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11th Annual Feline Fanciers Symposium
Use of Radiation Therapy in the Management of Feline Neoplasia

Cancer in the cat is less common than cancer in dogs and or humans. About 40 percent of feline cancers are related to the skin or the alimentary tract, particularly in the oral cavity. Feline leukemia is associated with about 25 percent of feline cancers. Dr. Sydney M. Evans, assistant professor of radiology, discussed the use of radiation therapy in the treatment of cancer in cats.

Cancer affects different parts of the body and tumors vary in their characteristics. For some types of tumors, treatment prognosis is quite good while others are difficult to eradicate or keep in check. To design the best treatment strategy, the veterinarian needs to know the type of tumor which can be determined through a biopsy by a veterinary pathologist.

Skin and oral tumors in the cat can be treated with radiation therapy. Dr. Evans explained that the same therapy options exist for animals as do for people. "The first line of treatment is often surgery. When this is not enough then additional treatment options are employed, such as chemotherapy, immunotherapy or radiation therapy. Sometimes two or three different treatment modalities may be employed successively or simultaneously." The first objective is to reduce the cancer mass. Once this is accomplished, either through surgery or chemotherapy, then radiation can be used to further shrink the tumor. In radiation therapy, ionizing radiation breaks the DNA in cells, causing their death. The form of ionizing radiation used at VHUP is x-rays. Other veterinary and human hospitals use higher energy radiation such as cobalt and linear accelerators.

Cancerous cells are sensitive to radiation because of their rapid growth rate. When exposed directly to radiation, cancerous cells die or become incapable of reproducing. Healthy cells are damaged by radiation but are able to heal themselves. Since radiation kills both normal and abnormal cells, careful treatment planning is required to eliminate the greatest number of tumor cells while sparing normal tissue.

The dose of radiation is carefully calculated for maximum effect on the cancer and minimum effect on healthy tissue. Many factors determine the number of treatments and thus the amount of radiation given. The most important consideration is the total amount of radiation that can be administered to a patient without compromising the ability of healthy tissue to heal.

For treatment, the animal is anesthetized to be perfectly still during the treatment. Treatments last from four to 18 minutes in length, depending on the tumor size, location and type. During treatment, the animal is monitored through a closed-circuit television. Most pets receive radiation therapy three times a week. (Monday, Wednesday, Friday) accumulating 10 to 15 treatments. This is as often as it is practical to subject the animal to sedation or anesthesia. It also provides rest time for normal tissue to recover from the effects of radiation. At times, more extensive rest periods are required.

The radiation treatment is not painful and the nausea/vomiting reported in humans does not occur in cats and dogs. There are two types of side effects of the radiation therapy: acute (immediate) and chronic (late or "burn"). The acute effects start near the end of treatment and last up to three weeks. The most common of these is radiation dermatitis or "burns". This is damage to the normal skin in the treatment area. At its peak, a radiation dermatitis looks like a serious sunburn in the treatment area. Animals may be moderately uncomfortable and need to be kept from rubbing or scratching the area. Appropriate medicines can be prescribed to keep the animal comfortable. This "burn" will heal on its own in two to three weeks. In cats receiving treatment in or around the mouth, bad breath and drooling may occur for two to three weeks. Teeth supported in an area of the tumor may be lost. Most common chronic or late skin changes consist of hairless and dry skin in the treatment area. If the eye is included in the treatment area, another late change, "dry eye" (lack of tear production) and cataracts may occur.

Most cats are sedated with two drugs, a narcotic and a tranquilizer. The advantage of this combination is that the effect of the narcotic can be eliminated by giving another drug, a narcotic antagonist. Even with this narcotic antagonist, occasionally the animal will be returned to the owner looking fairly awake but it will fall asleep during the ride home and may sleep through the afternoon. This is acceptable as long as the animal is able to eat that evening. Some pets may cry for a short time following treatment. They are not in pain but are recovering from the effects of the sedation. It is best to protect the animal from stairs or high furniture while it is under the effect of sedation so it cannot injure itself.

