32nd Annual Canine Symposium

The 32nd Annual Canine Symposium was held on Saturday, January 26 at VHUP.

The event was generously supported by Pedigree®. Six faculty members gave presentations on an array of medical problems in dogs

Following are summaries of the faculty presentations:

My Pet has Changed: Understanding Aging-Related Behavior Changes in Dogs

Dogs, like people, may experience dementia as they age. Fortunately, explained **Dr. Ilana Reisner**, assistant professor of behavioral medicine and director of the behavior clinic at VHUP, the behavior changes associated with age-related degeneration – termed "cognitive dysfunction syndrome" (CDS) – can be managed through medication, and environmental and behavioral modification. Dr. Reisner discussed the prevalence, pathogenesis, clinical manifestations, diagnosis and treatment of CDS.

The clinical signs of CDS result from a number of degenerative changes, including the death of brain cells secondary to oxidative damage. This leads to subsequent cerebral and cerebellar atrophy, and ventricular enlargement. The brain tissue is further compromised by decreased local blood flow and deposition of beta-amyloid protein. Mental capacity is physiologically altered by neurotransmitter and receptor dysfunction. "The brain pathology impairs the way affected dogs think and function. This results in behavioral changes," said Dr. Reisner.

The signs of CDS, which was first recognized in dogs about 10 years ago, include anxiety; disorientation (i.e., apparent confusion and memory loss, staring, aimless wandering, getting "stuck" in corners); inappropriate elimination (i.e., "accidents" in housetrained dogs, failure to adequately signal at the door, inappropriate elimination in view of owners, indoor elimination shortly after being outdoors); changes in social behavior (i.e., social detachment, irritability, decreased interest in interaction); changes in sleep-wake patterns (i.e., evening restlessness, decreased nighttime sleep, more frequent and deeper daytime sleep); and changes in activity level (i.e., decreased activity or increased activity with repetitive behaviors).

It is important to differentiate behavioral problems associated with CDS from those of other physical causes because, Dr. Reisner explained, "in the elderly dog, we can see behavioral changes that are manifestations of physical problems."

For example, decreased responsiveness, similar to that of CDS, can be caused by the expected sensory impairment of old age. Impaired mobility can result from osteoarthritis, cardiovascular disease and hormonal disorders. Inappropriate elimination can be a symptom of urinary tract or systemic disease, or of neurological impairment.

Nevertheless, CDS is a significant problem, particularly in light of the fact that there are some 18 million pet dogs over seven years of age in the U.S. In a recent prevalence study that surveyed owners of 180 dogs between the ages of 11 and 16, 28 percent of owners of 11-12-year-old dogs, and 68 percent of owners of 15-16-year-old dogs, reported one or more categories of cognitive impairment. In another study, 75 percent of owners of older dogs reported that their pets exhibited at least one sign of CDS, yet only 12 percent of owners said they had spoken to their veterinarian about it.

CDS is probably underreported by owners, said Dr. Reisner, because "people sometimes don't complain about behavioral problems that they view as normal and almost inevitable in old dogs."

Unfortunately, Dr. Reisner pointed out, CDS worsens with age, hence the need for timely diagnosis and treatment. A diagnosis of CDS, which is based on clinical signs, cannot be made until underlying medical causes for the behavioral changes have been ruled out or accounted for.

The choices for drug therapy for CDS are varied and diverse. Perhaps the most widely-touted is selegiline (Anipryl®), which enhances dopamine function in the brain. In a recent study of 200 dogs with CDS, selegiline administration significantly improved their activity levels, sleep-wake cycles and elimination habits.

Other drug categories used in the treatment of CDS include vasodilators, calcium-channel blockers, antidepressants and sedatives. Antioxidants (vitamins E and C, selenium), which scavenge free radicals and thereby reduce tissue damage, have been used with some success. In several studies, Hill's Prescription Diet® b/d™ – an antioxidant diet designed to reduce brain tissue damage – was associated with improvements in social interaction, discrimination tests and activity level in cognitively-impaired older dogs.

