CEH HORSE REPORT

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Understanding Cancer in Horses

Some Common Tumors and What to Expect

Advances in medicine and agriculture have saved vastly more lives than have been lost in all the wars in history. — Carl Sagan

The cancer problem that people tend to think of as a human phenomenon also affects the animals that live among us. Roughly half of U.S. households are home to companion animals—dogs, cats and horses. Like people, more and more companion animals are living longer due to better quality of life, better nutrition, preventive medical care and vaccinations. But in the language of cancer, a longer life usually means an increased chance of developing it.

Cancer is one of the top three disease killers in humans in the United States and among the top ten disease killers globally. In animals, it accounts for almost half of the deaths in pets over 10 years of age, according to the American Veterinary Medical Association. Dogs get cancer at roughly the same rate as humans, while cats get fewer cancers. Although horses seem to be less susceptible, the fact is that there is relatively little information on cancer in horses. Much of the existing information comes from pathology collections, often from veterinary schools, and does not provide information on incidence and prevalence rates.

*Remembering **Lost in the Fog**, 2/4/02 – 9/17/06*
A horse gallops with his lungs, perseveres with his heart, and wins with his character.

Dr. Alain Théon, Chief of Oncology at the UC Davis Veterinary Medical Teaching Hospital, believes that horses are no less susceptible to cancer than humans, dogs and cats. But because their lifespan is substantially greater than that of dogs or cats—and the incidence of cancer increases with age—it

Lost in the Fog won his last stakes at Churchill Downs on June 3, 2006, and ran his final race on July 15 before his cancer was discovered in August that year. The cancer was diagnosed as inoperable lymphoma that had invaded his spleen, kidney and chest cavity. The fact that he ran these races with the extensive cancer that was discovered attests to what a true champion he was.

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DIRECTOR'S MESSAGE

The Same Chances for Survival

Dr. Gregory L. Ferraro

A *Horse Report* on the subject of equine oncology is probably long overdue. Like many equine veterinarians, I have been reluctant to delve into the topic because of a general lack of knowledge or understanding of the subject. In my defense, it can be said that I am not alone in this state of ignorance. The equine medical field has until recently lagged far behind other species-specific medical specialties for diagnosing and treating neoplastic disease.

The adage "horses don't get cancer" has persisted for far too long. While equine medicine may have languished in this state of ignorant bliss, other veterinary researchers and oncology specialists, particularly small-animal specialists, have logarithmically increased the biological understanding of cancer and its therapeutic management. These specialists have now appeared on our threshold and have begun to bring the equine clinician kicking and screaming into the modern age. Here at UC Davis and elsewhere, modern oncologists are now making significant advances in cancer diagnostics and treatment for horses.

What follows in this issue of the *Horse Report* is a comprehensive look at what is now known regarding cancer in the horse and what the prospects are for future disease management and cure. We have endeavored to present a basic course in equine oncology. Our contributing authors and the *Horse Report's* editor, Barbara Meierhenry, have gone to great effort to take a very complicated subject and explain it in a way that all can understand. I hope that after taking the time to read and reflect upon what they have written that you, as I did, will come away with the feeling of having really learned something. Beyond that, we hope you will be encouraged by the realization that horses with cancer in this day and age can now enjoy the same level of expert therapeutics and have the same chances for survival as humans, dogs and cats.

In the community of living tissues, the uncontrolled mob of misfits that is cancer behaves like a gang of perpetually wilding adolescents. They are the juvenile delinquents of cellular society. — Sherwin B. Nuland (physician), 1994

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usually takes longer for cancer to develop in horses and is more difficult to detect due to their large body size. We can also conjecture that because horses die more often from other causes such as colic, laminitis or catastrophic injuries, we cannot know the true incidence of cancer. In any case, cancer is essentially the same disease in all species.

Veterinary oncology is recognized as a specialty by the American College of Veterinary Internal Medicine. This attests to the prevalence of cancer and the need for specialized research and training in diagnosis and treatment. Specialists in comparative oncology work to advance cancer treatments in animals and humans by studying similarities and differences in the behavior of tumors in different species. These types of studies have improved understanding of the biology of cancer as well as treatment options for both humans and animals. Because of comparative oncology, the standard treatments for cancer in humans—surgery, radiation therapy, chemotherapy and immunotherapy—have been adapted to help animals with cancer.

Defining Cancer

All cancers begin in cells, the body's basic unit of life. Normal cells grow and divide in a controlled way to produce more cells as they are needed to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells. With cancer, this orderly process breaks down. The genetic material (DNA) of a cell can become damaged or changed and affect normal cell growth and division. When this happens, cells do not die when they should, and new cells form when the body does not need them—a process called *uncontrolled cell proliferation*. The extra cells can form a mass of tissue known as a tumor.

