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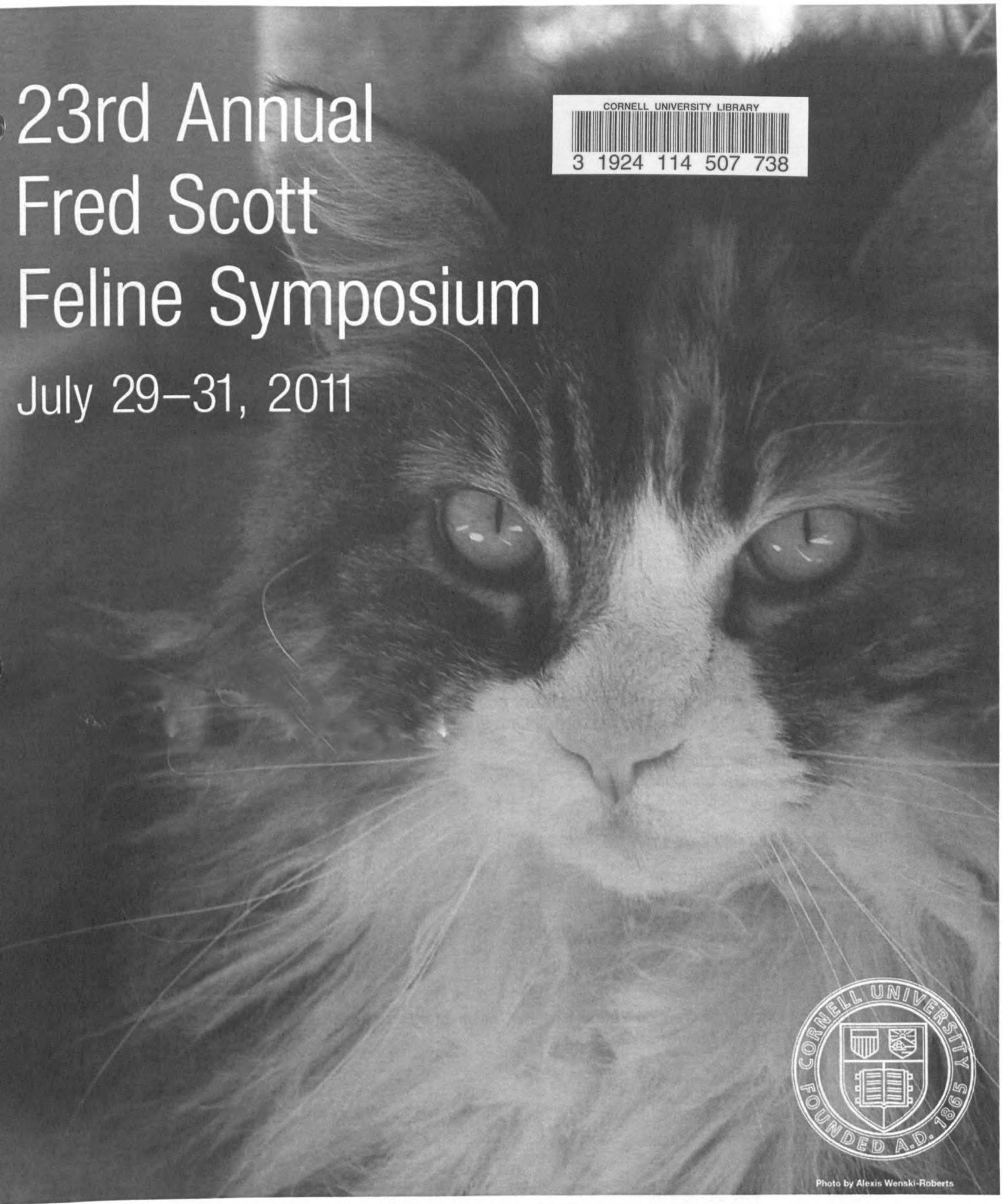
# 23rd Annual Fred Scott Feline Symposium

July 29–31, 2011





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Information about this conference and other continuing education programs offered by the College of Veterinary Medicine at Cornell University are available by contacting:

Office of Continuing Education
College of Veterinary Medicine
S2 113 Schurman Hall, Box 52
Cornell University
Ithaca, NY 14853-6401

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| Phone | 607-253-3200 |
| Fax | 607-253-3198 |
| Email | amm36@cornell.edu |
| Website | www.vet.cornell.edu/events |

Information about the Cornell Feline Health Center at the College of Veterinary Medicine at Cornell University contact:

Cornell Feline Health Center
College of Veterinary Medicine
Hungerford Hill Road
Cornell University
Ithaca, NY 14853

| | |
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# General Information and Logistics

## 23rd Annual Fred Scott Feline Symposium
## July 29 - 31, 2011

### Course Overview

This year's 23rd Annual Fred Scott Feline Symposium will educate and update veterinarians in feline oncology, gingivostomatitis, infectious diseases, and behavioral issues.

### RACE Accreditation and Continuing Education Credit

This program was reviewed and approved by the AAVSB RACE program for 19 hours of continuing education in jurisdictions which recognize AAVSB RACE approval. Please contact the AAVSB RACE program if you have any comments/concerns regarding this program's validity or relevancy to the veterinary profession.

You are asked to sign-in at the registration desk on the first day so that there is evidence of your attendance.

For questions about accreditation and continuing education credit please contact:

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| Office of Continuing Education | Phone | 607-253-3200 |
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| S2 113 Schurman Hall, Box 52 | Email | CVMERM@cornell.edu |
| Cornell University | Website | www.vet.cornell.edu/events |
| Ithaca, NY 14853-6401 | | |

### Evaluation

It is important for the Cornell Office of Continuing Education, faculty, corporate sponsors, and exhibitors to receive your feedback. We ask that you complete the evaluation form and return it to the registration desk before you leave the symposium. The information you provide us is essential in the development of future educational programs. We welcome and encourage your comments on all aspects of this symposium.

### Meals

Meal tickets are in the back of your nametag for:

- Lunch on Friday and Saturday. These lunch meal tickets are to be turned into the cafeteria cashier after you select your lunch on Friday and at the cafeteria entrance on Saturday.
- Lunch with Dr. Barbara Kitchell on Friday in S1 007 Schurman Hall. If you signed up to have lunch with Dr. Kitchell on Friday please turn in your ticket to the staff member at the room entrance.
- Lunch with Dr. Ralph Henderson on Saturday in S1 007 Schurman Hall. If you signed up to have lunch with Dr. Henderson on Friday please turn in your ticket to the staff member at the room entrance.

### Tours

If you registered to participate in a tour of the college during lunch on Friday you will find an admittance ticket in the back of your nametag. Please meet in the Atrium at the beginning of your lunch break.

### Course Materials

The course materials that are distributed during this symposium are under the auspices of the Office of Continuing Education at the College of Veterinary Medicine at Cornell University. Duplication of these materials is prohibited.

### Disclaimer

The lectures offered during this symposium will include some discussion of off-label use and commercial products and/or services. The opinion and recommendations expressed by the faculty are their own.

Agenda

# Agenda

## 23rd Annual Fred Scott Feline Symposium
## July 29 - 31, 2011

- All lectures will be held in Lecture Hall I in the Veterinary Education Center.
- Continental Breakfasts and breaks will be located in the Hagan Room.

### Friday, July 29, 2011

| | |
|---|---|
| 7:30-8:00 a.m. | Registration and Continental Breakfast<br>**Sponsored by IDEXX Laboratories** |
| 8:00-8:15 a.m. | Welcome |
| 8:15-9:05 a.m. | Feline Mast Cell Disease<br>*-Barbara Kitchell* |
| 9:05-9:20 a.m. | Break |
| 9:20-10:10 a.m. | Advances in Feline Lymphosarcoma Care<br>*-Barbara Kitchell* |
| 10: 10-10:25 a.m. | Break |
| 10:25-11:15 a.m. | ***James R. Richards, Jr. Memorial Feline Lecture***<br>The Difference Between Dogs and Cats with Cancer<br>*-Barbara Kitchell* |
| 11:15-11:30 a.m. | Break |
| 11:30 a.m.-12:20 p.m. | Multi-modal Therapy for Cancer: Fundamental principles and practice<br>*-Ralph Henderson* |
| 12:20-1:30 p.m | Lunch<br>Lunch with Dr. Barbara Kitchell (pre-registration is required) |
| 1:30-2:20 p.m. | Surgical Management of Specific Feline Neoplasms<br>*-Ralph Henderson* |
| 2:20-2:35 p.m. | Break |
| 2:35-3:25 p.m. | People-directed Aggression: Making the Diagnosis<br>*-Michelle Bamberger* |
| 3:25-3:40 p.m. | Break |
| 3:40-4:30 p.m. | Elimination Behavior Problems<br>*-Pamela Perry* |
| 4:40-5:30 p.m. | Inter-cat Aggression and Miscellaneous Behavior Problems<br>*-Pamela Perry* |
| 6:30-9:00 p.m. | Annual Picnic–Celebrations |

## Saturday, July 30

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|---|---|
| 7:30-8:00 a.m. | Continental Breakfast<br>**Sponsored by Fallon Wellness Pharmacy** |
| 8:00-8:50 a.m. | Injection Site Sarcomas Where Do We Stand in 2011?<br>*-Barbara Kitchell* |
| 8:50-9:05 a.m. | Break |
| 9:05-9:55 a.m. | Feline Carcinoma Management<br>*-Barbara Kitchell* |
| 9:55-10:10 a.m. | Break |
| 10:10-11:00 a.m. | Feline Cutaneous Oncology<br>*-Barbara Kitchell* |
| 11:00-11:15 a.m. | Break |
| 11:15 a.m.-12:05 p.m. | Supportive Care for the Feline Patient With Cancer<br>*-Cheryl Balkman* |
| 12:05-1:10 p.m. | Lunch - **Sponsored by Intervet Schering-Plough Animal Health**<br>Lunch with Dr. Ralph Henderson (pre-registration is required) |
| 1:10-2:00 p.m. | Feline Juvenile Gingivostomatitis - An Overlooked Disease<br>*-Jennifer Rawlinson* |
| 2:00-2:15 p.m. | Break |
| 2:15-3:05 p.m. | Parasites of the Feline Lung<br>*-Dwight Bowman* |
| 3:05-3:20 p.m. | Break |
| 3:20-4:10 p.m. | The Intestinal Conundrum Protozoal Package<br>*-Dwight Bowman* |
| 4:10-5:00 p.m. | Two cat killers: Cuterebra and Cytauxzoon<br>*-Dwight Bowman* |
| 5:00-6:00 p.m. | Wine and cheese cocktail hour<br>**Sponsored by ArthroDynamic Technologies** |

## Sunday, July 31

| | |
|---|---|
| 8:00-8:30 a.m. | Continental Breakfast<br>**Sponsored by Fallon Wellness Pharmacy** |
| 8:30-9:50 a.m. | Feline Pain<br>*-Andrea Looney* |
| 9:50-10:10 a.m. | Break |
| 10:10-11:30 a.m. | Vet Oncology Assessment and Treatment<br>*-Andrea Looney* |

# Corporate Sponsors and Exhibitors

23rd Annual Fred Scott Feline Symposium
July 29 - 31, 2011

## Corporate Sponsors

### ArthroDynamic Technologies
www.arthrodynamic.com

ArthroDynamic Technologies, based out of Lexington, Kentucky, is the maker of Polyglycan, A-CYST, Tandem Oral, Poly Chews, and Dyna Lyte. A-CYST is a patented formulation designed for temporary replenishment of the glycosaminoglycan layer in the bladder and contains naturally occurring components of the bladder epithelium. GAG deficiency contributes to clinical symptoms in diseases such as feline IC, FLUTD, and cystitis cause by infections, trauma, urolithiasis, urinary retention and neoplasia.

### Fallon Wellness Pharmacy
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Peace of mind is a precious commodity, and that's what you can expect when you rely on Fallon Wellness Pharmacy (one of the very few compounding pharmacies nationally that have earned Professional Compounding Accreditation Board (PCAB) accreditation. We strive to improve patient outcomes and experiences through compounding and wellness consultations.

### IDEXX Laboratories
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The purpose of IDEXX Laboratories is to be a great company that creates exceptional long-term value for our customers, employees and shareholders by enhancing the health and well-being of pets, people and livestock.

### MERCK Animal Health (formerly Intervet Schering-Plough Animal Health )
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As an organization, our core values are driven by a desire to improve human life, achieve scientific excellence, operate with the highest standards of integrity, expand access to our products and employ a diverse workforce that values collaboration.

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Merial is a world-leading animal health company. We are a forward-looking company with a proven track record, producing pharmaceutical products and vaccines for livestock, pets and wildlife. We are on the cutting edge of product development and innovation, providing millions of doses worldwide annually to keep livestock and pets healthy.

## James R. Richards, Jr. Memorial Feline Lecture

The James R. Richards Jr. Memorial Feline Lectures were established to honor the outstanding contributions that the late Dr. James R. Richards Jr., made to the field of feline medicine to improve the health and well being of cats everywhere. A series of state-of the-art lectures on various areas of feline medicine will be held (1) periodically at the College of Veterinary Medicine, (2) at the annual New York State Veterinary Conference, and (3) at the annual Fred Scott Feline Symposium.

Dr. Richards was Director of the Cornell Feline Health Center (1997-2007), and Past President of the American Association of Feline Practitioners. Funds contributed to the James R. Richards, Jr. Memorial Fund for Feline Health at Cornell University by his many friends and colleagues are being placed in an endowment fund, and the income from this fund will support these memorial lectures in perpetuity.

## Annual Picnic

The annual picnic will be held at the Celebrations Banquet Facility, the band will be the *7th Age Barons.* We will have a shuttle available for those that requested it.

## Exhibitors

ArthroDynamic Technologies
Companion Therapy Laser by LiteCure
Cornell Feline Health Center
DVM Solutions
Fallon Wellness Pharmacy
Heska Corporation
Hill's Pet Nutrition, Inc.
MERCK Animal Health
MERIAL
Rx Vitamins for Pets
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# Faculty

## 23rd Annual Fred Scott Feline Symposium
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### Cheryl Balkman, MS, DVM, DACVIM

Dr. Cheryl Balkman received her veterinary degree from Cornell University College of Veterinary Medicine. She completed an internship at the Animal Medical Center in NYC and a residency at Cornell University in small animal internal medicine. From there she pursued a two year oncology research fellowship and a non-conforming residency in medical oncology. Dr. Balkman has been a lecturer in the medical oncology section at Cornell University since 2003. Dr. Balkman is board certified in small animal internal medicine.

### Michelle Bamberger, MS, DVM

Dr. Michelle Bamberger received her DVM from Cornell University in 1985. Before attending Cornell, she earned her masters degree in pharmacology from Hahnemann University Medical College and then worked in equine research for two years at New Bolton Center, University of Pennsylvania Veterinary School. After graduating from Cornell, Dr. Bamberger studied at Oxford University and practiced small animal and exotic medicine and surgery in both Massachusetts and New York. Before opening Vet Behavior Consults, Dr. Bamberger returned to Cornell for training in the field of behavior medicine as a Visiting Fellow. Dr. Bamberger has a special interest in educating the public on veterinary topics. She has taught adult education courses and written two books on the topic of first aid. She spends much of her spare time documenting the impacts that hydraulic fracturing for extraction of hydrocarbons has on both animal and human health.

### Dwight Bowman, MS, PHD

As a parasitologist, the focus of Dr. Bowman's research has been on the biology of parasitic infections, testing of various agents for efficacy against parasites, disinfection of parasites in manures and sewage sludges, and improved diagnostics. In 2008, he was awarded the Distinguished Veterinary Parasitologist Award by the American Association of Veterinary Parasitologists. In 2009, he was awarded the Chancellor's Award for Excellence in Teaching from the State University of New York. Since 1987, Dr. Bowman has taught veterinary parasitology in the College of Veterinary Medicine at Cornell University. He has authored and edited four textbooks on the parasites of domestic animals. Dr. Bowman first entered the field of veterinary medicine as a postdoctoral student of Dr. Robert Grieve in the Department of Pathobiological Sciences at the School of Veterinary Medicine, University of Wisconsin, Madison. At Wisconsin, Dr. Bowman worked on improved diagnostics for ocular larva migrans. He received his MS and PhD in parasitology from Tulane University in New Orleans, La., in 1976 and1983, respectively. Dr. Bowman focused his graduate studies on zoonotic diseases due to ascaridoid nematodes. He then spent four years working on a survey of parasites in U.S. domestic sewage sludges in a grant funded by the U.S. Environmental Protection Agency. Dr. Bowman earned his bachelor of arts in biology, with honors, from Hiram College, Hiram, OH, in 1974.

### Ralph A. Henderson, DVM, MS

Dr. Ralph Henderson graduated from the University of Missouri in 1972, and joined the faculty of Auburn University College of Veterinary Medicine in the Department of Clinical Sciences as an intern. He continued as an instructor earning a masters degree and subsequently moved through the academic ranks becoming a professor in 1981. He was board certified by the American College of Veterinary Surgeons in 1978 and served various committees of that organization including the

governing Board of Regents. He was granted Charter Diplomate status by the American College of Veterinary Internal Medicine, subspecialty Clinical Oncology in 1986.

Dr. Henderson's clinical activity narrowed from general and orthopedic small animal surgery to focus on soft tissue and reconstructive surgery in 1980. His focus further narrowed in 1998 when the Department of Clinical Sciences established the Clinical Oncology Service and he assumed the role of a dedicated Surgical Oncologist. He has received the Norden Outstanding Teacher Award, SCAVMA Certificate for Teaching Excellence, Alumnus of the Year for the University of Missouri and was named the Robert and Charlotte Lowder Distinguished Professor of Clinical Oncology.

Dr. Henderson's research has involved broad areas of veterinary orthopedic and general surgery, critical care, and oncology. Highlights of his research include the original description of the "Tibial Compression Mechanism" which is the fundamental principle upon which the TPLO cruciate reconstruction procedure is based; a technique for intestinal tube feedings; an intermediate duration tracheostomy technique; a number of surgical oncology reconstructive procedures and in 2005 he and a graduate student discovered fundamental healing differences between dogs and cats. Dr. Henderson was a charter member of the Veterinary Cooperative Oncology Group and participated in a number of collaborative retrospective and prospective studies. In addition, Dr. Henderson has had opportunity to contribute directly to human health as an instructor for Basic Life Support, Advanced Trauma Life Support, and Laparoscopic and Thoracoscopic Surgery instruction.

He is the co-author of one textbook and author or co-author of 20 book chapters, and 72 scientific articles. He has presented 15 scientific presentations or posters and 146 continuing education seminars.

## Barbara E. Kitchell, DVM, PhD, DACVIM

Dr. Barbara E. Kitchell graduated from Purdue University School of Veterinary Medicine in 1979. Dr. Kitchell completed an internship at the University of Minnesota, then residency in Small Animal Medicine at UC Davis. She started an Oncology referral center at Special Veterinary Services, Berkeley, California in 1985. She received a Ph.D. degree (emphasis in Cancer Biology) from the Department of Comparative Pathology at UC Davis in 1994. In addition, Dr. Kitchell completed a postdoctoral fellowship in the Department of Comparative Medicine, Stanford Medical School from 1990-1994. She returned to academic medicine in 1994 as Assistant Professor in the Department of Veterinary Clinical Medicine, University of Illinois School of Veterinary Medicine. Dr. Kitchell joined the faculty of Michigan State University in 2004, where she is acting as Director of the Center for Comparative Oncology. Dr. Kitchell is an ACVIM Diplomate in the specialties of Internal Medicine and Oncology. She has received numerous awards including the National Cancer Institute Physician Scientist Award, the Dean's Postdoctoral Fellowship Award at Stanford, and the Gaines Cycle "Golden Fido" award for Veterinarian of the Year in 1993. She was a selected participant at 2 workshops (Molecular Biology of Cancer in 1993 and Methods in Clinical Cancer Research in 1997), sponsored by the American Association for Cancer Research and is an active member of that organization. She is currently president of the Veterinary Cancer Society. Dr. Kitchell is the author of numerous scientific publications and chapters, and keeps busy as a single mom of 5 active teenagers and is active in adoption, foster care and Transition to Independence for foster adolescents in Lansing, Michigan.

## Andrea Looney, DVM, DACVA

Dr. Looney graduated from the College of Veterinary Medicine at Cornell University in 1989. She was an instructor at Cornell University Hospital for Animals from 1990-1996 in the Departments of Anesthesiology and Community Practice Medicine. Following completion of her residency, she accepted a position at Angell Animal Medical Center where she worked for 10 years, prior to short returns to academia at both Tufts University Cummings School of Veterinary Medicine and Cornell University. She is currently at Upstate Veterinary Specialties in Albany where she works in emergency/ perioperative care, and rehabilitation.

## Pamela Perry, DVM

Dr. Pamela Perry was born and raised in Vermont. She went to Cornell University as an undergraduate (BS in Animal Science) and then continued on in veterinary school. Dr. Perry recently defended her PhD thesis at Cornell and graduated in May 2011. Her graduate work evaluated the effects of enrichment programs on the behavior, welfare, and adoptability of dogs in an animal shelter. Before pursuing graduate work, she was in private practice for 5 years working with both small and large animals. In addition, she lectured on behavior and welfare topics for seminars and conferences and is a lecturer for an Animal Welfare course at Cornell. Dr. Perry was also the primary instructor for a Farm Animal Behavior course in Animal Science for 6 years. She is currently a non-conforming behavior resident under Dr. Katherine Houpt, VMD, PhD, DACVB.

## Jennifer Rawlinson, DVM, DAVDC

Dr. Rawlinson graduated from Cornell University Veterinary College in 1998. After working as a small animal private practitioner for three years in the southern tier of New York, she returned to Cornell as a veterinary educator and course organizer. Over her next two years at Cornell, her interest in dentistry grew, and she accepted a residency position in the Dentistry and Oral Surgery section at the University of Pennsylvania. In 2005, she became a Diplomate of the American Veterinary Dental College and developed the Dental and Oral Surgery section at Cornell University. She has devoted the last 6 years to providing high quality dental service for all species, educating veterinary students in both small animal and equine dentistry, and developing a fledgling research program.

There were no pages

in this section

**Feline Mast Cell Disease**

*Barbara E. Kitchell, DVM, Ph.D., DACVIM*
*Michigan State University*

Normal mast cells are of hematopoietic origin and function as mediators of IgE specific inflammatory and hypersensitivity responses. Granules in the mast cells contain a number of vasoactive substances, including heparin, histamine, and seretonin, which induce the typical mast cell degranulation reaction of redness, pain, swelling, and itch. Malignant transformation of mast cells is a rare event in human beings but unfortunately a common event in dogs and to a lesser extent cats. Because the species in which the molecular pathogenesis of cancer is usually studied (humans) is not much affected by this disorder, research regarding the underlying cause of this disorder is scant. There is clearly a breed predisposition in canine mast cell disease, suggesting a genetic contribution. Environmental carcinogenesis for mast cell disease has not been well studied.

Mast cell tumor (MCT) occurs in the skin and in visceral sites in the cat. Skin tumor occurs in older (mean age 9 years) cats, with no observed sex predilection. Siamese cats are three times more likely than other breeds to develop cutaneous MCT, which are histiocytic in appearance and prone to spontaneous regression. Visceral MCT tumors occur in the spleen, mediastinum and nodes. There is no FeLV association. Cats also are prone to an aggressive intestinal form of MCT that is associated with vomition, weight loss, diarrhea and anorexia. Tumors in the intestine are composed of poorly differentiated cells. A recent report describes a form of intestinal MCT in cats that is associated with a significant stromal component, in which neoplastic mast cells are admixed with moderate to abundant dense stromal collagen (sclerosis). This entity has been named feline intestinal sclerosing mast cell tumor, and has a particularly poor prognosis.

Most cutaneous MCT of cats are well differentiated and benign, but occasionally have been reported to metastasize and often appear as multiple lesions in the skin. Mast cell infiltration was the most common cause of splenomegaly in cats, accounting for 15% of splenomegaly cases in one large retrospective study of 455 cats. Visceral MCT of the spleen may cause massive splenomegaly and vomiting due to GI ulceration from histamine release. When visceral organs such as spleen and liver are involved, mastocythemia and bone marrow involvement may be detected on staging evaluation. Occasionally cats with visceral MCT will develop multiple metastatic foci in the skin. Mediastinal involvement presents like thymic lymphosarcoma, with dyspnea and pleural effusion. Cytology of the pleural fluid reveals mast cells and eosinophils.

**Histologic Features and Molecular Pathogenesis** – Feline cutaneous mast cell tumors have been histologically classified as well-differentiated mastocytic types or atypical/poorly granulated lesions. Granules in feline mast cell tumors may not be evident through the use of Diff-Quik or H&E staining and thus additional stains such as Giemsa or Toluidine Blue may be required to fully characterize anaplastic mast cell tumors from cats. A poorly granulated histiocytic type of mast cell tumor has been described in young Siamese cats and this disease manifestation may be self-limiting. The

histologic grading system described for canine MCT has been shown in repeated studies not to be predictive of tumor behavior or of clinical outcome in feline MCT. Mitotic rate within feline tumors may be correlated with biologic behavior. In general, the prognosis in feline MCT patients is more closely tied to visceral involvement than to histologic appearance of the lesions. Additional prognostic features may be identified through use of proliferation markers such as mitotic index and Ki-67 are helpful in determining the potential for aggressive behavior. Additionally, positive immunohistochemical staining for CD117 (the c-kit receptor) as well as telomerase reverse transcriptase in feline mast cell tumors has been associated with poor prognosis and aggressive biologic behavior.

**C-Kit Mutation in Feline MCT** -The stem cell factor receptor c-kit is mutated by an internal tandem duplication mutation in the juxtamembrane domain region of exon 11-12 in a substantial proportion of canine MCT cases. In the cat, an internal tandem duplication mutation of 12 base pairs has been identified in the region corresponding to exon 8. This mutation results in a 4 amino acid insertion in the immunoglobulin-like domain of the receptor. Because this apparently activating mutation exists in at least some feline MCT cases, the potential for response to specific receptor tyrosine kinase inhibitors such as toceranib, masitinib, and imatinib is ongoing in feline oncology.

**Staging** –It is sometimes difficult to define the best staging procedures to recommend for feline mast cell tumor patients. Many cats have solitary or multicentric cutaneous lesions that are not systemically involved, although they may be recurrent or new lesions may arise over time. When multicentric tumors are discovered, systemic staging is indicated. Staging for MCT in cats involves a minimum database and buffy coat evaluation for occult mastocythemia, thoracic radiographs and abdominal ultrasound with fine needle aspiration of involved organs, and possibly bone marrow aspiration. Issues that are particular to the cat include the observation of mastocythemia and eosinophilia associated with visceral and intestinal forms of the disease. The ultrasonographic appearance of liver and spleen in cats with intestinal mast cell disease may appear to be of normal echotexture, so when intestinal lesions are discovered it may be prudent to perform fine needle aspirations of even normal appearing liver and spleen. A recent report suggests that intestinal mast cell tumors in the cat may have eccentric non-obstructive hypoechoic areas on the serosal surface of the bowel, appearing as dark outpouchings on the serosal gut wall. Mast cell tumors may also be a cause of intra-abdominal and intrathoracic lymphadenopathy in cats as in dogs.

**Treatment** -Treatment of dermal MCT is primarily through surgery, which occasionally must be multiple due to the tendency of cats to have multiple solitary tumors over extended periods of time. Because these tumors are well differentiated in general, surgery is curative most often for solitary lesions. Corticosteroids (1 mg/kg/day prednisolone) may be helpful. Intralesional triamcinolone injections have been helpful for individual solitary or multicentric cutaneous MCT lesions in the cat. A systemic dose of triamcinolone (1.2 to 1.8 mg/cat) can be administered intralesionally in cats at 2 week intervals, appears safe and tolerable, and may even eradicate small lesions.

Visceral MCT in cats is variable in behavior. Cats may present with massive splenomegaly, prompting the clinician to render a poor prognosis. However, we and others have observed that even splenectomy alone results in median survival times of 12 months for these cases, with some cats reported to live 3 years or more. Prolonged survival can be seen with splenectomy even when cats have evidence of hepatic mast cell infiltration on staging FNA.

Radiation therapy can be useful for non-resectable or invasive tumors. External beam irradiation is rarely necessary in cats as these lesions are frequently widespread and extensively multicentric and therefore not amenable to such therapy. Topical application of strontium-90 through plesiotherapy has been reported to be very effective in this setting. Unfortunately, plesiotherapy applicators are costly and highly regulated so this form of therapy is limited in availability.

Systemic chemotherapy may be useful for cats with disseminated MCT. Agents such as used for canine MCT may be tried. However, limited reports of prolonged survival as a result of chemotherapy are available. Vinblastine at 2.0 mg/kg IV weekly may also be helpful for treatment of multicentric feline mast cell tumors. We have employed lomustine (CCNU) chemotherapy at a dose of 10 mg capsule per cat Q 21 days with some positive responses observed. Rassnick et al reported on the use of lomustine at a dose of 50-60 mg/m2 PO in 38 feline cases. The mean number of doses administered to these cats was 2 (range 1-12 doses) These cats had a response rate of 50% (7 complete and 12 partial responses). for a median response duration of 168 days (range 25-727 days). Lomustine therapy was associated with neutropenia and thrombocytopenia in this group of cats.

Recently, the use of specific receptor tyrosine kinase inhibitors has been explored in cats. Imatinib mesylate (Gleevec) has been shown to improve outcomes in visceral MCT feline cases, at a dose of 10 mg/kg PO SID. In some cases, cats developed GI signs necessitating treated on an every other or every third day basis for quality of life concerns. Masitinib meylate has been administered to 20 healthy cats at doses of 50 mg/cat daily or every other day for 4 weeks. Adverse effects observed in these cats included proteinuria in 10% of cats and neutropenia in 15%. The potential for use of this drug for treatment of feline MCT is being explored but no response or toxicity data is yet available. Similarly, toceranib (Palladia) has been administered to 18 healthy cats in an exploratory pharmacokinetic study. Doses ranging from 2.5-6.5 mg/kg PO every other day for 10 days were associated with varying gastrointestinal signs and anorexia, which were reversible on discontinuation of the drug in this group of cats. One can anticipate further reports on the use of specific receptor tyrosine kinase inhibitors in feline MCT in the near future.

**Supportive Care** - Gastrointestinal signs and signs of systemic degranulation reaction are rare in cats, but can occur. Bruising at sites of MCT can be associated with heparin release, as in the dog. Very rarely cats with MCT can suffer sudden hypotensive crisis and death from degranulation after surgical manipulation of tumor or even a procedure as simple as fine needle aspiration. Normal mast cells in the airway of cats are associated

with signs of bronchoconstriction in feline asthma, and in addition to antihistamine administration, antiserotonergics such as cyproheptidine may be helpful adjuncts in feline mast cell disease. Interestingly, a recent research paper assessing the effect of H1 receptor antagonists terfenadine and loratadine showed inhibition of mast cell growth and even apoptosis when the drugs were applied to established cell lines and primary mast cell cultures from human and canine patients. However, famotidine, cimetidine, and ranitidine did not exert substantial growth- inhibitory effects on mast cells in culture. It is not yet known whether this approach would prove to have clinical benefit, and the drugs were not explored in feline mast cell tumors in culture. Treatment of gastric and duodenal ulcers is symptomatic as described in canine MCT, and would typically include the use of H2 blockers such as famotidine, or even sucralfate and omeprazole in severe cases. Intestinal MCT carries the poorest prognosis of all of these presentations. Intestinal MCT often is associated with systemic involvement and patients are debilitated from malassimilation before diagnosis. If possible, bowel resection with 5-10 cm margins should be performed. Corticosteroids may be palliative for these cats, but most with intestinal involvement die within 4 months of diagnosis.

**Advances in Feline Lymphosarcoma Care**

*Barbara E. Kitchell, DVM, Ph.D., DACVIM*
*Michigan State University*

**Epidemiology:** Among the domestic animal species, the incidence of lymphoma is relatively high in both the dog and cat. The incidence rate and disease presentation of this malignant disease in cats has changed since the advent of vaccines and diagnostic tests for the management of feline leukemia virus. The older literature reported rates of lymphoma in cats to be 200 cases of lymphoma or leukemia per 100,000 cats at risk per year. While definitive feline epidemiologic studies documenting the change in incidence rates of lymphoma and FeLV infection have yet to be carried out, it appears that the incidence rate of lymphoma in cats is around 20-25 cases per 100,000 cats at risk per year, which is similar to the rate seen in dogs and humans.

Lymphoma has traditionally been the most common malignancy of cats. Before vaccines for FeLV, approximately 50-70% of cats with lymphoma were FeLV positive. Recent studies of feline lymphoma patients in the 1990's suggest that only 8-14% of lymphoma cats are FeLV positive. There is also a relationship of the feline immunodeficiency virus with lymphoma in cats. The relative risks for developing leukemia/lymphoma were 5.6, 62.1, and 77.3 times greater in cats infected with FIV, FeLV, or with both infections, as compared to uninfected control cats. The average age at onset of lymphoma has been reported to be 5-6 years in cats, but this number may be misleading due to the biphasic peak in the age of incidence. Co-infected or FIV positive cats with lymphoma were significantly older than FeLV infected cats. In most recent clinical studies, the median age of lymphoma cats is 9-11 years, with the majority of cats having alimentary site lymphoma.

