

## Features

Therapeutic Options for  
Ferret Lymphoma:  
A Review .....1

Natural History of  
the Guinea Pig .....7

Bunny Behavior 101:  
Aggression .....9

Guidelines  
for Authors .....10

Abstracts .....11

## Departments

News You Can Use .....6

Book Review  
*Textbook of Rabbit  
Medicine* .....8

Designed and published by  
Veterinary Learning Systems,  
780 Township Line Road,  
Yardley, PA

Copyright © 2003  
Association of Exotic Mammal  
Veterinarians.

## Therapeutic Options for Ferret Lymphoma: A Review

**Peter G. Fisher, DVM**

*Pet Care Veterinary Hospital  
Virginia Beach, Virginia*

**Angela Lennox, DVM**

*Avian and Exotic Animal Clinic of Indianapolis  
Indianapolis, Indiana*

Malignant lymphoma is a common diagnosis in pet ferrets. In a retrospective study of 574 ferrets with neoplastic disease, Li et al<sup>1</sup> found that 15.2% were hemolymphatic in origin, and of these, 78% were malignant lymphomas. Clinical signs vary with the location of the disease as well as the age of the animal. Lymphoma can affect numerous tissues, with the visceral and peripheral lymph nodes, spleen, liver, mediastinum, bone marrow, lungs, intestines, and kidneys being most commonly affected. Less frequently involved are the stomach, pancreas, nervous system, and orbit. Ferrets also can develop a rare form of dermal cutaneous epitheliotropic lymphoma.

It is likely that lymphoma in ferrets, as in other species, stems from a variety of causes including genetic, environmental, and infectious etiologies. Occasional cluster outbreaks in siblings or cohabitating ferrets suggest an infectious etiology. Erdman et al<sup>2</sup> have described horizontal transmission of lymphoma where naive ferrets developed disseminated lymphoma after inoculation with malignant lymphoid cells or a filtered cell-free supernatant from cultured malignant lymphocytes, suggesting a viral etiology. A specific viral agent, however, has not been isolated.

Clinical features of lymphomas in ferrets have been linked with animal age and tumor location. The most common form of lymphoma is a lymphocytic variant (where neoplastic cells are mature, well-differentiated lymphocytes)

seen in ferrets older than 3 years of age.<sup>3</sup> Lymph nodes are affected most commonly, resulting in peripheral lymphadenopathy. Visceral spread and subsequent organ failure may occur as the disease progresses. Clinical signs vary with which organs or systems are affected; however, most mature ferrets with lymphoma present with chronic, nonspecific abnormalities including intermittent inappetence, lethargy, and weight loss.<sup>4</sup> Other signs may include peripheral lymphadenopathy, posterior paresis, splenomegaly, chronic vomiting, and diarrhea.

A juvenile form of lymphoma, affecting ferrets 1 to 2 years of age, is typically an acute onset, multicentric lymphoblastic form of lymphoma characterized by large immature lymphocytes that infiltrate the visceral organs early in the course of the disease.<sup>3</sup> Splenomegaly, hepatomegaly, and thymic enlargement may all occur; however, peripheral lymphadenopathy is not a common finding. Clinical signs in young ferrets are often acute in nature and may mimic signs of a gastric foreign body (i.e., vomiting, dehydration, anorexia, and wasting). Ferrets with mediastinal (thymic) lymphoma may cough and present with dyspnea. Ferrets with alimentary tract involvement may present with varying degrees of anorexia, vomiting, or diarrhea with or without melena.

A third, relatively uncommon immunoblastic polymorphous form of lymphoma is seen in ferrets of any age and is characterized by lym-

phadenopathy and visceral organ involvement with short survival time after diagnosis.

## DIAGNOSIS

Diagnosis of lymphoma involves biopsy of affected lymph nodes or visceral organs with direct visualization of neoplastic cells and evaluation of cellular morphology. While cytologic examination of lymph nodes, spleen, thoracic effusion, or bone marrow aspirates can provide a preliminary diagnosis, it is generally less informative than histologic preparations because of disruption of tissue architecture.<sup>5</sup> In addition, the large fat pads surrounding ferret peripheral lymph nodes make obtaining an adequate sample via fine-needle aspiration difficult.