Tumors are generally characterized as benign or malignant based on their histologic features (structure of the tissues as seen microscopically) and biological behavior. Benign tumors are not cancerous; they do not spread to other regions of the body, and they can be removed surgically and do not grow back. There are actually very few truly benign tumors in the horse.

Malignant tumors have three properties that differentiate them from benign tumors: the cells **grow out of control**; the cells are **invasive**—they invade and destroy adjacent tissues; and the cells may **migrate to other locations in the body**—a process called metastasis. To metastasize successfully, tumor cells must detach from their original location, migrate through normal tissue, and (1) form a new cellular colony, or (2) invade a lymphatic vessel or nerve sheath and establish a new tumor, or (3) invade a blood vessel and travel in the circulation to a distant site to colonize other organs.

Some tumors have seemingly benign and malignant properties. They may grow slowly (benign trait) and yet become locally invasive and destroy adjacent tissues (malignant trait). A good example of this dual biological behavior is the sarcoid tumor in horses. **Equine sarcoid,** regarded by some practitioners as a benign tumor because of its slow growth, **is in fact a malignant tumor because it is locally aggressive and may spread regionally via lymphatics.** It is classified by the World Health Organization as a low-grade fibrosarcoma (a malignant tumor).

To complicate the matter further, some benign tumors have the potential to become malignant. Therefore, classifying tumors based on known or anticipated biological behavior (benign or malignant) represents a gross oversimplification of the wide behavioral range exhibited by some tumors in terms of local aggressiveness and metastatic potential. For example, a papilloma, which is a benign skin proliferation also known as a wart, has the potential to progress into squamous cell carcinoma, a malignant tumor.

Tumors are classified according to the cell type of origin, as determined on a tissue specimen examined microscopically by a veterinary pathologist. In some cases, the tumor cells are so immature that they lack classic hallmarks of disease and can be difficult to diagnosis. In these instances, molecular analysis can be used to help refine the diagnosis and provide the information needed to differentiate different types of cancers like lymphoma, for example. This allows clinicians to select the most effective treatment based on the specific

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genes expressed in a tumor. See article on *State-of-the-Art Methods for Diagnosing Cancer*, page 12.

An important part of evaluating a cancer is also to determine its histologic grade in order to understand its expected behavior and responsiveness to treatment. One type of grading system classifies tumors as **high-grade** (tumor is immature, fast-growing and aggressive) or **low-grade** (tumor is usually mature, slow-growing and less aggressive).

The following table summarizes the major differences between benign and malignant tumors:

Horse owners are more aware of progress in cancer treatment and are becoming more demanding in seeking care for their horses.

More than 80% of tumors in horses affect the skin and subcutaneous tissues. Because skin tumors are easily seen and are often quickly brought to the attention of a veterinarian, the vast majority of these tumors should be appropriately removed very early on. Early detection and treatment are critical to preventing serious and more costly problems.

Sarcoids

Sarcoids are skin tumors and the most common tumors in horses. Early sarcoids can vary in appearance from an almost circular area of hair loss with a gray, scaly surface, to wart-like growth presenting as a skin thickening or small growths on a stalk. The most common sites are the skin of the head (eyelids, ears and junction of the mouth), neck, legs, and ventral trunk as well as any previously traumatized sites. Young adults and Quarter horses may be at higher risk.

Occult-type sarcoids appear as an almost circular area of hair loss with a gray, scaly surface that can be mistaken for a skin infection (ringworm) or keratosis.

Sarcoids are often considered benign tumors because many are slow-growing and initially cause little, if any, physical problems to the affected animal. Due to this misperception, they are often mismanaged, allowing progression of the tumor to

MAJOR DIFFERENCES BETWEEN BENIGN AND MALIGNANT TUMORS

Criteria	Benign	Malignant
Histologic (microscopic) features	More mature cells	Immature cells
Mode of growth	Expansive, contained	Infiltrative, not contained
Rate of growth	Slow, limited (years)	Rapid, uncontrolled (months)
Local effect on host	Mass effect (compression)	Invasion and destruction of normal surrounding tissue
Metastasis (ability to spread)	None	Potential for metastasis
Prognosis	Seldom lethal; cure after surgical removal	Often lethal (without treatment); frequent recurrence after surgical removal

Common Tumors in Horses

The occurrence of tumors in horses has been increasing, according to Dr. Théon. This phenomenon is attributed in part to horses living longer due to improved preventive and therapeutic medical practices. As a result, veterinarians are called upon more frequently to diagnose and manage horses with tumors.

Verrucous-type sarcoids (on ear) resemble warts, with thickened skin with a dry rough surface and loss of hair.

