerate progress in cancer prevention? Recently canine studies have helped define the dose of an antioxidant—the trace mineral selenium—that minimizes cancer-causing genetic damage within the aging prostate. The message from the dogs: when it comes to taking dietary supplements such as selenium to reduce your cancer risk, more of a good thing is not necessarily better. Elderly dogs given moderate doses ended up with less DNA damage in their prostates than dogs given lower or higher amounts. Comparative oncologists hold that dog studies conducted before large-scale human prevention trials are initiated can streamline the process of finding the most effective dose of cancer preventives and can enable oncologists to lob a well-aimed grenade at the cancer foe.

Pet dogs can assist in preventing human cancers in another way. For years, dogs in the research laboratory have advanced understanding of the acute and long-term effects of high doses of cancer-causing chemicals. But pet dogs, just by going about their daily lives, could serve as sentinels—watchdogs, if you will—to identify substances in our homes and in our backyards that are carcinogenic at lower doses. If something can cause cancer, the disease will show up in pets,

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with their compressed life spans, well before it will in people.

Take asbestos. Most human cases of mesothelioma (a malignancy of tissues lining the chest and abdomen) stem from asbestos exposure. Symptoms can appear up to 30 years after the incriminating exposure. Investigators have now documented that mesothelioma in pet dogs is also largely related to encountering asbestos, most likely through being near a master who came into contact with it through a hobby or work. But in dogs, the time between exposure and diagnosis is comparatively brief—less than eight years. So the appearance of the cancer in a dog can alert people to look for and remediate any remaining sources of asbestos. Also, closer monitoring of exposed individuals might lead to earlier diagnosis of mesothelioma and render these cancers curable.

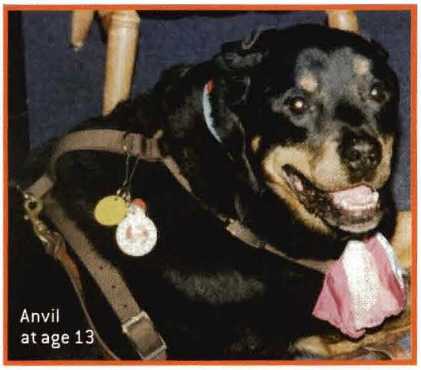
Pet dogs could assist in discovering other environmental hazards. Some well-documented geographic "hot spots" show an unusually high incidence of certain cancers. For example, women living in Marin County, California, have the country's highest breast cancer rate. Scientists typically try to identify the factors contributing to cancer in hot spots by comparing the genetics and behavior of people who become afflicted and those who do not. To advance the effort, comparative oncologists are now establishing cancer registries for pet dogs in those areas. If both pets and people living in a particular community experience higher-than-normal cancer rates, the finding would strengthen suspicions that these malignancies are being triggered by something in the environment.

Analyzing tissues of dogs could even potentially speed identification of the specific hazard. Many toxic chemicals, such as pesticides, concentrate themselves in body fat. So it might make sense to collect tissues from dogs during common elective surgical procedures (for example, spaying) or at autopsy. Later, if an unusually high number of people in an area acquire a certain form of cancer, investigators could analyze levels of different chemicals in the samples to see if any are particularly prominent and worth exploring as a contributing factor.

Why Uncle Bill Avoided Cancer

BECAUSE CANCER IN PET DOGS is so commonplace, the animals might be able to assist in solving an age-old mystery.

Cancer Resistance: Lessons from the Oldest Old

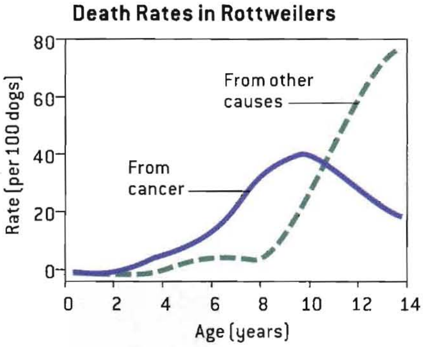


Anvil at age 13

The risk of most human and canine cancers increases dramatically with age. This pattern has led to the belief that cancer is simply the result of a time-related accumulation of genetic damage. But recent studies of people who live to be 100 years old (centenarians) reveal an intriguing paradox: the oldest old among us are much less likely to succumb to cancer than are people who die in their 70s or 80s. Do the oldest-old pet dogs share a similar resistance to cancer mortality?