**Lymphoma Classification:** Lymphoma is classified based on essentially 4 criteria: histologic type, anatomic location, cytologic appearance, and immunologic type of lymphocyte affected. In many cases, the anatomic location and cytologic appearance are used to establish the working diagnosis for treating cats affected with this disease. Cytologically, tumors have been classified in the older literature as stem cell, lymphoblastic, prolymphocytic, histiocytic and lymphohistiocytic types. Anatomic locations of this disorder in cats include alimentary, anterior mediastinal (thymic), multicentric, leukemic, and miscellaneous types (renal, ocular, neurologic, dermatologic, nasal, and various other less commonly seen locations).

The immunophenotype of feline lymphomas is rarely determined clinically. However, because FeLV attacks T lymphocytes, T cell tumors have been reported in the anterior mediastinal (thymic) and multicentric forms in about 80% of cases so tested. Proviral DNA has recently been discovered by nested PCR reaction in up ot 80% of T cell and 60% of B cell feline lymphomas, although antigen was only noted in 21% of T cell and 11% of B cell lymphomas. The presence of proviral DNA may be attributed to endogenous retroviral elements in the cat genome, while actual expression of these proviral elements to create detectable antigen is rare, as is naturally acquired FeLV infection. Differentiation between inflammatory bowel disease with lymphocyte

infiltration and true intestinal lymphoma can be difficult in cats. There is some debate as to the cell of origin of alimentary LSA in cats; current literature indicates a T cell predominance over B cell disease in cats with alimentary LSA, which is typically not associated with FeLV infection. However, in the case of gastric lymphoma in cats, B cell disease predominates almost exclusively. (Moore, Vet Path 2011 – epub; Vet Path 46(2): 259-68.) Nasal lymphomas have been reported to be more likely B immunophenotype. Cats are also known to suffer from large granular lymphocyte (LGL) lymphoma, which is notable for the presence of pink granules in the cytoplasm of the lymphocytes. These lymphocytes may be natural killer cells, or may be a subset of cytotoxic T lymphocytes. As they have different lineage ontogeny, they have a dichotomous behavior in that some of these lesions are indolent and while they do not respond well to therapy, they are slow to progress. Other of the LGL lymphomas of cats are rapidly progressive and fatal despite chemotherapy, with a median survival time reported to be 57 days (Vet Comp Oncol 6(2):102-10).

**Clinical Signs and Diagnostic Testing:** Clinical signs are variable and depend on tumor location, stage, and paraneoplastic effects. Definitive diagnosis of lymphoma requires cytology or preferably histology. Laboratory abnormalities are also variable in cats affected with LSA depending upon the stage of disease, anatomic site, and FeLV status of the patient. FeLV status should be determined by ELISA testing of blood or serum, or by immunofluorescence testing of blood smears. Normal hemograms are most often encountered, but atypical lymphocytes may be seen on careful examination in up to 62% of cats with LSA. Bone marrow aspiration for cytology or bone marrow biopsy is useful in staging and evaluating feline patients with LSA. In some studies, approximately 50% of cats with LSA are reported to have some marrow infiltration with malignant cells. Also, cats with FeLV infection may have myelosuppression and with anemia, granulocytopenia, thrombocytopenia, or immune mediated disease. However, bone marrow evaluation may not change the recommended therapy for cats with LSA.

**Staging:** The role of staging in clinical oncology is to define the extent of tumor in any given patient. Staging is accomplished through evaluation of the physical examination, radiographs, changes in laboratory values, and bone marrow cytology or biopsy findings. Staging is necessary for therapeutic decision-making in some types of cancer (for example, tumors which are localized require only local treatment, whereas cancer that is metastatic requires a systemic approach to therapy). We typically stage lymphoma cats by performing a CBC with careful cytologic evaluation for occult leukemia, a serum chemistry panel, urinalysis, thoracic radiographs and abdominal ultrasound evaluation. Intestinal and renal lymphoma will often be more apparent with abdominal ultrasound, which reveals loss of layering of changes in intestinal wall thickness, presence of mesenteric lymphadenopathy in GI lymphoma, or hypoechoic subcasular renal thickening as a fairly reliable indicator of renal lymphoma. Many cats have evidence of bone marrow disorders (lymphoma infiltration, retroviral illness, or the anemia of chronic disease), which must be evaluated in order to develop an appropriate and safe therapeutic course. Diagnosis of alimentary or abdominal site lymphoma in cats requires evaluation of the gastrointestinal tract either by ultrasound guided fine needle aspiration, endoscopy or by surgical exploratory for full thickness biopsy.

**Therapy:** The goal of therapy in LSA is palliation of symptoms by inducing remission, thereby improving the quality of the patient's life and prolonging the animal's life in comfort. Cure is sometimes achieved in LSA in cats, particularly in cases of localized disease such as in the case of intranasal lymphoma or renal lymphoma. In other cases with indolent or low-grade disease, long-term survival in cats is possible. Of course, high grade lymphoma or lymphoma associated with retroviral disease often has a rapidly progressive course and may only respond transiently to therapy. Type of therapy chosen depends largely on the presentation seen, and will be discussed in the context of region of involvement.

Local therapy may be used in patients with Stage I disease (localized to one site) with the potential to be curative. Radiation therapy to the local site or surgical resection may be helpful. The cases for which the tumor is locally confined to a single site are rare, however, nasal lymphoma in cats treated with radiation with or without chemotherapy have been reported to have very long survival times. In a paper from UC Davis, cats with intranasal lymphoma treated with 22-48 gy of radiation (median 42 gy) plus 6 months of chemotherapy had a progression free survival duration of 945 days, with approximately 60% of the cats alive and disease free beyond that point. Of the 19 cats treated in this report, 4 (23%) had local recurrence, while 17% had distant metastasis at some time. Involvement of the cribriform plate was found to be a negative prognostic factor (Vet Rad Ultra 2007 48(4):388 – 93).

Systemic therapy is the most important part of the therapy for LSA in cats. Several chemotherapy protocols have been published, with most reporting approximately 60 - 80% of cats obtaining a durable remission of lasting a median of 7-8 months. Approximately 20-30% of cats can be expected to live beyond one year. FeLV positive cats tend to be more sensitive to the myelosuppressive side effects.

Alimentary lymphoma is becoming the most common presentation seen in older cats. The intestines are reported to be involved in 70% of cases reviewed at Tufts University. Signs include vomiting, diarrhea, and anorexia with weight loss. Of 28 cats reported in the Tufts study to be treated with COP chemotherapy, 9 had complete response, 2 had partial remission, and 16 failed to respond to therapy. Median remission time for the 11 cats that responded to therapy was 213 days, but the overall median survival duration with chemotherapy was 50 days. Thus, most cats that failed to respond to therapy had extremely short survivals. However, 5 cats in the study lived beyond one year. More recently, as study from Cornell (JAVMA 2008 232(3):405-10) reported the use of oral prednisone and chlorambucil in 41 cats with low grade lymphocytic lymphoma, predominately of the gut. Of these cases, 56% achieved a complete response and 39% a partial response to treatment. Cats that achieved a complete response had a median remission duration of 897 days, while those with a partial response had a median remission duration of 428 days. All had improved clinical signs on therapy. Overall median survival time for the entire group was 704 days. Nutritional support becomes very critical for these cats, as gut involvement often is associated with malassimilation of some degree. Low serum cobalamin is frequently seen, as is anemia.

For cats with large cell high-grade lymphoma of the gastrointestinal tract, we institute therapy with prednisolone and l-asparaginase for 1-3 weeks in these cats, along with metronidazole therapy for bacterial overgrowth disease and intense nutritional support, before adding cyclophosphamide and vincristine, in an effort to minimize effects on gut mucosa or motility. Anecdotally, we have had several cats that were intolerant to cyclophosphamide but tolerant of chlorambucil in their induction protocol. Others have reported that mitoxantrone in cat lymphoma is without effect, but we have managed several cats with alimentary lymphoma on mitoxantrone (5.5 mg/M2 IV infusion over 1 hour) and prednisone therapy with success for several months. Doxorubicin therapy for high-grade disease may also be very helpful. While it seems contraindicated to apply radiotherapy to the feline intestine, we have successfully rescued out of remission GI lymphoma cats with focal irradiation to the intestine, using 4 gy/fraction dosing on two consecutive days.

Mediastinal lymphoma is becoming more rare in clinical practice due to the efficacy of FeLV vaccines. This form occurs most often in young cats and those that are FeLV positive. These cats have fairly good responses to combination chemotherapy with COP (79% complete remission rates with a median remission duration of 150 days, as reported by Cotter in 1983.) However, the cat with a mediastinal mass presented today is more rare, often older, and frequently is found to have a thymoma rather than a thymic lymphosarcoma. Accurate diagnosis is critical, as thymoma may not respond to therapy for lymphoma. Typical recommendation for true mediastinal lymphoma remains the use of combination chemotherapy, such as is detailed below, COP therapy, and also radiotherapy for local control.

Renal lymphoma has a variable biologic behavior. Those cats that present with solitary kidney involvement have better outcomes in response to treatment than those with bilateral disease, severe azotemia, or other sites of involvement in the abdomen. Association with spinal lymphoma has been noted for renal primary disease. Renal lymphoma cats with FeLV positive status have shorter survival duration also. In one study, 61% of renal cats had a complete response to chemotherapy with median remission duration of 127 days (range 20-2,542 days - or cure). These cats are treated with aggressive fluid and red cell support and must receive chemotherapy that does not require renal elimination initially until renal function is improved. Again, we generally administer prednisone or dexamethasone, l-asparginase, and vincristine to these patients. Cyclophosphamide and doxorubicin can be added when renal function is improved. Some of the longest survivors of feline lymphoma have renal lymphoma, with some cats surviving up to 4 years from diagnosis.

Spinal lymphoma often presents as posterior paresis in these patients. Severe pain is often a feature as well. The majority are FeLV positive and have concurrent bone marrow involvement. Chemotherapy with focal radiation therapy is the treatment of choice for these cats. Occasionally cats are diagnosed at surgical decompression and are found to have focal lesions. Decompression may be helpful to stabilize neurologic function in addition to appropriate anticancer therapy.

**Table 1 -Feline Lymphoma Staging**[1]

| | |
|---|---|
| Stage I | Single tumor (extranodal) or single lymphoid tissue including anterior mediastinum |
| Stage II | A single tumor (extranodal) with regional lymph node involvement; Two or more nodal areas or extranodal tumors on the same side of the diaphragm; a resectable primary GI tract tumor, with or without involvement of associated lymph nodes |
| Stage III | Two or more nodal areas or extranodal tumors above and below the diaphragm; all unresectable intra-abdominal disease; all paraspinal or epidural tumors |
| Stage IV | Liver and/or spleen involvement, with or without the above |
| Stage V | Stages I-IV with involvement of the bone marrow, CNS, or both |

[1]Mooney S., et al: Renal lymphoma in cats: 28 cases (1977-1984) JAVMA 191:1473, 1987.

**Table 2 - Diagnosis & Staging Tests for Feline Lymphoma**

- Minimum data base including CBC, serum chemistry panel, UA, FeLV and FIV tests; confirm FIV ELISA + test by immunoblot
- T: palpation, measurement, radiographs if anterior mediastinal location, cytology, biopsy
- N: palpation, FNA, biopsy
- M: thoracic radiographs 3 views, abdominal ultrasound. If patient is cytopenic, has circulating blast cells, or is feline retroviral positive, bone marrow aspiration should be performed

**Chemotherapy protocols for cats with lymphoma**

Cats are most often 0.25 mg/m$^2$ body surface area, therefore, doses of chemotherapy drugs given below are based on this calculation.

Low Grade Lymphoma protocol:

Prednisolone 5 mg PO BID initially, then EOD. Chlorambucil (Leukeran) 2 mg tablet twice weekly. Monitor the CBC on a monthly basis for myelosuppression, particularly increasing anemia or thrombocytopenia long term.

COP protocol

**C**yclophosphamide 25mg tablet, PO, twice weekly for 42 days (6 weeks)

Vincristine (**O**ncovin) 0.1mg, IV, q 7 days for 42 days (6 weeks)

**P**rednisone 5 mg, PO, sid for 1 week; then 5mg, PO, eod until relapse or adverse steroid effects in which case taper dose and discontinue

*CBC's and lymph node/mass measurements will be obtained weekly, in order to modify treatment if deemed necessary.*

**Feline version of the University of Wisconsin-Madison lymphoma protocol:**

| Treatment Week | Drug, Dosage, and Route | Treatment Week | Drug, Dosage, and Route |
|---|---|---|---|
| 1 | Vincristine, 0.5-0.7 mg/m$^2$, IV<br>L-asparaginase, 400 Units/kg, SQ<br>Prednisone, 2 mg/kg, PO | 11 | Vincristine, 0.5-0.7 mg/m$^2$, IV |
| 2 | Cyclophosphamide 200 mg/m$^2$, IV<br>Lasix 3 mg/kg, IV<br>Prednisone, 2 mg/kg, PO | 13 | Cyclophosphamide 200 mg/m$^2$<br>Lasix 3 mg/kg, IV |
| 3 | Vincristine, 0.5-0.7 mg/m$^2$, IV<br>Prednisone, 1 mg/kg, PO | 15 | Vincristine, 0.5-0.7 mg/m$^2$, IV |
| 4 | Doxorubicin, 25 mg/m$^2$, IV<br>Prednisone, 1.0 mg/kg, PO[a] | 17 | Doxorubicin, 25 mg/m$^2$, IV |
| 6 | Vincristine, 0.5-0.7 mg/m$^2$, IV | 19 | Vincristine, 0.5-0.7 mg/m$^2$, IV |
| 7[d] | Cyclophosphamide 200 mg/m$^2$, IV<br>Lasix 3 mg/kg, IV | 21 | Cyclophosphamide 200 mg/m$^2$<br>Lasix 3 mg/kg, IV |
| 8 | Vincristine, 0.5-0.7 mg/m$^2$, IV | 23 | Vincristine, 0.5-0.7 mg/m$^2$, IV |
| 9[b] | Doxorubicin, 25 mg/m$^2$, IV | 25 | Doxorubicin, 25 mg/m$^2$, IV |

[a]Prednisone is continued (1 mg/kg, PO) every other day from this point on.

COPLA protocol

**C**yclophosphamide 25 mg tablet, PO, twice weekly for 42 days (6 weeks)

Vincristine (**O**ncovin) 0.1 mg, IV, starting day 1, q 7 days for 42 days (6 weeks)

**P**rednisone 5 mg, PO, sid for 7 days; then 5mg, PO, eod until relapse or adverse steroid effects in which case taper dose and discontinue

**L**-asparaginase 400 U/kg, SC, on days 1 and 8

Doxorubicin (**A**driamycin) 20-25 mg/$m^2$, IV, weeks 6, 9, and 12

*CBC's and lymph node measurements should be obtained weekly beginning on day 8, in order to modify treatment if deemed necessary.*

COAP protocol:

**C**yclophosphamide 25 mg tablet/cat PO twice weekly for 42 days (6 weeks)

Vincristine (**O**ncovin) 0.1 mg/cat, IV, q 7 days for 42 days (6 weeks)

Cytosine **A**rabinoside 25 mg/cat SC, divided tid for 2 days

**P**rednisone 5 mg, PO, SID for 7 days; then 5mg, PO, eod until relapse or adverse steroid effects in which case taper dose and discontinue

NOTE: Cats with acute life threatening lymphoma (anterior mediastinal with respiratory compromise, or central nervous system disease) may be additionally treated with:

- Radiation therapy of affected area.

**For cats with CNS Lymphoma or Lymphoma with CNS signs:**

Cyclophosphamide 25mg, tablet PO, twice weekly for 42 days (6 weeks)

Vincristine (Oncovin) 0.1 mg, IV, q 7 days for 42 days (6 weeks)

Cytosine Arabinoside 25 mg/cat/day, continuous IV infusion for 2 days.

Prednisone 5 mg, PO, q 12 hours for 7 days; then 5mg, PO, q 24 hours until relapse or adverse steroid effects in which case taper dose and discontinue.

FELINE LYMPHOMA RESCUE THERAPY

Doxorubicin (Adriamycin) 20 - 25 mg/$m^2$, (or 1 mg/kg) IV, every 21-28 days

***OR***

Mitoxantrone 5.5 mg/$m^2$, IV, q 21 days

***OR***

CCNU (Lomustine) 10 mg/cat, PO, q21 -28 days for 4 cycles; alternately, can reformulate CCNU capsules to a dose of 60 mg/m2 and administer every 21-28 days depending on appetite and myelosuppression for intertreatment interval.

***OR***

The feline version of the MOPP protocol:

MOPP stands for:

| | |
|---|---|
| Mustargen | 3 mg/$m^2$ IV in 10 ml NaCl |
| Oncovin (Vincristine) | 0.6 mg/$m^2$ IV |
| Procarbazine (Matulane) | 10 mg PO once daily |
| Prednisolone | 5 mg orally twice daily |

Protocol Schedule:

- Day 1: Mustargen + Vincristine IV
- Day 7: Mustargen + Vincristine IV

- Day 1 through 14: Matulane + Prednisolone PO
- Day 15 through 18: Rest

Patients are rechecked on day 28 and the cycle is started again.

***OR***

DOMAC protocol

**(Cycle is repeated every 21 days)**

NOTE: This is a dose intense protocol; monitor closely for adverse GI or bone marrow side effects.

**D**examethasone 1 mg/kg, PO or SC, days 1, 8, and 15

Vincristine (**O**ncovin) 0.5 mg/m$^2$, IV, days 8 and 15

**M**itoxantrone 4 to 5 mg/m$^2$, IV infusion (over 3 to 4 hours) day 1

Cytosine **A**rabinoside 150 - 200 mg/m$^2$, SC, divided tid, days 8 and 15

**C**yclophosphamide 200 mg/m$^2$, PO, day 10

Other agents that have been useful in treatment of cat lymphoma include doxorubicin, idarubicin, and mitoxantrone. In 36 cats with lymphoma treated with COP therapy, eighteen achieved CR. Those that continued on COP therapy had a median remission duration of 83 days, while those that were given doxorubicin therapy for 6 months had a median remission duration of 259 days, according to Moore at Tufts. Idarubicin is an oral anthracycline that has been reported in cats, again by Tony Moore. Median remission of cats maintained with idarubicin (2 mg/day PO for 3 consecutive days every 21 days) after COP induction therapy and CR was 183 days (range 30-825 days). The idarubicin was associated with leukopenia and anorexia, but the drug is less cardiotoxic than doxorubicin. Idarubicin is as yet not commercially available in the US.

**The Difference Between Dogs and Cats with Cancer**

*Barbara E. Kitchell, DVM, Ph.D., DACVIM*

Like all other eukaryotes, the feline species is subject to development of a variety of malignancies. Despite being declared the most popular companion animals in the United States and in fact worldwide, feline cancer therapy and research has lagged behind that of the dog. As the old adage states, "cats are not small dogs," and perhaps this is nowhere better evident than in the cancers that arise in the cat, the biologic behavior of those tumors, and the peculiarities of feline metabolism as regards cancer therapies. Cats may have less or more aggressive malignancies of organ or tissue sites when compared to dogs, and individualization of feline care is important to successful outcomes.

The feline species is believed to have been domesticated as long at 10,000 years ago, from a potential list of 5 progenitor feline types. As phenotypic variation through selective breeding has not been particularly striking in domestic cats, the exact point of domestication of *Felis catus* is in some doubt. It is believed that the originating species include small wild felids, the African wild cat (*Felis sylvestri lybica*), the European wild cat (*Felis sylvestri*). It is believed that the original domestication event occurred in the Fertile Crescent in the Near East. The earliest known archeological record of human and cat cohabitation was found in a burial site in Cyprus, dated 9,500 years ago. In this site, there was evidence of funerary rites for a cat buried alongside a human. Egyptians are known to have mummified cats to accompany them to the afterlife as early as 2500 BC. Cats were likely less easy to domesticate than dogs, as cats do not have a hierarchical social structure that would adapt well to a human alpha. Thus, cats likely joined humans in a mutually beneficial symbiotic relationship based on the prevalence of rodent infestation in early agrarian societies. Humans have long manipulated the canine genome through artificial selection in breeding to result in the modern dog, which has the highest morphologic variance of any species on the planet. Cats overall display less physical and behavioral phenotypic diversity than do dogs. The feline genome consists of 38 chromosomes and roughly 20,000 genes, although the feline genome project has thus far published approximately 65% coverage of the sequence of an Abyssinian cat named Cinnamon in 2007.

Feline cancer research has lagged behind canine research due to the paucity of genomic data, lack of availability of feline specific antibodies for investigation, and a general perception that the domestic cat is less useful as a translational model species for research than is the dog. The unique aspects of feline hepatic metabolism have rendered them particularly challenging for pharmaceutical research as well. Cats are unable to mobilize lipid stores rapidly through liver metabolism, resulting in a tendency toward hepatic lipidosis in times of inanition. Cats have a relative deficiency in glucuronyl transferase activity, making them vulnerable to toxicity from specific drugs and toxins. Cats are unable to synthesize arginine, which make them susceptible to hyperammonemia during times of anorexia. Cats are particularly vulnerable to potentially lethal toxicities from several chemotherapy agents, including 5-fluorouracil and its oral analog capecitabine,

cisplatin, and temozolomide.

**Different Tumor Behavior**

Some of the tumors that arise in the cat are more likely malignant than benign when compared to the histologic counterpart diseases in dogs, as is true for masses that arise in the skin and mammary gland. Itis also true that the biologic behaviour of certain of the malignancies that arise in the feline species have apparently differing clinical courses than counterpart histologies in dogs or humans. Coupled with different underlying carcinogenic responses and biologic behaviors in cat tumors is the unique pharmacologic responses of the cat's metabolism and excretion of many drugs important in cancer chemotherapy. Feline oncology thus presents additional challenges in veterinary medicine. Because cats are so common as companion animals, veterinary oncologists must constantly evaluate novel drugs and strategies to improve outcomes for cats afflicted with malignant disease.

Examples of tumors with more aggressive biologic behaviors in cats that in dogs include skin tumors in general, which are reportedly malignant in 60% of cats compared to 30% of dogs, and feline mammary tumors are 90% likely to be malignant as compared to 50% of canine mammary tumors. Oral tumors in cats are generally malignant, with a reported rate of 95%, while 70% of similar oral tumors in dogs are malignant. While dogs are most commonly affected by oral melanoma, which carries a poor prognosis due to metastasis, cats rarely experience oral melanomas. Instead, the most common oral malignancy in cats is the squamous cell carcinoma, which has a low metastatic rate but is highly invasive into bone and generally detected too late in the course of disease to allow for complete resection. Oral squamous cell carcinoma lesions in dogs are rarely metastatic also, and may be surgically cured if rostrally located and detected early. Also, cats are unfortunately susceptible to formation of sarcomas at sites of tissue wounding and inflammation, such as the uvea after ocular injury or the development of injection site sarcomas. These inflammatory and wound healing associated tumors are rarely encountered in the dog.

Conversely, hemangiosarcomas in cats may be actinic and non-metastatic in behavior, although the rare visceral hemangiosarcoma lesion of the cat is highly metastatic. Appedicular osteosarcomas of cats, on the other hand, tend to have much lower rates of metastasis (10%) than do the same lesions of dogs, where metastasis is expected in greater than 90% of cases. Similarly, melanocytic lesions of cats are more rare, and cutaneous melanomas in cats are largely benign, although uveal and oral lesions can have malignant behavior. Pulmonary carcinomas of cats may have an unusual metastatic pattern of behavior, with cats sometimes presented for swelling of the distal digits and nail bed or digital metastasis being the primary presenting complaint while the primary pulmonary tumor may be an incidental finding on thoracic radiographs.

Lymphoma in the cat can have disparate forms, ranging from the aggressive high

grade multicentric and thymic diseases that arise spontaneously or as a consequence of retroviral infection, to the more indolent GI lymphoma forms. Dogs have not been discovered to have a retroviral causation for lymphoma. Before vaccines for FeLV, approximately 50-70% of cats with lymphoma were FeLV positive. Studies of feline lymphoma patients in the 1990's suggest that only 8-14% of lymphoma cats are FeLV positive. In the past, FeLV infection occurred in the young adult feline population, with onset of lymphomas displaying a biphasic peak at 2 and then 5-6 years of age. Now, the median age of lymphoma cats was 11 years, with the majority of cats having alimentary site lymphoma. Alimentary lymphoma is very rare as a primary tumor of dogs. Feline GI lymphoma is often of low grade, but in dogs lymphoma is largely a high-grade disease.

**Feline Paraneoplastic Syndromes are Different**

Hypercalcemia of malignancy is the most common paraneoplastic syndrome seen in the dog, and is commonly associated with lymphoma, anal sac adenocarcinoma, mammary carcinoma, and other less common neoplasms. Hypercalceima of malignancy is much more rare in cats and is seen in cases of oral squamous cell carcinoma, lymphoma, and rarely in other neoplastic syndromes. A very rare and unusual paraneoplastic cutaneous disorder is seen in cats that are affected by pancreatic and bile duct carcinomas. Bilaterally symmetrical alopecia of the ventral abdomen and medial limbs has a unique, shiny skin appearance with easily epilated fur. Lameness due to footpad lesions was also noted in some cases. Exfoliative dermatitis lesions may also be noted in cases of feline thymoma, particularly affecting the head, pinnea and ear canals. A brown waxy discharge is reported to occur in the feet as well as in the ear canals. Paraneoplastic syndromes are mitigated by resolution of the underlying neoplastic disease process in cats, as in other species.

**Difference in Chemotherapy Tolerance**

It has been well established that a handful of chemotherapy agents are not safe for use in cats. Among these are cisplatin, which causes a potentially fatal pulmonary edema syndrome of undetermined origin. Cats are apparently deficient in dihydropyrimidine dehydrogenase, which makes them vulnerable to potentially lethal neurotoxicity from 5-fluoruracil and its oral analog capecitabine. Even exposure to 5% 5-fluoruracil topical cream has been reported to cause seizures and death in one cat.

Doxorubicin has been reported to induce renal toxicity in cats, although there is debate about the significance of this assertion. The original report was based on 30 mg/m2 IV dosing of doxorubicin, which is likely an overdose. Since anorexia and gastrointestinal signs are prominent with high dose doxorubicin therapy, and since many cats with cancer are geriatric, it is conceivable that the renal toxicity that was observed could be attributed to acute-on-chronic renal insufficiency brought on by dehydration in cats with renal compromise. Adequate hydration and dosing at 1 mg/kg doxorubicin, with careful attention to renal status, means that many cats with marginal renal function may safely receive this important antineoplastic agent.

Cats overall appear to tolerate alkylating agents very well. Lomustine (CCNU) has been used to treat cats with a variety of malignancies. The dose range for this agent is reported to be either 60 mg/m2 or 10 mg/cat for cats between 3.5 and 7 kg body weight. Responses have been noted with this agent in a variety of tumor settings. The drug dacarbazine is a non-traditional alkylating agent that binds primarily to the 06 position of guanine to cause DNA injury. This drug has not been explored for use in the cat because it is a prodrug that requires hepatic microsomal activity to activate the primary cytotoxic effect. Because of the relatively unexplored states of hepatic cytochrome P450 activation in cats, it is generally thought that there might be pharmacogenomic issues with either overactivation of dacarbazine with excess toxicity, or insufficient activation that would limit the drugs efficacy. Recently, an oral analog of dacarbazine called temozolomide has been introduced to veterinary oncology. This new drug has the advantage of being an already activated form of dacarbazine with high bioavailability and volume of distribution, including crossing the blood-brain barrier. However, we have discovered a subset of cats that develop pleural and pericardial effusion when treated with temozolomide either as a single agent or in combination with an anthracycline agent such as doxorubicin. This effect was seen in 3 of 13 cats, which resulted in early closure of the clinical trial. Until the exact mechanism for this effect is determined, we advocate caution in treating cats with this agent.

Several new drugs and protocols have become available to treat cats with non-resectable or metastatic solid tumors. Cats with injection site sarcomas, mammary tumors, and a variety of carcinomas have been managed with varying degrees of success using traditional chemotherapy agents as well as with drugs that are relatively new to veterinary medicine. The standard broad-spectrum chemotherapeutics in feline oncology include doxorubicin, which is typically administered at a dose of 1 mg/kg IV over 20-30 minutes in cats on a 21-28 day basis. Mitoxantrone may also be substituted for doxorubicin when there is concern for cardiac or renal compromise in the cat. Carboplatin is used exclusively in cats as cisplatin causes potentially lethal pulmonary toxicity. Carboplatin has some level of efficacy against a variety of neoplasm in the cat. The dose we use at MSU ranges from 180-240 mg/m2 IV bolus on a 21day basis. We have also evaluated a combination doublet therapy with gemcitabine and carboplatin in the cat. The protocol is administered as follows: Day 1- Gemcitabine 2 mg/kg IV over 20 minutes, followed by a 4 hour period to allow for prodrug activation, then carboplatin at 10 mg/kg IV bolus Day 8 - Gemcitabine 2 mg/kg IV over 20 minutes Day 15 -CBC only; Day 21 –If CBC is recovered, administer the next cycle of the protocol. We have seen a modest response rate with this protocol, including complete remission of a biopsy confirmed pancreatic adenocarcinoma in a 10 year old that that has remained durable over 15 months.

Ifosfamide is a third generation alkylating agent that is similar to cyclophosphamide. This agent has been efficacious in some cats with metastatic

carcinomas and sarcomas in our hands. This drug is somewhat unique in the cat, in the while the canine dose is 375 mg/m2, the feline dose is 900 mg/m2. Itis unclear why the maximally tolerated dose is so high in the feline species. It may be due to the relative inefficiency of activation of the prodrug in the cat as compared to humans and dogs. The drug is both nephrotoxic and a potent inducer of sterile hemorrhagic cystitis. Thus, it must be given with extensive fluid diuresis and with the drug MESNA administered as a urothelial protectant. The protocol is as follows:
Normal (0.9%) saline IV diuresis at a fluid rate of 6 times maintenance over 30 minutes (18.5 ml/kg/hr)
Ifosfamide diluted to 20 mg/ml or less over 20 minutes
Normal saline IV diuresis at 6X maintenance over 5 hours
MESNA urothelial protectant at 1/5 the patient's calculated mg dose at time 0 (immediately before ifosfamide administration), and repeated 2 and 5 hours after ifosfamide administration.
This therapy may be repeated on a 21 day basis.

A new version of vinca alkaloid called vinorelbine (Navelbine) has been used in the cat for the treatment of a variety of malignancies. Doses have ranged from 7.5 to 9.0 mg/m2 administered as a rapid intravenous bolus, on a 5 weeks on, one week off schedule of administration.

Paclitaxel (Taxol) has been used successfully in the cat particularly in the setting of metastatic mammary carcinoma. The dose that has been recommended for cats is 80 mg/m2 as a slow IV infusion, with careful attention paid to the potential for anaphylactoid reaction to occur. This agent is anaphylactogenic, although, in our hands, it appears to induce this response less frequently in the cat than in dogs. It is therefore recommended that the premedication protocol used in dogs be applied to cats, as follows: For 5 days preceding the anticipated date of paclitaxel administration, administer prednisolone (5 mg/cat SID PO), Diphenhydramine 1 mg/kg PO BID, and famotidine 0.5 mg/kg PO SID. Immediately prior to instituting the paclitaxel infusion, dexamethasone sodium phosphate is given as a 2 mg/kg IV bolus, as is famotidine (1 mg/kg IV) and diphenhydramine (4 mg/kg 1M). Anaphylactoid response should result in transient discontinuation of the infusion, followed by additional premedications as determined by the clinician, and reinstitution of the infusion at a slower rate. However, the longer the duration of the infusion, the greater the likelihood of increased GI and myelosuppressive toxicity.

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# SURGERY IN MULTI-MODAL CANCER THERAPY

*Objective: Description interaction of surgery, radiation, chemoimmunotherapy and alternative therapy in multimodal therapy. Unless otherwise noted, the only disease considered is malignant neoplasia; however, these principles may also overlap with specialty care of other diseases.*

## Principles

First Treatment. The first treatment is the one that has the greatest opportunity for success. It must be implemented as early as possible and must accomplish certain necessary minimum criteria for success. Intentional delay of diagnosics or treatment is considered to be the first treatment. When there is uncertainty of appropriate course, obtain consultation or refer.

Diagnosis and Staging. Definitive cancer treatment(s) must be preceded by sufficient effort to make a diagnosis, obtain a pathological grade and define the extent of disease (stage and volume).

Goals. Once an owner is advised of diagnosis, stage, treatment options and response possibilities, goals are mutually established. Though definitive treatment (maximal response sometimes called curative intent) is always desirable; however, based on the stage of disease, patient health or owner ability and wishes, it may not be possible. The alternatives are palliation when the patient is suffering or attempting to alter the rate of progression of disease.

Failure. Treatment should only be undertaken when its objective is clear. The objectives of surgery toward cancer management are: Diagnosis, Cure, Palliation, Adjuvant Care and, perhaps, Prophylaxis. (These objectives will be further defined later.) In the process of treatment, new findings can cause goals to be modified, but the new goal should still remain clear. Whenever the goal of treatment is not achieved, the treatment has failed. The author believes that high surgical standards (and planning) result in fewer failures. Whenever surgery that is intended to achieve a cure leaves cancer cells in the tissue, the surgeon has failed. And, when the harvest of tissue is intended to assist in diagnosis, but renders none, the surgeon has failed and, worse, treatment is delayed.