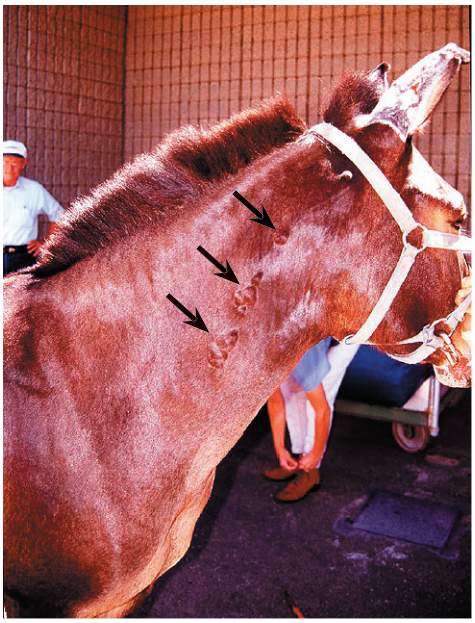
advanced stages that may not be treatable and result in euthanasia. Therefore, **early surgical removal of sarcoids *when they are small* is strongly recommended.**

Early stage sarcoid (left) vs. advanced stage (right).

Advanced sarcoids referred to as nodular (lumpy) sarcoids may appear as a large mass with a surface that will progress from scaly and hairless to ulcerated. This type of sarcoid is locally invasive, destroying adjacent tissues, and should be managed as a malignant tumor.

Advanced sarcoids occasionally can spread regionally through the lymphatic system. Although not contagious to other horses, a tumor can be transferred mechanically to a different part of a horse's body by chronic rubbing with an ulcerated lesion (similar to grafting).

Contact metastasis of sarcoid tumor. Tumor appeared originally at the base of the ear prior to surgery (left) and spread by chronic rubbing of the tumor on the leg (right).



Regional metastasis of sarcoid tumor. Mule with a sarcoid on the ear was treated successfully with radiation therapy (white area). Although the tumor was locally controlled, it metastasized via the lymphatics (arrows).

Melanoma

All melanomas are malignant. They appear as firm, dome-shaped bumps on the skin or mucous membranes anywhere in the body, especially in the region around the anus, tail and external genitalia. They may also originate from melanin-producing cells of the eye. Melanomas grow slowly over a number of years (up to 10 years), enlarging or spreading until they mechanically interfere with defecation, urination or locomotion—a common cause of euthanasia in gray horses.

Melanomas develop most frequently in gray and white horses with dark skin and only occasionally in horses with other coat colors. About 70% of these gray and white horses will develop melanoma. A high incidence has been observed in Arabians, Lipizaners and Percherons.

Three different types of melanomas have been identified: dermal melanoma, melanomatosis, and anaplastic malignant melanoma. In horses with dermal melanoma and melanomatosis, lesions become aggressive and locally invasive and metastasize after many years of apparently benign behavior. All anaplastic melanomas as well as

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30% of dermal melanomas metastasize to regional lymph nodes, lungs and other organs.

Generally, fast-growing tumors and tumors located at the root of the tail and salivary gland area tend to be locally more aggressive and/or metastasize. Tumor size is related to the degree of malignancy. Large tumors are more likely to metastasize than small tumors. **Therefore, early management of small tumors is highly recommended.**

Examples of dermal melanoma.

Multiple melanoma or melanomatosis.

According to Dr. John Robertson, Director of the Center for Comparative Oncology at the Virginia-Maryland Regional College of Veterinary Medicine at Virginia Tech, about two-thirds of all melanomas will initially behave as tumors that will grow slowly at their site of origin. These small, local tumors may cause no problems or they may interfere with work, bodily functions such as defecation, or create cosmetic problems for affected horses and their owners. "We know from evaluation of biopsies that even the small, locally growing tumors will grow into surrounding tissue, making early treatment of small lesions desirable (before they grow extensively)."

Regional metastasis of melanoma. Original melanoma on lower eyelid progressed to a large facial mass that eventually metastasized to the parotid lymph nodes.

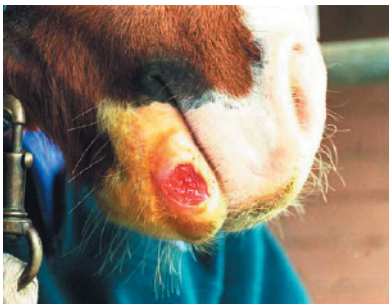
Other equine melanomas will display a malignant pattern of growth very early in the course of disease. These tumors can occur at several sites in the body at once, or they may spread throughout the body from a primary tumor. They are likely to kill the horse outright or may necessitate the humane destruction of the affected animal. Since some veterinarians consider melanomas to be benign (based on outdated concepts about these tumors), they do not usually biopsy the tumors or remove them in time to control the serious problems associated with the growth of the tumor. Dr. Robertson emphasizes that it is important to biopsy tumors for accurate diagnosis and treatment planning.