Radiation therapy can only be employed against local tumors. Lymphosarcoma generally is not treated this way since the cancer cells are usually spread throughout the body. If the disease is confined to one lymph node, then radiation therapy can be employed. One of the more common tumors treated with radiation therapy is a localized nasal tumor. If recently metastasized, this tumor can invade the bones surrounding the nasal cavity. The tumor is thought to occur in one out of every 100 cats. Signs include nasal discharge, sometimes bloody, tearing eyes and facial masses. In a recent study, Dr. Evans determined that the average survival rate of cats treated for nasal tumors with surgery and radiation therapy is two years or longer.

Radiation therapy is not inexpensive; it runs about $800 to $1,200 for 10 to 12 treatments. The length of survival is increasing as treatment modalities improve. "Here at Penn we are on the cutting edge of new treatments. Feline squamous cell carcinoma, a very common, sun-induced skin tumor on the tips of the ears or on the nasal plate responds well to radiation treatment. If the tumor occurs in the mouth the outlook is not so optimistic. Dr. Evans explained that some conditions may give the appearance of a squamous cell carcinoma, but are not. To be sure, a biopsy has to be performed. The outcome of the treatment is more favorable if the tumor is treated early. This is particularly true if the tumor occurs in the oral cavity because it can attack bone as well as soft tissues. Early detection and treatment are important in all tumors."
The Feline Diabetic Patient

The first speaker, Dr. Douglas K. Macintire, assistant professor of medicine, discussed diabetes in the cat. She said that the emergency service at VHUP sees about 30 such cases annually and that feline diabetic patients usually are presented as emergency cases.

Diabetes mellitus is an endocrine disease of the pancreas resulting in a relative or absolute deficiency of insulin. In humans, two types of diabetes are recognized: Type I diabetes (insulin dependent), and Type II diabetes (non-insulin dependent). Type I diabetics require insulin injections. Type II diabetics can be managed with diet and oral hypoglycemic agents, except in time of stress, when they become prone to ketoacidosis, similar to the Type I diabetics. Type I diabetics may not permanently require insulin injections if the underlying illness is treated and the cause of stress removed.

Diabetic dogs are Type I diabetics and require life-long insulin injections. Cats, on the other hand, may be either Type I or Type II. Some cats become transient diabetics during episodes of severe stress and then spontaneously recover from their insulin dependence.

Insulin is an anabolic hormone. It promotes storage of fat in adipose tissue, and storage of glucose in the liver as glycogen. Insulin is necessary to permit entry of glucose into fat and muscle cells. Insulin release is stimulated by high glucose levels in the blood stream. When insulin is absent, blood glucose levels become very high, but the cells are unable to use this glucose for energy. To provide extra sources of energy, muscle protein and fat are broken down. As a result, weight loss occurs. In the absence of insulin, glucose levels in the blood stream are so high that excess sugar is filtered through the kidneys and lost in the urine. The large amount of sugar in the urine pulls body water with it. Therefore, one of the classic signs of diabetes mellitus in animals is excessive urination and increased thirst.

Stress can exacerbate diabetes because hormones are released which increase glucose formation through breakdown of body tissues. Diabetes has decreased immunity and are prone to infection, especially in the urinary tract. Infection or underlying disease often cause elevated levels of stress hormones which can result in two emergency conditions: 1) ketoacidotic diabetes and 2) hyperosmolar diabetes.

In ketoacidotic diabetes, breakdown of fatty tissues results in high levels of ketone bodies in the blood stream. Although these substances can be used for energy, the body becomes overwhelmed when they are produced in large numbers. Ketone bodies are acidic and they lower the pH of the blood. As a result, the animals become nauseous and vomit. They are unable to keep up with the tremendous water loss in the urine and they become rapidly dehydrated. Ketoacidotic diabetic animals are a medical emergency. Without intravenous fluid therapy and insulin, they will die. Even with proper veterinary care, these animals are very critical and the prognosis is guarded.