In dogs suffering from CDS, psychopharmacology must be combined with environmental modification. For example, said Dr. Reisner, senescent dogs that are eliminating indoors should be treated like pups: Restrict access to indoor areas, do not rely on signaling behavior, reward outdoor elimination and modify feeding schedules.

In conclusion, she added, behavioral problems in elderly dogs rarely exist in isolation, so any concurrent medical problems must be diagnosed and treated. Behavioral changes should be closely monitored, and veterinary visits increased to every three or four months, she stressed, because "our aged pets deserve our full commitment and care."

Chemotherapy for the Canine Cancer Patient

Chemotherapy has served to expand both the length and quality of life for dogs with cancer. **Dr. Jennifer Baez, V'92**, assistant professor of oncology at VHUP, described the pathogenesis of cancer, and chemotherapy and other treatment options in dogs.

Cancer, the manifestation of uncontrolled cell growth, occurs as a result of genetic damage and/or changes in a cell. Such changes can be caused by innate genetic factors, as in the case of certain cancer-prone breeds like boxers, German shepherds, golden retrievers and Scottish terriers. In these breeds, oncogenes – genes that initiate the cancer process – have been inadvertently selected for over time. Cancer can also result from DNA damage by hormones and carcinogens (chemical, physical, radiation, foreign bodies, viruses). In healthy animals, cells that are damaged undergo apoptosis, or natural cell death. Cancer cells, however, have lost this ability and therefore grow uncontrollably. The course and rate of this growth is determined by cancer tissue type (i.e., hemangiosarcoma vs. thyroid carcinoma).

Cancer is a significant disease in dogs, said

32nd Annual Canine Symposium

Dr. Baez. Nearly one-quarter of all dogs, and 45 percent of dogs older than ten years of age, will die of cancer. The incidence of canine cancer appears to be on the rise, which could be partially accounted for by increased life span and better diagnostic methods.

Treatment strategies for cancer in dogs differ somewhat from those employed in people. In the latter, the goal is a cure, and very aggressive regimens are often used, resulting in severe side effects that may require intensive supportive care. In dogs, on the other hand, the goal of therapy is to extend a good quality of life, so treatments are generally less aggressive.

Treatment is based on histologic grade, which determines tumor aggressiveness and disease progression, or staging. Low-grade tumors, which are slow to metastasize, generally carry a good prognosis and are often treated with radiation and/or surgery. High-grade tumors, conversely, are fast to metastasize, and are normally treated with chemotherapy and/or surgery to prolong survival. Cancer is staged using a variety of diagnostic tests, such as blood work, radiography, ultrasound, CT and MRI.

Surgery is most effective when a tumor is low-grade and/or when it is localized with no evidence of metastasis. Further, the tumor should be in an area where there is enough skin and tissue to secure adequate tissue margins. Radiation, which damages and kills rapidly-dividing cells, can be used as primary therapy or to purge surgical margins of any remaining tumor cells. Radiation works best in cancers that are sensitive to it, when metastasis has not yet occurred, and when tumor location is not proximate to tissue that, if damaged by radiation, could be life-threatening for the patient.

Chemotherapy is employed when cancer is present in multiple locations. It is most effective for cancers that are sensitive to chemotherapy, in cases where only microscopic disease is present, and in patients that are otherwise healthy and feeling good. Chemotherapy works at different stages of the cell cycle to halt replication of rapidly-dividing cells, which includes cancer cells. Many classes of chemotherapy exist, each working by a slightly different mechanism.

Chemotherapy can be used as a primary agent, such as for lymphoma, or as an initial treatment to shrink a tumor prior to surgery or radiation. Chemotherapeutic agents can be administered systemically, intralesionally, via inhalation or intracavitarily. Many new chemotherapeutic agents are available or under investigation for use in animals.