Squamous Cell Carcinoma

Squamous cell carcinoma is a malignant tumor and the second most common skin tumor in horses, accounting for about 30%. Although it can develop at any location on the skin, it occurs most frequently in nonpigmented areas in horses 12 years and older, especially on the head (eye, eyelid, lip, nose) and genitalia. Depending on the location, squamous cell carcinoma can be very

Distant metastasis of melanoma. Primary melanoma in parotid lymph node area (top photo) that metastasized to the lungs (bottom photo). Note the large size (approximately 2 to 3 inches) of the tumors in the lung (arrows).

hard to treat (on the eyelid, for example), so early treatment is important.



Squamous cell carcinoma.

A high incidence of squamous cell carcinoma occurs in lightly pigmented horses such as some draft horse breeds, Appaloosas, American Paints, and Pintos. Factors contributing to the development of squamous cell carcinoma include long-term sun exposure, inflammation associated with trauma (poorly healing wound, burn) and viral papilloma infection.

Sunlight-induced skin carcinomas develop from precancerous lesions known as actinic keratosis. It is important to recognize and treat these early lesions before they become cancerous. Because of the known association with sun exposure, we highly recommend sheltering light-skinned horses from exposure to full sun.

Actinic keratosis (thickening of the skin with scaly or crusty patches) is a precancerous lesion that is easy to treat. It can progress to a carcinoma in situ (arrows), which will in turn progress to squamous cell carcinoma if untreated.

Lymphoma

Lymphoma refers to tumors that originate from the lymphoid system—the lymph nodes, thymus, spleen, and other lymphoid tissues including those lining the digestive, respiratory and urogenital tract. Lymphomas are always malignant. There are four forms of lymphoma in horses:

Generalized or multicentric lymphoma is more common than the intestinal and thoracic forms. Clinical signs may include severe depression, weight loss, loss of appetite, enlarged lymph nodes, and edema (swelling) due to impaired lymphatic drainage.

Alimentary or intestinal lymphoma usually involves the small intestine and is the most common tumor of the intestinal tract in horses. It can occur in young and older horses. Clinical signs may include weight loss, swelling (edema), mild colic and diarrhea.

Mediastinal/thoracic or thymic lymphoma is usually seen in adult horses. Common clinical

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signs include nasal discharge, lung sounds not related to normal breathing, excess fluid around the lungs, vena cava syndrome (enlarged chest/ swollen legs), cough, and sometimes respiratory distress.

Cutaneous lymphoma refers to tumors that are usually confined to the skin and regional lymph nodes. These can appear as single or multiple skin bumps that are firm and not painful.

Lymphoma in horses is rarely diagnosed early, except for the cutaneous (skin) type. Cutaneous lymphoma may be an indication of internal malignancy; therefore, a thorough examination is important. Historically, lymphoma has almost always carried a poor prognosis. Today, improved treatment options can offer a better chance for a good prognosis if caught early enough.

Diagnosing Cancer

Although the appearance, location and growth pattern of a lesion may give a veterinarian a high degree of suspicion as to whether or not it is a tumor and the type of tumor involved, a definitive diagnosis must be made in time for the horse to receive the appropriate treatment. The most common diagnostic procedures are tissue biopsy and cytology.

Biopsy

A biopsy is the removal of a small section of a tumor for examination under a microscope. Obtaining a biopsy specimen is possibly the most important step in the management of all tumors. Not only will the biopsy provide a definitive diagnosis that is used to predict the biological behavior of the tumor, it will help in selecting the most appropriate treatment and in determining the prognosis.

When should a biopsy be performed? A biopsy is recommended whenever there is:

• An active lesion that is not responding or temporarily responding to medical treatment.

• A chronic (persistent) lesion of unknown origin and duration.

• A lesion that interferes or will interfere with local body function.

If a horse owner decides to proceed with a biopsy, it is essential that the owner be committed to treatment if the diagnosis reveals a tumor, because the biopsy is part of managing the tumor. There is no medical contraindication for a biopsy unless the procedure may endanger the patient or an effective treatment cannot be provided.

Cytology

Cytology is the microscopic analysis of cells from a suspected tumor to see their formation and structure. It is generally used as a screening tool to distinguish between cancerous and inflammatory lesions. Cytology cannot be a substitute for biopsy and histopathology because it does not provide any information about the biological behavior of a tumor.

Treatment Options

Cancer treatment in horses is an art. Because of the limited number of research studies that have been conducted compared with other species (humans, dogs, cats), treatment decisions are based more on the integration of "what we see, what we know, what we have experienced personally, and what is known about other species" than on verified protocols. By contrast, humans and dogs have been treated for cancer for many years. Progress is being made, albeit slowly, but there is a pressing need for more research to build on the current level of understanding.

Treatment options can be grouped broadly into **ablative** (surgery, laser vaporization), **cytotoxic** (radiation therapy, chemotherapy) and **biological** (immunotherapy). Treatments for the primary tumor mass include ablative treatments to remove all tissues that may contain tumor cells, radiation therapy and local chemotherapy (intratumoral

chemotherapy, directly into the tumor mass); those directed at the tumor and metastases or multiple tumors include systemic chemotherapy and immunotherapy.