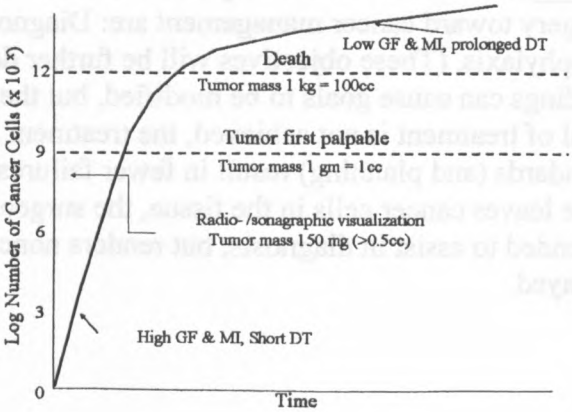
Owner Consent. Informed consent should include at minimum a description of the diagnostic or therapeutic procedures to be performed, prognosis, aftercare required, estimate of cost, and manner and timing of communication.

Planned Surgery. Surgery for the treatment of cancer has been defined as "planned" or "unplanned". Planned surgery is based upon knowledge of tumor microscopic examination (cytology or histopathology) and, as appropriate, imaging of the surgical field which assist in determining the volume of normal tissue to remove as a margin. Procedures that do not have the guidance of microscopy are defined as unplanned.

India Ink Margin
with Scored Neoplasm

Surgical Margin. The quantity of margin obtained is important in describing the efficacy of excision. Because of tissue elasticity and the dehydrating effect of tissue processing, margins measured at surgery will be larger than the margins measured by the pathologist. How pathologists define and report margins vary, but some of the following terms are common: Marginal or "capsular" (dissection was at the tumor-normal tissue interface), "Narrow" (implies several mm), and "Wide" (implies 1 to several cm). To aid the pathologist, the surgical margin should be distinguished from trimmed or artifactual cuts by marking the surgical borders (India ink or Davidson's System) and tagging important foci by suture(s) with description for the pathologist. Depending upon the particular neoplasm, a narrow margin composed of dense muscle fascia may be equal to a wide margin of fatty subcutis so the surgeon must consider the imperviousness of the planned margin when considering the pathologist's findings. It is important to remember that a layer of muscle fascia (fasciectomy/ myofasciectomy) is usually a barrier for mast cell tumor, but not for feline injection-site sarcoma. Whenever neoplasms are intentionally invaded for diagnostic purposes, placement of the incisions (and any other intentional wounds such as drains) must be placed to facilitate future treatments including surgery and radiation.

Malignant Development. Malignancy culminates from unregulated, rapidly dividing cells, characterized by a gradually diverging genotype expressed phenotypically within limits that are based on the cell of origin. Neoplastic transformation and early growth may depend upon escape of the neoplasm from detection until the size of the neoplasm results in autonomy. During early development, most cells in the neoplasm are dividing and the growth rate (doubling time, DT, growth fraction, GF) is rapid as expressed in the Gompertzian growth curve diagrammed in this section. This may be noted in the pathologist's interpretation by reporting the number of mitoses (number of mitoses per field(s)). As a neoplasm enlarges, the blood supply is often compromised and the neoplasm core becomes ischemic or necrotic. Many cells enter resting state (G0). The principle growth fraction is the portion at the surface of the neoplasm. Differential oxygen content and vascularity reduce the proportion of cells dividing thus, lowering the growth fraction. This status also influences the efficacy and distribution of



therapy. Contrasted imaging and biopsy would confirm ischemia. The earliest visible neoplasm by routine detection mechanisms (inspection, sonography, radiography) will have undergone between 20 and 30 doublings ($10^6$ to $10^8$ cells). The sequence of neoplasm development is important clinically because volume, vitality and growth rate influence the outcomes of various treatments.

Multi-modal Treatment. Although chemotherapy and immunotherapy are occasionally used for local treatment, most commonly, they are used for systemic therapy. Conversely, although radiation has been used for whole body treatments, it is most commonly employed for local treatment. Surgery is also aimed primarily at localized neoplasia. The efficacy of each of these treatments can be compromised (limited) by the aforementioned volume, vitality, and growth rate as well as location. Each of these treatments often have limitations that can be mitigated by combining them in specific sequences. These strategic sequential interventions with multiple treatments are termed multi-modal therapy.

In multi-modal treatment, one treatment modality usually has a dominant role and it is the "primary" treatment. It could be looked at as the key treatment needed for cure (even though cure may not be believed to be possible apart from an extraordinary response – and these do occur). Treatments that make the "primary" treatment more effective are adjuvant (helper) treatments and may be given neoadjuvant (Greek neo = before) or following the primary treatment. Based on treatment response, the relative roles of treatments may change from adjuvant to primary.

Surgery is most effective when precise neoplastic margins are palpable and when a margin of normal tissue taken with the neoplasm will not jeopardize important structures. Surgery is especially capable of "curative" treatment of localized neoplasia. In otherwise optimum clinical presentations, causes of failure include undetected metastasis and the more commonly encountered iatrogenic failures of too conservative margins (fear), contamination of the surgical wound (contamination of gloves and instruments by ulcerated neoplasms or cut neoplasms) and hydraulic propulsion by proximate injection of local anesthesia. For the surgeon, the most effective chemotherapeutic agent is 10% buffered formalin.

Irradiation is most effective for well-vascularized, oxygenated neoplasias and is advantageous in that important structures can often be included in the radiation field. Specifically, with most neoplasms, irradiation targets cellular DNA by direct damage or by free oxygen radical formation so that a cell may die acutely or when it tries to divide. By comparison, radiation is more time consuming (multiple treatments) and expensive than surgery. Radiation kills logarithmically. For example, even when radiation kills 99.99% of a neoplasm, a half kilogram neoplasm (500,000,000,000 cells) is reduced to 50,000,000 cells which is still far above the level of autonomy. Large volume neoplasias are more likely to exhibit the natural resistance factors of hypoxia and cell-cycle arrest (G-0 stage) which renders them more resistant to irradiation.

In general chemotherapy and immunotherapy are more effective for highly sensitive, small volume neoplasia with high growth fractions and good circulation. Similar to radiation therapy, the efficacy of chemotherapy and immunotherapy of large volume disease is limited to log-kill.

**Surgical Scenarios for Multi-modal Therapy**

Multi-modal planning acknowledges that no single therapy will be effective alone and the best results for the patient will be achieved with multiple treatment modalities. All of the following scenarios accept that curative intent surgery will be ineffective or less effective. In the real world, not only are knowledge of diagnosis and stage important, but the "want to" and "financial ability to" of the client must be considered in addition to the systemic health of the animal. The veterinarian serves as a broker between these three diagnostic areas (disease, vital reserves, owner) attempting to achieve the best outcome after a thorough discussion of the options.

In each of the following scenarios, the treatment will be built around the most important or "primary" treatment for stage and disease and other treatments will serve as adjuvant therapy. Palliation is not a goal of these scenarios.

Primary Surgery (Reoperation) with Adjuvants if needed. Most surgical failures result from unplanned operations, iatrogenic contamination (inoculation of the wound with exfoliated cancer cells), and undetected dirty margin. Such surgical failures are realized through histopathologic may be detected by margin examination or by recurrence. At the time of consultation, there may or may not be an apparent mass, the type and intent of the previous surgery may or may not be known, and the opinion of the surgeon may not be available. The best treatment for failed surgery is often a planned re-operation guided by diagnosis and imaging, but there are alternatives that must be considered based on completed histopathology (if tissues were processed), metastatic risk, and whether clear margins can be obtained:

- Planned reoperation – Best used when effective margins seem possible with a reoperation
- Add adjuvant (radiation, chemotherapy, immunotherapy) – if second surgery fails or is not possible
- Adjuvant(s) only – sensitive low volume neoplasia of moderate to high grade
- Surveillance only – low /no volume with low grade; negative cytology; owner reluctance

Neoadjuvant Surgery plus Irradiation: Some neoplasia is radiation sensitive and an owner might prefer to spare tissue. Surgery can be intentionally planned for the purpose of rending irradiation more effective by cytoreduction of the cells that are necrotic, hypoxic, or in resting stage – typically the center of the neoplasm. It is worth mentioning that through ctyoreduction, oxygenation improved, toxins of necrotic tissue are removed and residual G0 cells may shift to active status rendering them more sensitive to radiation.

- Teletherapy (beam irradiation) with photons (gamma or x-rays) and electrons are the most common treatments. Photons (linear, through-and-through, full-thickness penetration) are highly effective for neoplasms surrounded by intermediate (vascular endothelium) to non-mitotic tissue (muscle, nerve, bone). The surgical goals are cytoreduction and primary wound healing with no more than a 2 to 3 week healing delay. The internal margins of the surgical field are marked with skin staples or vascular clips to show extent of dissection margins.
- High-energy electrons are used when highly mitotic tissue (sensitive, GI-tract, lung) is beneath and in-line with the field containing the neoplasm. The depth of penetration of electrons can be pre-determined. Because the tissues absorb the electrons, dosimetry is complicated by inhomogenity (variation of geometry, thickness or density) of the surgical

wound. When electron-based neoadjuvant irradiation is anticipated, the surgical goals are 1) uniform final wound thickness, 2) compactness of the wound, and 3) avoidance of wounds passage around a body curvature, and 4) Marking clips should be limited to the four internal corners of the wound because stainless steel can protect neoplastic cells by blocking electrons.

Neoadjuvant Surgery plus Chemotherapy or Immunotherapy: When animals with large volume and high grade neoplasms that have metastasized are considered for treatment, chemotherapy (or immunotherapy) will be the cornerstone of efficacy or the "primary" treatment. Surgical cytoreduction can benefit treatment by removing less sensitive necrotic, hypoxic, and resting stage cells that usually occupy the center of the neoplasm. Cytoreduction should be aimed at proximate and rapid wound healing with minimization of factors that could contribute to infection and chemotherapy induced sepsis. Similarly, when planned with metronomic chemotherapy (anti-angiogenic therapy), rapid healing should be a goal as metronomics pose a problem for surgical healing and should not be instituted until healing is complete.

Neoadjuvant Therapy plus Surgery: Some neoplasms might be judged as too advanced for surgical care because the margins required would result in wounds that are too large to reconstruct or tissues that are vital for function would need to be removed to achieve curative intent. The goal of treatment is to render the neoplasm operable through an appropriate neoadjuvant to achieve tumor consolidation (compaction and reduction of size). When effective, the surgical excision will be easier. To what extent a surgical margin might be reduced is controversial. One argument is that a lesser margin is needed; however, the controversy is that even though many cells have been killed by the neoadjuvant, there may be sufficient remnant cells that would remain outside the lesser margin to repopulate the neoplasm.

- Chemotherapy can be employed when the primary neoplasm is known to be sensitive. Such treatment might be considered for an otherwise inoperable feline mammary carcinoma. Owners may be unable to afford radiation therapy and chemotherapy sensitivity may be unknown. It is possible to initiate a regimen of chemotherapy to evaluate for neoplasm responsiveness and to reduce local margin involvement prior to surgery. Injection-site sarcoma or mast cell tumor may be considered for such treatment because it also affords the opportunity to evaluate for potential chemotherapeutic efficacy prior to excision of the neoplasm and as an alternative to more expensive irradiation.
- Radiation might also consolidate a neoplasm prior to surgical excision and can be combined with chemotherapy. In this setting surgery is still considered the primary treatment. This approach might be effective for injection-site sarcoma, invasive thyroid and certain oral neoplasms, etc. The risk of a lessened surgical margin remains a consideration and a new risk imposed is that surgery within irradiated fields is more difficult resulting in a 30% to 50% complication rate of healing and secondary infection. This is the reason many surgeons, the author included, try to avoid operating in irradiated tissues.

## Surgical Technique

Most veterinarians operate as well as they can, never considering how the mix of their personal fundamentals can influence the outcome of their procedures. After years of observing novice and experienced surgeons (as well as some personal floundering), several transferrable technical

principles have emerged that might benefit you. Many of these suggestions relate to improved visualization - if you can see better, you will operate better. Some suggestions are unique to surgical oncology; however, most are of more general nature. Of special importance are the principles of dissection – the main operation. Admittedly some of these are very simple, but even Coach Lombardi started the Packers with the famous, "Gentleman this is a football."

Planning:

- Visualization
  - Both direct and indirect lighting will influence visualization. A means to aseptically change the light position is helpful.
  - If you have a magnifying loupe, use it. The use of a surgical operating loupe of about 2.5x will initially drive you crazy, but gradually you will recognize structures you have never seen before. Ideally, the focal length will match your comfort (usually 20 to 25 cm; a dental loupe focal length may only be 10 to 15 cm).
  - Transilluminate. Light transmitted from the trans (far) side of a structure (mesentery or fascia) can illuminate in silhouette vascular and neural structures
- Reconstruction – *Double-mindedness during excision leads to failure.* Dirty margins are most likely to occur because of fear of inability to close a wound. When considering repair/ reconstruction, plan for 2 options
  - The first based on the "what you think may transpire – what is the needed margin?"
  - The second based on the "worst case scenario" (grafts, more complex flaps)
  - Then concentrate on the excision rather than question the possibility of closure
  - It may be fun, but adventure is not the main goal – so use the simplest closure with the greatest safety
- Positioning:
  - Protect the spine (when rolling) and joints (over flexion/ extension) of old animals under anesthesia/ sedation during movement or positioning. Old patients are unable to protect themselves by muscle control and may suffer fractures of arthritic joint or spondolytic bridging when the spine receives torque, and postoperative discomfort if the joints are stressed while anesthetized.
  - The operative field should usually be at the surgeon's elbow height
  - The surgical site should be the highest point when positioning the patient. Roll a towel as needed to improve access
- Local Anesthesia:
  - Effective for analgesia, remain distant from the mass
  - Fluid dynamics may push neoplastic cells away from the excision field

Incision:

- Cover ulcerated tissue – Fear may be the foremost cause of recurrence through conservative dirty margins and the second is transplantation of exfoliated neoplastic cells from ulcerated neoplasms or neoplasms cut during surgery (curiosity, accidental)
- Draw/ Plan on the skin with skin marker or Sharpie
  - First mark the border of the neoplasm
  - Second mark a reasonable surgical border for clear margins

    - Third, mark the line(s) of excision
- Suggested Margins
    - Benign (rare in cats) – at margin or few mm
    - In Situ – 0.5 to 1.0 cm
    - Malignancies 1.0 to 2.0 cm
    - Injection Sarcoma 5.0 cm
- Tense skin for incision
    - Follow the marked line for excision.
    - If it is curved, use a pencil grip with minimum scalpel surface contact (15 blade) for curved incisions.
- Linear Incisions
    - The minimum skin incision should be 1.5 times mass for linear incisions;
    - Incisions can be shortened by using curvilinear incision flaps to increase exposure (incision length remains approximately the same)

Dissection:

- Wound Retraction
    - Primary wound retraction improves visualization
    - Simple instruments (Gelpi, Weitlaner, Sutures, Allis tissue or Towel forceps)
- Tissue division
    - Sharp scalpel, scissor, electrosection, laser, blunt fracture
    - Avoid incision of neoplasm (another source of exfoliant cells)
- Hemostasis – visualization
    - Electrosurgery/ laser
    - Exsanguinating tourniquet
    - Ligate drainage as early as possible
- Traction with counter-traction (assistant or pt weight) –
    - Develops tissue plane
    - Gentle manipulation of neoplasm (tumor embolization)
- Don't "undercut" – avoids accidents
    - Mistaken incision of structures/ tumor
    - "Roll" neoplasm off as possible

Closure:

- Confirm adequacy of hemostasis,
- Determine need for drain (IPFs, unsuturable deadspace, drains are negatives in oncology wound closure).
- As needed, use buried tension (pulley) sutures while obliterating dead space.

Evaluating a Previous Surgery:

- Compare opinion of the surgeon and pathologist on thoroughness of excision
- Scar becomes softer and flatter over time. Proliferative scar is rare in dogs and cats.
- When a mass is present, any re-excision should include all coadjacent tissue wounded in the previous surgery if it was within 3 months

- Contrast imaging reveals vascular leakage/ abnormality, but neoplastic infiltration may extend beyond imaging changes by several mm or more.

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# SURGICAL MANAGEMENT OF SPECIFIC FELINE NEOPLASMS

*Objective: Several elements of feline surgical oncology are different from the dog. Using the tool of critical thinking, this lecture will emphasize the unique needs of the feline surgical patient: Wound healing, maxillofacial surgery, injection site sarcoma, and unique situations in feline surgery.*

Critical Thinking: Critical thinking is a 1980s concept to explain some of the ills of the American education experience. Educational curricula had become inflexible and bloated by an over-emphasis on teaching factual knowledge. Educators from the counter-culture of critical thinking emphasized that students should be taught the understanding of processes, concepts and methods while encouraging learning through curiosity, self-expression and creativity. This new method of analysis called critical thinking has been defined by Webster as *the mental process of actively and skillfully conceptualizing, applying, analyzing, synthesizing, and evaluating information to reach an answer or conclusion.* This method began to penetrate veterinary medicine as a sub-component of the 1989 Pew Report. Some veterinary curricula which were new at this time were dramatically different from traditional curricula and even traditional curricula began a gradual modification, but not without resistance. Some educators maintained that knowledge could be "possessed", and graduation and the passage of national board examination was the "license to practice". Those of the counter-culture however emphasized "possessed knowledge" was already outdated and that "lifetime learning" was the future of education.

Critical-thinking coincided with the beginning of the information age. Through the early days (ARPANET, FreeNet) to the present (WWW), the quantity and quality of information available increases daily and has far surpassed the ability of individuals to acquire, filter, process and use. As advancements in technology improve information processing, newer advancements provide even more information. Critical analysis has vastly improved some areas of our lives such as weather forecasting, information sorting (web searches), shopping. Society-wide, critical thinking has become synonymous with the kind of thinking that strategists in business, finance, industry and medicine use to "see the future". At its core, it is the kind of thinking that separates factual elements from assumptions, randomness, and rationalizations while accommodating important feelings and beliefs that would influence the use of those facts. Critical thinking does not depend on technology; however, in medicine, the concept of evidence-based practice fits definition. And veterinarians use it daily to plan diagnostics, treatments and prognoses while accommodating clients' concerns and financial abilities.

Critical Thinking in Feline Wounds. The seminal publication of feline wound healing as compared to the dog (Bohling, Vet Surg 35;2006:3) reported that cats healed differently than dogs. At 21 days, the wounds were similar, but along the way, they were not. Because this was a new area of research, the most important events of feline wound healing were unknown. The major finding was that cats depended more on the integrity of subcutaneous tissues than did the dog. If subcutis was removed from cat wounds, the wound healed slower than in dogs. In the presence of subcutaneous tissue, epithelial migration occurred, but suffered a lag time awaiting granulation. The feline granulating wound differed from the dog as well. Granulation in the cat began at the edges and grew centripetally, whereas the caning granulation seemed to be produced across the wound at a near equal rate. So cat open wound contraction began slower and gradually sped up catching up with the dog at about 3 weeks. Cats also have a propensity to "pseudohealing" which is defined as healing of the skin to skin but not having reattachment of the skin to the underlying tissues.

Chronic wounds in the cat are among the most difficult to manage. If subcutaneous tissue is absent, granulation is slow to occur and is thin – often effecting little to no benefit. Experience teaches that it is better to avoid chronic wounds in cats. With dogs, we often manage a wound on the basis of delayed closure, knowing that a canine wound cared for properly will granulate and readily accept closure by wound contracture and epithelialization, or surgical skin advancement, flaps and grafts. Cat wounds must also be managed openly sometimes, but experience has also taught that extensive debridement is likely to promote a slow to non-healing wound. When this occurs, it is often necessary to shift a complex myocutaneous flap so that a defect is filled with vascularized muscle, subcutis and skin simultaneously. In some body sites, this is far more difficult than others.

A second feline wound healing paper paper (Mitsui, AJVR 70;2009:532) reported enhancement of granulation in feline wounds if the muscle fasica was incised (fasciotomy) or removed (fasciectomy) but not so with simple abrasion of the fascia. The control time to development of robust granulation was 18.5 days, but the treated groups were shortened to 9.6 days. Simple abrasion developed similar granulation in 16.7 days.

So based on present knowledge, critical thinking suggests incorporation of all of these elements as the wound might dictate. Initial judicious debridement, accurate closure, consideration of fasciotomy or fasciectomy if subcutis is absent, consideration of subcutaneous suction drains or walking-type sutures to improve contact of the skin to underlying tissue to help re-establish continuity and prevent pseudohealing, consideration of complex flap closures for difficult wounds and, finally, despite even the advanced care of referral centers some wounds are not going to heal. This latter group may be benefitted by growth promoting factors, but this is still unknown.

Interestingly cat skin seems resistant to the acute effects of radiation. Few cats suffer acute irradiation inflammatory change; however, irradiated cat skin that is wounded can be more difficult to heal. When irradiation is planned, we have often performed tumor excision followed

immediately (same day) with irradiation and linear wounds seem to heal normally. However the healing of complex reconstructions may be compromised by irradiation and are allowed to heal two to three weeks before irradiation.

Critical Thinking in Feline Maxillofacial Surgery. Maxillofacial surgery began to advance rapidly in the early 1980s and surgeons were often amazed at the resilience of dogs to major reconstructive procedures. In 2006 the complications of mandibular surgery were reported for 42 cats (Northrup, JAAHA 42;2006:350). This seminal paper mostly affirmed the experience of those of our profession who had been performing oral surgery on cats - it was understood that feline oral surgery was often more challenging than for dogs – and most veterinary surgeons were much more reserved about performing oral surgery in cats compared to dogs. Several factors contributed to this problem: Cats hid their disease better than dogs so they ovften presented with more advanced disease, the differentials were fewer, but equally malignant (mostly squamous cell carcinoma ~50% to 75%, fibrosarcoma, and osteosarcoma), the site of origin was often in the bone rather than on the bone, less labial tissue was available in the cat for reconstruction, and sharp canine teeth that became malaligned as a result of surgery caused trauma and pain. Postoperative contrasts were dramatic. Dogs usually only missed the meal withheld for surgery as they readily ate postoperatively; whereas, cats were not likely to eat postoperatively, sometimes for a week which posed risks for other metabolic problems and the need for alimentary support. Earlier reports that included dogs and cats had far fewer cats in the studies and the results for the feline portion were often overshadowed by the number of dogs. The recurrence rates for dogs were lower than for cats

How does critical thinking fit this clinical scenario? Veterinarians learn surgery by rote: Step 1, Step 2, etc. Reconstructive surgery and surgical oncology don't fit this model well. A standard operation is often changed completely by changing the depth of the lesion or moving the wound or the neoplasm 2 inches in any direction. Instead these types of surgery are taught by teaching concepts built on "standard" surgical procedures: Create a margin of normal tissue, don't cut into the neoplasm, don't manipulate roughly, ligate vessels early, irrigate frequently, don't contaminate gloves with cancer cells, avoid exfoliant cells, mark the internal extent with stainless clips AND don't leave clips in the wound, remove a layer of fascia, remove a layer of muscle with fascia, remove the full thickness of the body wall, accommodate wound tension, close the wound, delay closure of the wound, avoid a biological tourniquet during closure, place sutures in or otherwise mark sites of interest for the pathologist – all of these principles are not useful in every procedure and some countermand the others – the ones incorporated are those which indicated. It is the surgeon's job to coordinate based on importance and other treatments preceding or to follow. It requires an analysis of the peculiarities of a specific operation – critical thinking. To make it even more complicated no one even knows if the successful critical thinkers do it the same way.

One way to discover how to do things better is to study what went wrong. The chief problems reposted by Northrup in the 38 cats followed long term were dysphagia or inappetance 16,

ptyalism 9, mandibular drift 14, tongue protrusion 11, pain 0, difficulty grooming 7, dehiscence 0, malocclusion with palate injury 7 (only criteria that increased from acute to long term), temporomandibular joint crepitus 1, death 2. Only 9 cats has no long term complications. The results were still encouraging: Despite acute morbidity of 98% and 76% long term morbidity, 83% of the owners were satisfied with the outcome of mandibulectomy. Of greatest concern was the 12% of cats that never regained the ability to eat.

The critically thinking surgeon would evaluate these findings and structure the surgery to minimize potential morbidity. It is not always possible to prevent some problems such as ptyalism or tongue protrusion with rostral mandibulectomy, but a feeding tube should be considered for cats with anticipated eating problems or cats that already exhibit reluctance to eat. For unilateral mandibulectomy, plan for amputation with vital pulpotomy or extraction of the contralateral canine teeth that are likely to cause pressure problems. Unilateral mandibulectomy should be accompanied by cheilorraphy of the upper and lower lip to the level of the first premolar to reduce tongue lolling and ptyalism.

Critical thinking analysis of operative complications can often be used to design an operation to minimize the occurrence of complications – of course these are the complications that have been reported or experiences. There will always be newly experienced complications – may we think critically enough to avoid them a second time.

**A Short Glossary** – *What are we talking about anyway?*

- Names for the Disease Process – These are commonly misused/ confused.
  - Neoplasm – Unregulated tissue growth Malignant or Benign
  - –oma – "swelling" a suffix indicating a neoplasm of benign character
  - –sarcoma – "fleshy" a suffix indicating a mesenchymal neoplasm of malignant character
  - –carcinoma – "hard" a suffix indicating an epithelial neoplasm of malignant character
  - Cancer – A malignant neoplasm
  - Invasion – A mode of growth in which malignancy grows into adjacent tissue; sometimes referred to as "local metastasis"
  - Malignant – Capable of spread or of causing death
  - Metastasis – Malignancy that has spread by blood, lymph, airway, or via body cavity to a distant site and by direct invasion to an adjacent organ. Retrograde, intransit, inflammatory are other descriptors.
  - Benign – Usually incapable of causing death. Site dependent
  - Mass – An undiagnosed swelling of /on the body
  - Tumor – An undiagnosed swelling of /on the body
  - Paraneoplastic - A "side-effect" of neoplasia usually caused by the biochemical action of a protein, protein class, cytokine, chemokine, hormone or hormone-like substance
- Nomenclature for Outcome Analysis – Accepted abbreviations
  - Average – The sum of outcomes divided by the number of outcomes
  - Median – The middle animal in a population
  - Disease Free Interval (DFI) – Normally reported as a median, it is the time from treatment to recurrence
  - Median Survival Time (MST) – Reported as a median, it is the time from treatment to death
- Multi-modal - Using more than one treatment to attack the disease at several levels. The toxicity should not generally be overlapping/ cumulative
- Neoadjuvant – From the Greek "before" rather than the Latin "new", this is adjuvant care given before the primary care rather than after as is more common
- Margin - The edge of a neoplasm or tumor submission.
  - Clean margin – absence of neoplastic cells at the edge
  - Dirty margin - Tumor cells are at the edge of the section
  - Margin composed of normal tissue - clean margin
  - Tumor cells abut the margin - dirty martin
  - Wide margin – larger than 1 to 3 cm. May still be dirty if the primary neoplasm was large (sampling error).
- Metaplasia – Abnormal transformation of one type of cell into another usually due to tissue chemical mediators or changing genotype.
- *Mitoses - cells caught by fixation in the process of dividing. Except for certain germinal tissues, this is a very unusual finding in normal tissue

- Mitotic index - the number of mitoses seen in a section of tissue usually expressed per 10 high power fields (400x), but is subject to pathologist variation (per field; per 600x field, etc.)
- Pathologist's Terms – Commonly encountered terms from pathology that are used to interpret the pathology report and to assist in making a prognosis)
    - *Anaplastic - poorly developed cellular differentiation
    - *Anisocytosis – Differently sized cells/ within a specimen
    - *Anisokaryosis – Differently sized nuclei within a specimen
    - Atypia – Cell variation beyond normal. Occ. very early precursor of neoplasia
    - *Desmoplastic - Containing abundant fibrous connective tissue (see scirrous)
    - Dysplasia – Cells that exhibit evidence of stress or other phenotypic alteration of abnormal development, but not (yet) neoplastic
    - Grade – Terminology to define the relative malignancy of a neoplasm
    - *High grade - Malignant neoplasm that is associated with rapid cell division and likely to metastasize early
    - Low grade - Usually well-differentiated neoplasm that is associated with somewhat slower progression or risk
    - Intermediate grade - Of intermediate differentiation and risk
    - Hyperplasia – Increase in the number of cells
    - Hypertrophy – Increase in the size of cells
    - In situ – Growing above the basement membrane (not yet invasive)
- *Pleomorphism – the occurrence of multiple shapes and forms of cells usually indicative of unregulated differentiation during neoplasia
- Prophylaxis - The treatment should reduce the risk of neoplasia
- Rescue - Treatment of a neoplasm that has come out of remission
- Rescue (alternate use) - Administration of an intentionally lethal overdose of chemotherapy with the intent of following with a reversal agent such as methotrexate followed by calcium leukovorin
- *Scirrous – Inducing or containing abundant fibrous connective tissue
- Surveillance – Observation for a specific event with a planned action
- Treatment Intent – Goals of therapy (plus above terms to describe treatment response)
    - Adjuvant - a means of assisting another form of treatment
    - Control - Achieving Remission, Partial Remission or Progression
    - Curative - Elimination of all neoplastic disease
    - Palliation - Relief of pain or secondary signs
    - Cytoreduction - Reduction of neoplasm volume to benefit another treatment
    - Debulking - Cytoreduction
- Treatment Response– Terms used to describe treatment response
    - Cure - Elimination of all neoplastic disease
    - Remission - No detectable neoplasm; Apparent complete resolution of neoplasm
    - Partial Remission - Reduction of greater that 50% neoplasm volume
    - Progression - More than 25% increase in neoplasm volume
    - Stable Disease - Less than 50% decrease in neoplasm volume
- Tumor emboli - malignancy has invaded blood or lymphatic vessels

**Terms that relate to malignancy. Increasing expression of these changes usually indicate relatively increasing malignancy.*

# PEOPLE DIRECTED AGGRESSION: MAKING THE DIAGNOSIS

MICHELLE BAMBERGER, MS, DVM

Vet Behavior Consults

1. Medical and Nutritional Rule Outs
   A. Pain
   B. CNS
   C. Sensory decline
   D. Endocrine imbalances
   E. Cognitive dysfunction
   F. Drug-related
   G. Diet

2. Making the Diagnosis

3. Types of Aggression
   A. Aggression as a result of lack of socialization
   B. Pain-induced
   C. Irritable
   D. Petting-induced
   E. Play
   F. Predatory
   G. Maternal
   H. Fear
   I. Status
   J. Territorial
   K. Pathophysiological
   L. Idiopathic
   M. Learned
   N. Redirected

4. Case Discussion

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# Feline Elimination

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## Feline Elimination Problems

- House soiling
  - Urinating or defecating on horizontal surfaces outside the litter box
- Urine marking
  - Usually manifested as spraying
  - Some cats mark on horizontal surfaces
  - Middening = fecal marking (rare)

## Determine What the Cat is Doing

- Urination or defecation or both
- Surface where urine is found
  - Vertical versus horizontal
- Posture
  - Standing with tail twitching = spraying
  - Squatting = elimination or marking
- Volume of urine
  - Usually smaller amount voided with spraying

## Identifying the Perpetrator

- Direct observation
- Videotaping

## History

- When and where problem began
- Changes in cat's environment
- Urine and/or feces
- Surfaces soiled
- Frequency of house soiling
- Other behavior changes
- Solutions attempted

## Determine Scene of the Crime

- Have owners draw a map of the house
  - Site of soiling
  - Site of litter box
  - Favorite resting spot of each cat
  - Windows, doors, beds, couches, etc. indicated
  - Feeding stations

## Feline House Soiling

- Eliminating outside the litter box
- Males = females
- Random, or a specific location or substrate
- Risk factors
  - History of previous urinary tract infection
  - Use of scented litter
- Long-haired cats may be predisposed to fecal soiling

## Feline House Soiling Differentials

- Medical
- Litter box aversions
- Substrate aversions / preferences
- Location aversions / preferences
- Accessibility
- Geriatric issues

## Feline House Soiling Differentials

- Anxiety – social interactions
  - Ambush by other cat
  - New pet, new person, new baby
  - Passive or active inter-cat aggression
  - Change in owner's schedule or long absence

## Litter Box Aversions

- If cat urinates AND defecates outside litter box, often a problem with the box
- Hygiene
  - Odor: waste, disinfectants
- Type / size of box
- Negative experience associated with box

## Substrate Aversion

- Type of litter
  - Clumping vs. non-clumping
  - Scented vs. unscented
  - Plastic "pearls"
  - Texture – size of granules
- Depth of litter
  - Deeper usually better

## Preferred Litters

- Ever Clean®
- World's Best Cat Litter™
- Swheat Scoop®
- Fresh Step® with Carbon
- Agway's Clumping Litter

## Location Aversions

- Environment near litter pan
- Traffic or noise
- Other animals
- Negative association
  - Pain while in box
  - Medicated in box
- Accessibility

## Preferences

- Surface preference
- Location preference
- If only defecates outside box
  - Rule out medical issues
    - Constipation or colitis

## Substrate Preference

- Carpet
- Bed or couches
- Clothes or shoes
- Plastic bags
- Soil in house plant
- Hard surfaces – porcelain

## Weather

- Outdoor cat forced to be indoor cat
- Outdoor cat doesn't want to go outdoors

## Feline House Soiling

- Eliminating on horizontal surfaces can be marking behavior
  - High cat density
  - Stress/anxiety – investigate other changes in cat's behavior

## Treatment

- Rule out medical issues
- Remove the cause
- Re-establish litter box use
- Prevent access to soiled areas

## Rule Out Medical Problems

- Urinalysis
- Culture
- Radiograph or ultrasound
- Endoscopy
- Assess water intake and urine frequency
- Dysuria
- Stool evaluation – diarrhea, blood/mucus, hard stools, constipation

## Remove the Cause

- Treat medical condition
- DO NOT PUNISH!
- Treat underlying anxiety / social issues
  - Keep cat's environment consistent and predictable
  - Schedule daily interaction time

## Re-establish Litter Box Use

- Add litter boxes
  - 1 box per cat *plus 1*
  - Bigger is better
- Litter cafeteria to determine preference

## Re-establish Litter Box Use

- Don't use liners
- Litter box hygiene
  - Scoop 1-2x daily (discard non-clumping daily)
  - Wash pans weekly with mild detergent / replace litter

## Prevent Access to Soiled Areas

- Change behavioral function of previously soiled areas
  - Place food bowls, bedding, toys in area

## Prevent Access to Soiled Areas

- Make areas undesirable
  - Scat mat
  - Plastic carpet runner, nubby side up
  - Foil, plastic, or double-sided sticky tape

## Prevent Access to Soiled Areas

- Make areas inaccessible
  - Barriers
  - Water in bathtub
  - Place litter box over soiled area

## Treatment

- Confine cat to small area temporarily
  - Reinforces habit of using litter box
  - Let cat out to socialize and play, but must be supervised 100%
  - Reward for using box
- Large cage with perch or shelf
  - Cover floor with litter
  - Gradually introduce litter box

## Cleaning Soiled Areas

- Bacteria / enzyme combinations
  - Anti-Icky-Poo
  - Outright Veterinary Strength
  - KOE
  - Feline Odor Neutralizer
  - Planet Urine
  - Zero Odor

## Urine Spraying

- Urine sprayed on vertical surfaces
  - Some mark on horizontal surfaces
- Sexually dimorphic behavior
  - Males > females
  - Intact > neutered
- Related to number of cats in the home

## Who Sprays?

- 100% intact males
- Intact females in heat
- 10% of castrated males
- 5% of spayed females

## Why Do Cats Spray?

- Sexual – hormonal
- Outside cats
  - Odor
  - Sight
- Multiple cat household – high population density
- Anxiety – usually social issues
  - Coping mechanism or sign of stress?