Resistance to chemotherapy is the most common cause for treatment failure, as cancer cells can develop mechanisms for excreting or inactivating the drug. Chemotherapy delivers the bad with the good, as it damages other rapidly-dividing cells like bone marrow, intestinal and, occasionally, hair cells. Side effects of chemotherapy include low white blood cell counts, vomiting, diarrhea, and hair loss. But, Dr. Baez said, "Our canine patients are amazingly tolerant of the procedure."

A fourth, newer, treatment modality exists for the treatment of cancer in dogs: biotherapy, which includes immunotherapy, angiogenesis inhibition and growth factor modulation. Biotherapy, Dr. Baez declared, is where the future of veterinary oncology likely lies. However, she added, "Because cancer is so multifocal and complex, there is never going to be a single magic bullet to cure cancer."

Interventional Radiology – a New Tool for Difficult Cases

An established tool in human medicine, interventional radiology has tremendous potential for the treatment of serious maladies in pets. **Dr. Chick Weisse, V'98**, resident in surgery at VHUP, described several interventional radiology procedures and their potential applications in a variety of serious medical conditions in dogs. "These techniques have revolutionized disease treatment in human medicine," Dr. Weisse said of interventional radiology procedures, "and now we're looking at their potential applications in veterinary medicine." He is working closely with **Dr. Jeff Solomon**, an interventional radiologist at the Hospital of the University of Pennsylvania, who donates his time and expertise.

Interventional radiology utilizes fluoroscopy to visualize the placement of catheters, stents, balloons, and coils into blood vessels and other tubular structures. These procedures are still largely experimental in animals. As a diagnostic and treatment modality, interventional radiology has many potential advantages over conventional techniques like surgery: minimal invasiveness, minimal anesthesia time, decreased morbidity/mortality, reduced hospital stay and lower cost. Interventional radiology is under investigation at VHUP for many different applications in animals.

Dr. Weisse presented the case of "Prince", the Yorkshire terrier, whose respiratory distress was incited by degeneration of his tracheal cartilages. Interventional radiology was successfully employed to place a stent to keep the trachea open.

In large-breed dogs prone to intrahepatic portosystemic shunts, it is a debilitating condition in which a shunt carries non-detoxified blood from the portal supply directly into the systemic circulation. Affected dogs suffer neurologic conditions such as seizures and head pressing as well as urolithiasis and stunted growth. Surgery for this condition carries a reported 15%-66% percent mortality rate. Under fluoroscopy, a contrast agent is used to aid in passing a catheter into the shunting vessel. Thrombogenic coils are then passed into the shunt to occlude blood flow and return the circulation to normal.

Embolization can be used to obstruct blood supply to tumors, reduce hemorrhage, and provide pain relief. Currently performed to shrink uterine fibroids in women as an alternative to hysterectomy, embolization would be particularly useful in animals with fibroids or other tumors that are so invasive as to render surgery ineffective.

For malignant tumors, a procedure called chemoembolization can be performed to localize drug concentrations to the desired site by delivering chemotherapeutic agents directly into the vessels feeding a tumor. Embolizing particles are then deposited into these vessels, thereby reducing blood supply to the tumor and hampering the tumor's ability to excrete the drug. Dr. Weisse presented the case of "Bobo" the cocker spaniel, who had a nonresectable tumor eroding through the orbital bone into the nasal cavity and skull. Chemoembolization was delivered through a catheter placed in the femoral artery and fed up into the superficial temoporal artery in the head. Three weeks later, the tumor was almost undetectable. In another case, a dog with osteosarcoma had one affected leg amputated. When a second tumor later appeared, amputating the other affected leg was not an option. A catheter was inserted into the femoral artery and a microcatheter then fed into the circumflex humeral artery. After embolization was

performed, an angiogram confirmed that the blood supply to the tumor was successfully terminated. A palliative rather than a curative approach, chemoembolization may need to be repeated if tumors grow back.