Surgery

The complete surgical removal of localized tumors cures more patients than any other form of treatment. Depending on the type of tumor and whether the tumor can be removed completely, surgery may be used in combination with other treatments such as chemotherapy.

Chemotherapy

Until recently, chemotherapy was a very expensive treatment option in horses primarily because of the cost of drugs and their potential toxicity. Today, low-cost generic drugs are available and new routes of drug administration have been developed to increase the therapeutic benefits and reduce toxic side effects. Tumors that are easily accessible can be treated with local chemotherapy, including topical and intratumoral (administering the drug directly into the tumor) chemotherapy.

Most systemic chemotherapy protocols for horses use a single drug, even though the benefit of using combination chemotherapy protocols has been shown in humans and small animals. The anticancer drugs are administered intravenously. More research in horses is needed to determine safe dose levels of combination drugs as well as their combined effect.

Radiation Therapy

Radiation therapy is the use of x-rays to kill cancer cells. In horses, radiation therapy is used primarily to treat localized tumors that are large or deep, invade the bone, or are located in the oral or nasal cavity with bony involvement. All treatments are done while the horse is under short-term general anesthesia to immobilize the horse and allow for accurate positioning.

One form of radiation therapy called *intensity-modulated radiation therapy* (IMRT) is designed to accurately target tumors with optimal radiation dosages while avoiding damage to normal tissue. Computer software is used to design three-dimensional treatment plans based on CT and MRI scans and to position the beam of a high-power linear accelerator. Radiation is distributed exactly as needed, depending on both the shape and location of a tumor. UC Davis is one of only a few veterinary schools in the nation that has this capability.

Dr. Alain Théon treating a horse with intensity-modulated radiation therapy at UC Davis. The treatment area includes a specially designed equine recovery room.

Immunotherapy

Immunotherapy is based on the idea that the immune system can be trained to attack tumors in the same way that it targets infectious agents. Unlike more traditional vaccines, which prevent diseases from occurring (usually by targeting the infectious virus or bacterium that causes disease), the goal of therapeutic cancer vaccines is to prevent recurrence after cancer has been detected and treated through more conventional means (surgery, chemotherapy, radiation therapy).

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Lowering the Cancer Risk in Horses

As with all forms of cancer, the key to successful treatment is early diagnosis. Regular grooming and care of the horse will reveal any small lumps or bumps; these should be treated seriously and examined as soon as possible by a veterinarian. Reducing smegma accumulation in the sheath (by regular sheath cleaning), reducing exposure to excessive sunlight in light-colored horses, and general cleanliness are important for prevention of tumors, especially squamous cell carcinoma. It is important to seek early veterinary assistance if you notice any skin abnormalities that persist over a period of a few weeks, or a new lesion develops around the original lesion or in a new location on the body.

Since long-term sun exposure is a major factor contributing to the development of squamous cell carcinoma in light-skinned horses, we highly recommend providing shelter (shed or shade trees) to protect the horses from exposure to full sun. Baby sunblock (to prevent skin and eye irritation) can also be used, and some fly masks may reduce UV exposure. ❄

Important Facts to Know About Cancer in Horses

What is Cancer?
Cancer is an uncontrolled growth of abnormal cells on or within the body. These growths may be benign or malignant. They may be localized or they may invade adjacent tissue and spread throughout the body.

How Common is Cancer in Horses?
We don't know the true incidence of cancer in horses because information is lacking. However, skin tumors are quite common in horses, and the risk for all types of cancer increases with age.

How Is It Diagnosed?
Most cancers require a biopsy (a removal of a piece of tissue) for a definitive diagnosis. A biopsy is also needed to grade the level of malignancy.

Is Cancer Preventable in Horses?
Unfortunately, the cause of most cancers is not known and therefore prevention is difficult. However, as with humans, **early detection and appropriate treatment are the best ways to manage cancer in horses**.

How is Cancer Treated in Horses?
Each type of cancer requires individual care and may include a combination of treatment therapies such as surgery, chemotherapy, radiation therapy, or immunotherapy. The type of treatment selected depends on the exact diagnosis of the cancer. Your veterinarian will discuss the best treatment options for your horse. In some instances, he or she may refer you to a veterinary oncologist (cancer specialist).

What is the Success Rate?
This strongly depends on the type and extent of the cancer and the effectiveness of the treatment. Some cancers can be cured and almost all patients can be helped to some degree. ***The best chance for success lies in early detection and treatment.***

Common Types of Cancer in Horses

Skin tumors—80% of all tumors in the horse arise from the skin. Horses should be examined thoroughly by a veterinarian on a regular basis. Skin tumors are highly curable ***if they are caught early***. The treatment of skin tumors as early as possible is most economical and effective and avoids the risk of euthanasia.