## Why Do Cats Spray?

- Environmental stimuli
  - Changes in household, new person, novel objects
- Relationship with owner
  - Changes in schedule/interactions
  - Punishment

## Treatment of Spraying

- Identify and remove triggers
- Neuter
- Deter outside cats from visiting
- Cover windows
- Separate household cats
- Indoor/outdoor access
- Cat diapers

## Treatment of Spraying

- Decrease cat population
- Litter box hygiene
- L-shaped boxes or spray panel
- Medication – CBC/chem panel first
  - SSRI
  - TCA
- Feliway™ as adjunct
  - Cat unlikely to spray over cheek gland secretions

# Inter-Cat Aggression

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## Feline Social Structure

- Highly variable
- Adults solitary when hunting for prey
- Can adapt to living in large groups where food is readily available
- Hierarchy in feral cats determined by body size in females and age in males

## Why are Cats Social?

- Temperature regulation
- Kitten care
- Mutual defense

## Territories

- Male has larger territory
  - Spray urine to mark territory
- Females have smaller territories – usually encompassed by dominant male's
- Cats may sleep together, but are active alone
- Female groups are stable, but strangers are rejected

## Inter-Cat Aggression

- Status
- Territorial
- Re-directed
- Fear

## Status Aggression

- Cats that bite or attack owners or other cats in order to control a situation or resource
- Controls access to furniture or other resource
- Assertive, pushy behavior
- May bite when petted too long

## Territorial Aggression

- Attacks visitors or other cats to expel them from their territory
- Seeks out victim

## Re-directed Aggression

- Occurs when the cat is aroused and cannot reach the intended target
- An innocent bystander (another cat) becomes the victim
- Very acute, intense, and uninhibited

## Fear Aggression

- Cat perceives someone or something as a threat
- Can quickly escalate to aggression if cat is unable to escape

## Fear Aggression

- Can occur in victim cat – perpetuates aggression cycle

## Treatment of Acute, Serious Feline Aggression

- Isolate cat
- Keep in quiet, darkened room
- Assess every few hours; bring tasty food
- To take cat to veterinarian, put cardboard box over cat and slide cookie sheet under cat
- Protect victim
  - File canines
  - Onychectomy

## Treatment of Inter-Cat Aggression

- Separate
- Medicate – if necessary
  - Buspirone for victim
  - SSRI or TCA for aggressor
- Odor exchange
  - Feliway – the cat cheek gland pheromone
  - Rub each cat with same towel
- Re-introduce ***slowly***

## Treatment of Inter-Cat Aggression

- Give aggressor smaller or less desirable place of confinement
- Give victim larger, more desirable place

## Reintroduction

- At least one week of total separation
- Feed meals, not free choice
- Reintroduce only at mealtime (continue to separate otherwise)
- Have cats on opposite ends of room; both cats or only aggressor in carrier or tethered

## Reintroduction (continued)

- If cats eat with no sign of aggression – growl, hiss, caterwaul, etc. – feed an inch closer
- Continue until cats can eat right next to one another

## Reintroduction (continued)

- Repeat three times
  1. Aggressor in carrier
  2. Aggressor wearing harness and tethered
  3. Aggressor wearing harness, but not tethered
- Gradually increase time that cats are together after meals

## Treatment of Inter-Cat Aggression

- Instruct owners on feline threats
  - Stares
  - Posture
- Interrupt threats
- Bell aggressor as warning to victim

## Pica

- Ingestion of non-food items
  - Wool or other fabric
  - Plastic
  - Cords
  - Wood

## Pica

- Relation to early weaning

## Plants

- Cats may eat plants
  - Make sure it is a safe plant

## Treatment of Pica

- Clomipramine
- Cat garden
- Bones
- Kangaroo meat

## Cat Gardens

- Edible grasses
- Available from most pet stores

## Geriatric Issues

- House soiling
- Excessive vocalization – esp. at night
- Wandering aimlessly
- Sleeping
- Purring
- Demanding attention
- Increased affection
- Decreased activity

## Possible Medical Causes

- CNS disease
- Orthopedic issues
- Dental disease
- Renal disease
- Hepatic disease
- Pain
- GI issues
- Endocrinopathies
- Sensory loss
- Cognitive decline

## Behavior and Health

- Behavior problem remains after medical condition is treated
- Learned associations
  - E.g., litter box aversion after UTI
- Behavior modification may be more difficult

## Incidence from Vet Behavior Practices

- Cats
  - 73% house soiling
  - 6% aggression, vocalization, restlessness

## Senior Pet Visit

- 7+ years
- Minimum database
  - Complete blood count
  - Serum chemistry
  - Thyroid values if physical or behavior signs
  - Urinalysis if physical or behavior signs
- Questionnaire – have owner fill out every year
  - Best method to detect minor aging changes

## Brain Aging Basics

- Brain function declines with age
  - Cognitive abilities worsen
- Decline in brain function is associated with tissue and behavioral changes
- Underlying cause of these changes may be related to oxidative damage from toxic free radicals

## Hypothesis for Brain Aging

- Free radical theory of aging
  - Reactive oxygen species (ROS) cause cumulative damage with age
  - Protein: Impaired metabolism and function
  - Fats: Decreased membrane fluidity
  - DNA: Increased mutations
  - Carbohydrates: Decreased cellular function

## Mitochondria, ROS, and Aging

- Produces energy
- Generate free radicals as by-products
- Anti-oxidant defenses
  - Decrease with age
- Aged mitochondria
  - Less efficient
  - Produce even more free radicals
  - Eventual cell death

## House Soiling

- VERY common in older cats
- Look for patterns in certain locations
- Stranguria, pollakiuria, hematuria, PU/PD
  - Medical workup
- Cognitive dysfunction

## House Soiling

- Treat underlying medical conditions
- Management
  - More litter boxes
  - Easier access
  - Low sides
  - Confine to smaller area
  - Address any inter-cat conflict

## Vocalization

- Excessive night-time vocalization common in older cats
- Pain, discomfort
- Sensory impairment
- Response to outside stimuli
- Owner response – reward or punishment
- Daytime stimulation, medications

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**Feline Injection Site Sarcomas – Where Do We Stand in 2011?**

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**Historical Background**: Feline injection site sarcomas (FISS) were originally referred to as vaccine-associated sarcomas (VAS). An increase in observed incidence of feline soft tissue fibrosarcomas was first noted by veterinary pathologists Hendrick and Goldschmidt at the University of Pennsylvania in the late 1980's. This increased incidence paralleled two temporally- related events. First, in 1985, was the introduction and widespread use of two killed adjuvanted vaccines that had not been previously approved for use in cats. These vaccines were a subcutaneously administered, aluminum-adjuvanted killed rabies virus vaccine and an aluminum-adjuvanted killed feline leukemia virus vaccine. Second, in 1987 the State of Pennsylvania enacted a law requiring rabies vaccination for cats. This effectively increased the number of cats at risk for development of FISS due to an increase in number of cats vaccinated.

Public concern and rumors of lawsuits prompted the California Veterinary Medical Association to bring together a panel of experts to address the issue of feline FISS in August 1996. In November 1996, an organization was formed to promote research and educational efforts for this emerging disease problem. Charter organizations which supported the formation of what is now known as the Vaccine-Associated Feline Sarcoma Task Force (VAFSTF) include the American Veterinary Medical Association, the American Animal Hospital Association, the American Association of Feline Practitioners, Cornell Feline Health Center, and the Veterinary Cancer Society. The VAFSTF has since sponsored many research projects to explore the etiology, pathogenesis, diagnosis and treatment of this disease. The VAFSTF has worked towards development of recommendations regarding vaccination protocols and education of veterinarians and the public with regard to vaccine-site reactions and tumors that form at sites of vaccination.

**Epidemiology:** Investigations have led to a better understanding of the physical, biological, and histological characteristics of these tumors. Estimation of the frequency of feline FISS varies between retrospective studies, and ranges from 1 case/10,000 vaccinates to 1.3cases/1,000 vaccinates. The interval between vaccination and the development of tumors is highly variable. Tumor latency intervals have been reported to be as short as one month and as long as 10 years from vaccination (McEntee, 2001). Kass *et al.* showed a causal and temporal association between feline sarcomas and use of rabies and feline leukemia vaccines. Kass' study also revealed an increased risk of fibrosarcoma development with increased number of vaccines administered. In fact, the risk of developing a fibrosarcoma from a single injection in the cervical/intrascapular region was close to 50% higher than that of nonvaccinates. Risk escalated to 127% when 2 vaccines were administered and climbed to 175% when 3 or 4 concurrent vaccinations were given in the same anatomic site. Kass also observed that vaccines with adjuvants other than aluminum as well as vaccines without adjuvants, were associated with fibrosarcoma development. Epidemiologic studies have implicated an association with feline leukemia (FeLV), rabies, and feline viral rhinotracheitis/calicivirus/panleukopenia virus (FVRCP) vaccines, with monovalent and polyvalent vaccines, and with non-

adjuvanted as well as adjuvanted types. (Kass, 1993) These tumors are now called injection site sarcomas because they have also been reported in association with long acting antibiotics and corticosteroid injections, a lufenuron injection, non-absorbable suture material, and also at sites of microchip implantation. (Hendrick, 2011). Thus these lesions are presumed to be due to chronic inflammation and tissue wound healing responses gone awry, rather than to the specific injected material. They are also associated with the specific reactions seen within individual cats in response to these tissue wounding factors. (Martano, 2011)

Hendrick *et al.* followed their original observation with a study that compared fibrosarcomas that developed at vaccination sites with those arising at nonvaccination sites. This retrospective analysis revealed an association of sarcomas at rabies, FVRCP, and FeLV vaccination sites. These authors hypothesize that normal resident feline fibroblasts and myofibroblasts are induced to proliferate in response to injected adjuvants or other vaccine components. Myofibroblasts are believed to represent a transitional stage through which fibroblasts and macrophages pass during the process of wound healing. (Martano, 2011) In some cats, these cells ultimately undergo neoplastic transformation.

**Histologic and Biologic Behavior:** Through histologic evaluation of feline FISS tumor specimens, Hendrick recognized a characteristic inflammatory component associated with these sarcomas that was similar to the granulomatous and lymphoid infiltrates seen in non-malignant injection-site reactions. Many FISS tumors contain spindle cells and multinucleated giant cells with a high degree of nuclear pleomorphism and cellular atypia. Pathology studies what were then called comparing vaccine-associated sarcomas (VAS) and non-vaccine associated sarcomas (NVAS) reveal that VAS lesions exhibit histological features consistent with more aggressive behavior than do their NVAS counterparts. Characteristics such as intratumoral necrosis, mitotic activity, and cellular pleomorphism have been shown to be more pronounced in FISS than in NFISS.

Retrospective histologic evaluation of a number of tumor samples revealed a shiny, amorphous, grey-brown material present in the central necrotic zones and within macrophage cytoplasm in 40% of specimens examined. Electron-probe analysis identified this foreign material to be aluminum, a common adjuvant of vaccines.

Immunohistochemical analysis is generally positive for immunoreactive vimentin, the mesenchymal cell intermediate filament, and smooth muscle actin. This immunohistochemical profile supports a fibroblastic or myofibroblastic origin for FISS. Histologically, FISS tumor types include fibrosarcomas, malignant fibrous histiocytomas, rhabdomyosarcomas, soft tissue osteosarcomas, and chondrosarcomas.

These FISS tumors are grossly characterized as well-demarcated, pseudo-encapsulated masses. The biologic behavior of FISS is consistent with local aggressiveness and a high incidence of local recurrence. Furthermore, metastasis is seen in 10-25% of patients. It is observed that FISS is more likely to become metastatic than non-FISS sarcomas.

**Pathogenesis:** Research studies supported by the VAFSTF and also by the Morris Animal Foundation have been directed toward understanding the etiology of this

form of cancer. Retroviral elements, either endogenous or exogenous, do not appear to be associated with FISS. Ellis *et al.* investigated 130 suspected FISS from cats. In this population, all 130 suspected FISS were negative for the intratumoral FeLV gp 70 antigen on the basis of immunohistochemistry. One hundred FISS were also examined using polymerase chain reaction and were negative for the FeLV long terminal repeat region. This study decreased the concerns of a retroviral etiology for FISS.

Many groups have explored possible growth factors and oncogenes involved in the pathogenesis of FISS tumor development. Nambier *et al.* evaluated 40 FISS for expression of nuclear p53 protein by immunohistochemistry (IHC) to detect any correlative association of the p53 tumor suppressor gene in FISS. In 42.5% (17/40), tumor cell nuclei were stained darkly; in 20.0% (8/40), tumor nuclei were stained palely; and in 37.5% (15/40), tumor nuclei were unstained by IHC. This suggests mutations of the p53 gene may play a role in the pathogenesis of these tumors. Further investigation by the University of Minnesota found point mutations in p53 to be relatively rare in FISS and only one of the 20 tumors examined actually harbored the mutation. When these researchers compared matched sets of tumors and blood samples by automated DNA sequence analysis, they demonstrated a loss of heterozygosity at p53 in 39% of cases. This loss had a significant association with increased tumor size. (Banerji, 2006). Research at the University of Pennsylvania revealed that FISS exhibit a mild to strong positive staining for platelet-derived growth factor (PDGF), whereas NFISS have a negative or faint positive reaction. Further, lymphocytes in FISS were positive for PDGF but lymphocytes in normal lymph nodes and Peyer's patches were negative. Macrophages in the area stained positive for PDGF receptor. Hendrick *et al.* surmised that lymphocytes in vaccine-associated lesions may secrete PDGF to recruit macrophages, and thereby cause fibroblast proliferation as a collateral effect. Researchers at the University of Pennsylvania also identified overexpression of *c-jun*, a proto-oncogene. This gene codes for the transcriptional protein AP-1, which is critical to cellular proliferation. Further investigation is ongoing to characterize the resident intratumoral and peritumoral leukocyte population including lineage (T or B) and subset (CD4 vs. CD8, $T_H1$ vs. $T_H2$). Wound healing cytokines such as transforming growth factor- beta and acidic fibroblast growth factor and basis fibroblast growth factor are released by the inflammatory cells and are involved in excessive wound healing response. (Martano, 2011) Also, the c-Kit receptor has been identified to be upregulated in FISS. (Smith, 2009)

The concept of tumor development secondary to inflammation and wounding is not new. In fact, many such examples can be found in the human literature including tumors associated with metallic implants, soft tissue sarcomas associated with aluminum oxide hip implants, and angiosarcomas associated with foreign body material. The veterinary literature also provides examples, including esophageal sarcomas associated with *Spirocerca lupi* in dogs, post-traumatic ocular sarcomas in cats which are histologically similar to FISS, fracture associated sarcomas, and radiation-induced osteosarcomas. Solitary case reports include a liposarcoma associated with a glass foreign body and an osteosarcoma associated with total hip arthroplasty.

Another focus of research has been in the prevention of FISS tumor development. Work done in chickens infected with the Rous Sarcoma virus indicated that if the post-wounding inflammation was inhibited, tumor development was also inhibited.

Investigators concluded that inflammatory mediators play a critical role in providing the ideal environment for oncogene integration and activation that leads to tumor development.

**Diagnostic and Therapeutic Considerations:** Many investigators have focused on the diagnostic and therapeutic aspects of this tumor. Veterinarians at the University of California-Davis set out to assess the use of advanced imaging in diagnosis and treatment planning. This group used computed tomography (CT) to evaluate cats with presumed FISS prior to treatment. These CT scans revealed a larger area of involvement detected by contrast-enhanced CT as compared to the pre-contrast images. These investigators surmised that FISS are highly aggressive from the onset, are not impeded by fascial planes, and affect multiple muscle groups at the time of diagnosis (McEntee, M, personal communication, VCS 19th Annual Conference, 1999). This study supports the importance of advanced imaging to determine the extent of surgery and/or the size of the radiation field needed for optimal treatment.

Optimum treatment for FISS is still under investigation. We now know that aggressive first surgical excision provides the best chance for a cure. Hershey *et al* (2000) examined 61 FISS cases treated with surgical excision alone and learned that radical first excision yielded significantly longer median time to first recurrence (325 days) than did marginal first excision (79 days). This study also concluded that cats with tumors located on the limbs had a longer median time to first recurrence (325 days) than cats with tumors located at other sites (66 days). While it is important to note these differences, it is also vital to realize that only 13.8% of these cats had longer than 2-year survival. This study therefore emphasizes the need for effective adjunctive therapy.

The importance of adjunctive therapy such as radiation and chemotherapy has also been evaluated. Cronin *et al* (1998) examined 33 cases treated with radiation therapy followed by surgery. This retrospective analysis found the only variable that influenced treatment success was the presence of tumor cells at the margin of resected tissue. Kobayashi et al reported on 92 cats treated with preoperative radiation therapy for FISS at NCSU. Cats received 48 Gy RTH in a total of 16 radiation fractions, with the intended target volume being the entire gross tumor plus a 3 cm margin of normal tissue in all planes. Tumors were excised 2-4 weeks after radiation therapy was completed. The median time to first event (MTFE – defined as local recurrence or metastasis) for this patient cohort was 587 days, and if the surgical margins were declared free of tumor cells the MTFE was 986 days vs. 292 days if margins were dirty. Metastasis occurred in 21.7% and treatment with a combination of RT and carboplatin chemotherapy resulted in a MTFE of >986 days. This study confirms the benefit of combined modality therapy for FISS. (Kobayashi, 2002)

Cytotoxic chemotherapy agents, including carboplatin, doxorubicin, mitoxantrone, cyclophosphamide, ifosfamide, CCNU, vincristine, and immunotherapy with interferon omega have been evaluated by various groups. (Cohen, 2001, Rassnick 2006, Hampel, 2007, Poirier, 2002) Although sarcomas in cats are not very chemo-responsive in general, both partial and complete responses have been seen in FISS. Because growth factor signaling pathways through platelet-derived growth factor appear to be upregulated in FISS, interest in using specific receptor tyrosine kinase inhibitors is

being followed with clinical studies. A study from UW-Madison successfully utilized imatanib mesylate (Gleevec) to inhibit PDGF in FISS cell lines in vitro. Thus far it appears that cats can take Gleevec with minimal adverse consequences, as compared to dogs that have potentially lethal hepatotoxicity with the drug. However, no clinical responses have been reported in FISS. (Katayama, 2004) Other new RTKI agents such as masitinib and toceranib may also prove useful.

Unfortunately, complete cures remain unpredictable even with the use of aggressive multiple modality treatment. It seems that the best method of treatment of FISS is prevention by avoiding unnecessary vaccination, and prompt aggressive surgical resection of early lesions. (Martano, 2011)

**Prevention and Early Intervention:** Current recommendations for vaccination may necessitate a change in our thought processes and practice habits. Veterinarians have come to appreciate the need for more rational vaccination guidelines and practices. The VAFSTF and other organizations such as The American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines have advocated proactive changes in standard vaccination protocols. First, no vaccination should be given in the interscapular space. Instead, rabies vaccines should be administered in the distal aspect of the right hind limb, the FeLV vaccine should be administered in the distal aspect of the left hind limb, and all other vaccines should be administered distally in the right shoulder region. These recommendations were made to increase the potential for complete resection by limb amputation. All vaccines should be administered subcutaneously, as this allows earlier detection of these growths. (AVMA guidelines 2009 http://www.avma.org/vafstf) Use of these new injection site guidelines has resulted in a shift from forequarter tumor predominance to more distribution over the rear legs, which has the potential to allow for curative intent surgery through amputation. (Shaw, 2009)

Another critical question is the appropriate approach to postvaccination masses, which are most likely benign. Some types of rabies and FeLV vaccines have been associated with postvaccinal reaction masses in 100% of vaccinated cases. Fortunately, most of these masses resolve by two to three months postvaccination. The current recommendation, developed by the VAFSTF, for dealing with vaccination site reactions is to record the anatomic location, shape, and size of all masses that occur at the site of an injection. The group also recommends that all masses that develop in an injection site be managed as if malignant until proven otherwise. A diagnostic biopsy should be performed if the lesion persists for longer than 3 months post-injection, is larger than 2 cm in diameter, or is increasing in size beyond one month post-injection. All biopsies should be performed in such a way that subsequent surgical removal of the biopsy site and tract will not be hindered. (VAFSTS Roundtable, JAVMA 2005) Once a FISS has been confirmed, a consultation with an oncologist for current treatment recommendations is critical to optimize treatment planning. Adequate diagnostic assessment combined with multiple modality therapy currently provides optimum chance for cure or long-term remission of these difficult and life threatening tumors (Table 1 and Table 2).

**Table 1: Current guidelines for the diagnosis of suspected sarcomas.**[a]

| Diagnosis |
|---|
| 1. Accurately record location, shape, and size of all masses that occur at injection sites. |
| 2. Assume all masses that occur at injection sites are malignant until proven otherwise. Further diagnostics and management are indicated if:<br>• The mass persists for more than 3 months following injection.<br>• The mass is greater than 2cm in diameter.<br>• The mass is increasing in size beyond one month post-injection. |
| 3. If a mass displays any one of the criteria listed above, a diagnostic biopsy should be performed without compromising future definitive therapy. Fine needle aspiration cytology is considered unreliable in the diagnosis of FISS. |

[a] This information is adapted from the current recommendations of the Vaccine Associated Feline Sarcoma Task Force Guidelines.

**Table 2: Current guidelines for the treatment of suspected sarcomas.**[b]

| Treatment |
|---|
| 1. Complete staging including pre-operative lab tests and thoracic radiographs should be performed. |
| 2. For optimal outcome, FISS should have advanced imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) performed for therapeutic planning. |
| 3. Never "shell out" a sarcoma. Incomplete surgical removal can result in treatment failure. |
| 4. Consultation with an oncologist will aid in the initiation of optimal treatment planning, which may include multi-modality therapy. |
| 5. Submit the entire specimen for histopathology. |
| 6. Report all histologically confirmed FISS to the manufacturer and to U.S. Pharmacopeia Veterianry Practitioners' Reporting Program. (1-800-487-7776) |

[b] This information is adapted from the current recommendations of the Vaccine Associated Feline Sarcoma Task Force Guidelines.

**Managing Feline Carcinomas**

*Barbara E. Kitchell, DVM, Ph.D., DACVIM*

Carcinomas arise in cells of ectodermal and endodermal embryonic origin. These cells have the propensity to malignant transformation because they contain cells with high replicative rates throughout the lifetime of the animal, and also because these cells are on the "front line" of environmental carcinogen exposure. Epithelial cells are protected against malignant transformation by a lifestyle that include the capacity for transformed cells to slough away under physiologic conditions. However, when carcinogenic hits occur to progenitor cells in the basal layers of skin, gut, airway, or urinary system, cells may proliferate inappropriately to form a carcinoma. Carcinomas are known to undergo successive molecular injuries to progress from induced cells with a primary carcinogenic injury, to adenomas to carcinomas in situ and ultimately to invasive and metastatic carcinoma. These malignancies are relatively common in cats.

**Feline mammary tumors** - Mammary tumors represent the third most common feline tumor, after lesions of the skin and lymphomas. Mammary tumors are seen in both female and male cats. Progesterone may play a larger role in mammary carcinogenesis in cats than in the dog, as cats are known to develop carcinomas of mammary tissue after exposure to pharmaceutical forms of progestational agents administered for estrus control or behavioral issues. In queens, cats ovariectomized at 6 months to one year of age were up to seven times less likely to develop mammary carcinomas than cats that were unspayed. Mammary tumors in cats with an overall more aggressive biologic behavior than the disease seen in dogs. When a mammary mass develops in a feline patient, it is 80-90% likely to be malignant, with the majority of these tumors being adenocarcinomas. Feline mammary tumors are characterized as being tubular, papillary, solid or cribriform types. Other histologies are more rare. Inflammatory carcinoma, though rare, can occur in cats and carry an extremely grave prognosis. Median age at onset is 10-12 years, and Siamese cats have an increased risk of mammary tumor development, with an earlier age at onset than other breeds. Mammary carcinoma cells from cats are more likely to express progesterone receptors than are dogs or humans. Most feline mammary cancers are locally invasive and have lymphatic infiltration and ulceration may be a feature of these tumors. Size of tumor is prognostic, in that cats with smaller tumors have longer disease-free intervals and survival times.

In cats, surgical excision is the treatment of choice for local control. Uni- or bilateral radical mastectomy has been demonstrated to lead to longer disease-free intervals but not necessarily longer overall survival times. Cats frequently develop local recurrence after mastectomy; it is not uncommon to manage these by multiple surgeries before eventual metastasis.

Doxorubicin and cyclophosphamide have been demonstrated to be effective as an adjuvant therapy to palliate advanced mammary carcinoma in one third to one half of treated cats. One study reported a Median survival time of 448 days and 1 and 2 year survival rates of approximately 60 and 38%, respectively, in 67 cats treated with 1 mg/kg doxorubicin every 21 days for 5 treatments. We have found roughly equivalent rates of

disease regression for cats treated with mitoxantrone or carboplatin for mammary tumors. **Note that fluorouracil is contraindicated for use in cats because of fatal neurotoxicity;** the FAC protocol is indicated for canine use only.

**Oral Tumors** In the cat, the oral location accounts for 3% to 10% of all cancers. In the dog, malignant melanoma and squamous cell carcinoma of the mouth are the most common presentations. In cats, 75% of feline oral neoplasias are squamous cell carcinoma. Lingual tumors are most likely squamous cell carcinoma in the cat. Fibrosarcomas are the next most common, accounting for roughly 20% of malignancies. Other oral malignant tumors seen in cats include adenocarcinomas, fibrosarcomas, hemangiosarcomas, lymphomas, and melanoma. Odontogenic tumors are rare in the cat, but have been seen. Benign inflammatory lesions such as polyps may be confused with neoplastic lesions, so biopsy is essential for accurate diagnosis. The most obvious rule-outs for oral swelling are tumor or infection.

Although the etiology of oral tumors remains largely unknown, several risk factors have been identified in the cat. Risk factors include use of flea control collars, diet, and potentially exposure to environmental tobacco smoke. In fact the latter may associated with p53 mutations and over-expression of the mutated form of the gene. Clinical signs associated with oral tumors include inappetance, difficulty in prehending or masticating food, dysphagia, ptyalism, halitosis, nasal discharge or oral hemorrhage. Unfortunately, animals often hide their signs and may be diagnosed with oral tumors when they are in an advanced state. Careful oral examination might reveal a mass, but occasionally incidental tumors are noted in the course of routine dentistry. Diagnostic radiographs should be taken under anesthesia, to determine the extent of boney involvement and the potential for resectability. Fine detail dental radiographs are helpful for lesion on the rostral mandible or maxilla, but more caudal and maxillary tumors are best imaged with computed tomography or magnetic resonance images. A biopsy is in order, because of the potential for radical therapy with surgery or radiation therapy for cancer vs. long-term antibiotic or antifungal therapy for osteomyelitis of the mandible. Withrow recommends a large incisional biopsy because of the potential for misdiagnosis. Most oral masses are infected, inflamed, or necrotic. Scalpel biopsy instead of electrocautery is recommended because the potential for distortion of the sample by electrocautery. Specimens should be taken from the center and the edges of the mass to increase diagnostic yield. The biopsy site should be situated such that the tract can be removed at the time of definitive surgery. As a general rule, the biopsy should be obtained through the labial mucosa and not through the skin, in order to preserve the latter for facial reconstruction. Culture for bacterial organisms may not be fruitful, as the oral cavity is a contaminated site. Careful examination and palpation of regional nodes and tonsils is important for staging. Fine needle aspirates of nodes for cytology, or node excision for biopsy should be considered in the case of enlarged nodes that may be infiltrated with cancer cells or merely reactive, inflammatory nodes because of a necrotic and infected oral mass. Thoracic radiographs for detecting metastatic disease in the lungs is appropriate, but the potential for systemic dissemination of oral squamous cell carcinoma is very low.

**Treatment options** -Most oral tumors are treated by a local form of therapy, such as

surgical excision, radiation therapy or cryosurgery. Radical surgeries, such as mandibulectomy, are the most economical, fastest and potentially most curative modalities. Unfortunately, for most malignant SCC lesions the 2-3 cm margins of normal tissue recommended to prevent local recurrence is difficult if not impossible to attain. Withrow, in his chapter on oral neoplasia in *Withrow and MacEwen,* recommends the widest possible margins for feline squamous cell carcinoma, because of the extremely high local recurrence rate. Thus, many feline squamous cell lesions are non-resectable. Radiation therapy may be useful for at least palliating non-resectable tumors, or for eliminating residual disease when the tumors have been incompletely resected. Radiation therapy is rarely curative alone. Hyperfractionation or accelerated fractionation schemes for the delivery of radiation therapy to these tumors is currently being investigated. Hypo-fractionated radiation therapy has shown limited efficacy in feline oral tumors, inducing non-durable responses. Systemic chemotherapy has not been effective in local control of oral malignancy. Piroxicam may be used in SCCs as a single agent, providing symptomatic treatment and potentially partial remissions. Gemcitabine or carboplatin may be added as radiosensitizers. Most recently aminobisphosphonates such as pamidronate 2 mg/kg IV in a 2-hour saline infusion every 28 days, have been applied to feline oral tumor patients to mitigate the bone invasive nature of oral SCC. With standard fractionation or hyperfractionation schemes, increased survival duration requires the use of the endoscopic or percutaneously placed esophageal or gastrostomy feeding tube (PEG tubes). These tubes allow cats to be nutritionally managed with ease, allowing for longer survivals in the situation of poorly responsive oral malignancy.

**Salivary gland tumors** are observed in cats, and most particularly in Siamese cats. Median age at onset is 12 years. Cats present with non-painful swellings in the region of the salivary gland that are often invasive and fixed to underlying tissues. Cats may have metastasis and advanced disease at time of diagnosis. Radiation therapy and chemotherapy with doxorubicin or carboplatin and gemcitabine may offer some benefit to patients with metastatic disease or as an adjunctive therapy to surgery and radiation. Median survival time has been reported to be 516 days for cats with salivary carcinoma.

**Feline nasal tumors** - Cats also incur carcinomatous nasal tumors, although not as commonly as dogs. Radiation therapy is the treatment of choice, and the probability of survival is excellent, especially if the tumor is of lymphoreticular origin. Nasal lymphoma is much more common than in nasal epithelial tumor in the cat. Local radiotherapy to total fraction doses of greater than 32 gy have been associated with complete durable local control of nasal sinus lymphoma in cats. Systemic chemotherapy may be needed for disseminated disease, however.