Interventional radiology is a safe alternative to surgery for a variety of other procedures, said Dr. Weisse. Angiograms can be used to locate internal areas of hemorrhage, and embolization can then be performed to control bleeding. To dissolve blood clots, thrombolytic drugs can be delivered to the thrombus site via catheterization and fluoroscopy. Interventional radiology can also provide less invasive means for inserting nephrostomy and gastrostomy tubes, and performing liver biopsies.

New Perspectives on Osteoarthritis

Debilitating though osteoarthritis may be, the disease occurrence and course can both be influenced by environmental modulation. **Dr. Gail K. Smith, V'74**, professor of orthopedic surgery and chairman of the department of clinical studies at VHUP, discussed the pathogenesis of hip dysplasia and subsequent osteoarthritis, and presented a yet-unpublished, landmark study conducted at Nestle-Purina that clearly demonstrated an association between dietary regulation and development of joint disease.

Hip dysplasia, which was first described in 1935, is a condition in which the femoral head ("ball") does not fit tightly into the pelvic acetabulum ("socket"). Excess wear develops in the joint, leading to synovial membrane inflammation, cartilage damage, subchondral bone sclerosis, and formation of bony proliferations called osteophytes. Osteoarthritis can occur in other joints as well, and is a significant source of discomfort.

"We care about osteoarthritis because it causes pain and disability in dogs and in people," Dr. Smith explained.

Hip dysplasia is a polygenic trait and therefore very complex. The breeding community has taken great efforts to reduce the incidence of the disease through careful breeding. However, said Dr. Smith, in spite of these efforts, they have not been very successful. In a prevalence study reviewing Orthopedic Foundation for Animals (OFA) figures from 1981-1988, 21 percent of surveyed German shepherds had hip dysplasia. During the subsequent eight years, that figure was 23 percent. Likewise, the occurrence rates for Rottweilers, and Labrador and golden retrievers – which hovered in the range of 24 percent – did not significantly fall over time, as might have been expected if selective breeding were effective. In a study of Airedale terriers in Berlin, the prevalence rates of hip dysplasia in 1981, 1991 and 1996 were 45, 50 and 45 percent, respectively. A Finnish study of 10,335 German shepherds between 1981 and 1997 also showed no genetic headway in reducing the occurrence of hip dysplasia.

"Genetically, we're not getting anywhere fast," Dr. Smith concluded. "But can we do things environmentally? The answer is yes."

Limiting the forces on a joint that is genetically predisposed to hip dysplasia and/or osteoarthritis can reduce the occurrence and severity of disease, he said. Several studies in the past have shown that restricting weight gain, growth rate and exercise can produce small decreases in the occurrence of degenerative joint disease.

Our understanding of hip dysplasia may be revolutionized by a longitudinal study conducted at Nestle-Purina for which Dr. Smith was a coinvestigator. It demonstrated for the first time that limiting a dog's intake of commercial dog food throughout its life significantly reduces the occurrence and severity of hip laxity and/or osteoarthritis. The study, which has not yet been published, tracked 24 paired littermates of Labrador retrievers maintained at Nestle-Purina for 14 years. For each pair of dogs, one was fed ad libitum for 15 minutes daily, while the other ("limit-fed") dog was fed 75 percent of the quantity the first dog consumed. To increase the reliability of the results, the hips were uniformly scored using several different diagnostic methods.

At two years of age, 16 of the dogs fed ad libitum, and only seven of the leaner, limit-fed dogs, had hip dysplasia. Other joints were affected by diet as well: At eight years of age, 19 dogs in the ad-libitum group, and 12 dogs in the limit-fed group, had osteoarthritis of the shoulder. In fact, 68 percent of the ad-libitum dogs and ten percent of limit-fed dogs had both hip and shoulder affected, and 77 percent of the ad-libitum dogs and ten percent of the limit-fed dogs were affected in any two joints. Clearly dietary restriction has a protective effect on other joints as well.