Further parameters to consider when making a diagnostic and treatment plan for ferret lymphoma include a complete blood count (CBC), platelet count, serum chemistry profile, bone marrow aspirate, whole-body radiographs (two views), and abdominal ultrasonography. In both the adult and juvenile forms, absolute lymphocyte counts may be elevated, normal, or below normal. Lymphocytosis is significantly more frequent in younger ferrets; lymphopenia is significantly more frequent in older ferrets.<sup>4</sup> Persistently elevated lymphocyte counts may also result from chronic antigenic stimulation, and the ubiquitous nature of *Helicobacter* or coronavirus infection in the U.S. ferret population has tremendous potential for inciting this nonspecific change in ferrets.<sup>3</sup> Mild anemia is common, and hepatic enzyme activity, hypoglycemia, and hypercalcemia have all been reported in ferrets with lymphoma.<sup>4</sup> Diagnostic aspirate or biopsy of the bone marrow is useful in diagnosing and assessing the progression of diseases of the hematopoietic system, including ferret lymphoma, and should be performed with any ferret with persistent lymphocytosis ( $>8,000$  cells/ $\mu\text{l}$ ). Abdominal radiographs or ultrasonography may reveal various degrees of visceral lymphadenopathy and organomegaly. Imaging of thymic lymphoma will often reveal pleural effusion and a cranial thoracic mass that displaces the heart and lungs dorsally and caudally.

## TREATMENT

Lymphoma should always be considered a systemic disease even if confined to a solitary organ, and treatment decisions should follow a careful evaluation of the patient's age, concurrent diseases and therapy, type of lymphoma, and distribution and staging of tumors. Unfortunately, in the past 30 years, numerous classification schemes with a disparity of terms have been proposed, making it difficult for investigators to compare lymphomas between species. However, objective histologic and phenotypic analysis should facilitate interspecies comparisons.<sup>6</sup> Use of the National Cancer Institute's Working Formulation<sup>7</sup> to classify lymphomas of ferrets into low, intermediate, or high grades has proven useful for predicting the biologic progression of these tumors in ferrets. In general, younger ferrets tend to have more rapidly

progressive high-grade lymphoma, whereas older ferrets may have either high- or low-grade lymphoma.<sup>5</sup> Classification of ferret lymphoma by anatomic location may also serve as a tool in determination of disease severity, prognosis, and potential response to therapy. Stage I has been defined as involvement of a single site of tumor; stage II has been defined as involvement of multiple sites on the same side of the diaphragm; stage III has been defined as involvement of spleen and lymph nodes on both sides of the diaphragm; and stage IV has been defined as involvement of multiple sites on both sides of the diaphragm.<sup>4</sup> In general, lymphomas involving the liver, intestine, stomach, and/or bone marrow seem to respond poorly to chemotherapy. The lymphoid cells of animals that have received glucocorticoids for an extended period may develop resistance to the antitumoral effects of the steroids<sup>8</sup>; therefore, patients receiving prednisone for insulinoma or inflammatory bowel disease may be refractory to further chemotherapeutic treatment.

Treatment choices for ferret lymphoma include surgery, chemotherapy, radiation, alternative therapy, or combination therapy involving these modalities. Surgery may be considered as an alternative or an adjunct to chemotherapy in ferrets affected with a solitary abdominal mass or cutaneous lesion. In ferrets with splenomegaly in which the spleen occupies more than 50% of the abdominal cavity, performing a splenectomy may augment treatment and patient comfort.

## Chemotherapy

Chemotherapy for ferret lymphoma involves single-agent or combination drug therapy to suppress tumor growth. The goal of most veterinary oncologists when using chemotherapy is to control the cancer and prolong survival while maintaining a good quality of life for the patient. It is important for the client to understand the difference between complete remission and cure.

Aggressive combination chemotherapy is based on the rationale that unrelated drugs simultaneously attack tumor cells at different stages of the cell cycle with different mechanisms of action. These factors interact to prevent or delay the emergence of resistant tumor cells and result in a greater fractional kill per cycle of chemotherapy without additive host toxicity.<sup>9</sup>

A number of generalizations can be made regarding the use of chemotherapeutic agents in ferrets. The clinical status of the patient must be monitored frequently for signs of drug toxicity and to assess physical condition. Many chemotherapeutic drugs alter the CBC and platelet count, and a CBC prior to each chemotherapy treatment is recommended to ensure a minimal level of at least 2,000 neutrophils/ $\mu\text{l}$  and 50,000 platelets/ $\mu\text{l}$ . In the authors' experience, the most common chemotherapy-associated complications are lethargy, fever, and varying degrees of vomiting and diarrhea associated with leukopenia. In most cases, patients respond favorably to supportive care including IV fluids, antibiotics, gastrointestinal protectants, and syringe feeding.