Osmolality is a measure of particles in the blood such as electrolytes, glucose, and urea in comparison to body water. Some diabetic animals become extremely hyperosmolar as a consequence of high blood glucose, dehydration, and impaired kidney function. Hyperosmolality is associated with abnormalities of the central nervous system including restlessness, staggering, incoordination, twitching, tremors, seizures, coma and death. The hyperosmolar diabetic is also a medical emergency. In these patients, serum osmolality must be lowered very gradually with intravenous fluids and insulin. If it is corrected too fast, serious brain swelling and deterioration of mental status may result.

Diabetes mellitus occurs more frequently in dogs than in cats. However, the majority of dogs are uncomplicated diabetics, while the cats are usually quite ill. Most cats are presented to the veterinarian in a ketoacidotic or hyperosmolar state, either because the signs of diabetes were not noticed or because of the rapid progression of the disease in cats. Early signs of diabetes include increased thirst and urination accompanied by weight loss. Other diseases, such as hyperthyroidism and kidney failure, have similar signs and should be ruled out with blood testing by the veterinarian.

As the disease progresses, common signs include depression, weakness and loss of appetite. If the cat becomes ketogenic, dehydration, vomiting and rapid respiration are common. Hyperosmolar cats may exhibit various degrees of abnormal brain function including stupor, coma and seizures.

The goals of treatment include restoration of electrolyte and acid-base balance, replacement of body fluids and lowering the blood glucose. Short-acting (regular) insulin must be used at this stage of treatment. At VHUP regular insulin is administered as a slow continuous intravenous drip. An infusion pump is used to deliver the proper dose, and these patients are closely monitored. The cat should remain on the intravenous drip until urine ketones are negative, which often takes 24 to 36 hours.

When ketones are negative and the cat begins to eat, a longer-acting insulin should be administered subcutaneously. In cats NPH insulin has a peak effect 2-4 hours after administration with a duration of 4-10 hours. It is usually given to cats twice daily. PZI insulin has its peak effect 4-10 hours after administration and has a duration of 12-30 hours. One daily administration of PZI insulin is effective in most diabetic cats.

Cat owners should practice giving insulin injections under the veterinarian's guidance until they feel comfortable with measuring and injecting insulin. Saline can be used to practice giving injections. The insulin syringes have very small needles and most cats do not mind the injection. Cats will learn to stand still for the injection if it becomes part of their daily routine and they are fed immediately following the shot. For fractional or excited cats, a "cat bag" can be made from a towel with a slit to allow for injections in the back area.

An infusion pump is used to accurately deliver the proper dose of intravenous insulin. After the cat is stable, the infusion is discontinued and subcutaneous injections of longer-acting insulin are administered.

Reagent strips can be used to test the cat's blood or urine for glucose or ketones. These strips allow for more accurate regulation of the insulin dose. A veterinarian should be consulted if the cat's urine is positive for ketones, or if consistently high glucose readings are obtained.

Diabetic cats should be fed twice daily. Semi-moist foods should be avoided because of their high sugar content. Medications such as steroids and megesterol acetate (Ovaban®) should be avoided since they induce insulin resistance. Cats should also be neutered or spayed for better control of the diabetes.

It is a good idea to keep the cat a normal weight. Increased water intake and urination may indicate that the diabetes is not well controlled. The urine should be periodically checked with test strips for glucose and ketones. The veterinarian should be called if ketones are present, or if glucose is persistently present. To get a urine sample, plastic wrap can be placed over cat litter.

Certain cats may develop hypoglycemia (low blood sugar). Insulin should be administered. These patients may exhibit fatigue, mental confusion or dullness, staggering, incoordination, and seizures. If these are seen, Karo syrup should be given orally immediately, and food offered if the cat is able to eat. If the cat is seizing or no improvement is seen, veterinary attention should be sought.