To answer this question, my colleagues and I consulted pet owners and veterinarians to construct lifetime medical histories of a large cohort of rottweiler dogs living in North America. We found that the likelihood of dying from cancer within two years rose with age during adulthood until dogs reached about 10 years but then declined after that. Moreover, exceptionally old dogs (those older than 13 years) were much less likely to die of cancer than were dogs with usual longevity even though the risk of dying from other causes continued to rise.

These findings raise the exciting possibility that studies comparing oldest-old dogs to those with usual longevity might reveal genes that regulate cancer resistance. Gene variations (so-called polymorphisms) responsible for cancer resistance and exceptional longevity in dogs could then be evaluated to see whether they are also overrepresented in the oldest-old humans. If they are, scientists can try to learn how the



IN ROTTWEILERS who live past 10 years, getting older means having better odds of avoiding death from cancer.

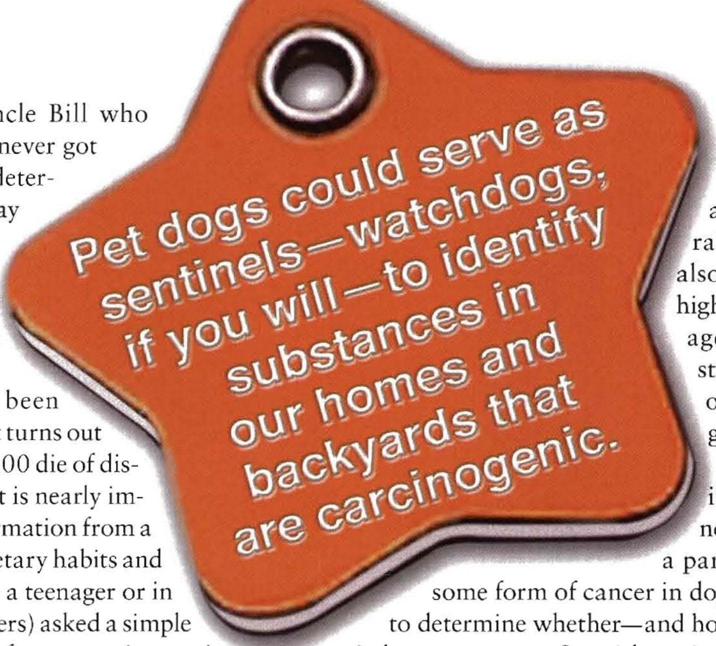
Grace Fair at age 103

molecular interactions regulated by these genes alter cancer susceptibility at the tissue level.

At present, the precise nature of cancer resistance in human centenarians is poorly defined. Detailed autopsy studies of oldest-old dogs are currently under way to explore this issue. These studies should determine whether cancer resistance reflects a complete suppression of the biological events that give rise to cancer—for example, through increased repair of DNA damage—or whether tumors actually arise but are of the nonlife-threatening variety. By better understanding the genetic and pathological basis of cancer resistance in the oldest old, scientists will be better positioned to develop practical interventions that will reduce the average person's cancer risk. *—D.J.W.*

COURTESY OF DONNA RICE (*rottweiler*); COURTESY OF THE NEW ENGLAND CENTENARIAN SOCIETY (*woman*)

Almost everyone has an Uncle Bill who smoked two packs a day and never got lung cancer. So what factors determine cancer resistance? One way to tease out the answer is to find populations resistant to cancer and study them closely—their genetics, their diet and their lifestyle.



Such a population has been found—human centenarians. It turns out that most folks who live to be 100 die of disorders other than cancer. But it is nearly impossible to collect reliable information from a 102-year-old woman on her dietary habits and physical activity when she was a teenager or in her mid-40s. So one of us (Waters) asked a simple question: Is this phenomenon of cancer resistance in the oldest old operational in pet dogs? The answer is yes [*see box on opposite page*]. Now by interviewing owners of very old pet dogs, comparative oncologists can construct accurate lifetime histories of "centenarian" dogs. Combine this prospect with the ability to collect biological samples (such as blood for genetic analysis and for tests of organ function) from very old dogs as well as from several generations of their offspring, and you have a unique field laboratory for probing the genetic and environmental determinants of cancer resistance.