The study also demonstrated that the incidence of hip dysplasia increases linearly with age such that normal hip conformation at two years of age is not necessarily predictive of hip dysplasia risk in later years: About half of the dogs with normal hips at two years of age became dysplastic later in life. The study concluded that for dogs kept lean there was a 6:1 reduction in hip osteoarthritis by two years of age and a 2:1 reduction by end of life. The study also showed that leaner dogs that experience hip dysplasia generally have a lower severity of the condition, and dysplastic dogs that are kept lean maintain better use of their limbs, require less pain medication… and have a better quality of life.

Canine Eye Diseases and their Treatment

A dog's eyesight is subject to a variety of potential problems. **Dr. Elaine Holt**, lecturer in ophthalmology at VHUP, discussed several common inherited ophthalmic conditions in dogs.

Dogs' vision differs somewhat from that of people because of unique architectural features of the canine eye. Dogs have fewer cones – the photoreceptors for color vision, and so cannot perceive color as well as people can. Dogs' eyes are adapted to seeing light and movement. The canine retina is comprised primarily of rods, the photoreceptors that detect dim light and movement. They also have a reflective layer called the tapetum lucidum, which appears as iridescent green. It is thought that this reflective layer "allows the retina to get sort of a double exposure of light back to the eye," Dr. Holt explained.

Progressive retinal atrophy (PRA) is a common disease inherited in several breeds,

32nd Annual Canine Symposium

including the cocker spaniel, Irish setter, Labrador retriever and miniature schnauzer. A disease of the rod photoreceptors, PRA typically presents as loss of night vision and usually progresses to complete blindness. An irreversible condition for which there is no treatment, PRA can be diagnosed by fundic exam, electroretinogram and, in some breeds, genetic testing.

Vision loss in dogs can also be caused by glaucoma, a disease of the optic nerve that usually presents in dogs as an elevation in intraocular pressure. Glaucoma usually results from an anatomic or physiologic abnormality in the drainage angle, rendering it unable to siphon off fluid from the aqueous humor. Fluid then builds up in the anterior chamber, causing the eye to stretch. The disease, which usually affects both eyes, irreversibly damages the retina and optic nerve. Common in cocker spaniels, Basset hounds and Chow Chows, acute glaucoma presents with pain, ocular cloudiness/redness, pupillary dilation and vision loss. Glaucoma is diagnosed with either a Schiotz tonometer or a Tonopen, handheld instruments used to measure intraocular pressure. Topical and systemic drugs are available to decrease intraocular pressure, but medication alone is rarely successful over the long term. Surgical treatment – cyclophotocoagulation – employs a laser to destroy the aqueous-producing organ, the ciliary body. This is more often an eye-saving, rather than a vision-saving, procedure. Alternatively, enucleation can be performed to remove the eye.

The most common cause of blindness in dogs is cataracts, which are opacities in the lens of the eye caused by irreversible alterations in the lens metabolism, such as diabetes mellitus. Not all cloudy lenses are cataracts, Dr. Holt cautioned. Nuclear sclerosis, a normal old-age change characterized by hardening of the lens, can be mistakenly diagnosed as cataracts. Not preventable or treatable with medication, cataracts can be surgically removed by a process called phacoemulsification: Ultrasound is applied directly to the lens to shatter the lens fibers, which are then aspirated out. Eighty percent successful (complications like glaucoma and retinal detachment occur in about one in five cases), phacoemulsification returns functional vision to the eye, but without an intraocular lens implant the ability to focus is poor.