Occasionally, effective control of diabetes cannot be achieved. Reasons for poor control include excessive frequency of insulin, inadequate mixing, improper injection technique, improper dose, insulin, resistance, and rapid metabolism of insulin. After ruling out problems with insulin or injection technique, the veterinarian should be consulted if the problem persists. The cat will probably have to be admitted into the hospital to determine a 24-hour glucose curve. There is a great deal of individual variability among cats in their response to insulin. By determining the time period of peak activity and the duration of the insulin, it is possible to more finely regulate the diabetes. In general, the blood glucose should not drop below 100 mg/dl or increase above 250 mg/dl.

Although diabetes mellitus cannot be cured, it can be controlled with proper management. Diabetic cats may live for years as happy, functional pets. There are many diseases of small animals which can be controlled but not cured with medication (i.e., chronic skin disease and arthritis). Diabetes is unique in that the medication must be given by regular hypodermic injections rather than orally. Once the technical aspects of hypodermic injection have been mastered, however, it is really less trouble in most cases than giving a cat a pill.

Feline Reproductive Problems

The first speaker of the afternoon session, Dr. Vicki Meyers-Wallen, discussed feline reproductive problems. She briefly described the normal male and female cat and explained that the sex of an animal is determined by chromosomes. A female has two X chromosomes and a male has an X and a Y chromosome. Early during embryonic development animals with the XY configuration develop testes which produce testosterone, a hormone which promotes development of the male reproductive organs. This hormone also plays an important role in the development of male characteristics and behavior when the animal reaches puberty.

Sometimes, during meiosis (formation of the eggs or sperm), at fertilization or during early embryonic development, the chromosome distribution is disturbed. As a result animals may have two X chromosomes and one Y chromosome, or they may have just one X chromosome. An XXY animal outwardly appears like a male, but it will not be fertile. The XXY defect is common, since it is known to appear in one out of every 700 human male births. In cats, it is the most frequent karyotype found in male calico cats. Chromosome karyotyping can help to make a positive diagnosis of this defect. An XO cat will appear to be a female, but it is too infertile.

In addition to defects attributable to chromosomal errors, there can be a number of other inborn errors continued on page 8.
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which prevent a cat from reproducing. Cats with a male appearance can be born with a uterus and cats which outwardly appear to be female can have testes. There can also be physical defects of the external genital organs which prevent reproduction of the animal.

In addition to these defects, the sperm may be defective such as having coldd tails; being incompletely formed, or being immobile. Such conditions are often not diagnosed until the cat has failed to impregnate a queen. Then a semen analysis is done. This is not easy in cats that are not trained to accept semen collecting during sexual mating. Most animals need to be anesthetized and then electro-ejaculated to obtain sperm for examination. For this reason it is advisable to use the male first with a proven female, if that is not successful then these tests are the next step. Because of the difficulty of routinely obtaining sperm from male cats, artificial insemination is rarely used.

Female cats are highly seasonal in their breeding cycle. They need 12 to 14 hours of light a day to cycle. If an animal is kept indoors in a darkened room, it will not cycle. When a female cat (queen) is in season, behavioral changes occur. These are the only indication that the animal is ready to breed. Cats are induced ovulators, unlike dogs which ovulate spontaneously during their heat cycle. The stimulation of the breeding process causes the brain to release luteinizing hormone, a substance which causes the follicles to release the ovum. Thus for ovulation to occur, the stimulation of mating is necessary. In some animals the stimulation to induce ovulation needs only to be slight. The process of taking a vaginal smear may induce ovulation in some queens.

Such smears can be of some assistance, but they may not provide an accurate picture of the stage of the queen's cycle. A more accurate method is monitoring the level of estradiol in the bloodstream. The level of this hormone is high during estrus (heat). This method is currently expensive and not practiced for most queens since the bloodtest has to be run every day.