**Primary lung tumors** are rare in dogs and cats and tend to occur in older animals. Adenoarcinomas are the most prevalent lung tumor. The frequency of carcinomas has been increasing; this may relate to an increasing life span of companion animals or to an increased number of necropsies being performed. Exposure to environmental carcinogens, including passive smoking, may influence the rate of occurrence. These lesions may be found incidentally during the course of thoracic radiography, but cats may be symptomatic with dyspnea, cough, lethargy, anorexia, weight loss, and fever. The

lung-digit syndrome is unusual to cats. In this disease manifestation, cats are lame and have swelling , paronychia and apparent pododermatitis due to metastasis to nail beds. Primary lung tumors may be solitary, but these lesions are also prone to intrapulmonary metastasis. In this scenario a larger mass is found in association with multiple smaller masses distributed throughout the lung fields. IT has been reported that more than 75% of feline pulmonary carcinomas are metastatic at the time of diagnosis. Lesions may be associated with pleural effusion due to breaking through the pleural surfaces. Tracheal bronchial or perihilar node involvement may be of small size, and this dissemination, along with very small intrapulmonary metastasis, may be bested detected by pulmonary CT scans. Fine needle aspiration cytology is not recommended for solitary lesions, as this may compromise complete surgical excision, but FNA is often used in cases of multicentric disease not amenable to surgical resection. Primary lung lesions are normally treated with surgical excision via complete or partial lobectomy. Carcinomas of the thoracic cavity, including carcinoma metastatic to lung and pulmonary carcinomas that are non-resectable, can be treated with chemotherapy. A variety of agents may show limited efficacy, including: doxorubicin; cisplatin; carboplatin; or with agents such as gemcitabine and the taxanes. Dose escalation studies of gemcitibine single agent chemotherapy and carboplatin gemcitibine combination therapy are ongoing. A new version of vinca alkaloid called vinorelbine (Navelbine) has been used in the cat for the treatment of a variety of malignancies. Vinorelbine is particularly interesting for treatment of lung cancers as it has been reported to 14 times greater pulmonary concerntrations than other vinca alkaloids. Doses have ranged from 7.5 to 9.0 mg/m2 administered as a rapid intravenous bolus, on a 5 weeks on, one week off schedule of administration. Piroxicam or meloxicam NSAID therapy may have some anti-angiogenic and analgesic affect and thus are often used adjunctively to other therapies for pulmonary carcinoma.

**Carcinomas of the gastrointestinal system -** Most tumors of the stomach, intestine and colon in cats are lymphomatous, but carcinomas can be seen. Gastric carcinomas are vanishingly rare in cats, but intestinal carcinomas may be seen and have a breed predisposition for Siamese cats. Small intestinal adenomatous polyps have been identified in the cat. Lesions may arise at the ileocecocolic junction with some degree of frequency, and metastasis to mesenteric nodes is common. Even with nodal involvement, intestinal carcinoma cases in cats should be managed by surgical resection and long survivals (5-15 months) have been reported from surgery alone. Intestinal carcinoma lesions are reported to be metastatic to nodes in 50% of cats, to the mesenteric surfaces in 30% (carcinomatosis) and to the lung in 20% of cases. Chemotherapy may not be helpful for all cases, but survival benefit has been noted for some cats with metastatic carcinomas. Doxorubicin, carboplatin, gemcitibine, and vinorelbine have been administered. Intracavitary carboplatin has been used to treat cases with abdominal carcinomatosis.

Although the incidence of colorectal and perianal neoplasia in feline patients is relatively low, the location of these neoplasms provides unique challenges with respect to therapy. In general, the tumor types found in colorectal cancers of the dog and cat are the same histologically as those found in small intestinal

neoplasia in these species, and include adenocarcinoma, leiomyoma and leiomyosarcoma, and lymphosarcoma. History and clinical signs associated with colorectal neoplasia in the dog and cat include anorexia, weight loss, vomiting, diarrhea, hematochezia, tenesmus, and dyschezia. Tumors of the perianal region of dogs and cats can include any form of cutaneous tumor, including melanomas, mast cell tumors, lymphomas, and squamous cell carcinomas. Several reports indicate that rectal or perirectal location in these neoplasms, particularly mast cell tumors and melanomas, can be associated with more aggressive biologic behavior of the tumors. Perianal adenomas and adenocarcinomas are not commonly found in the cat, although rare cases have been reported.

Anal sac apocrine gland adenocarcinoma is rare in cats but has a highly malignant behavior, with an invasive and ulcerative local involvement that makes surgical resection particularly challenging in cats, and early metastasis to the sublumbar and iliac lymph nodes. Hypercalcemia is rarely a feature of this neoplasm in the cat, and arises due to production of a parathyroid-related protein (PTHrp) that induces hypercalcemia and hypophosphatemia. Although surgical excision of the primary tumor is recommended, surgery is often difficult due to the size of the tumor and its invasiveness. Complications include fecal incontinence, wound infection, and sepsis. Local excision followed by adjuvant radiation therapy is recommended, with sublumbar lymph nodes included in the radiation field. Chemotherapeutic strategies to control distant metastases have included the use of doxorubicin, actinomycin D and carboplatin can also be employed as palliative therapy for relatively long-term control.

**Bladder tumors** comprise less than 2 %of all feline malignancies. It is more common in the dog than the cat, and in the cat the tumor is seen in very geriatric individuals with a male predominance. Clinical signs most often associated with bladder tumors include hematuria, pollakiuria, and stranguria. Other clinical signs include polyuria, polydipsia, urinary incontinence, urinary obstruction, abdominal pain, tenesmus, ribbon-like stool, and lethargy. Bladder tumors may be symptomatically similar to feline lower urinary tract disease, and thus cats with recurrent or non-remitting signs should be evaluated with diagnostic imaging. Physical exam findings may reveal caudal abdominal mass, bladder distention or obstruction, abdominal pain, and weakness. Most often, routine blood work and physical examination are normal and the bladder mass cannot be detected by abdominal palpation. Urinalysis may often be consistent with a bacterial cystitis (bacteruria, pyuria, hematuria, and proteinuria). Neoplastic cells can be identified in the urine sediment. There can be over interpretation of the criteria of malignancy in cells in the urine sediment as inflammation by itself can cause changes that closely mimic malignancy. Secondary bacterial infection may confound the diagnosis, and there is often reported an initial response to antibiotic therapy followed by a return of the clinical signs when antibiotic therapy ceases. This is a particularly troublesome finding in the cat as they are less prone than dogs to bacterial UTIs and any recurrent bladder infection bears investigation in this species. Radiography is a valuable tool in the diagnosis of bladder tumors.

Plain radiographs of the abdomen usually do not provide the diagnosis, however, positive and negative contrast cystograms readily identify mucosal irregularities, filling defects, and masses. Bladder tumor lesions in the cat tend not to be localized to the trigone, in contrast to the common canine presentation. Ultrasound can be used as a diagnostic tool to look for bladder masses as well as evaluate the kidneys for evidence of hydroneprhosis, ureters, and sublumbar lymph nodes for metastatic disease. Further, masses within the bladder can be easily measured at each ultrasound and used to evaluate response to treatment. Intraveneous urograms are often not necessary to diagnose bladder masses unless urethral obstruction prevents urinary catheter passage. Itis estimated that 20% of dogs with TCC have metastasis at the time of diagnosis, although this metastasis may be confined to sublumbar lymph nodes, while metastasis is more rare in the cat. Thoracic radiographs to detect evidence of lung metastasis should be performed at the time of diagnosis. Most typical patterns of pulmonary metastasis seen with TCC are interstitial nodular and diffuse interstitial patterns. While much can be gained from performing the above diagnostic tests, the final diagnostic step should include biopsy. Biopsy can be obtained by cystoscopy, traumatic catheterization, or cystotomy via laparotomy. Surgical resection, if possible, is the treatment of choice and can be curative for small tumors located distant to the trigone. Feline tumors are more amenable to surgical resection than are canine tumors. Ifthe cancer is located in the apex of the bladder, a very wide full-thickness partial cystectomy may be attempted. More than 80% of the bladder can be removed with eventual return to normal function and capacity. Even if surgical resection is possible, most patients will have local recurrence or metastsis within one year. Piroxicam or meloxicam are nonsteroidal anti-inflammatory agent that acts as a non-selective cyclooygenase inhibitors. Use of these agents may provide some anti-tumor and anti-angiogenic effect and palliative analgesia. The mechanism of anti-tumor activity is thought to be blockade of PGE2-mediated immunosuppression, but there is also some evidence to support cyclooxygenase-2 signaling as a direct growth stimulant to urothelial cells. This effect has not been well studied in the setting of feline TCC. Doxorubicin, mitoxantrone, carboplatin and gemcitibine have all been used to treat feline TCC with limited success. There are few reports on the effectiveness of radiation therapy use in the control of bladder tumors in cats.

**Feline Cutaneous Neoplasms**

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Cats are vulnerable to the development of skin tumors, as are other species. The skin is at risk for carcinogenesis because of its continually replicating pattern of cell growth, and because of its location as a primary barrier against environmental carcinogenesis. Skin tumors may arise from any cell residing in the skin and subcutaneous tissues, and therefore may be epithelial, mesenchymal, melanocytic, or round cell in nature. Mast cell tumors are discussed elsewhere. The frequency of feline cutaneous tumors has been reported to be ranked as follows: Basal cell tumor (15-26%, of which 1% are reported to be malignant carcinomas); Mast cell tumor (13-21%) Squamous cell carcinoma (10-15%); Fibrosarcoma (15-17%); sebaceous adenoma (2-4%); Fibroma (3%); Apocrine adenocarcinoma (3-5%) with all other lesions being less prevalent. The tendency for cats to develop cutaneous malignancies means that any mass lesion in a cat should be investigated vigorously.

Cutaneous tumors is usually readily identified on physical examination due to their surface location. Owners may identify masses, non-healing wounds, ulceration or scabbing at the site of a skin tumor in cats. Body maps are made to facilitate tracking benign skin lesions over time. Any masses in the skin should be measured, aspirated, and recorded on a body map to serve as an objective record of the lesions. This way, additional lesions or changes in pre-existing lesions can be noted on sequential veterinary visits over time. Cytology and/or biopsy are indicated for masses that are growing, changing in appearance or are newly identified. Biopsy may be incisional or excisional, depending on size and location of the mass. For some lesions, immunohistochemical staining and more precise histologic assessment of growth rate (intratumoral necrosis, mitotic index, proliferation markers) are required to fully characterize the skin tumor.

For most cutaneous lesions, surgical excision is the appropriate therapy. For multicentric lesions, biopsy for diagnosis followed by topical or systemic therapy may be more appropriate. Topical immunostimulatory therapy with imiquimod may be useful for treatment of superficial squamous cell carcinoma, as may strontium 90 plesiotherapy or cryotherapy. Basal cell tumors are common but generally not threatening and may be resected if they are bothering the cat or at the owner's discretion. This histologic designate may encompass several types of epithelial tumors, including cell of epidermal, follicular, and adnexal origin. Trichoblastomas are often classed as basal cell tumors. Basal cell carcinomas are characterized by a predisposition to lymphatic spread that occurs early in the course of the disease. Wide surgical excision of local tumor along with draining lymphatics and affected nodes can be curative for these lesions. Sebaceous adneomas and adenocarcinomas are much more rare than are basal cell tumors,

but are similarly managed when they are encountered. Apocrine gland tumors are found in the anal sac of cats, and also in the foot pads. These tumors are associated with an invasive biology and rapid metastasis as seen in dogs.

Squamous cell carcinoma is a common skin malignancy in cats and can arise from excess exposure to sunlight (actinic SCC), which is seen in cats that lack pigment on the eartips, eyelids, nasal planum, and pre-auricular regions of the face. These lesions typically occur in outdoor cats in highly sunny areas, such as the Southern US or in mountain regions. These lesions may be preceded by flaky skin with an inflammatory appearance, and it is not uncommon for clients to original attribute the lesions to non-healing cat fight injuries. These lesions can progress to become proliferative mass lesions or erosive, ulcerative lesions that can destroy normal tissue architecture. Actinic SCC may be metastatic to lymph nodes when in an advanced stage, but in general the most significant problems associated with these lesions are local disease progression. Animals with chronic actinic SCC may have elevated serum globulin levels, but the lab work is otherwise unremarkable. Differentials include infection with fungal organisms, non-healing traumatic wounds, and actinic dermal hemangiosarcoma or hemangioma that arises in the same location. . Therapy for actinic SCC is surgical when possible, and can include pinnectomy either therapeutically or prophylactically in the case of actinic keratosis, as well as resection of the nasal planum. Imiquimod cream may be helpful as a topical inmmunotherapeutic agent for superficial SCC lesions, but this agent can cause crustiness, scabbing , and discomfort in the treated cats through the ability of the drug to recruit a macrophagic inflammatory response. Cox-2 inhibition with agents such as piroxicam or meloxicam can be palliative for pain, anti-inflammatory, anti-angiogenic, and in rare cases may actually facilitate remission of the SCC cells themselves. Laser ablation, and electron or photon radiotherapy can also be used to control these lesions. Strontium 90 plesiotherapy with a local radiation applicator has been successful in treating cats with SCC. Investigationally, intralesional chemotherapy using a purified bovine collagen-based repositol delivery system for treatment with 5-FU and cisplatin proved efficacious in 85% of cats treated, but this agent is not commercially available. Using free 5-FU or cisplatin is contraindicated in cats due to potentially lethal neurologic and pulmonary toxicities, respectively. Injection of carboplatin or bleomycin directly into the lesions is tolerable but efficacy is not as successful as with the time-release collagen delivery vehicle.

Multicentric squamous cell carcinoma in situ (feline Bowen's disease) is a form of SCC that arises in haired skin and is associated with papillomavirus infection in cats. These lesions are typically crusted and very superficial. They can arise at any location over the cat's body and are not associated with sunlight exposure. The lesions are identified by the fact that they do not invade the epidermal

basement membrane. Papillomavirus DNA has been identified in these lesions. Bowen's disease lesions are typically treated with a course of imiquomod (Aldara) therapy and will resolve over several weeks as the papillomavirus antigen is recognized by immune cells that home to the site of inflammation caused by the agent. Plesiotherapy with strontium 90, intralesional chemotherapy, and surgical resection can also be helpful for these lesions. Nail bed (paronychial) tumors in cats are most likely SCC, although cats also suffer from a digit-lung syndrome wherein the primary pulmonary carcinoma colonized the paronychial vascular or lymphatic plexus to create multicentric mass lesions. Primary digital SCC of cats warrants a guarded prognosis, with median survival time of approximately 3 months despite digital amputation. Primary nail bed SCC is usually solitary while lung-digit syndrome affects multiple toes.

**Melanoma** – Most cats are not particularly subject to occurrence of dermal melanoma, although uveal melanoma can be problematic for some animals. Biologic behavior of these lesions in cats is somewhat unpredictable. These lesions can be metastatic although some benign lesions do arise. In a study of 45 cats with cutaneous melanoma treated by surgery, most (22/45) cats that died during the study had local recurrence, while 16 cats have metastasis.

Cats are rarely affected by dermal plasma cell tumors or histiocytic tumors. Cutaneous lymphosarcoma is noted in cats, and can respond favorably to standard of care chemotherapy with a CHOP-based protocol.

**Supportive Care for the Feline Patient with Cancer**

Cheryl Balkman, DVM

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Common clinical signs associated with variety of cancers

- Anorexia or decreased appetite
- Vomiting
- Diarrhea
- Weight loss

Management of these clinical signs will best be accomplished by treating the underlying disease but in some cases prior to obtaining a definitive diagnosis or while initiating appropriate therapy supportive care is necessary to allow the patient the best possible chance of recovery. These clinical signs can also be associated with cancer therapy. This brief overview will address some common issues associated the treating cats with cancer.

**Appetite**

Anorexia and hyporexia (reduction in appetite rather than total loss) can be due to many causes such as:

- Pain associated with eating or chronic pain associated with tumors elsewhere in the body
- Anosmia associated with nasal tumors
- Concurrent respiratory disease/dyspnea
- Nausea – primary disease associated or treatment associated (chemotherapy/radiation)
- Decreased appetite associated with inflammatory cytokines secondary to a neoplastic condition (IL-1, IL-6, TNF-alpha and others)

Appetite and satiety are controlled by complex interactions between the central nervous system, the gastrointestinal tract, and environmental factors.

Neurotransmitters controlling appetite

- Stimulatory
  - Norepinephrine through alpha2- adrenergic receptors
  - Dopamine through D1 receptors
- Inhibitory
  - Serotonin (5-HT)
  - Dopamine
  - Catecholemines through beta-adrenergic receptors

**Appetite stimulants**

Appetite stimulants can be tried in clinically stable patients that have a decreased appetite but are still eating. We often use them in patients that have a decreased appetite associated with chemotherapy administration.

Cyproheptadine

- Antihistamine with antiserotonin properties
- Inhibits serotoninergic receptors that control appetite
- Oral bioavailability – 100%, elimination half-life 13 hours
- Dosage: ¼ to ½ of 4mg tablet per cat SID-BID PO

Mirtazapine

- Significant anti-nausea, anti-emetic, and appetite stimulating properties
- Presynaptic alpha2-adrenergic receptor antagonist
- Increases noradrenergic and serotonergic neurotransmission by blocking presynaptic inhibitory receptors, resulting in increased norepinephrine release into the synaptic cleft and increasing postsynaptic availability
- Serotonergic effects occur through 5-HT1 receptor-like activity as well as enhancement of serotonergic transmission by norepinephrine
- Potent postsynaptic 5-HT3 and 5-HT2 antagonist
- Dosage: 1/8 – 1/4 of 15mg tablet (1.88mg – 3.75mg) PO every 3 days
- Drug half-life of 1.88mg dose – approximately 9 hours
- Drug could theoretically be given daily to *healthy young cats* based on the short half life and the limited pharmacokinetic/pharmacodynamic studies available. Studies on geriatric or clinically ill cats have not been published to date.

**Feeding tubes**

Feeding tubes are recommended for patients that have complete anorexia or a chronic history of hyporexia and a *treatable* form of cancer. It is especially important for patients that will be receiving therapy that may cause or exacerbate a poor appetite (chemotherapy, radiation therapy).

Types of feeding tubes:

- Nasoesophageal (NE) tubes
- Esophagostomy (E) tubes
- Gastrostomy (G) tubes

Nasoesophageal (NE) Tubes:

- Short term nutritional support (<14 days) or for patients that are not candidates for general anesthesia
- Easy to place, inexpensive
- Should not be placed in patients that are vomiting or have a decreased gag reflex
- Small diameter limits diet selection to liquid enteral formulas
- Radiographic confirmation of proper placement essential
- Complications
    - Epistaxis
    - Rhinitis
    - Tracheal intubation (secondary aspiration pneumonia)
    - Tube can be dislodged by coughing, sneezing, vomiting, scratching or pawing (e-collar necessary)

Esophagostomy (E) Tubes:

- Requires general anesthesia
- Relatively quick procedure
- Specialized equipment not required
- Confirmation of correct placement with radiographs essential
- Can be used for extended period of time (weeks to months or longer in select cases)
- Tube diameter allows for wider selection of diets
- Complications
    - Infection at ostomy site
    - Kinking or obstruction of tube
    - Tracheal intubation
    - Vomiting
    - Displacement of the tube (especially if patient vomits)
    - Swelling of the head (rare)

Gastrostomy (G) tubes:

- Requires general anesthesia
- Can be placed surgically or via endoscope (percutaneous endoscopic gastrostomy) PEG
- Bypass esophagus
- Allows for prolonged feeding (although e-tubes have been used for >1year in some patients)
- Larger bore tube – increased selection of foods
- Complications

- Cellulitis around ostomy site
- Gastric pressure necrosis
- Tube migration
- Pyloric outflow obstruction
- Inadvertent tube removal
- Leaking food around ostomy site
- Vomiting/secondary aspiration pneumonia

**Vomiting**

Vomiting can be associated with the primary disease process or treatment associated. The potential for chemotherapy induced vomiting is determined by the particular drug, dose and individual sensitivity. Typically gastrointestinal side effects of chemotherapy are mild and self limiting and occur 3-5 days after administration. Some drugs can cause immediate emesis during administration or shortly thereafter.

Pathophysiology of vomiting:
Vomiting is a reflex initiated by stimulation of the vomiting (or emetic) center in the medulla oblongata of the brain. The vomiting center receives afferent input from peripheral receptors in viscera, the chemoreceptor trigger zone in the floor of the 4$^{th}$ ventricle, the vestibular apparatus, and from higher centers of the cerebral cortex.

Complex pathways can trigger vomiting:

Humoral pathway – initiated by blood borne substances, plays an important role in chemotherapy induced nausea and vomiting

- Activation of the chemoreceptor trigger zone (CRTZ) in the area postrema
  - Blood brain barrier – less effective in this area
  - Allows the CRTZ to be exposed to chemical stimuli found in circulation
  - Chemotherapy, chemotherapy metabolites, other drugs, uremic toxins, electrolyte, osmolar, and acid-base disorders, other metabolic derangements
  - Feline CRTZ dopaminergic receptors are poorly developed however stimulation of alpha2-adrenergic receptors stimulates CRTZ

Neural pathways

- Afferent vagal
- Sympathetic
- Vestibular
- Glossopharyngeal
- Cerebrocortical

Peripheral receptors found throughout the body - can be triggered by directly by chemotherapy drugs or indirectly when chemotherapy is causes substances released by peripheral tissues

- Duodenum contains highest concentrations of these receptors
- Disease/irritation of the GI tract, other abdominal organs, or peritoneum can directly stimulate vomiting through vagal afferent pathways
- Receptors found in kidneys, uterus, urinary bladder send afferent impulses via sympathetic nerves
- Receptors located in the pharynx and tonsillar fossae transmit impulses through afferent fibers of the glossopharyngeal nerve
- CNS disease may directly stimulate the vomiting center through extension of inflammatory stimuli, hydrocephalus, or space-occupying lesions
- Supramedullary receptors may also influence the reactivity of the vomiting center
- Psychogenic vomiting – arise from cerebral cortex and may occur as a result of fear, stress, or pain
- Some chemotherapy drugs may cause a direct release of serotonin from the small intestine causing emesis mediated through vagal nerves or direct stimulation of centrally located 5-HT3 receptors
- NK-1 receptors located in the emetic center, chemoreceptor trigger zone, and enteric plexus is stimulated by the neurokinin known as substance P resulting in emesis

Mild self limiting nausea/vomiting can be treated conservatively at home by withholding food and water for 8 – 12 hours with or without the administration of anti-emetic drugs, and then slowly introducing water and bland, low-fat diet. Subcutaneous fluids can be given to patients that are mildly dehydrated or have other underlying metabolic conditions such as renal insufficiency. Anti-emetics can be given prophylactically to patients with a known sensitivity to certain chemotherapy agents.

**Anti-emetics**

Metoclopramide

- Prokinetic – release of acetycholine in gastric and small intestinal smooth muscle
  - Increased gastric emptying
  - Increased intestinal motility
- Central acting antiemetic
  - Antagonist at dopamine receptors of the chemoreceptor trigger zone
  - Also inhibits 5-HT3 receptors
  - May not play a role in feline vomiting through these receptors
- Other central antiemetics may be more effective for uremia, pancreatitis and chemotherapy induced vomiting

- Dosage:
  - 0.2 – 0.4 mg/kg SC or PO every 6-8 hours
- May be more effective as a constant rate infusion 1-2 mg/kg/day
- Reduce dose in cats with renal failure by 50% or more
- High plasma concentrations
  - Frenzied behavior or tremors
  - Discontinue drug until signs resolve
  - Consider reinstituting at half previous dosage

Ondansetron and dolasetron

- 5-HT3 receptor antangonist - central nervous system and gastrointestinal tract
- Effective as a prophylactic for chemotherapy induced vomiting, refractory vomiting in pancreatitis, hepatic lipidosis, severe inflammatory bowel disease, gastrointestinal neoplasia, cholangitis
- Dosage:
  - Ondansetron - 0.5mg/kg every 12 hours
  - Dolasetron – 0.6 mg/kg – 1.0 mg/kg IV or PO SID

Prochlorperazine and chlorpromazine

- Phenothiazine central antiemetics
- Antagonism of dopamine, histamine type 1, alpha2-adrenergic and muscarinic receptors
- Inhibit vomiting at the chemoreceptor trigger zone and directly at the emetic center
- Used for refractory vomiting in patients with pancreatitis, GI neoplasia, chemotherapy in conjunction with intravenous fluid support
- Dosage:
  - 0.1-0.5 mg/kg SC every 8 hours
- Can cause sedation, hypotension (due to alpha adrenergic blockade)
- Not recommended for empirical outpatient use or in dehydrated patients
- Risk of tremors due to dopamine antagonism – especially when combined with Metoclopramide

Maropitant (Cerenia)

- Neurokinin-1 (NK-1) receptor antagonist
- Inhibits substance P binding to NK-1 receptors located in the emetic center, chemoreceptor trigger zone, and enteric plexus
- Dosage:
  - 1 mg/kg SC or PO every 24 hours for 5 days followed by 2 days of rest

- Can cause pain at injection site (may be less painful when refrigerated)
- Should not cause cumulative side effects in combination with Metoclopramide or 5-HT3 antagonists
- Approved for dogs only however studies have shown efficacy in cats as well

**Diarrhea**

Diarrhea can be associated with primary cancers of the gastrointestinal tract or a side-effect of chemotherapy. As with vomiting, chemotherapy induced diarrhea is usually mild and self-limiting and occurs 3-5 days after the administration of certain chemotherapy drugs.

For mild cases empirical treatment usually involves increasing fiber in the diet, metronidazole, and occasionally probiotics. Rarely patients will need to be hospitalized for fluid therapy to combat dehydration and electrolyte imbalances.

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# Feline Juvenile Gingivostomatits: An Overlooked Disease

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## Most Common Oral Pathology

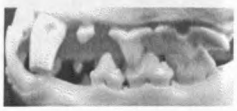
- Gingivostomatitis
  - Juvenile Gingivostomatitis (JGS)
  - Chronic Gingivostomatitis (CGS)
- Periodontal Disease
- Tooth Resorption
- Neoplasia
  - Squamous cell carcinoma

## History

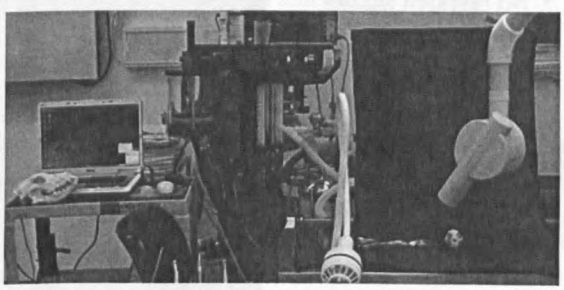
- History
  - Change in food preference
  - Appetite but loses interest
  - Frustration during eating
  - Decreased grooming
  - Reclusive behavior
  - Ptyalism +/- blood

## Oral Exam

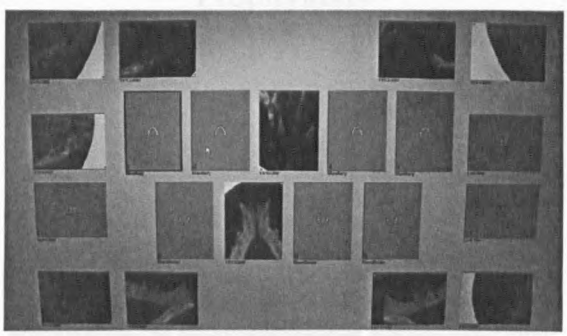
- Go slow and look before tissue manipulation
- Slight opening of mouth for mandibular M1
- Opening mouth
  - Examine mucocutaneous junction first
  - Respect the stop
  - Glossopalantine arch
  - It may not be worth it!



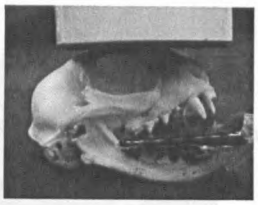
## Intraoral Radiographs – A Necessity



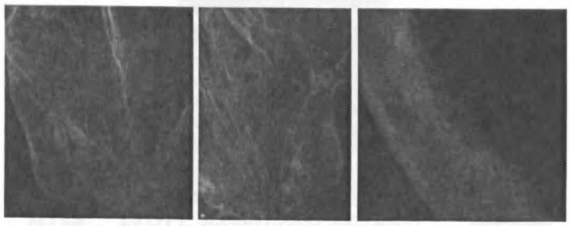
## Ideal Series: Digital System



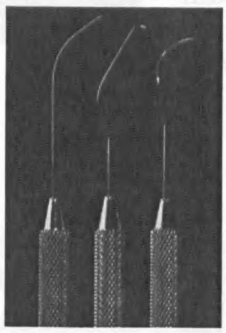
## Looking for Tooth Roots?

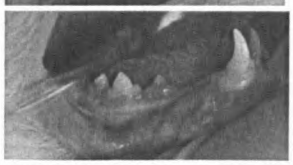




## Ahhhh …. Tooth Roots



## Anesthetized Oral Exam



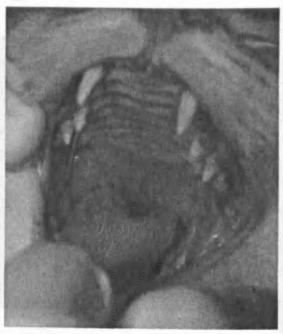


## Gingivostomatitis

## Gingivostomatitis (GS)

## Juvenile GS

- No research studies describing pathology
- Two sentence mention in Wiggs and Loprise's *Veterinary Dentistry*
  - Severe inflammation of the gingiva
  - Resolves at around 3 years of age.



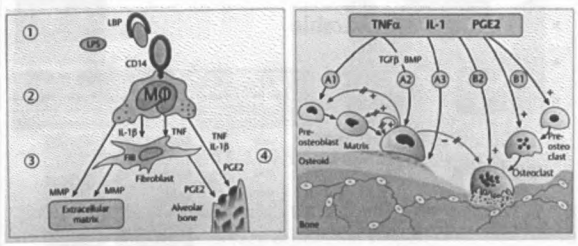
## Juvenile GS

- Unexplained etiology
  - Exfoliation of deciduous teeth
    - Pseudopocket formation
    - Increase detrimental bacterial population (gram negative bacteria)
  - Associated with calicivirus infection
  - Genetically "sensitive" inflammatory response
- Halitosis!!!
- Bloodwork normal

## Pathogenic Gram-Negative Organisms

- Direct tissue injury
  - enzymes: hyaluronidase, chondroitin sulfatase, proteolytic enzymes
  - cytotoxins: organic acids, ammonia, hydrogen sulfide, lipopolysaccharides (LPS)
- Inflammation-inducing bacterial by-products
  - LPS most important
    - stimulates macrophages, endothelial cells and fibroblasts to produce cytokines
    - helps to activate complement pathway
    - antigenically stimulating

## Destruction of Connective Tissue and Bone Resorption by Inflammation



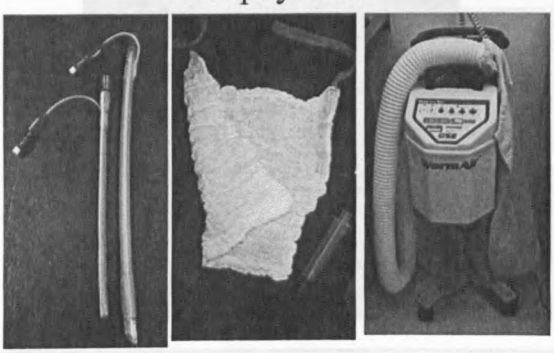

## Prominent Host Factors

- Host factors
  - Biofilm – can only be removed physically
  - Inflammatory and immune response - connective tissue destruction and loss alveolar bone
  - Host sensitivity – individual's pro-inflammatory (TNFα, IL-1, IL-6, PGE2, MMP) to inflammation-reducing (IL-10, TGFβ, MMP-inhibitor) cytokine ratio
  - Genetics – animals born with their predisposition to periodontitis
  - Environmental – stress, systemic health, housing (second-hand smoke)
- Significantly influence susceptibility, expression (type and severity) & progression of gingival inflammation

## Juvenile GS - Treatment

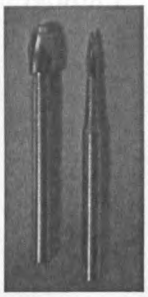
- Control inflammation and change bacteria
  - Anesthetized oral exam and radiographs
  - Dental cleaning +/- periodontal therapy

## Complications from Dental Prophylaxis



## Juvenile GS - Treatment

- Control inflammation and change bacteria
  - Gingivectomy
    - Reduces pseudopockets associated with gingival overgrowth
    - Promotes healing
    - Incorporates scar tissue into gingiva
  - Procedure
    - Dental bur and a careful hand
    - CO2 laser but beware of thermal damage to tooth!