Melanoma (also a skin tumor)—affects 70% of gray and white horses with dark skin. Melanomas can arise from the skin or mucous membranes anywhere in the body. In horses, they most frequently affect the skin around the anus, tail and external genitalia.

Tumors of the reproductive tract—ovary, penis, vulva. The most common are tumors of the ovary and external genitalia (vulva and perineum, penis, prepuce and scrotum). Testicular tumors are uncommon.

Lymphoma or cancer of the lymphoid tissue—Affects 5% of horses. Lymphomas can occur in various regions of the body (lymph nodes, thymus, spleen, gastrointestinal tract, chest, skin). Except for the skin form, lymphomas are usually caught late and the disease is often advanced at the time of diagnosis. Without treatment, the prognosis is poor.

Common Signs to Watch For

- **Abnormal swellings that persist or continue to grow**
- **Sores that do not heal**
- **Active lesion not responding or temporarily responding to medical treatment**
- **Weight loss**
- **Loss of appetite**
- **Unexplained fever**
- **Bleeding or discharge from any body opening**
- **Offensive odor**
- **Difficulty eating or swallowing**
- **Hesitation to exercise or loss of stamina**
- **Persistent lameness or stiffness**
- **Difficulty breathing, urinating, or defecating**

State-of-the-Art Methods for Diagnosing Cancer

Many advances have been made in the prognosis and treatment of cancer in humans and companion animals due in large part to the progress made in diagnostic methods. Chief among these has been the development of molecular techniques that enable pathologists to characterize the genes, proteins and biochemical pathways within a cancer cell. The use of these molecular techniques to define genetic profiles for cancer has been a significant benefit for delivering more effective treatments for cancer. For some cancers, clinicians can select the most effective therapy based on the specific genes expressed in a tumor.

This new approach to understanding the biology of cancer has been made possible by the completion of different genomes, including those for the human and the horse. Every organism has a genome that contains all of the biological information needed to build and maintain a living example of that organism. The biological information contained in a genome is encoded in its DNA and is divided into discrete units called genes. Genes code for proteins that attach to the genome at the appropriate positions and switch on a series of reactions called gene expression.

Molecular diagnostics is the study of how genes and proteins interact in a cell; it focuses on gene and protein activity patterns in different types of cancerous or precancerous cells and reveals sets of changes or mutations that may have occurred. These changes are known as *expression patterns* or *molecular signatures* and are used to give a more detailed picture of a cancer type.

Traditional diagnostic methods rely on categorizing cancer cells from tissue samples by their appearance under a microscope. A description of these cells contains information about their size, shape and appearance. Information about different types of cells can be obtained by using a variety of tissue-staining techniques to determine where the cancer started, distinguish among different cancer types, or help diagnose and classify different types of lymphomas.

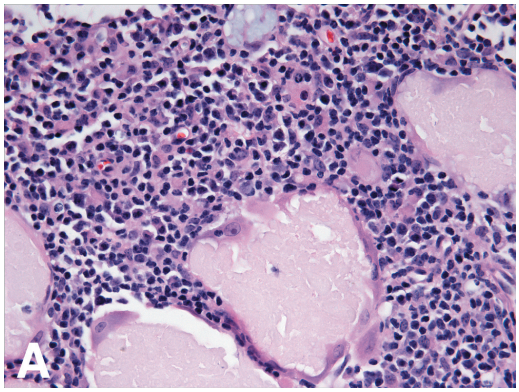
Because tumors of the lymphoid system (lymphomas) can be difficult to diagnose using traditional methods, molecular profiles can be used to improve the diagnoses made by pathologists. Although a clear diagnosis is "easy to make in the majority of cases, about 5 to 10 percent of tumors lack classic hallmarks of disease and can be confused with another tumor type, leading to an incorrect diagnosis," according to a research scientist at the National Cancer Institute. Molecular profiles can be used to help refine the diagnosis and provide the information needed to differentiate these different types of lymphoma.

A perfect example of this is the case of Lost in the Fog, 4-year-old Lost Soldier colt who won over many hearts with his remarkable performance, intelligence and character. After a stunning but short-lived career, Lost in the Fog was brought to the UC Davis Veterinary Medical Teaching Hospital for what was believed to be a mild bout of colic. Instead, a large, cancerous mass was found and diagnosed as inoperable systemic lymphoma. The initial histopathology results (traditional method) were suggestive of lymphoma, but it was not possible to confirm the diagnosis with 100% certainty. Moreover, traditional diagnostic methods did not specify the exact type of cell involved, and this would be critical in determining the most effective treatment strategy.