Keratoconjunctivitis sicca (KCS), "dry eye," is a common canine problem to which toy breeds, like Lhasa apsos and shih tzus, are prone. In cases of KCS, the lacrimal (tear) glands are unable to produce adequate moisture for the cornea. Signs of KCS include ocular redness and cloudiness, thick discharge and recurrent eye infections. KCS is diagnosed with the Schirmer tear test, which measures tear production. Most affected dogs respond well to medical treatment, which includes cyclosporine – a tear stimulant, artificial tears, antibiotics and anti-inflammatory drugs.

The eyelids can also be the source of ocular problems, Dr. Holt added. Entropion – inversion of the eyelid(s), occurs commonly in wrinkled breeds like bulldogs, shar peis, Chow Chows and Rottweilers. Entropion is damaging to the eye because it allows the hair from the face to rub against the surface of the eye, leading to excessive squinting, tear production and corneal Ulcers. Entropion is repaired with surgery to evert the affected eyelid(s).

Antibiotic Resistance: Malice in Wonderland

Ever since Ehrlich reported in 1907 that *Trypanosoma brucei* became resistant to parosaniline after repeated exposure, we have had a sense of the resistance faculties of bacteria. **Dr. Shelley Rankin**, research assistant professor in microbiology at the School, discussed the unique mechanisms of bacterial resistance.

Bacteria are single-celled organisms with a cell wall, cell membrane, single chromosome, DNA fragments called plasmids, protein-producing ribosomes and, in some cases, flagella that provide motility. Plentiful and ubiquitous, bacteria exist in greater quantity on a human hand than people exist on the entire earth. And no natural environment is too harsh for them – from hot springs to Antarctic ice. Earth's very first inhabitants, bacteria are its true pioneers. As such, they have developed sophisticated survival skills.

Dr. Rankin uses a single word to describe the staying power of these hardy organisms: MALICE (Microorganisms Always Live In Challenging Environments). Perhaps their biggest environmental challenge is each other, she said. "They are competing for food sources. If they can produce something that is going to kill their neighbor, then they will get all of the food."

Millions of years ago, soil bacteria developed the genetic mechanisms to produce their own antibiotics to fend off these hungry neighbors. In turn, the neighbors developed resistance mechanisms to allow them to survive these assaults. This micro-armory consists of everything from barriers to nets, pumps to explosives. These sinister mechanisms have also hampered man's every attempts to use antibiotics. Case in point: penicillin. The first penicillin extract was produced in 1940. Within a year, a substance was identified in in *E. coli* that could inactivate penicillin. Sulphanilamide resistance was also reported in *Streptococcus*. Subsequently, some bacteria were found to possess surface modifications that decreased their permeability to fluoroquinolones, others to modify their binding sites in order to resist antibiotics like rifampin and vancomycin. And still others were found to have enzymes like beta lactamases that could inactivate or modify certain antibiotics.

At one time, it was thought that a random gene mutation produced an independent event of resistance to one drug. Today, we know that the acquisition of resistance involves more than a simple mutation. Rather, it involves several key players: R-plasmids, autonomous DNA elements, promote the transmission of resistance mechanisms. Transposons are mobile DNA elements that can move genes to a plasmid for later transmission to other bacteria. Integrons, which are present on transposons, constantly accept new genes, which further helps to build the armory of drug resistance.

When we overuse antibiotics, Dr. Rankin explained, we create an environment in which the few bacteria that possess antibiotic resistance can flourish and propagate. "There is this pool of genes subject to selection pressure, with the potential for further evolution."

The hospital environment, where antibiotic use is heaviest, has hosted the development of staphylococcus that can inactivate the penicillinase-resistant methicillin. And triclosan, an antibacterial agent present in many household items like deodorant, toothpaste and carpeting, is not helping the situation. Triclosan's ubiquity, Dr. Rankin said, will undoubtedly promote the evolution of multi-drug-resistant organisms. Though we try to keep up with their progress, bacteria may always be one step ahead of us, she said.

"We will never win. There is nothing we can throw at them that they haven't already encountered in their 3.2 billion years on earth."

—Joan Capuzzi Giresi, V'98