## Control Infection and Promote Change in Bacterial Population

- Three week course of an antibiotic
  - Clavamox:
    - 13.75 mg/kg po bid
  - Clindamycin
    - 5-10 mg/kg po bid
  - Metronidazole
    - 10-30 mg/kg po bid
  - Doxycycline
    - 5 mg/kg po bid

## Juvenile GS - Treatment

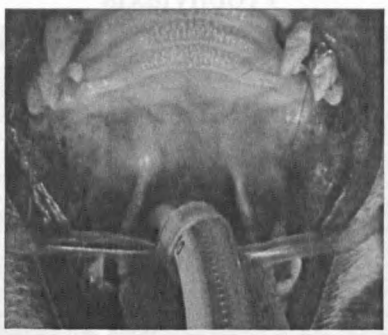
- Maintain oral health at home
- Retreat as needed (3-9 months)
  - Most need just 1 to 2 treatments
- Spontaneous remission 2-3 years
  - Without inflammation control severe periodontal disease will result

## Oral Hygiene Therapy

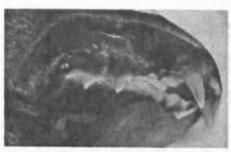
- T/D diet or comparable
- Biotene gel
- CHX gel or rinse
- Biotene drinking water additive
- CET chews



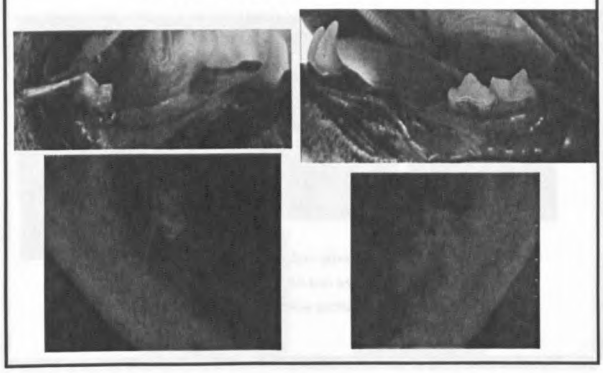
## End Stage Juvenile GS



## End Stage Juvenile GS

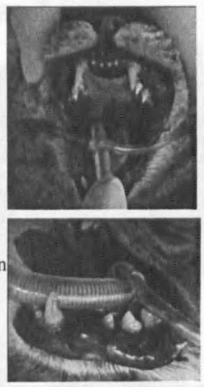


## End Stage Juvenile GS



## Chronic GS

- Exaggerated inflammatory reaction to bacteria associated with dental structures
- Multifactorial disease:
  - Bacteria (Bartonella henselae)
  - Viral (calicivirus, herpes, FIP, FeLV, FIV)
  - Genetic (breed predisposition and familial)
  - Nutrition
  - Environment (secondary smoke)
  - Domestication
- Bx: Lymphocytic-plasmacytic stomatitis
- Bilateral, near symmetric oral distribution
- Rule out systemic disease
- High TP and globulin
  - Usually polyclonal (monoclonal spike)





## Chronic GS - Treatment

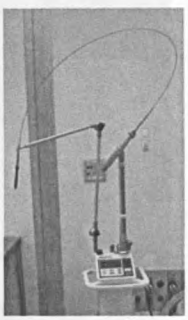
- Prognostic indicators
- Medical
  - Oral Hygeine
  - Antibiotic Therapy
  - Immunosuppression
    - Prednisolone 0.5-2 mg/kg sid with taper to lowest effective dose
    - Methylprednisolone 20 mg q 3weeks for 3 months
    - Cyclosporin (dosage depends on supplier)
      - Neoral (Novartis) 2 mg/kg po bid
      - Take blood levels q 4-6 weeks!!!

## Chronic GS - Treatment

- Surgical extraction
  - ALL DENTAL STRUCTURES MUST GO!
  - Full or caudal mouth extractions
    - 60% clinical remission
    - 20% significant improvement with no medication
    - 13% medication still necessary
    - 7% no improvement
- Proliferative tissue debridement: CO2 laser
- Interferon omega therapy

## CO2 Laser Thermoablation

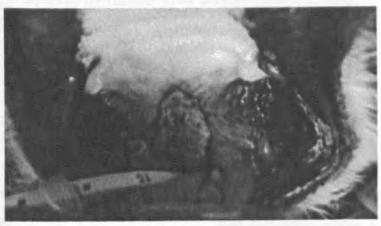
- Uses
  - Gingivectomy
  - Mucosal debridement
- Advantages
  - Bactericidal
  - Removal proliferative tissue
  - Fibrosis
  - Decreased pain sensation



## CO2 Laser Thermoablation

- Settings
  - Gingivectomy
    - 3-8 W continuous with 0.8-1.4 ablating
  - Mucosal debridement
    - 2-6 W continuous with 0.8-1.4 ablating

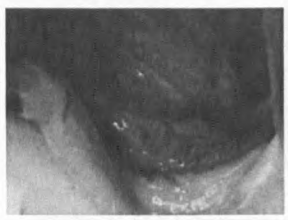
## CO2 Laser Themoablation



## Interferon Omega

- Effectiveness anecdotal
- Import
- Expensive ($120/vial)
- Needs refrigeration
- Treatment regimen
  - Intralesional injection 5 MU
  - Remaining 5 MU diluted with 100 cc sterile saline
    - Divide: 10 ml per 10 sterile vials
    - 1 vial refrigerator; freeze rest till needed
    - Give 1 ml po sid alternating sides of mouth for 3+ months


## Adult Onset GS – Refractory?

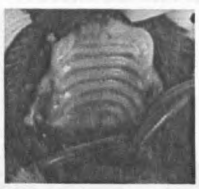


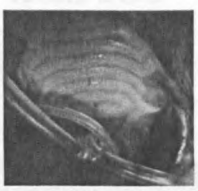
## Typical Case Presentation

## Chronic GS with Diabetes Mellitus (DM)

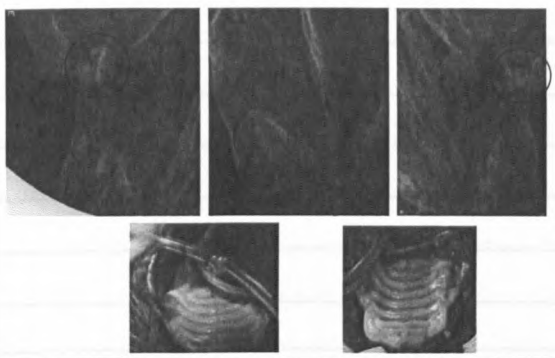
- History
  - Management of CGS 6 yr
    - Medical - Depomedrol 20 mg SQ every 4 weeks
    - Surgical - caudal mouth extraction followed by maxillary canine extraction
  - Develops DM
    - unable to control DM - ever increasing dose insulin

## Anesthetized Oral Exam

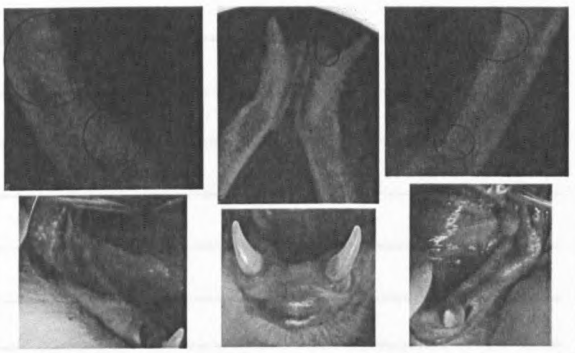




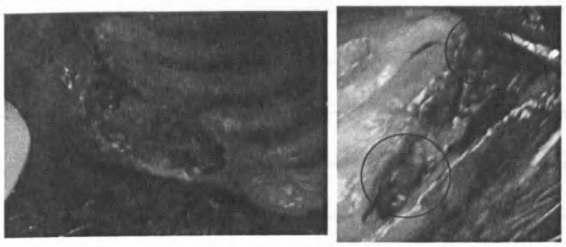
## Intraoral Radiographs - Maxilla



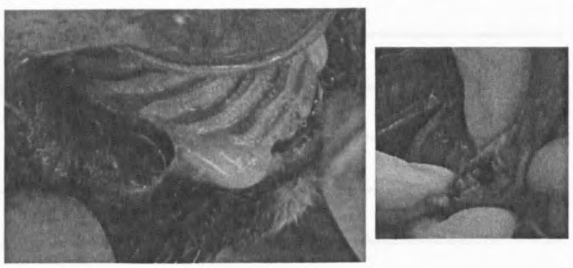
## Intraoral Radiographs - Mandible



## Surgical Extraction
## 13 Retained Roots



## Surgical Debridement



## Post-operative

- Post-op
  - IV fluids and Unasyn
  - Buprenorphine x 2
    - 0.01 mg/kg IV q 6 hr
  - Fentanyl patch
    - 12.5 mcg/hr
  - Insulin with glucose monitoring
  - A/D slurry
- To go home
  - Convenia 8 mg/kg q 7 days (1-3 weeks)
  - 5 additional days Buprenorphine post-patch
  - Insulin and glucose monitoring with rDVM

# Parasites of the Feline Lung

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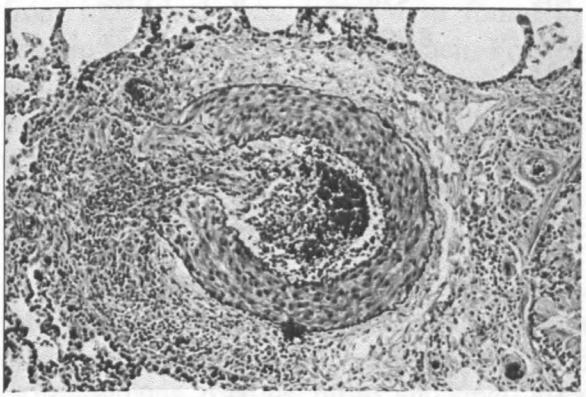
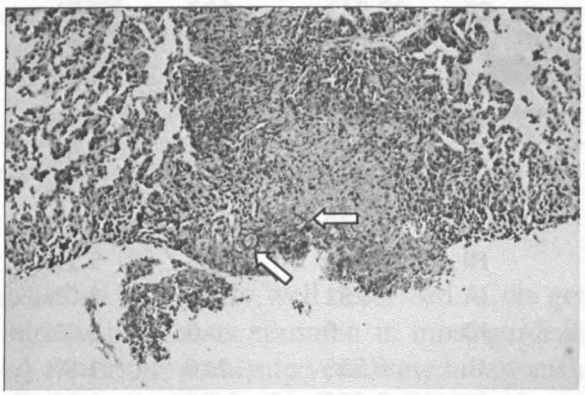


**Histosection of lung of cat showing medial hypertrophy of the pulmonary artery due to natural *T. canis* infection**



**Histosection of lung of cat naturally infected with *T. canis* with sections of larva**

There are three parasites of cats that are routinely relatively overlooked relative to their effects on the feline lung. These parasites are the canine heartworm *Dirofilaria immitis*, the feline lungworm *Aelurostrongylus abstrusus*, and infections of cats with roundworms of the genus *Toxocara*, both *T. cati* of the cat and *T. canis* of the dog. Cats tend to respond in the lungs to helminth infections, even if the infections do not mature, with a significant reaction that includes cellular infiltrate and the development of significant hypertrophy of the vessels in the lung. Such manifestations are common with all three of these infections which are much more common than typically considered.

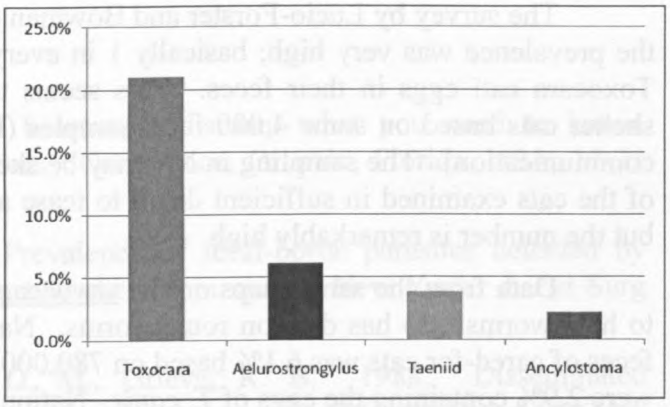
Recent data (Table) that has been collected from the laboratories of IDEXX, Antech, and Banfield Pet Hospitals (appearing on the interactive maps on www.capcvet.org) reveals that feline heartworm is much more common in cats around the nation than previously recognized. Actually, when the data on some 250,000 cats is compared to data collected on some 5 million canine samples from around the country, there are only 5 states, Arkansas, Louisiana, Mississippi, Oklahoma, and Texas, where dogs have a higher percentage of animals testing positive for heartworms. This might be due to the prevalence of cats being inflated by the "good clinician" syndrome, i.e., where veterinarians make a diagnosis based on clinical signs and then order the test in cats to verify their clinical suspicion, but the numbers are still quite staggering in their content. The fact that 2.7% of the cats tested around the nation are antigen positive for heartworm is an indication that a fairly large percentage of cats entering veterinary clinics around the United States have living heartworms in their pulmonary arteries. The antigen testing representing the true status of heartworm infection in cats is, however, supported by surveys examining shelter cats at necropsy for the presence of heartworms (Ryan and Newcomb, 1995).

| Results of Antigen Tests on 249,597 Cats around the United States | | | | | | | |
|---|---|---|---|---|---|---|---|
| STATE | Number samples | Number. positive | Percent Positive | STATE | Number Samples | Number Positive | Percent Positive |
| AK | 108 | 3 | 2.8% | MT | 0 | 0 | 0.0% |
| AL | 3,638 | 178 | 4.9% | NC | 13,279 | 364 | 2.7% |
| AR | 58 | 1 | 1.7% | ND | 0 | 0 | 0.0% |
| AZ | 4540 | 84 | 1.9% | NE | 713 | 8 | 1.1% |
| CA | 27,943 | 823 | 2.9% | NH | 574 | 9 | 1.6% |
| CO | 6,657 | 170 | 2.6% | NJ | 8,299 | 221 | 2.7% |
| CT | 4,519 | 102 | 2.3% | NM | 1,445 | 50 | 3.5% |
| DC | 757 | 15 | 2.0% | NV | 1,916 | 53 | 2.8% |
| DE | 1,678 | 44 | 2.6% | NY | 11,398 | 299 | 2.6% |
| FL | 43,147 | 1,390 | 3.2% | OH | 4,514 | 59 | 1.3% |
| GA | 11,639 | 407 | 3.5% | OK | 2,311 | 59 | 2.6% |
| HI | 634 | 33 | 5.2% | OR | 3,389 | 47 | 1.4% |
| IA | 251 | 5 | 2.0% | PA | 10,214 | 180 | 1.8% |
| ID | 0 | 0 | 0.0% | RI | 747 | 19 | 2.5% |
| IL | 6,515 | 116 | 1.8% | SC | 5,304 | 161 | 3.0% |
| IN | 3,129 | 56 | 1.8% | SD | 0 | 0 | 0.0% |
| KS | 679 | 10 | 1.5% | TN | 4,745 | 221 | 4.7% |
| KY | 1,263 | 24 | 1.9% | TX | 17,567 | 535 | 3.0% |
| LA | 1,761 | 78 | 4.4% | UT | 793 | 11 | 1.4% |
| MA | 8,856 | 202 | 2.3% | VA | 9,729 | 210 | 2.2% |
| MD | 7,114 | 128 | 1.8% | VT | 373 | 21 | 5.6% |
| ME | 0 | 0 | 0.0% | WA | 3,628 | 45 | 1.2% |
| MI | 5,605 | 113 | 2.0% | WI | 510 | 6 | 1.2% |
| MN | 4,647 | 54 | 1.2% | WV | 0 | 0 | 0.0% |
| MO | 2,662 | 74 | 2.8% | WY | 0 | 0 | 0.0% |
| MS | 349 | 9 | 2.6% | **Total** | **249,597** | **6,697** | **2.7%** |

We now also are aware that cats suffer from disease due to the presence of young adult heartworms in the heart even if they do not mature; the disease has come to be called HARD for Heartworm Associated Respiratory Disease (Blagburn, 2009). Results indicate that lesions and signs of are associated with death of pulmonary stages of *D. immitis* resemble those of other diseases such as feline asthma or other cause of tracheitis/bronchitis and interstitial lung disease. Thus, we now know that heartworm infections in cats even if the worms are not their long enough to stimulate an antigenemia in infected cats are still likely to induce disease in these cats. It should not be forgotten when considering feline heartworm disease that the worms that enter the heart of the cat after 70 to 100 days of development are 2 to 3 cm long when they arrive at the pulmonary arteries. Again, cats tend to over react to the presence of nematodes in their lungs with the indication of sever lung changes which in HARD are also associated with medial hypertrophy of the pulmonary vessels.

Both these findings, the high number of infected cats and the present of HARD in cats, are further verification of the need to provide cats with heartworm prevention. This lung disease is preventable if the cats are on heartworm preventives. These preventives are also likely to protect cats from infections from pulmonary disease due to lungworms and roundworms.

The feline lungworm of cats, *Aelurostrongylus abstrusus*, is a parasite that is often considered rather rare and unusual. It would appear that this may not actually be the case. In a survey of two shelters from Cortland and Tompkins County New York, of the 1,322 samples that were examined from individual cats, 6.2% were found to contain larvae of A. abstrusus (Lucio-Forster and Bowman, 2011). In this work, it is expected that since the manner of diagnosis was centrifugal flotation with zinc sulfate flotation that the number of cases detected was actually lower than the true prevalence.



**Fecal results of 1322 cats from two shelters in upstate NY**

The biology and disease caused by *A. abstrusus* has been fairly well described. Cats get infected with this lungworm by eating molluscan intermediate hosts common in most gardens (slugs or land-snail, e.g., *Deroceras*, *Arion*, *Helicella*) or various paratenic vertebrate hosts, such as amphibians, reptiles, birds, and small mammals. Larvae are shed in the feces of infected cats in slightly more than a month after the infection is initiated. The larvae are only infective to another host if they pass through a snail. The adult worms live in the terminal respiratory bronchioles and alveolar ducts. The disease is due to the presence of the worms and, probably even more so, to the eggs that are laid in the surrounding tissue in which the larvae develop and hatch. Cats with mild infections often have only minimal clinical signs, but heavily infected cats can present with severe bronchopneumonia and open-mouthed abdominal breathing. This worm seems restricted to felids, and does not pose any known risk to people.

We know that we can use certain products off-label to treat cats infected with *A. abstrusus*. Cats can be successfully treated with either a single treatment with moxidectin at the routine dose as in the monthly preventive for cats and by a three-day course of fenbendazole (Traversa et al., 2009). Thus, it would appear that Advantage Multi for cats may act as a preventive for this infection. We do not know if the dose in the heartworm products containing ivermectin, selamectin, or milbemycin oxime would be effective in treating and preventing feline infections with this lungworm.

Diagnosis of lungworm infection in cats is not always easy. It is by finding the larvae in the feces. Methods used include direct smears, zinc-sulfate or sugar flotation, and the use of a Baermann funnel method used to harvest the motile larvae from larger volumes of fresh feces. The direct smear and funnel method have the advantage that they provide the observer with actively motile larvae that aid in identification. The larvae obtained in zinc-sulfate flotations are characterized by the dorsal spine on the tail. In sugar, the larvae may be hard to visualize, because they are crenated by the osmotic pressure of the sugar solution, but they can often still be recognized if the tail can be found.

*A. abstrusus* is only one example of a good reason why it is necessary for pets that are on good all-year-round health parasite prevention to have regular fecal exams. An indoor cat may be more likely to eat an infected mouse in the winter than the summer, so seasonality may not play a major role in when infections with this parasite appear. A cat that gets to go outdoors is always at risk of getting infection if it hunts.

The survey by Lucio-Forster and Bowman (2011) cited above on cats in NY revealed that the prevalence was very high; basically 1 in every 5 cats in the shelters were found to be have Toxocara cati eggs in their feces. This seems to match almost exactly a national survey of shelter cats based on some 4,000 fecal samples (Dr. B. Blagburn, Auburn University, personal communication). The sampling in NY may be skewed by the fact that we did not know the ages of the cats examined in sufficient detail to tease apart what percentage of the cats were kittens, but the number is remarkably high

Data from the same maps on the www.capcvet.org website that was cited above relative to heartworms also has data on roundworms. Nationally, the prevalence of *T. cati* eggs in the feces of cared-for cats was 6.1% based on 780,000 samples. For the 4 million dog samples, there were 2.9% containing the eggs of *T. canis*. Nationally, there were only 4 states, Alaska, Arizona, Nevada, and California where there was a lower percentage of cats infected than dogs. In New York and Pennsylvania (some 144,000 samples), nearly 10% of the fecal samples were positive for *T. cati*.

What is often not realized is the effect that *Toxocara cati* has on the lungs of the infected cat. The majority of work done in this regard was published only in the form of a thesis submitted in 1969 (Swerczek, 1969). In this work, it was presented in great detail that the experimental infection of cats with *T. cati* induced severe lesions, medial hypertrophy of the pulmonary vessels, in the lungs. It was concluded that these studies showed "that the lesion is produced earlier and is much more extensive than in *A. abstrusus* infection. The earliest change noted in the arteries was mild intimal proliferation 2 weeks post infection, and medial hyperplasia was observed as early as 3 weeks and was severe by 6 weeks postinfection." It was felt that the observed lesions seen in random-sourced cats was probably most commonly caused by *T. cati*. Also, the lesions did not clear in cats that had been infected, and it was considered that the induced lesions were irreversible. Also noted in these cats, like with *A. abstrusus* infections, was the occurrence of peribronchial mucus gland hyperplasia. A single egg inoculum caused the lesion, and repeated reinfection simply caused them to worsen and to persist for longer periods.

Swerczek also reported on the disease induced in cats after their experimental infection with the eggs of the canine roundworm, *Toxocara canis*. About this infection, he stated that "the focal pneumonia associated with the migration of *T. canis* larvae was much more severe than that seen in *T. cati* infection." and "Muscular hyperplasia of the bronchioles and terminal alveolar ducts was also seen and was more severe in cats with evidence of sever ascarid infection." A cat was found naturally infected with larvae identified as those of *T. canis* with very large granulomas in the kidneys that also had significant lesions is the lungs (Figures on page 1) similar to those described by Swerczek in his thesis (Parsons et al., 1988). The lesions in the cat were similarly reproduced in cats that were experimentally infected with *Toxocara canis*, and these lesions also included severe lung disease with medial hypertrophy of the pulmonary vessels (Parsons et al., 1989).

Overall, based on the high prevalence of *T. cati* seen in cats, the knowledge that this parasite causes lung lesions, and the fact that infections with *T. cati* and *T. canis* can occur all season long, is an argument for keeping cats on preventive therapy. When coupled with the amount of lung disease associated with heartworms and lungworm, the three together argue very strongly for year-round heartworm and broad spectrum parasite control in cats.

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# The Intestinal Conundrum Protozoal Package

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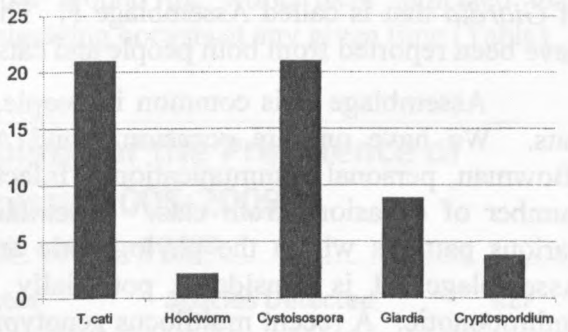
There are four protozoa parasites of cats that garner a good deal of attention for different reasons. The different species of *Cystoisospora*, *C. felis* and *C. rivolta*, are of interest because they are so very common. *Giardia* organisms are commonly found in cats, and infections sometimes causes diarrhea, but this genus of parasites gets most attention due to the concern that it might be a zoonotic agent. The *Cryptosporidium* species in the cat, Cryptosporidium felis, likewise garners attention because it is a potential zoonotic agent. Finally the fourth species, Tritrichomonas foetus is now known as a pathogen that may cause large bowel diarrhea in cats.




Fecal flotation results on 1322 shelter cats in upstate NY
% Positive Samples

## *Cystoisospora* species

The feline coccidia, *Cystoisospora felis* and *Cystoisospora rivolta,* undergo enteric development only in the intestinal mucosa of the domestic cat and perhaps other felids. There has been very little work in recent years on the potential of different species occurring in wild felids to be shared with the domestic cat. Also, it is not uncommon for no attempt to be made in the fecal examination of cats to distinguish between *C. felis* and *C. rivolta.* A survey in Germany reveals that 5.4% of 3,167 cats were shedding oocysts (8.2% of cats less than 1 year of age) (Barutski and Schaper, 2003) and a study in shelter cats in upstate New York revealed that 21% of the shelter cats were shedding oocysts (Lucio-Forster and Bowman, 2011). Cats can be infected directly by the ingestion of the oocysts that have sporulated in the environment after passage in the feces of a cat or indirectly by the ingestion of paratenic hosts, typically rodents or birds that have cystozoites in their tissues. After infection, oocysts are shed by the infected cat about a week later. In most cats the period of oocyst shedding will last about a month at the most.

Cystoisosporosis is a disease caused by the destruction of the epithelium and perhaps some lamina propria cells in the mucosa of the small and large intestines. In cats, clinical signs include soft, mucoid feces, and infections in young kittens can induce enteritis, emaciation, blood-tinged feces, and death. Disease can be severe and deadly in kittens that are not yet weaned. The diagnosis of the infection is by the finding the oocysts on fecal flotations.

Treatment has been examined most carefully in dogs where sulfadimethoxine is approved as a treatment for "bacterial enteritis associated with coccidiosis in dogs." Toltrazuril (10, 20 or 30 mg/kg of a 5% suspension for three days) and ponazuril (20 mg/kg daily for one to three days) have also been shown to clear abrogate oocyst shedding and to improve clinical signs. It must be remembered that oocysts which have already formed within the intestinal mucosa will not be affected, because the anticoccidials are not capable of penetrating the oocyst walls.

**Giardiasis**

Cats (and dogs) have been put forth by many as regular sources of human infection with *Giardia duodenalis* and as carriers of this "zoonotic" agent (reviewed by Bowman and Lucio-Forster, 2010). Such an assessment can have major effects on the acceptance of pets within a household and significant effects on hospital and elderly/shut-in visitation programs by pets, possibly increasing program costs or causing their cancellation. Some occupational health and safety officers want to or already have instituted regular fecal screening for *Giardia* cysts of all personnel who work with dogs and cats within a facility. Typically, cats are infected with a form of *Giardia* that is called Assemblage F. There are two additional Assemblages, A and B, that have been reported from both people and cats.

Assemblage B is common in people, and has only rarely been reported from dogs and cats. We have on rare occasion found Assemblage B in fecal samples from shelter cats (Bowman, personal communication). Infections with Assemblage A have been reported on a number of occasions from cats. Assemblage A is divided into sub-Assemblages based on various patterns within the phylogenetic analyses using different allozymes or genes. Sub-Assemblage AI is considered potentially zoonotic and sub-Assemblage AII is considered anthroponotic. A recent multilocus genotyping study using the sequence analysis of four genes (ssrRNA, β-giardin, glutamate dehydrogenase, and triose phosphate isomerase) of *Giardia duodenalis* recognized a third group, sub-Assemblage AIII, that is restricted to wild hoofed stock. There has been only a single report of AII from a cat. Part of the problem with defining host associations to the different sub-Assemblages is that they remain somewhat still in a state of flux as to their definition. Overall, however, cats are infected with Assemblage and F and on occasions, AI. The finding of B in some shelter cats is a bit worrisome, but this may require that we work to identify the sub-Assemblage and then determine if it is cat adapted or an actual zoonotic agent.

*Giardia duodenalis* is one of the most common parasites of cats around the world. A recent survey in Australia found *Giardia* cysts in 2.0% of 1,063 feline samples (Palmer et al., 2008). A survey of cats in the United States using a commercial ELISA-based test revealed a positive antigen result in the feces of 10.8% of 4,978 cats that were considered symptomatic by the testing clinic (Carlin et al., 2006). Cats in metropolitan Rio de Janeiro have been reported to be infected at a rate of 6.1% (Serra et al., 2003). In Tehran, Iran, 11.6% of cats were found to be infected (Zarebavani et al., 2006).

*Giardia* infections in cats are common in apparently normal animals, and thus, with the development of the new patient-side ELISA test from IDEXX Laboratories, veterinarians realized what veterinary parasitologists had known and told them for a long time: the prevalence of *Giardia* infections in these hosts is high, typically, anywhere from 10% to 40%, or higher. Giardiasis can sometimes make dogs and cats sick, but animals with signs are atypical. The stools of dogs and cats with apparent signs of giardiasis do not have the same frothy and foul-smelling features associated with the stools of symptomatic people. Practitioners do see cases that require treatment and which respond to treatment. Unfortunately, there are no approved drugs for cats: giardiasis is often treated with formulations of nitroimidazoles (metronidazole) and/or benzimidazoles (fenbendazole or the pro-benzimidazole febantel).

***Cryptosporidium felis***

The species of *Cryptosporidium* occurring in the cat is *C. felis*. It is hard to impossible to infect cats with *Cryptosporidium parvum*. On rare occasions, the murine gastric species of *Cryptosporidium*, *C. muris*, may be found in cats, but it may be due simply to prey ingestion.

Cats do not shed for long periods, so surveys give mainly an indication of what cats are shedding at any given time, not an indication as to what percentage of cats may have been infected with this parasite. Basically, studies from around the world have indicated that somewhere between 0 to almost 30% of cats can be shedding oocysts at any given time (Table)

## Recent Reports of Feline Sampling for the Prevalence of *Cryptosporidium* oocysts (2005-2009)

For earlier data see Santin and Trout 2008

| Country | % Positive Samples | Method/notes | Species Detected | REF |
|---|---|---|---|---|
| **North America** | | | | |
| Canada | 7.3% (3/41) | BFM[2] and FecAg Detection[3] | ND | Shukla 2006 |
| USA | 12.0% (30/250) | IFA[4] and PCR | *C. felis* | Ballweber 2009 |
| USA | 4.7% (16/344) | IFA and FecAg Detection | ND | Mekaru 2007 |
| **South America** | | | | |
| Brazil | 3.9% (2/51) | BFM | ND | Coelho 2009 |
| Brazil | 11.3 % (37/327) | BFM | ND | Funada 2007 |
| Colombia | 13.0% (6/46) | PCR | *C. felis* & *C. muris* | Santin 2006 |
| **Europe** | | | | |
| Italy | 24.5% (49/200) | BFM | ND | Rambozzi 2007 |
| Netherlands | 4.6% (1/22) | BFM | ND | Overgaauw 2009 |
| Romania | 29.4% (53/180) | BFM and FecAg Detection | ND | Mircean 2007 |
| Spain | 4.0% (2/50) | BFM | ND | Gracenea 2009 |
| UK | 0% (0/57) | BFM | ND | Gow 2009 |
| UK | 1.0% (13/1355) | BFM | ND | Tzannes 2008 |
| **Australia** | | | | |
| Australia | 2.4% (26/1063) | BFM and PCR | *C. felis* | Palmer 2008 |
| Australia | 7.0% (3/46) | BFM | ND | O'Calaghan 2005 |

1. Positive Samples % (Positive Samples/Total Samples Examined)
2. BFM: Bright-Field Microscopy, including DIC and/or phase microscopy, stationary and/or centrifugal fecal flotation methods, centrifugal sedimentation methods, and/or acid-fast, malachite green, or methylene blue gram safranin staining.
3. FecAg Detection: Includes various enzyme immunoassays (EIA), and 2 were nonenzymatic immunoassays
4. IFA indirect fluorescent antibody assay (may include direct fluorescent assays)

Most cats do not develop disease from an infection with C. felis. Occasionally, a cat, especially in a closed colony, may develop diarrhea due to its infection. There is no treatment currently registered in the USA for Cryptosporidium infection in cats. Tylosin has been used successfully in cats, but requires a long course of treatment; nitazoxanide is registered for the

treatment of cryptosporidiosis in children and also reduces oocyst shedding in cats (Lucio-Forster et al., 2010).

A recent review of Cryptosporidium in humans and companion animals (Lucio-Forster et al., 2010) has reported on studies concerning the distribution of *Cryptosporidium* spp. in humans. In the USA, of 228 cases of cryptosporidiosis where genotyping was done, 143 cases (63%) were linked to *C. hominis*, 78 to *C. parvum* (34%), six to *C. felis* (2.6%) and a single case to *C. canis* (0.4%); which was similar to that reported from the UK. *C. felis* was isolated only from HIV-positive adults in the USA, but it has been seen in immunocompetent humans in other countries, especially in children in developing countries where 3.3% of cases were due to *C. felis*. In total, there have only been 97 *C. felis* cases reported in people (6 in the USA). Thus, molecular epidemiologic data to date support the belief that the risk of zoonotic transmission of *Cryptosporidium* spp. from cats to people. Veterinarians and physicians can inform their clients of this minimal risk, but nevertheless advise them to minimize contact with pet feces, especially if their clients or other members of the household are immunosuppressed.

***Tritrichomonas foetus***

For a long time, it was considered that *Tritrichomonas foetus* was a parasite of the genital tract of cattle. However, it has recently been shown using molecular and other methods that the form present in the feces of cats with diarrhea is the same as the species in cattle. Amongst cats, there is no known breed or sex predilection; although diarrhea is more commonly seen in younger animals. *T. foetus* was diagnosed in the stools of 31% of 117 purebred cats from 89 catteries attending a show. In a study of catteries in which infection was found, more cats had diarrhea when there were more cats per square foot of floor space (Gookin et al, 2004). An examination of the feces from 100 feral cats and 20 healthy indoor cats using microscopy and protozoal culture of feces failed to reveal any cats infected with this parasite suggesting that it is not commonly found in cats outside of the cattery-type housing environment.

The life cycle is direct. Transmission is fecal-oral, with trophozoites passing between hosts. Trophozoites survive for short periods in fresh feces. Following experimental infection, some cats began to shed trophozoites in their feces as early as 2 days after oral inoculation with the organisms (Gookin et al., 2001). Infections without clinical signs can be prolonged, years, without the animals having clinical signs of infection (Foster et al., 2004)

Infections with this pathogen cause chronic large bowel diarrhea. The diarrhea tends to occur sporadically and may on occasion contain fresh blood or mucus. Typically, however, in spite of transient diarrhea, the cats remain in good health with good body condition. The feces tend to be semi-formed and considered malodorous. It has been noted that in very young cats held in poor housing conditions that the anus may appear edematous, erythematous, and painful; this may be associated with involuntary dribbling of feces. On rare occasions rectal prolapse can occur. Diarrhea tends to be associates mainly with cats that are one year of age or younger.