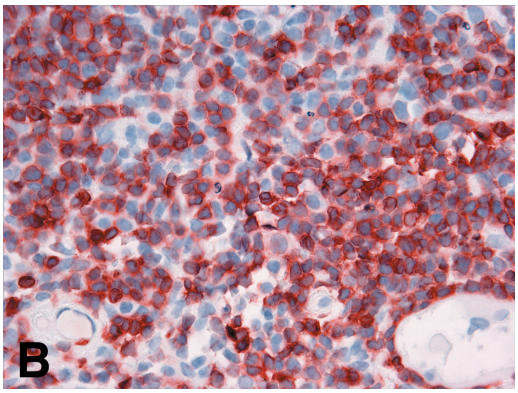
While all lymphocytes are descendents of a common lymphoid stem cell, they differentiate into two main families (B-cells and T-cells) during development. Descendents of these progenitor (immature) B-cells and T-cells then develop further to generate many families of lymphocyte subtypes that each play a specific role in the body's coordinated immune response to infectious agents and other challenges. Each family and subfamily of lymphocytes expresses unique identifying markers on their surface.

Many years of painstaking research performed by pathologist Dr. Peter Moore and his colleagues in the UC Davis School of Veterinary Medicine has recently resulted in the production of antibodies that allow pathologists to examine biopsy samples and to not only identify that a suspected tumor is of lymphocyte origin but also to precisely define the subfamily of lymphocytes involved. In Lost in the Fog's case, traditional histopathological examination of the small surgical biopsy specimen initially could not provide the needed information.

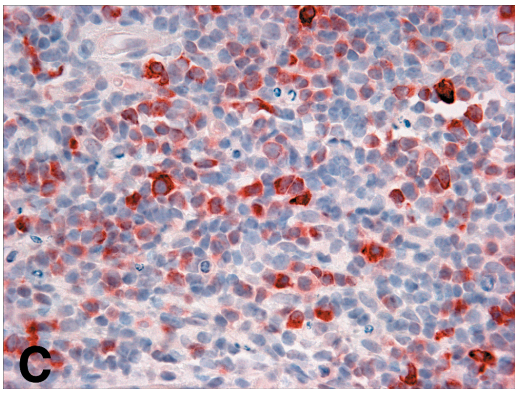
Horse with skin masses, diagnosed as cutaneous lymphoma.



Traditional histopathology section as seen under a microscope. Pink deposits are amyloid protein produced by the tumor lymphocytes.



Immunohistochemical stain for T lymphocytes (red). These are the most numerous cells and are reacting to the presence of the tumor lymphocytes.

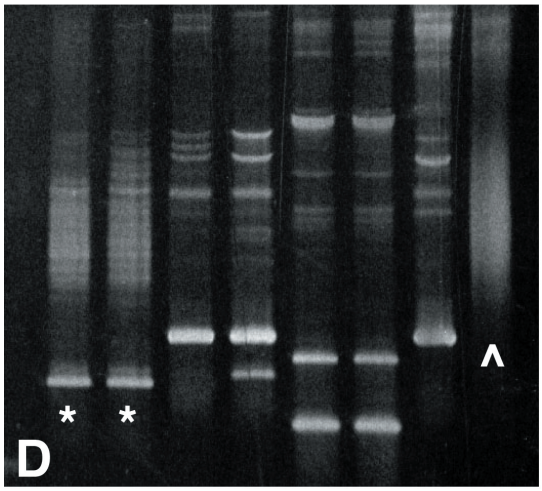


Immunohistochemical stain for B lymphocytes (red). These are the tumor cells and are a minor population numerically. They produced the amyloid protein shown in Photo A.

Fortunately, Dr. Moore was able to reach an accurate definitive diagnosis using immunohistochemical and molecular clonality techniques to classify the lymphocyte lineage and the disease process. Results of these tests indicated that Lost in the Fog's tumor was a lymphoma of B-cell origin.

Molecular clonality testing is not a primary diagnostic assay but is used as an adjunct to traditional histopathological examination and immunohistochemical diagnostic assays. It is used to differentiate malignancies from other processes (such as cells reacting to infections) in lymphocytes. During development, B cells make unique surface receptors for antigens (infectious agents, allergens, etc.). As a result of this process, each B cell essentially creates a molecular fingerprint in its immunoglobulin gene locus that differs from the fingerprints created by other B cells. In a random population of B cells that might assemble to fight an infection, the immunoglobulin gene fingerprints are quite variable (polyclonal = many clones). In the case of B cell lymphoma, the cancer develops from a single transformed cell whose descendants share an identical immunoglobulin gene fingerprint, which indicates the presence of a single clone of B cells.

So while tremendous advances have indeed been made in the methods used to diagnose and subsequently treat different kinds of cancer, cancer continues to be an insidious disease because there are many components that still are not understood. Years of basic research have brought a number of successes to the diagnosis and treatment of cancer, but more work is needed to continue making improvements. ❄



Molecular clonality assay. Amplification of the immunoglobulin heavy chain locus (IGH) from the lymphoma reveals a single-size band (*), indicating a clonal B cell population (derived from a single cell). Amplification of IGH from normal lymph node shows a heterogeneous smear (^) consistent with a polyclonal B cell population.