It is best to breed a queen repeatedly to induce ovulation. Studies have found that the luteinizing hormone peaks within 90 minutes of repeated breedings. It is recommended to leave the queen and the male together for some time so they can breed more than once.

Once the queen has ovulated, progesterone levels in the blood rise. If the animal is pregnant, the level stays high for the first half of the pregnancy and then gradually declines by the time of birth (64 days). If the cat ovulates but does not become pregnant, the progesterone level will drop earlier (45 days) and the queen will come into season again. A cat can also have a false pregnancy.

The gestation period is about 64 days. In a difficult to breed queen, it is important to determine whether the animal ovulated and whether it is pregnant. Pregnancy can be detected as early as 20 days after ovulation through ultrasonography, but is generally performed at 21 to 28 days. Palpation can also detect embryos between 21 to 28 days of gestation. A number of things can interfere with a successful gestation. The animal can have an undetected uterine infection or embryos may die due to chromosomal defects. It is possible for a queen to lose a litter later in pregnancy (abortion). This can be due to viral disease, such as a herpes infection, or to hormonal disorders. Thus early pregnancy detection is important as it helps the veterinarian with a diagnosis. Failure to carry full term presents a risk to the queen. Prostaglandin treatment is only recommended for breeding queens. The recommendation for pet cats with this condition is ovariohysterectomy (spay).

Cats should not be bred until they are mature and have reached their adult size and weight. Dr. Meyers-Wallen explained that young queens generally are not good mothers. Cats can be bred twice a year if they are in prime health. She said that, although cats usually do not cycle while nursing, it is possible for this to occur. She emphasized that good records are a great help to the veterinarian should problems arise. She also stated that vaccinations during pregnancy are not recommended, and that it is best to have the cat vaccinated and wormed prior to breeding.

Dr. Meyers-Wallen is assistant professor of reproduction at the School. She is in the section of medical genetics and deals with generic, pediatric, and reproductive problems of cats and dogs.

A Line of Dwarf Mice

Researchers at the Laboratory of Reproductive Physiology at the School have developed a line of dwarf mice produced by genetic ablation of growth hormone expressing cells. For the last two years, Dr. Ralph L. Brinster and Dr. Richard R. Behringer here at Penn, and Dr. Lawrence S. Mathews and Dr. Richard D. Palmiter of the University of Washington, have been developing a method for selective ablation of specific cell lines in transgenic mice. Genetic ablation is a technique which utilizes genetic engineering to delete specific cells.

In multicellular organisms the diverse cell lineages which develop into organs, bone, tissues, etc., are generated from a hierarchy of stem cells. By using ablation techniques to delete specific cells, the relationship between stem cells and cell lineages can be studied. Such a system would be very valuable in studying the origin of distinct populations of cells which form tissues or organs in the body.

In these experiments, the switching region of the growth hormone gene was fused to part of the diptheria toxin gene, and the hybrid gene was introduced into the animal's chromosomes by microinjecting the gene into the egg from which the animal developed. When the cells that make growth hormone began to differentiate in that animal and to make growth hormone, they also made the toxin. This killed any cell that made growth hormone but no other body cell. Thus the growth hormone cells never developed, and no cell that might arise from a growth hormone cell could be formed. A dwarf mouse developed. This demonstrated the utility of the method and established a model for dwarfism.

The dwarf mice are about one-third to one-half the size of normal mice. Growth hormone could not be detected in these animals and insulin-like growth factor 1, the blood level of which is stimulated by growth hormone, was reduced eight-fold in comparison to normal animals. The researchers found that the dwarf mice cease growth at approximately six weeks of age, maintaining a weight of 10 to 15 grams.

The research demonstrated that the genetic ablation of specific cell types in transgenic mice can be a useful method for understanding cell lineage relationships and the role of particular cell types in morphogenesis. It was also demonstrated that cell type produces a hormone, one can generate a hormone deficient animal model. The technique should be valuable in generating unique models of human and animal disease.