Trophozoites should be looked for in fecal smears prepared with saline rather than water to prevent the lysis of the parasite. The directional swimming motion of the trophozoites can be used to distinguish them from the trophozoites of *Giardia felis* that move but tend to be unable to orient under most conditions. A very useful method for obtaining cultures of trophozoites is the In-Pouch TF kit (BioMed Diagnostics Inc.), typically used for diagnosing trichomoniasis in

cattle. There are also molecular methods used in several laboratories for the diagnosis of *Tritrichomonas foetus* infections.

There has not been a satisfactory modality of treatment that has been identified. Many antimicrobial drugs (metronidazole, fenbendazole, albendazole, sulfadimethoxine, trimethoprim–sulfadiazine, furazolidone, tylosin, enrofloxacin, amoxicillin, clindamycin, paromomycin, and erythromycin) have been utilized in therapy, often without success (Gookin 2004). In some cases cats will not be cleared of their infection by treatment, but the signs may imporve while on therapy.

In a long-term study of 26 cats that had diarrhea and were infected with *Tritrichomonas foetus*, 23 of the cats had a resolution of their clinical signs within 2 years of the onset of the diarrhea (median time to resolution 9 months) (Foster et al., 2004). More than have of the cats with clinical signs still had infection detected by PCR a median of 39 months after it had been reported that their Trichomonas foetus associated signs of diarrhea had cleared.

The trophozoites are highly labile and probably die under most circumstances within hours after being passed in the stool. The trophozoites will lyse in clean water and are likely to be killed by the application of heat, either dry, out of heated high pressure washers, or from steam cleaning. Most disinfectants, soap, bleach, ammonia, etc., are going to rapidly kill the trophozoites of this parasite.

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# Two Cat Killers: *Cuterebra* and *Cytauxzoon*

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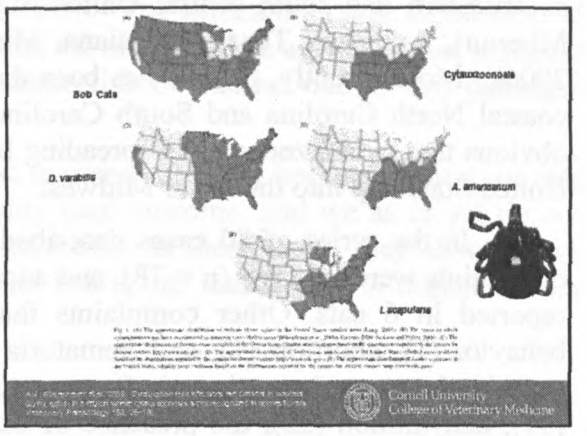
This parasite first appeared in domestic cats in Missouri in 1973, and the concern at that time was that it was an introduced species of importance to agriculture, perhaps related to *Theileria parva* (Wagner, 1976). It was also at this time described as a new species: *Cytauxzoon felis* Kier, 1979. *Cytauxzoon felis* used to be thought to be transmitted to cats from bobcats, *Lynx rufus*, by the bite of the American Dog Tick, *Dermacentor variabilis* (Blouin et al., 1984). We have more recently learned that the vector is the lone star tick, *Amblyomma americanum* (Reichard et al., 2009). This matches what is known about where the disease is located, it occurs in the overlapping ranges of the bobcat and the lone star tick, not in the overlapping areas of the *Dermacentor* and the bobcat ((Birkenheuer et al., 2008). The sexual stages occur in the tick which inoculates sporozoites into the host when it bites. So now, the reservoir host is the bobcat, and the vector is the lone star tick.




In the cat, there are two important life cycle stages, schizonts and merozoites (Meier and Moore, 2000). Schizonts are found in histiocytes and macrophages of the bone marrow, veins, and venules of various organs, including the lungs, liver, spleen, lymph nodes, brain, and kidneys. Merozoites occur in circulating red blood cells later in the infection, and therefore, often will not be found in cats dying of acute disease.

Disease occurs in cats that are bitten by the vector. In the cat, schizonts develop within monocytes, which become markedly enlarged. Cats with acute disease typically develop anemia, depression, fever, dehydration, and icterus. The majority of cats die within nine to 15 days of infection. The cause of death is occlusion of veins and venules with schizont-laden macrophages. Hematologic changes may be severe, and result from displacement of hematopoietic tissue within the bone marrow. If the cat survives for more than six days, erythrocytes become infected and the merozoite stage develops, typically with no more than 1% to 4% of red blood cells infected. In the case of the bobcat, the schizogonous stage is shortened, and they become prolonged carriers of the erythrocytic stage (Blouin et al., 1987).

One of the main sites of disease in the cat is the lung. An examination of lungs from 148 cats that had died of cytauxzoonosis were examined in Oklahoma from retrospective samples collected between January 1995 and June 2005 (Snider, 2010) Evaluated parameters included the presence of interstitial pneumonia, increases in the number of alveolar macrophages, degree of intra-alveolar hemorrhage, neutrophils infiltrating peribronchial and septal interstitium, and degree of vascular occlusion. Overall, interstitial pneumonia was moderate; alveolar macrophage numbers were mild, and vascular occlusion was moderate to severe with prominent

pulmonary edema. The findings shed light on the fact that the pathogenesis of cytauxzoonosis is due to vascular occlusion by macrophages that are enlarged by the schizont stages of the parasite.

In a survey of cases from the mid-Atlantic states of the US, of 34 cats infected with *C. felis*, 32 succumbed to the infection (Birkenheuer et al., 2006). The most common signs are pancytopenia and icterus. During the acute disease, organisms can be identified in smears of bone marrow or in biopsy specimens. Chronic disease is diagnosed by finding the merozoites in red blood cells. No treatments are consistently efficacious during the acute stage of the disease. Antiprotozoals with supportive care and antibiotics are often administered, but the prognosis remains poor. This is a disease that is currently best prevented by keeping cats indoors in areas where the ticks are active or using products that will kill or repel ticks.

Natural cases of cytauxzoonosis in cats have typically been described from the southeastern and south central United States, cases being reported from Kansas, Oklahoma, Missouri, Arkansas, Texas, Louisiana, Mississippi, Georgia, and Florida (Jackson and Fisher, 2006). More recently, *C. felis* has been diagnosed in Kentucky, Indiana, Tennessee (70 cases), coastal North Carolina and South Carolina (Jackson and Fisher, 2006). Thus, it is becoming obvious that cytauxzoonosis is spreading beyond its typical confined range in the south-central United Stated up into the lower Midwest.

In the series of 80 cases described by Cohn et al. (2011) the most common historical complaints were lethargy (n = 78), and anorexia (n = 60). Vomiting (usually once or twice) was reported in 6 cats. Other complaints that were reported were unsteady gait (3), abnormal behavior (1), abortion (1), and hematuria (1). The most common abnormalities on physical examination were hyperthermia (temperature >39.2 C; n = 72), icterus (31), elevated nictitans (31), dehydration (22), the presence of ticks (22), tachypnea (respiratory rate >40 breaths per minute; 20), tachycardia (heart rate >200 beats per minute; 13), pallor (9), murmur (8), vocalization (5), discomfort on abdominal palpation (5), lymphadenomegaly (5), and splenomegaly (5). Abortion, stupor, gallop rhythm, muscle wasting, ear mites, abscess, and disorientation were each found in a single cat. Temperature range in the 78 cats with legible recorded temperature was 38.3–41.7 C (101.0–107.01F).

Diagnosis has been improved through the development of PCR assays (Brown et al, 2010), and this has led to the ability to detect infections in asymptomatic cats. It may be that there are different strains of *C. felis* circulating in the wild and domestic populations with some being deadly and some being relatively benign. However, the risk remains. This is actually a very good argument for cats being kept indoors in areas where the disease is known to occur.

Treatment now appears to be best through the use of atovaquone (15 mg/kg PO q8h) and azithromycin (10 mg/kg PO q24h, with heparin, fluids, and supportive care (Cohn et al., 2011). Previously treatment had been with imidocarb (3.5 mg/kg IM). In an open-label, randomized prospective study, of 53 cats treated with the atovaquone and azithromycin, 60% survived to discharge. Unfortunately for the 27 cats treated with imidocarb, only 26% of the cats survived to discharge. The mean temperature of cats randomized to receive atovaquone and azithromycin (104.5 $\pm$ 1.1 F; 40.3 C) was identical to that of cats randomized to receive imidocarb (104.5 $\pm$ 1.1 F; 40.3 C). Of 80 cats included in data analysis, 39 survived and 41 died. Of the 41 that died, 5 were euthanized because of severe clinical deterioration and moribund condition. Twenty-four of 41 cats that died did so the day of or the day after presentation for care; only 3 cats died or were euthanized more than 3 days after presentation. Overall, survival was greater in cats treated with

atovaquone and azithromycin than in cats treated with imidocarb (P = 0.0036; odds ratio 7.2; 95% CI 2.2, 24.0).

As more and more people move into housing developments on the fringes of tick areas, it can be expected that more and more cases of this and other tick-transmitted diseases will be seen. This is due in part to the continued expanding range of the American bobcat, particularly in the Midwestern and several mid-Atlantic States U.S. Fish and Wildlife Service website). The range is increasing and the numbers are increasing. It is estimated that there are now at least some 1.5 million bobcats in the United States, but this may be an underestimate due to poor animal sighting abilities by census takers (Harrison, 2006). The annual harvest for fur was about 35,000 per year in the mid 1990s (US Fish and Wildlife Service website). In recent years, there has been an increase in the harvest due to the demand of the fashion industry, but this does not seem to be decreasing populations in any areas (Harrison, 2006). The expanding range of the host of the parasite and the vector would be expected to expand the range of both agents. Thus, it should be expected that cats will be under greater and greater risk of disease due to this pathogen throughout the United States.

It would seem that in areas where this disease is present that the best prevention for cats is an indoor existence. The disease often has a highly fatal outcome, and we as of yet do not have a perfect tick preventive for cats. If cats do go outside in these areas, they should have some form of tick prevention applied, but the lone star tick is one that is hard to dissuade from attacking and biting a host if it so chooses.

**Cuterebriasis**

*Cuterebra*, a genus of dipteran obligate parasites of rodents and lagomorphs in North America, undergoes an obligatory deep migration through the tissues of its host before the third-instar larva appears in a subcutaneous boil where it undergoes rapid growth before dropping to the soil to pupate (Sabrosky, 1986). Surprisingly in the rodent and lagomorph hosts, there is actually very little loss of fitness of the host from infections with these parasites that can appear strikingly large in comparison to the host (Slanksy, 2007). There are 34 species of *Cuterebra* throughout North America (Sabrosky, 1986), and dogs and cats are known to sometimes have the larvae develop into mature larvae within the lesions in their skin, nasal cavity, or eyelid (Scott et al., 2001).

***Cuterebra* larva removed from the retro-orbital region of a cat in upstate New York**

In the northeastern United States there is the seasonal appearance of neurologic disease in cats that has been associated with the migration of *Cuterebra* larvae through the spinal cord or brain (Glass et al., 1998). The larvae cannot be identified to species, and while third-stage larvae can be identified to subgenus, first and second instars cannot be identified morphologically beyond the generic level (Sabrosky, 1986). Thus, it is unknown if the disease in cats seen in the northeastern USA is due to one or more than one of the six species of *Cuterebra* that occur in this area: three species in the subgenus *Trypoderma* that use lagomorphs as their typical hosts,

*C. T. abdominalis*, *C. T. buccatta*, and *C. T. cuniculi*, and three in the subgenus *Cuterebra* that used rodents as the typical hosts, *C. C. emasculator*, *C. C. fontinella*, and *C. C. americana*. The flies all have univoltine life cycles with the females laying eggs on blades of grass in spring or early summer near the entrance to the host's burrow, and the larva then leaves the egg to get onto the host when it is passing by and enters the host through one of the body's orifices. The migratory patten in mice experimentally infected with *C. C. fontinella* revealed that whether the larvae first entered the host via the nares or anus, they migrated first to the trachea and thoracic region before migrating through the abdomen to the site of development in the subcutaneous tissues of the postero-ventral abdominal region (Gingrich, 1981). A mature larva in a rodent or rabbit requires some 3 to 8 weeks including the migratory phase of the life cycle (Bowman et al., 2002).

In cats, the disease usually presents between late June and the first killing frost in October. In most cats, and dogs, it seems that the larvae ultimately reach the subcutaneous tissues and mature (although they seem incapable of producing viable adults after pupation), and in these cases the diagnosis of infection is simply the finding of the larva in the subcutaneous boil. Unfortunately, in some cats, the infection produces respiratory signs followed by neurologic disease that is often fatal. In late summer to early fall, cats can develop an acute onset of neurologic disease that may be preceded by upper respiratory signs one to two weeks previously. These cats can present with depression, blindness, and behavioral changes. Lesions may be in the cerebrum or cerebellum in association with feline ischemic encephalopathy, but in some cases the larvae are found within the spinal canal.

Diagnosis is typically based on signs, response to treatment with high doses of ivermectin and corticosteroids, imaging with computerized axial tomography or magnetic resonance, or by necropsy. Treatment remains high-dose ivermectin, often with corticosteroids, or surgical removal of the offending bot. Work is underway to develop a means of assisting the diagnosis with the utilization of an ELISA for *Cuterebra*-specific IgG and IgM in cats with known and suspected disease. It is hoped that this will ultimately prove useful in ruling out the infection in cases where cats present with signs other than a bot within a subcutaneous lesion.

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# What's new in pain control and anesthesia for cats

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Pain management and rehabilitation service, CUHA

# How is pain defined?

- An unpleasant sensory or emotional experience
- Associated with actual, perceived, or potential tissue damage
- A physiologic and psychological experience
- A very subjective experience
  - Formed by a neural matrix
  - Evolving=Subject to change
    - immediate
    - long term

# "New age" definitions

- **Acute pain**
  - Known causative factor
  - Treatment usually satisfactory
  - Examples:
    - Myocardial pain
    - Traumatic MS pain
    - Headache

- **Chronic pain**
  - Causative factors?
    - Known
    - Unknown
  - Ongoing duration
  - Difficult to treat
  - Examples:
    - Oncologic pain
    - Osteoarthritis
    - Diabetic pain
    - Nerve injury pain

# What do these new definitions mean to us clinically?

- There's no straight line from tissue alteration to pain response
- A tiny insult can result in exponential damage
  - Autonomic changes
  - Supportive and neural Tissue changes
    - Structural
    - functional

- What decreases these problems?
  - Early aggressive treatment of pain
  - Preventative treatment of pain=preemptiv
  - Multimodal treatment of pain

# Why bother treating pain?

- Immediate effects
  - Increased sympathetic tone
  - Hypercoagulability
  - Increased myocardial work
  - Diminished pulmonary function
  - Translocation and altered GI blood flow
- Long term effects
  - Thromboembolic disease
  - Chronic pain
  - Myocardial disease
  - Immune supression
  - Poor wound healing

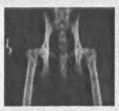
Lascelles B, 1999. A survey of current british veterinary attitudes to perioperative analgesia for cats and small mammals

- Veterinarians asked their opinion on an exploratory laparotomy in dogs and cats
  - Most considered this procedure painful in both species
  - Only 56% cats received analgesics
    - Compared to 71% of dogs

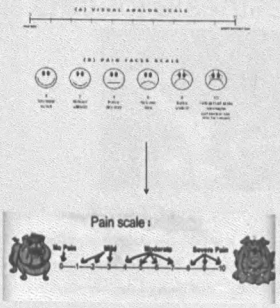
•www.royalcanin.co.uk

## Why are cats undertreated?

- Difficulty in recognizing signs of pain in this species
- Limited number of analgesics with label indications for cats
- Perceived frailty of the species
- Fear of adverse side effects
- Lack of published information



## Assessment of pain is important




## Normal cat spontaneous behaviors

- Stretching
- Back arching
- Climbing
- Grooming
- Laying lateral or curled up
- Yawning
- Wide eyed and slow blinking
- Tail movements
- Play or trouble making!

www.animalfriendsrescue.org

## Pain assessment

- Acute vs. chronic
- Physiologic and behavioral signs
- Knowing the norm for the animal
- Experience the animal outside the acute environment (in the case of chronic pain)

## Common clues to the presence of pain in cats

- Decreased movement
- Scratching or overgrooming affected areas
- Poor coat quality
- Lack of grooming and hair matting
- Decreased appetite and water consumption
- Hiding and isolation
- Escape attempts
- Slow cautious movement

## Common clues to the presence of pain in cats

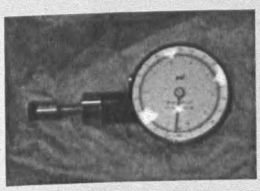
- Facial expression
  - Half mast pinna position
  - Squinting eyes
- Failure to urinate and defecate
- Toaster position
- Over sleeping
- Quietness or voice changes
- Drooling or difficulty prehending or chewing

## Systematic approach to determining pain in cats

- Detailed history
  - Typical day, current medications, recent life changes, vaccinal history
- Observation from a distance
  - Cat on the ground, dim lights
- Assess response to owner's approach
- Stranger interaction
  - Your Non invasive interaction
- Physical exam
  - Area of interest last

## Other more objective means of identifying pain

## Fisher algometer



## The bottom line in feline pain determination

- Acute pain
  - Respiratory rate
  - Respiratory character
  - Heart rate
  - Interactive behavior score near and far from area of interest
  - Adminster an analgesic and watch response
- Chronic pain
  - Appetite?
  - Movements?
  - Interaction with owners normal?
  - Urinary and bowel habits?
  - Administer an analgesic and watch response

## A great way to determine the presence or absence of pain

- Document pre-existing state
- Administer an analgesic
- Note and document response
  - Spontaneous behaviors
  - Induced or reactive (interactive) behaviors
  - Physiologic parameters
    - Heart rate and rhythm
    - Respiratory rate and character

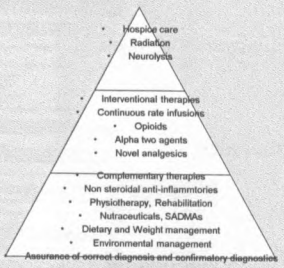
## What to administer?

- Hydro or Oxymorphone 0.05-0.1mg/kg SQ
- Buprenorphine 0.01-0.02mg/kg SQ or lingual
- Morphine 0.1-0.2mg/kg IM
- Meloxicam 0.1-0.2mg/kg
- Dexmedetomidine 5-10mcg/kg lingual, SQ, or IM

## Other factors which have great impact on pain control for cats

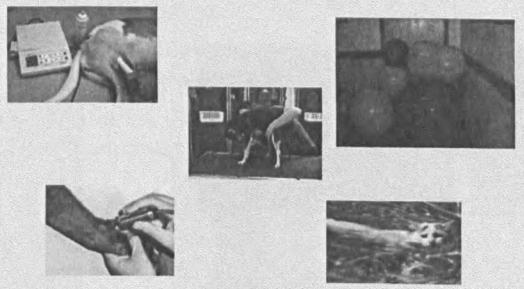
- Hydration and volume status
- Blood presure control
- Stress reduction
- Nutrition
- Electrolytes
- Glucose
- Movement
- Urinary and bowel habits
- Sleep

## Drugs and therapies used to treat feline pain

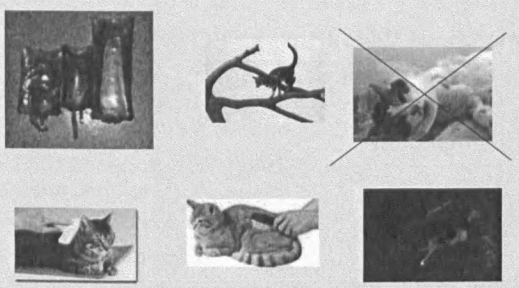



## Slow Acting Disease Modifying Agents

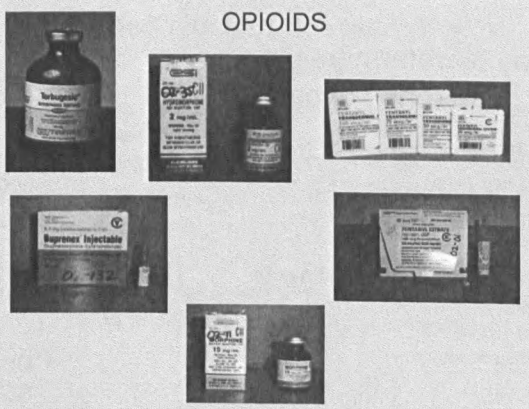

## Feline physiotherapy



## Feline physiotherapy



## OPIOIDS



## Opioid usage

**For typical acute analgesia**

- Buprenorphine 0.02mg/kg lingual, SQ, IM, IV q. 12 hr
  - Alternate with nsaid and/or dexmedetomidine
- Morphine 0.1-0.2mg/kg IM or SQ q. 12 hr
  - Alternate with nsaid and/or dexmedetomidine

**For typical premed, pre anesth**

- Buprenorphine 0.02mg/kg IM or IV
- Hydromorphone 0.05mg/kg IM, IV, SQ
- Morphine 0.1-0.3mg/kg IM
  - All with dexmedetomidine and/or nsaid

## Opioid usage

- For typical chronic analgesia:
  - Buprenorphine 0.01-0.02mg/kg buccal mucosa sid to bid
  - Oxycodone 5mg/5ml syrup: 0.05-0.1mg/kg orally sid to bid
  - Methadone 0.05-0.1mg/kg sq sid to bid
  - Oxymorphone 0.05-0.1mg/kg sq sid
  - Fentanyl patch 12.5 and 25mcg/hr q. week

## ALPHA TWO AGENTS


## Alpha two agonist usage

**For typical acute analgesia**

- Dexmedetomidine 3-10mcg/kg q. 12 hr buccally, SQ
- Medetomidine 7-15mcg/kg q. 12 hr buccally, SQ
  - either alternate with opioid of choice +/-nsaid sid

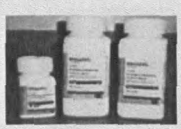
**For typical premed, preanesthesia**

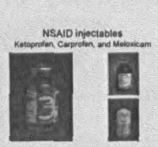
- Dexmedetomidine 10-20mcg/kg
- Medetomidine 20-30mcg/kg
  - Either with opioid of choice +/- nsaid

## Alpha agonist usage

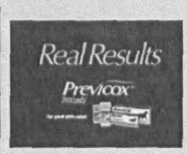
- For typical chronic analgesia
  - Dexmedetomidine 3-10mcg/kg buccally sid to bid
  - Given alternating with
    - opioid
    - nonsteroidal of choice

## NSAIDS



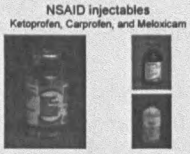







## My favorite acute NSAID options

- Meloxicam 0.1mg/kg SQ, IV, PO q. 2 days for 2-3 doses
- Carprofen 1mg/kg SQ, PO q. 2 days for 2-3 doses
- Flunixin 0.25mg/kg SQ q. 2 days for 2-3 doses
- Ketoprofen 1mg/kg SQ q. 2 days for 2-3 doses



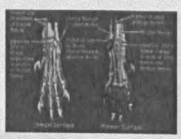

## My favorite chronic NSAID options

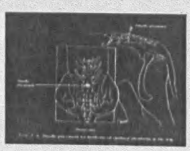
- Meloxicam 0.05-0.1mg/kg PO q. 2-4 days
- Aspirin 5-10mg/kg PO q. 2-4 days
- Ketoprofen 0.2-1m/kg PO q. 3-5 days
- Carprofen 1mg/kg PO q. 2-4 days

## Adequan for cats

- Indications
  - Osteoarthritis
  - Tendonitis
  - Polymyositis/myopathy
  - Chronic toxoplasmosis
  - Chronic cystitis
- Doses
  - 4mg/kg lean bw sq every 4-7 days for one month

## LOCOREGIONAL BLOCKS

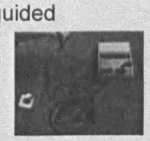





## Locoregional blockade can be performed blindly or guided

- Blind blockade
  - Pick nerve or plexus
  - Dilute local anesthetics
  - Deliver
    - with eyes open
- Ultrasound guided

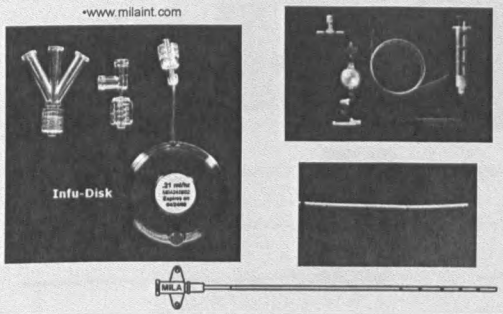
- Electrostimulation guided



## Common blocks, common doses

- Bupivicaine 0.2mg/kg with Lidocaine 1mg/kg and saline to dilute if needed
- Saline:
  - Reduces toxicity potential
  - Reduces sting
  - Spreads the love

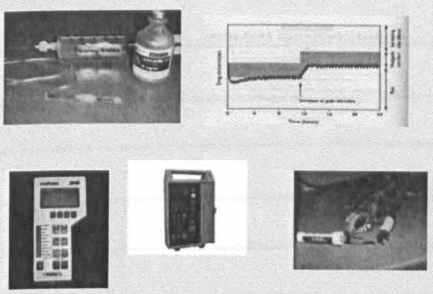
## Catheters extend life of local blockades for acute pain




## Different additives extend the life of local blockades for chronic pain=neurolytic blocks

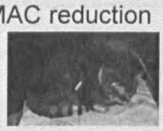
- Sarapin
- Alcohol
- Ammonium chloride
- Triamcinalone
- Methylprednisone

## Continuous rate infusions



## My favorite intraop infusion rates

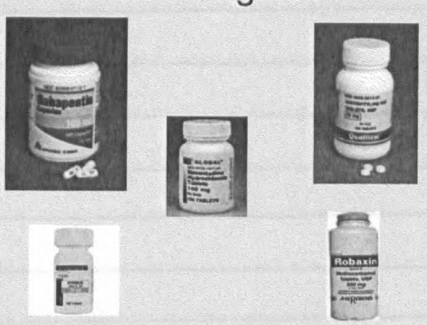
- Fentanyl-expect MAC reduction
  - 0.3-0.5mcg/kg/min
- Remifentanil-expect MAC reduction
  - 0.3-0.7mcg/kg/min
- Ketamine
  - 3 mcg/kg/min
- Dexmedetomidine-expect MAC reduction
  - 0.5 mcg/kg/HOUR



## My favorite post op infusion rates

- Fentanyl
  - 0.1mcg/kg/min
- Lidocaine
  - 5mcg/kg/min
- Ketamine
  - 1-3mcg/kg/min
- Dexmedetomidine
  - 0.5-2mcg/kg/HOUR

## Novel agents



## Transdermal gels

## Going into feline practice? Have these by your side

# Veterinary Oncology Pain Assessment and Treatment

Andrea Looney

## Where does oncologic pain originate?

- Etiologies:
  - That produced directly by the tumor (70%)
    - What you will learn about in next couple o' slides
  - That due to various modalities of therapy (20%)
  - That related to chronic debility (10%)
  - That related to non malignant concurrent disease (10%)

**TABLE 3–1 Chemotherapy-Induced Dysfunction and Pain Syndromes**

| Chemotherapeutic agent | Toxicity | Impact on pain |
|---|---|---|
| Vinca alkaloids (vincristin, vinblastin) | Neurologic | Peripheral neuropathy (glove and stocking distribution), autonomic neuropathy (abdominal pain, constipation, paralytic ileus, urinary retention, and orthostatic hypotension) |
| Paclitaxel/Docetaxel | Bone marrow depression, neurologic | Neutropenia, mucositis (painful mouth ulcerations), peripheral neuropathy |
| *Platinum complexes (cisplatin, carboplatin)* | *Renal, bone marrow depression, neurologic* | *Decrease creatinine clearance, peripheral neuropathy* |
| Etoposide | Bone marrow depression | Leukopenia, thrombocytopenia, mucositis (high dose) |
| Nitrogen mustards (mechlorethamine, chlorambucil, cyclophosphamide, ifosphamide) | Bone marrow depression | Leukopenia, thrombocytopenia, hemorrhagic cystitis (cyclophosphamide) |
| Anthracycline antibiotics | Bone marrow suppression, cardiac | Leukopenia, thrombocytopenia/anemia (less severe), stomatitis, cardiac arrhythmias, congestive heart failure |
| Mitoxantrone | Bone marrow suppression | Mucositis |
| Cytarabine | Bone marrow suppression, neurologic | Granulocytopenia/thrombocytopenia, peripheral neuropathy (high doses) |
| *Methotrexate* | *Bone marrow suppression, renal* | *Pancytopenia, mucositis (early indicator of toxicity), chronic renal failure* |
| Bleomycin | Pulmonary | Mucositis (dose-related), lung fibrosis |

Miguel RV Initial approach to the patient with cancer pain in De Leon-Cassasola OA ed. Cancer Pain, Saunders Philadelphia 2006.

**How much pain do various tumors cause?**

De Lorimier LP, Fan TM. Understanding and recognizing cancer pain in dogs and cats, 2005

## Chronic cancer pain is more difficult to evaluate (vs. acute pain)

- Quality of life scores, scales and questionnaires
- Behavior characteristics assessment
- Owner input essential
- *Abnormal gait or posture*
- Sleep or insomnia
- Altered appetite
- General attitude
- Care for daily activities
- Tail and ear carriage
- Family interaction
- Agitation potential
- Urinary and bowel habits

## Edmonton Staging System for Cancer Pain

- *Mechanism of Pain*
  - Nociceptive, neuropathic, mixed and unknown
- Pain characteristics
  - Nonincidental or incidental
  - Breakthrough
- Anxiety
  - Little or major
- Tolerance
- Overall health

Stage 1: good prognosis
Achieves a lot of relief with Simple analgesics
OR
Stage 2: poor prognosis
Achieve some relief with analgesics

## The physical exam of a chronically painful veterinary patient: extras related to cancer diagnosis and treatment

- Where are we in the animal's cancer treatment protocol?
- What are the implications of the protocol on the animal, its pain, its treatment options?
- What clinical conditions can I expect with the cancer and with the protocol?
- *Any new pain in a patient with a history of cancer is a recurrence of the cancer until proven otherwise*

**TABLE 3–3 Clinical Conditions in the Cancer Patient**

| Dysfunctional Organ System | Etiology | Impact on Pain Therapy |
|---|---|---|
| Constitutional | Tumor-induced wasting, anorexia, nausea/vomiting chronic fatigue syndrome, anemia of cancer/chemotherapy | Hypoalbuminemia (decreases protein binding, increases plasma free fraction), tolerate oral medications |
| Hematologic | Anemia, thrombocytopenia, neutropenia | Excessive fatigue, coagulopathy and interventions, infections with analgesic implants |
| Head, eyes, ear, nose, and throat | Irradiation, postsurgical (laryngectomy) | Difficulty/inability swallowing oral medications, xerostomia (oral transmucosal medications) |
| Lung | Smoking history, asthma, chemotherapy (bleomycin [pulmonary fibrosis]) | NSAIDs, central alveolar hypoventilation (opioids) |
| Cardiac | Hypertension, coronary artery disease/prior myocardial infarction, prior mediastinal irradiation, chemotherapy (daunorubicin, doxorubicin) | NSAIDs hypertension, edema, congestive heart failure, adrenergic antidepressants, electrocardiogram changes |
| Renal | Idiopathic, chronic (e.g., long-standing hypertensive), chemotherapy/NSAID-induced | Drug elimination/toxicity, diagnostic studies with contrast |
| Neurologic | Postsurgical, chemotherapy (cisplatin, vinca alkaloids, peripheral neuropathy), central nervous system irradiation, sleep disturbances | |
| Gastrointestinal | Postsurgical (e.g., "short gut," ostomies) | Drug absorption (e.g., slow release opioids) |

NSAID, nonsteroidal anti-inflammatory drug.

Miguel RV Initial approach to the patient with cancer pain in De Leon-Cassasola OA ed. Cancer Pain, Saunders Philadelphia 2006.