The Promise and Obstacle in Horse Cancer Research

by Xinben Chen, BVM, PhD

Humans today live longer than ever before. Since cancer is closely associated with old age in humans, the incidence of cancer in a person's lifetime is increased by about 50%. Likewise, as the quality of life has improved for horses and they now live longer, the cancer incidence in horses is increasing and becoming an issue in equine health.

Cancer formation and progression are controlled by two major genetic factors: oncogenes and tumor suppressor genes. Oncogenes in general promote tumor formation, whereas tumor suppressor genes inhibit it. Many oncogenes have been found to be activated while tumor suppressor genes are inactivated in tumors.

P53 is a major tumor suppressor gene. In human cancer, we have found that mutation of p53 is the most frequent genetic alteration, occurring in approximately 50% of all human cancers. Mutation of p53 inactivates its tumor suppressor function. In addition, mutant p53 is an oncogene and promotes cancer formation. Furthermore, mutation of p53 has been found to be hereditary in a small portion of human populations. Thus, investigation of p53 is a significant part of cancer research.

It is likely that p53 is frequently mutated in equine cancer as well, but few studies have been done in horses. The possibility also exists that a germline mutation of p53 might be responsible for a breed that is prone to multiple tumors with an early onset.

Sarcoids are one of the most common tumor types in horses. Bovine papillomavirus (BPV) and equine papillomavirus (EPV) may play a role in sarcoid development. The E5 gene in BPV and EPV may be responsible, but other viral oncogenes may also be involved, including the E5 and E7 oncogenes. Interestingly, the E6 oncogene is known to inactivate p53 tumor suppressor. Again, very few studies have been performed to confirm the viral gene(s) responsible for sarcoids in horses. Once the gene is identified, a vaccine can be developed to combat the disease. In addition, gene therapy can be developed to eliminate the viral oncogene.

The Center for Comparative Oncology is located within the Center for Companion Animal Health, UC Davis School of Veterinary Medicine.

The cancer research laboratory is state-of-the-art and is near the companion animal cancer clinic.

At the UC Davis School of Veterinary Medicine, the Center for Comparative Oncology — a cancer-specific research center — has been created to improve our understanding of cancer in animals. While cancer investigations have been conducted for many years in dogs and cats, few studies have been done in horses. It is hoped that the Center for Comparative Oncology can help change this by finding answers to the problem of equine tumors such as sarcoid, melanoma, and lymphoma. ❄

DONOR SUPPORT

2007 Peray Memorial Endowment

Congratulations to Dr. Stephanie Bell for being awarded the 2007 Peray Memorial Endowment! Dr. Bell's research will focus on analyzing a strain of the equine herpesvirus-2 using DNA sequencing.

Dr. Stephanie Bell

Equine herpesvirus-2 (EHV-2) infection has been implicated in the development of keratoconjunctivitis, malaise, fever, pharyngitis, and enlarged lymph nodes in young horses. However, due to the widespread nature of EHV-2 infection in horse populations, it has been difficult to establish a causal relationship between EHV-2 and various diseases. Identification of EHV-2 strains associated with respiratory disease in foals would be very helpful in understanding its clinical relevance.

An increased understanding of the effects of genetic heterogeneity on the ability of herpesviruses to cause disease would also have direction application to studies of EHV-1.

2007 John Hughes Memorial Endowment and 2007 Dan Evans Memorial Endowment

Congratulations to Dr. Emily Haggett for being awarded both the 2007 John Hughes Memorial Endowment and the 2007 Dan Evans Memorial Endowment! Dr. Haggett will be investigating the immune system of neonatal foals and their susceptibility to infectious diseases such as *Rhodococcus equi*.

Dr. Emily Haggett

Dr. Haggett attended the University of Bristol in England and graduated with a degree in Veterinary Science. She then worked in general practice before completing an 18-month internship at the Liphook Equine Hospital in Hampshire. She is now in her second year of residency at UC Davis. She has a special interest in neonatology and is currently undertaking research in neonatal maladjustment and the neonatal immune response.

Upcoming Events

The Equine Medicine Club at UC Davis presents

An Apple A Day: Wellness and Preventative Health for your Horse

May 17, 2008

This year's annual symposium sponsored by the Student Chapter of the American Association of Equine Practitioners (SCAAEP) will cover a variety of health-related talks and wetlabs conducted by UC Davis faculty and residents for the general horse owner. Proceeds from the symposium will help fund wetlabs and other activities.

For more information and a schedule of activities, visit their website at
www.vetmed.ucdavis.edu/clubs/emc/symp.html

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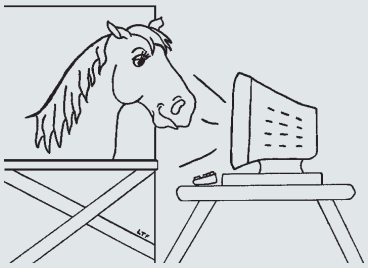

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