The puzzle of cancer resistance can also be addressed in another way—by examining differences in cancer susceptibility between dogs and humans. In people, obesity and diets rich in animal fat are known to increase risk for colon cancer. In contrast, colorectal cancer in dogs is uncommon, even though many pet dogs are obese and consume a high-fat diet. Scientists are now contemplating the use of dogs as a "negative model" of colon cancer in the hope of identifying factors able to confer cancer resistance to people whose style of living strongly favors colon cancer development. Knowledge of resistance factors could suggest new interventions for nonresistant individuals.

A Growing Effort

HISTORICALLY, comparative oncology research has been conducted in university-based hospitals and laboratories where veterinary oncologists are trained. But other organizations have begun to recognize the potential for this kind of research to translate into better care for people, and these institutions are now actively engaged in comparative oncology research.

The Gerald P. Murphy Cancer Foundation began in 2001 to accelerate the discovery of improved methods for preventing and treating prostate and bone cancers affecting both people and pets. The Animal Cancer Foundation in New York City has funded comparative oncology studies and has recently established a repository of biological specimens of diseased and healthy animals as a resource for researchers chasing biological indicators of cancer risk. And in 2003 the National Cancer Institute developed the Comparative Oncology Program, which designs trials involving dogs with naturally occurring cancers and also provides researchers with high-quality, canine-specific reagents needed for in-depth studies of the molecular biology, protein chemistry and genetics of dog tumors.

Moreover, the sequencing of the canine genome is now complete. Discovery that a particular gene is involved in some form of cancer in dogs will enable investigators to determine whether—and how—the same gene operates in human cancers. Scottish terriers with bladder cancer, rottweilers with bone cancer and golden retrievers with lymphoma—each breed can help elucidate the calamitous combinations of genes and environment that lead to cancer.

Of course, there are limitations inherent in the use of animals to mimic human cancer—whether you are talking about rodents, dogs or other species. No single, ideal animal model for cancer exists [*see box on page 6*]. The best science is done by asking good questions and then using the research tools most likely to yield meaningful answers. At times, following that rule in cancer research will mean turning to dogs to track down that hard-to-win knowledge.

The intriguing similarities between the cancers of people and pets—once a mere curiosity—are now being systematically applied to transform cancer from killer to survivable nuisance. Comparative oncologists are not inducing cancer in animals but are compassionately treating pet dogs suffering from the same kinds of lethal cancers that develop naturally in both man and man's best friend. They are putting our canine companions on the trail of a killer in ways that can save both pets and people. SA

JANA BRENNING

MORE TO EXPLORE

Exceptional Longevity in Pet Dogs Is Accompanied by Cancer Resistance and Delayed Onset of Major Diseases. D. M. Cooley, D. L. Schlittler, L. T. Glickman, M. Hayek and D. J. Waters in *Journal of Gerontology*, Vol. 58, No. 12, pages B1078–B1084; 2003.

Phase I Dose-Escalating Study of SU11654, a Small Molecule Receptor Tyrosine Kinase Inhibitor, in Dogs with Spontaneous Malignancies. C. A. London et al. in *Clinical Cancer Research*, Vol. 9, pages 2755–2768; 2003.

Herbicide Exposure and the Risk of Transitional Cell Carcinoma of the Urinary Bladder in Scottish Terriers. L. T. Glickman, M. Raghavan, D. W. Knapp, P. L. Bonney and M. H. Dawson in *Journal of the American Veterinary Medical Association*, Vol. 224, No. 8, pages 1290–1297; 2004.

Spontaneous and Genetically Engineered Animal Models: Use in Preclinical Cancer Drug Development. K. Hansen and C. Khanna in *European Journal of Cancer*, Vol. 40, pages 858–880; 2004.

Comparative Oncology Program of the National Cancer Institute (including information about clinical trials for dogs): **http://ccr.cancer.gov/resources/cop/**