## Acute and chronic pain syndromes with cancer

- Acute pain syndromes
  - Commonly due to diagnostic and therapeutic interventions
  - Easier to diagnose

  - Epidural puncture soreness
  - Prostatic biopsy pain
  - Postoperative pain
  - Cytotoxic infusion pain
  - Mucositis
  - Radiation burn
  - Joint and neuropathy pain
  - Infection pain
  - Thrombosis pain

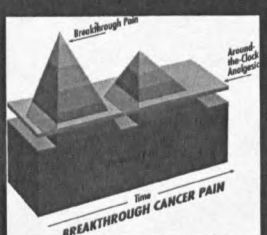
## Acute and chronic pain syndromes with cancer

- Chronic pain syndromes
  - Caused by direct tumor infiltration
  - May be caused by surgery, chemors, radiation therapy
  - May be caused by pathology unrelated to cancer (debilitating disease)
  - Difficult to diagnose

  - Bone pain
    - Metastases
    - Spinal or epidural compression
  - Arthritides
  - Muscle or trigger point pain
  - Headache
  - Neuropathy
  - Post surgical pain
  - Post radiation pain

## Acute and chronic pain syndromes with cancer

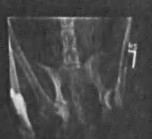
- Acute pain syndromes
  - Breakthrough pain
  - ½ to 2/3 of cancer pain patients experience
  - Episodes are usually short in duration but become more frequent as disease progresses
  - Types
    - Incident
    - Spontaneous
    - End of dose failure




## Poor prognostic factors for cancer pain management

Mneumonic: RAPID-N (Rapid Acceleration of Pain Indicates Damaged InterNeurons)

Rapid accelerating pain
Alcoholism
Psychological issues
Incidental or breakthrough Pain
Delirium or mental obtundation
Neuropathic Pain

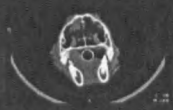


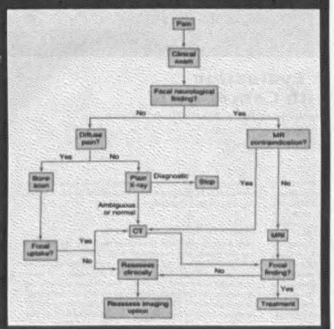
## Common diagnostics utilized

- Bloodwork
  - CBC, Chemistry, UA, urine C&S
- Sampling
  - Centesis, FNA, Biopsy, CSF analysis
- Imaging
  - Radiology, Ultrasound, Fluoroscopy, MRI, CT
- Special diagnostics
  - EMG, NCV
  - Scintigraphy
  - Thermography
  - Force platform and gait analysis
  - Muscle girth measurement
  - Behavioral assessment
  - -Algometry
  - -Goniometry
  - -Diagnostic nerve blocks
  - -Video analysis

## Oncologic pain imaging

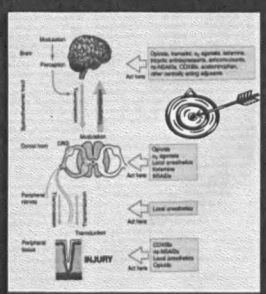
- Alberico RA, Abdel-Halim A, Husain SHS Neuroradiologic evaluation of the patient with cancer pain in deLeon-Casasola OA Cancer Pain, Saunders Philadelphia 2006






## Generalities regarding cancer pain treatment

- Basics of multimodal therapy
  - Drugs
  - Techniques
- Body offers different targets
  - We choose the arrows
  - We choose which target(s) to aim at
- Constant reassessment necessary
  - Rotation of drugs and techniques
  - Be open minded
  - Owners are resourceful and knowledgeable




## Acute care management

- The more acute or severe the pain, adherence to rules of critical care in initial evaluation and treatment is required

- Fluid balance
- Oncotic pressure
- Glucose
- Electrolytes (calcium, sodium, chloride, potassium, magnesium)
- Oxygenation and ventilation
- Level of consciousness and mentation
- Blood pressure
- Heart rate, rhythm and contractility
- Albumin
- Coagulation
- Red blood cell /hemoglobin concentration
- Renal function
- Immune status, antibiotic dosage and selection, WBC count
- GI motility and mucosal integrity
- Drug dosage and metabolism
- Nutrition
- Pain control
- Nursing care and patient mobilization
- Wound /bandage care
- Tender loving care

## Generalities regarding cancer pain therapy

- Goal is to stay one step ahead of pain
- The more unlikely solving the pain (terminal cancer pain!)
  - The more reasonable to remain on constant regular medication
    - Lowest dose and frequency possible to control the pain
    - Expect to increase both over time
    - Expect breakthrough pain
- Pain is what the owner says it is
  - Have them keep a diary
    - Location, actions of pet, when pain occurs, what makes it worse, what eases the pain,
  - Regularly scheduled recheck visits
    - Quality of life assessments important!

## Generalities of QOL care

- Lifetime nutritional management
- Supplements/nutraceuticals can really assist
- Eliminate environmental carcinogens
- Talk to the family, change the environment
- Prevent nausea, vomiting, diarrhea, constipation
- How is the bladder working?
- What is the animal's sleep and awake cycle?
- Prevent anorexia and cachexia; engage the nutritionist
- Assure mental stability; treat stress

## Generalities of QOL care

- Complementary treatments imply just that
- Complementary treatments are useful
- Transdermal medications may work
- Home parenteral care may be needed
- Mucositis needs to be treated aggressively
- Dermatologic disease needs to be treated aggressively
- Watch your white blood cell counts
- Learn to embrace imaging modalities
- Prepare the owner for realistic outcomes

## How to treat cancer pain

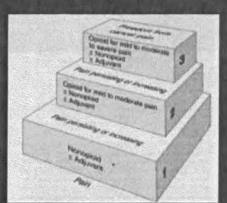
- Severity based treatment
  - WHO ladder treatment philosophy

You are here

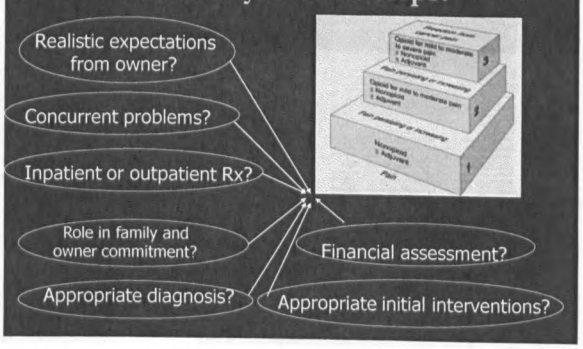
- Mechanism based treatment
  - Ex. Rapid DNA typing that guides antibiotic therapy

## Problems with the WHO ladder and veterinary oncology pain therapy

- Why the WHO ladder no longer works
  - Multidimensional aspects of modern cancer and pain treatment >> a more complex ladder
  - Imaging modalities have taught us much
  - Replace it with escalator based on
    - individual needs
    - Multimodal therapies
    - Preferences
    - likely responses based on what we know

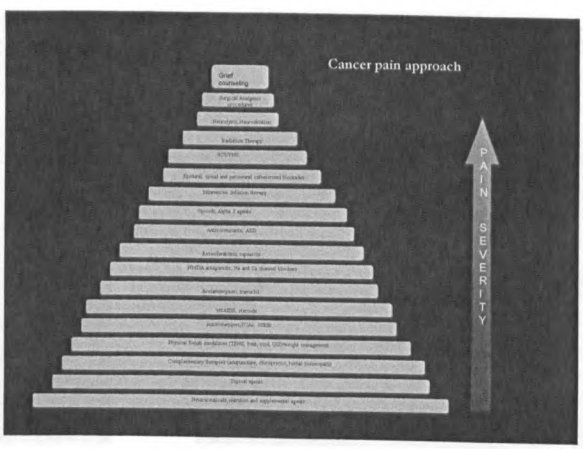


## The veterinary pain ladder has unsteady bottom steps!




## How to treat cancer pain

- Sequence of analgesic therapy should be based on taxonomy of INDIVIDUAL cancer pain
  - Rather than an epidemiologic based approach based on intensity of pain (WHO ladder)
  - Therapy should be guided by classification systems
    - IASP
    - Edmonton
    - Overall health/lifestyle of patient
    - Cancer therapies outside of pain management



# Typical cancer pain relief agents

OPIOIDS

ALPHA AGENTS

NSAIDS

## Opioids in vet oncology pain therapy

- Best pain relievers for acute and severe pain
  - PURE MU AGONISTS
- Side effects
  - GI
  - GU
  - Resp depression?
- Can be used parenterally, orally, neuraxial, locally
- Reversible if needed
- Controlled!
- Oral forms limited
- Few if any contraindications

FIRST LINE ANALGESICS for SEVERE PAIN REGARDLESS Of animal's health status

Kappa agonist, Mu antagonist

More potent Mu agonist

Mu agonist

## Which are the best opioids?

Partial Mu agonist


Most potent Mu agonist

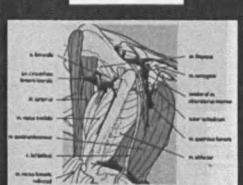

## Neuraxial opioids

Spinal or epidural opioids

- Little systemic absorbtion
- Decreased side effects
  - Less nausea
  - Less ileus
  - Urinary retention +/-
- Analgesia for days to weeks
  - With catheters
  - With automated pumps
- Can be used at home for patients

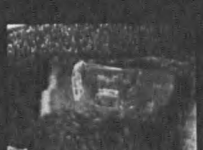

## Locoregional opioids

- Buprenorphine added to the local anesthetic for axillary brachial plexus block prolongs postoperative analgesia. Candido KD, Winnie AP, Ghaleb AH, Fattouh MW, Franco CD: Reg Anesth Pain Med. 2002 Mar-Apr;27(2):162-7
- [1]2 The addition of opioids to local anaesthetics in brachial plexus blocks: the comparative effects of morphine, buprenorphine and sufentanil. Bazin JE, Massoni C, Bruelle P, Fenies V, Groslier D, Schoeffler P: Anaesthesia. 1997 Sep;52(9):858-62



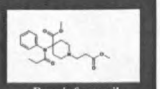
## Fentanyl transdermal patches

- Applied to shaved, cleaned areas
- Even though a potent form of narcotic, one of the poorest delivery methods
  - Provides "background" analgesia
  - Needs to be supplemented
  - Expensive
  - Variable absorbtion
  - Duration
    - 3 days canine
    - 5-6 days feline

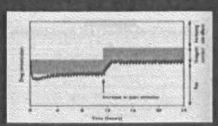



## Opioids in continuous rate infusions

- Best pain relievers for acute severe pain
- Titrability key factor
- Fentanyl and remifentanil of great benefit for ICU/CCU patients
- Often combined as part of mixed analgesic infusions (ex. MLK or FLK)
- Caution with metabolites, potency, accumulation



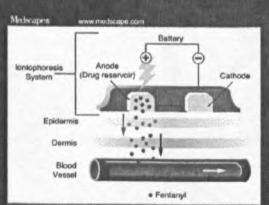
Reminfentanil



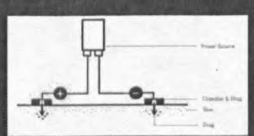
## Transmucosal buprenex in cats


- Robertson SA, et.al. 2002
- Alkalinity of saliva
- Systemic uptake of buprenorphine after buccal administration
  - Comparable to IV administration
- Pharmacokinetic data suggests 100% bioavailability
- Thermal threshold increased

## Fentanyl iontophoresis systems

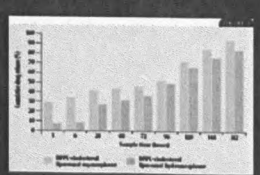






*Extended-Release Liposomal Opioids for Treating Pain in Dogs 2005*

**Lesley J. Smith, DVM, DACVA**
**Dept of Surgical Services, SVM, University of Wisconsin, 2015 Linden Dr., Madison, WI 53706**



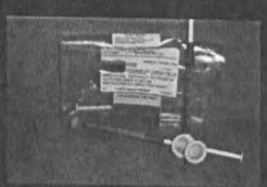
## Suppository opioids

- **Pharmacokinetics, pharmacodynamics, and analgesic effects of morphine after rectal, intramuscular, and intravenous administration in dogs.**
- Barnhart MD, Hubbell JA, Muir WW, Sams RA, Bednarski RM.
Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University
Columbus 43210, USA

- Bioavailability not much improved compared to oral use

## PLO transdermal gels and cremes with opioids

- Compounded regularly
- Ease of use for animals with limited oral intake
- Side effects lessened
- Danger with human absorbtion
- Therapeutic blood concentrations rarely met at similar parenteral doses
- Subjective owner assessment variable
  - Good to very good for selected agents
  - Usually requires a higher dose vs. oral dosing



## Oral opioids

- Tramadol 1-3mg/kg po tid to 3-5mg/kg po tid
  - Not that effective
  - *Not for cats*
- Codeine 0.1-1mg/kg po bid
  - Constipation in dogs
  - Combined with tylenol usually
- Hydrocodone 0.05-0.2mg/kg po bid
- Oxycodone 0.1mg/kg po sid-tid
- ER morphine 0.1mg/kg po sid

## Methadone

- Mu agonist opioid
- NMDA antagonist
  - Added benefit
- Similar to morphine
  - More panting
  - Less nausea and vomiting
  - Less dysphoria
- Used extensively in Europe

Lebetseder EN. A comparison of epidural and IV methadone on intraop isof and postop analg requirements in dogs VAA 2006

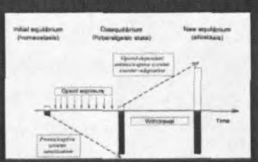
Rohrer Bley C. Comparison of perioperative racemic methadone, levomethadone, and dextromoramided in cats VAA 2004

## Opioid hyperthermia in cats

- Often seen with hydromorphone use
  - Repetitive dosing
- Can be seen with morphine use
- Common when opioids combined with other drugs
  - *ketamine*
- What to do?
  - Stop opioid
  - Fluids
  - Phenothiazines
  - Environmental methods
  - Tincture of time (3-6 hours)

## Opioid hyperalgesia

- Increasing pain in patients that have been "well controlled" on opioids
- First sign of tolerance
- Proposed mechanisms
  - Imbalance between anti and pronociception
  - Toxic effects of metabolites
  - Activation of NMDA receptors via glutamate
- Most likely seen with
  - Morphine
  - Hydromorphone

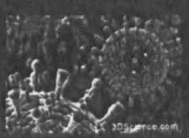


**Angst MS, Clark JD Opioid Induced Hyperalgesia. Anesthesiology 2006**

**Diagnosis: increase dose of opioids and see increased pain**

## Opioid immunosuppression

- Activation of CNS opioid receptors
  - Activates HA axis
- Inhition of NK cells
  - PAG area
  - Sympathetic outflow implications
- Endogenous opioids
  - *Increase* production of Th2
  - Inhibit macrophage cytokine IL-12
  - IL-12 necessary for Th1 production
- Exogenous opioids
  - Inhibits production of IL-10 and IL-12



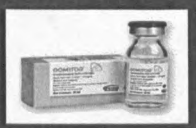
## Opioid histamine release

- **Evaluation of histamine release during constant rate infusion of morphine in dogs.**
  - Gonzales AG, Riede LP, Rider MA
- Department of Veterinary Clinical Science, College of Veterinary Medicine, University of Minnesota, *Saint Paul, MN*
- OBJECTIVE: To evaluate histamine release and selected physiologic variables during constant rate infusion (CRI) of morphine in dogs. ANIMALS: Five healthy, conscious, intact female dogs. MATERIAL AND METHODS: Using a Latin square, repeated measures design, dogs were randomly assigned to three treatment groups to receive a 4 hour CRI of saline (SAL), or a loading dose of morphine at 0.3 mg/kg/ IV (LM), or 0.6 mg/kg/ IV (HM), followed by an infusion of 0.17 mg/kg/ IV hour/ IV (LM) and 0.34 mg/kg/ IV hour/ IV (HM) respectively. Dogs received each of the three treatments at intervals of at least 7 days. Plasma histamine concentration, skin flushing, edema and wheals, heart rate and rhythm and non-invasive arterial blood pressure were measured before the loading dose and at 1, 2, 5, 15, 30, 60, 120, 180 and 240 minutes during the CRI, or at the time of cessation. RESULTS: The loading dose induced the highest histamine release in the HM group being statistically higher than the SAL group. The histamine release obtained in the LM group after the loading dose did not differ from SAL. During the infusion, plasma histamine levels were numerically higher in the LM group. Besides one dog that developed hypotension for 2 minutes after the loading dose in the HM group and one dog that showed occasional ventricular premature contractions during both morphine infusions, cardiovascular variables were similar among the three treatment groups. CONCLUSIONS AND CLINICAL RELEVANCE: Both doses of morphine induced variable histamine release with minimal adverse cardiovascular effects in these conscious, healthy dogs. The plasma histamine levels obtained may be associated with significant hemodynamic changes in patients with limited cardiovascular reserve and sympathetic nervous tone.

## Alpha two agonist agents in vet oncology pain therapy

**Dexmedetomidine**

- Provides analgesia and stress/anxiety relief
  - Alleviate dysphoria!
- Potent cardiovascular side effects at even mini-dose
- Used for moderate to severe pain
- Reversible
- Not controlled
- Usually given as part of a balanced regimen
- Relative and absolute contraindications
- Micro or mini dose employed

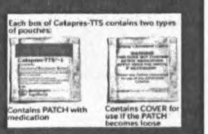


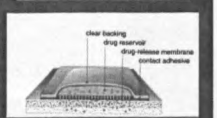
## The beauty of dexmedetomidine for chronic pain control

- Can be given mucosally
  - Works excellent in cats and exotics, moderately well in dogs
- Provides stress relief, relaxation, sedation
  - Things the opioids don't provide
- Provides rotation from opioids
  - Given opposite to opioids
- Problems: human absorbtion from mm, injectable only avail, cardiac output decrease (is this a problem???)

## Clonidine

- Antihypertensive agent
- Used in human cardiovascular and pain management
  - oral, epidural, local and transdermal forms
- Significant cardiovascular effects possible
  - ?probable
  - Dose related
- Often used in combination with other agents
  - Epidurals
  - Local block cremes
  - Patch




## Alpha two agonist side effects

- Decreased cardiac output
  - Bradycardia
  - Initial hypertension followed by hypotension
  - Unlike the opioids, alpha two agents are not "cardiac soothing"
- Mild respiratory depression
- Mild gastrointestinal effects

## NSAIDs in vet oncology pain therapy




NSAID=nonsteroidal anti-inflammatory drug

- Antipyretic
- Anti-inflammatory
- Analgesic
- Anti-thrombotic
- Used for mild to moderate pain
- Not regulated or controlled
- Oral and injectable forms available
- Relative and absolute contraindications

## NSAIDs in vet oncology pain therapy


## Classes of NSAIDS (terminology)

- ***NONselective NSAIDS***
  Inhibit both COX-1 and COX-2
  Ex. Aspirin, Flunixin
- ***Preferential NSAIDS***
  Inhibit COX-1 and COX-2, but less COX-1
  Ex. Carprofen, meloxicam
- ***Dual acting NSAIDS***
  Inhibit both COX-1, COX-2 and LIPOXYGENASE
  Ex. Tepaxolin
- ***Selective NSAIDS***
  Inhibit COX-2 only
  Ex. Deracoxib, firocoxib

## NSAID side effects are due to "good" COX & LOX enzyme inhibition

- Interference with PG of normal gastric homeostasis → Gastric ulceration
  - Increases gastric acid
  - Decreases gastric mucous production
- Interference with PG of renal blood flow → Renal ischemia
  - Reduced renal medullary blood flow
  - Renal papillary necrosis
  - Controversial whether to use preoperatively
- Inhibition of platelet function → Coagulopathy
  - Inhibits platelet plug by inhibiting thromboxane $A_2$
  - Aspirin affects are permanent (life of platelet)

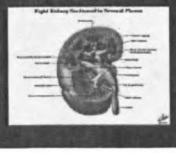
## Contraindications for use of NSAIDS

***Avoid use in:***

- Renal failure
- Dehydration, hypovolemia, hemorrhage
- Severe liver dysfunction
- History of gastric ulceration
- Coagulopathy
- Pregnancy
- Neonatal patients

***Use with caution, reduced dose or increased dosing interval in:***

- Renal insufficiency
- Impaired liver function
- Asthmatic patients



## Use of NSAIDS as part of cancer therapy

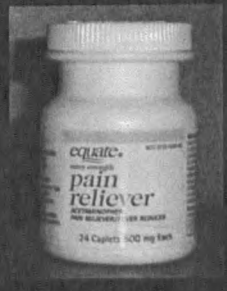
- Many NSAIDs possess antiangiogenic properties
- COX-2 is expressed in many cancers
  - Epithelial in origin tumors
  - In stromal tissues surrounding tumors
- In vitro work shows enhanced activity of chemo and radiation rx with cox-2 inhibitors
- NSAIDs seem able to protect and prevent against gastric and esophageal tumors


## COX-3 isoform

- Simmons D, et.al. Proc Nat Acad Sci 2002
- COX-1 variant or isoform expressed in high amounts in brain and heart
  - Constituitively and pathologically
- Acetaminophen (mechanism of action)
  - Poorly inhibits COX-1 and COX-2
  - Greatly inhibits COX-3
- May be a Partial COX-1 or COX-1 pre-protein
  - abundant in canine brain

## Acetaminophen

- Not an anti-inflammatory!
  - Grouped with NSAIDS
- Good analgesic in dog
- Excellent antipyretic in dog
- Will not cause GI ulceration, renal disease or platelet dysfunction
- Inhibits COX-3 or COX variant
- Inhibits NO synthetase
- Hepatic function (glutathione) must be adequate



## Cats and nonsteroidals

- Generally use lower doses than in other species
- Consider specific need (antithrombotic vs. anti-inflammatory vs. antipyretic) and modify dose
- Use longer dosing intervals (2-7 days) with chronic use
- Assess for subclinical renal impairment
- Provide fluid support perioperatively
- DO NOT USE ACETAMINOPHEN in cats!!!!


## NSAID transdermal patches

- Maziere B. Drugs R D. 2005
  - Topical ketoprofen patch.
  - Although oral nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the treatment of a variety of acute and chronic pain conditions, their use may be associated with serious systemic adverse effects, particularly gastrointestinal disorders. In order to minimize the incidence of systemic events related to such agents, topical NSAIDs have been developed. Topical NSAIDs, applied to gels, creams or sprays, penetrate the skin, subcutaneous fatty tissue and muscle in amounts that are sufficient to exert a therapeutic effect on peripheral and central mechanisms in the absence of high plasma concentrations. Data indicate that topical NSAIDs are effective at relieving pain in a number of acute and chronic pain indications. This review article discusses the pharmacokinetics, efficacy and tolerability of a new formulation of ketoprofen available as a topical patch. The topical patch containing ketoprofen 100mg as the active principle has been developed using a novel delivery system that dispenses therapeutic doses of the drug directly to the site of injury. Pharmacokinetic data indicate that although plasma levels of ketoprofen are higher when the drug is administered as a patch versus a gel, the total systemic bioavailability of ketoprofen 100 mg administered via a patch is no more than 10% of that reported for ketoprofen 100 mg administered orally. Because the patch facilitates ketoprofen delivery over a 24 hour period, the drug remains continually present in the tissue adjacent to the site of application. High tissue but low plasma ketoprofen concentrations mean that while tissue concentrations are high enough to exert a therapeutic effect, plasma concentrations remain low enough to not result in systemic adverse events caused by elevated serum NSAID levels. Phase III clinical trials in patients with post-articular distortions and traumatic painful soft tissue ailments showed that the topical ketoprofen patch was significantly more effective than placebo at reducing pain during daily activities and spontaneous pain after 7 days' treatment. Moreover, the topical ketoprofen patch was well tolerated; adverse events were primarily cutaneous in nature and occurred in a similar number of ketoprofen and placebo recipients, suggesting that these events were related to the patch itself rather than the active ingredient. The incidence of gastrointestinal adverse events was low (< 8% of all patients), and occurred in a similar proportion of patients receiving ketoprofen and placebo. Thus, the topical ketoprofen patch appears to be a simple, effective and safe therapeutic option for the treatment of local painful inflammation.

## NSAID transdermal cremes

- 1% diclofenac in a liposomal crème
- Shown to improve lameness scores in horses
- Reduces systemic side effects
- Must be applied with gloves
- Studies performed in canine patients
  - Budsberg SC, Lynn RC unpublished results in dogs
  - No statistical difference in force plate analysis
  - Subjective difference noted by owners for dogs using crème

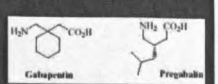


## NOVEL AGENTS FOR CANCER PAIN RELIEF

## Gabapentin

- Anti-convulsant drug
- GABA analog
- Used to manage peripheral and central neuropathic and chronic pain
- Recommended in chronic pain that is unresponsive to NSAIDs

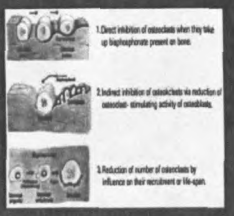

## Pregabalin=lyrica




- Another anticonvulsant
- Calcium channel modulator
- Similar to gabapentin except…
  - Less side effects
  - Lower effective dosage 0.1-0.2mg/kg po bid
  - "opioid" like effect
  - Controlled
  - Expensive

## Bisphosphonates for vet oncology pain therapy

- Inhibit osteoclast activity
  - Altered morphology
  - Via clinging (tightly) to calcium phosphate crystals in bone
- Best are administered IV over a 2 hour period monthly (pamidronate)
- Animal needs good renal function or diuresis to receive
- Also used to treat hypercalcemia of malignancy




http://www.roche.com/pages/facets/9/osteo.htm

## Long term Locoregional blockade for vet oncology pain therapy

- Neurostimulation location
- Ultrasound location
- Catheter placement

- Surgical blockade
- Palliative blockade
- Neurolytic blockade

## Infusion systems for indwelling epidural, spinal and nerve catheters

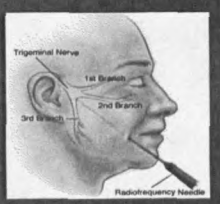


## Long term or neurolytic blockade constituents

- Local anesthetics
  - Butamben
  - Lidocaine 2 and 5 %
  - Bupivicaine
- Saline
- Microdose
  - alpha two agonist
  - steroid
  - NMDA antagonist
- Alcohol/phenol
- Glycerol
- Ammonium salts
- Sarapin

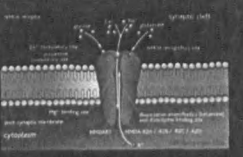
## Radiofrequency blockade for analgesia

- Originally used for disk related pain
- Destruction of nerves that transmit or perpetuate pain should relieve pain
- Compared with direct current
  - Uniform lesioning
  - Predictable lesioning
  - Not complicated by gas of electrolysis
- Useful for Well defined localized area of pain
- May be associated with motor deficits




## NMDA blockade for vet oncology pain therapy

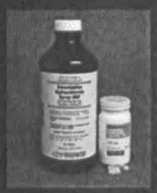
- NMDA receptor
  - One of main excitatory pathways for nerve transmission
    - Via glutamate activation
    - Via calcium influx
- Function
  - Passage of calcium, sodium, and potassium
    - Calcium influx causes central sensitization or "windup"
- NMDA antagonists help to reduce chronic pain
  - Ketamine, Amantadine, Memantine
  - Noncompetitive blockade
  - Reduces calcium influx



## NMDA blockade for vet oncology pain therapy

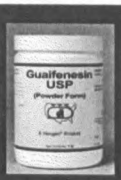
### Amantadine

- Anti-viral drug
- Non-competitively blocks NMDA receptors
- Blocks amplification of pain signals and prevents wind-up (central hypersensitization)
- Treatment of pain of neuropathic origin



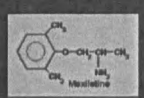
## NMDA blockade for vet oncology pain therapy

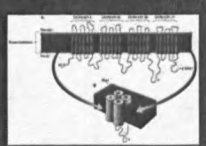
- Dextromethorphan
  - 1-2tsp per dog TID
  - 1-2 mg/kg TID-QID cats and dogs
- +/- guaifenesin
- Weinbroum AA Cancer 2002
  - 75 patients with bone and soft tissue malignancies
  - 3 groups
  - Dextromethorphan groups
    - 50-80% less sub pain
    - 50-70% less PC morphine
    - 70% less sedation


## Sodium channel blockade in vet oncology pain therapy

- Sodium channel
  - TTXr subtype
  - TTXs subtype
- Blockade via
  - Prevention of upstroke of axon action potential
- Peripheral and central activity
  - Anti-inflammatory action as well
- Na channel blockade results in analgesia
  - Neuropathic and nociceptive pain



## Lidocaine infusion for chronic pain

INTRAVENOUS LIGNOCAINE INFUSION For
NEUROPATHIC PAIN IN CANCER PATIENTS– A PRELIMINARY STUDY

INDIAN JOURNAL OF ANAESTHESIA, OCTOBER 2002 360 Indian J. Anaesth. 2002; 46 (5) : 360-364

Dr. Anjum S. Khan Joad, Dr. Jyoti Burad,Dr. Charu Mehta

The effectiveness and duration of pain relief with a continuous lignocaine infusion was observed in 10 cancer patients. All the 10
patients were suffering from pain of neuropathic origin, having two or more of the symptoms: burning, aching, allodynia, reduced
sensitivity to touch or pain, hyperaesthesia, nightly exacerbation and sleep disturbance. The patients received intravenous lignocaine
in a dose of 5mgkg-1 in 1mlkg-1 of normal saline over 60 minutes. Significant relief in pain (t value> t at 0.01), dysaesthetic
sensations, paraesthesias and nightly exacerbations were seen in the majority of patients upto 14 days. Statistical analysis were
performed using the unpaired 't' test and analysis of variance (through application of x2 test).
Keywords : Lignocaine infusion, Neuropathic pain, Cancer pain.

## Lidocaine infusion for chronic pain

**Efficacy of 5-day continuous lidocaine infusion for the treatment of refractory complex regional pain syndrome.**

Pain Med. March 2009;10(2):401-12.
Robert J Schwartzman, Mona Patel, John R Grothusen, Guillermo M Alexander

Chronic regional pain syndrome (CRPS) is a severe pain condition that usually results from an injury or surgical procedure. The pain in CRPS often spreads from the site of injury, and with time becomes refractory to conventional therapy. The present study was undertaken to evaluate the effects of 5-day continuous intravenous lidocaine treatment in patients afflicted with CRPS. METHODS: Intravenous lidocaine was administered in an escalating dose schedule to 49 severely affected CRPS patients in a monitored setting over 5 days. Evaluation of pain parameters and other signs and symptoms of CRPS were obtained during the infusion and at 1, 3, and 6 months following therapy. RESULTS: The majority of patients demonstrated a significant decrease in pain parameters and other symptoms and signs of CRPS. The pain reduction lasted an average of 3 months. Lidocaine may be particularly effective for thermal and mechanical allodynia. Less clinically significant effects were documented on the motor aspects of the syndrome. DISCUSSION: Intravenous lidocaine administration titrated to 5 mg/L demonstrated: 1) a significant decrease in mechanical and thermal allodynia for three months, 2) lessened associated inflammatory components of CRPS, and 3) only minimal side effects and no severe complications.

## Lidocaine patches

- 5% lidocaine patches
- Applied to intact skin
- Used in humans for treatment of postherpetic neuralgia and shingles
- Studies show little systemic uptake in dogs, cats, and horses
- Depth of penetration limited
- Used extensively for musculoskeletal and trigger point therapy

## Calcium channel blockade in vet oncology pain therapy

- Calcium channels expressed on dorsal horn neurons
  - P/Q and L type Ca channels
  - N type Ca channels
- Neurotoxins which block the N Ca channel
  - Ziconotide (snail)
  - Huwentoxin (chinese bird spider)
- Other receptors decrease Ca flow through N channels
  - GABA via vagal neurons
  - NMDA receptors

## Resiniferatoxin and capsaicin in vet oncology pain therapy

- Resiniferatoxin
  - Derivative of cactus Euphorbia
  - Long lasting (permanent?) blockade
- Capsaicin
  - Active component to chili peppers
- TRPV1 receptor agonists
  - Peripheral
  - DRG
  - ganglia
- Induce calcium cytotoxicity
- Blocks inflammatory hyperalgesia and neurogenic inflammation

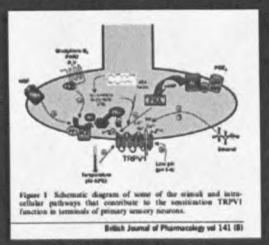



Figure 1 Schematic diagram of some of the stimuli and intracellular pathways that contribute to the sensitization TRPV1 function in terminals of primary sensory neurons.

British Journal of Pharmacology vol 141 (8)

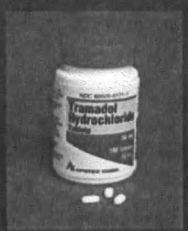
Geppetti P, Trevesani M Br J Pharmaco 141, 2004

## TCAs, SSRIs in vet oncology pain therapy

- Analgesic effects independent of anti-depressant effects
- Analgesia occurs at lower doses than expected for rx of depression
- Analgesia occurs due to
  - Blockade of NE and serotonin reuptake
    - Enhanced descending inhibition
  - Interaction of other types of receptors (ion channel, NMDA, histamine, cholinergic)

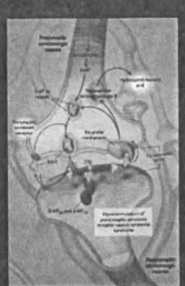
## Tramadol

- Analgesic and antitussive
- Weak mu partial agonist
- Inhibits 5-HT and NE reuptake
- Alpha-two agonist-like effect
- Metabolite (M1) is primarily responsible for analgesic effects.
- Partially reversible with naloxone or yohimbine
- Not a scheduled drug as compared to other opioids




## Serotonin syndrome

- Common Mechanisms of serotonin toxicity ="syndrome"
  - Stress or amphetamine like drugs increase serotonin release
  - Inhibition of serotonin metabolism by mao inhibitors
  - L-tryptophan or L-tryptophan precursors increases 5-HT production
  - Increases in synaptic 5-HT via reuptake inhibition



N ENGL J MED 352;11 WWW.NEJM.ORG MARCH 17, 2005

## Palliative radiation for vet oncology pain therapy

- Mechanisms of relief for osseous pain
  - Not well known
  - Cell kill?
  - Tumor shrinkage?
  - Inhibition of prostanoid secreting cells within microenvironment
  - Induction of TGF-B
- Basic approaches
  - Moderate dose regimen protracted
  - Low dose single shot

## Hospice

- Mobility
- Appetite
- Bowel and bladder function/control
- Vomiting/nausea/regurgitation
- Skin care and cleanliness
- Bleeding
- Sleep cycles
- Neurologic state