Remission times vary from case to case. The response to

chemotherapy depends on several factors, including the location of the disease, extent of disease (clinical stage), presence or absence of clinical signs, histologic grade, immunophenotype (T-cell versus B-cell), exposure to previous chemotherapy or corticosteroids and subsequent development of multidrug resistance, proliferation rate of the tumor, and presence of concurrent medical problems or paraneoplastic conditions such as adrenal disease, insulinoma, hypercalcemia, weight loss, and liver insufficiency.<sup>10</sup> As with lymphoma in other species, treatment is not aimed at obtaining a cure of the disease but rather a remission of clinical signs. Remission is obtained when clinical signs improve, CBC parameters normalize, and organ/lymph node enlargement or palpable masses decrease in size. Remissions can last from months to years in ferrets with adult-onset lymphoma; however, the prognosis for ferrets with acute-onset juvenile lymphoma remains guarded.

Caution must be exercised in handling chemotherapeutic agents to minimize risk to veterinarians and technicians. All IV chemotherapeutic agents should be delivered through an IV catheter to minimize patient hazard. Vincristine and doxorubicin can only be given intravenously, and even minimal extravasation of either drug has the potential to cause significant harm to the surrounding tissue (e.g., sloughing or damage due to self-mutilation). Indwelling catheters placed in the cephalic vein can be utilized to insure IV administration. Subcutaneous venous access ports have been used successfully.<sup>11</sup> Cost of therapy depends on drug selection, frequency of administration, costs of testing to monitor patients, and supportive care in the event of toxicity.

Numerous chemotherapy protocols have been used for the treatment of lymphoma in ferrets, and the authors recommend consulting with a veterinary oncologist, preferably one who has experience working with ferrets, for an opinion on the most up-to-date and practical protocols. It is important to note that all published protocols have resulted in remissions of varying lengths in ferrets with lymphoma, and becoming familiar with one or two protocols may be the most practical approach for the practicing clinician. Unfortunately, retrospective studies of individual chemotherapy protocols with numbers of patients, lists of toxicities, and outcomes in the form of months of remission achieved are lacking. Case reports often feature reasonably favorable outcomes, while treatment failures are likely underreported. While combination chemotherapeutic protocols have shown to improve patient longevity, the authors note that not all clients can afford aggressive combination therapy and pred-

**TABLE 1. New York State College of Veterinary Medicine Ferret Lymphoma Chemotherapy Protocol (reported in 1989)**

| <i>Week</i>   | <i>Drug</i>                    | <i>Dose</i>   |
|---|--------------------------------|---|
| 1   | L-asparaginase<br>Prednisone   | 400 IU/kg IP<br>1.6 mg/kg PO sid  |
| 2   | Cyclophosphamide<br>Prednisone | 336 mg/m <sup>2</sup> PO divided over 4 days<br>1.6 mg/kg PO sid  |
| 3   | L-asparaginase<br>Prednisone   | 400 IU/kg IP<br>1.6 mg/kg PO sid  |
| 4, 6, 9, 11, 13   | Cyclophosphamide<br>Prednisone | 252 mg/m <sup>2</sup> PO divided over 3 days<br>1.6 mg/kg PO sid  |
| 17, 20, 23, 26<br>and every 3<br>weeks thereafter<br>or until relapse | Cyclophosphamide<br>Prednisone | 168 mg/m <sup>2</sup> PO divided over 2 days<br>1.6 mg/kg PO sid for 36 weeks,<br>then every other day thereafter |

Hemograms monitored prior to each treatment.

nison (1.0 mg/kg PO q12h), which binds to cytoplasmic receptors and inhibits cell division, can be used as a single-agent drug resulting in various remission success depending on the stage and type of lymphoma.

As early as 1989, Dugan et al<sup>12</sup> reported on the chemotherapeutic remission of multicentric lymphoma in a ferret using a protocol derived from various aspects of canine treatment regimens taken from Cotter<sup>13</sup> and MacEwan et al<sup>14</sup> (Table 1). The case report demonstrated the use of L-asparaginase, oral prednisolone, and oral cyclophosphamide in bringing about complete remission as judged by radiographic and ultrasonographic evaluation after 21 weeks of chemotherapy. In 1993, Brown<sup>15</sup> gave an account of a ferret chemotherapy protocol (Table 2) used successfully by oncologists at the Animal Medical Center in New York City. One year later, Rosenthal<sup>16</sup> reported on another chemotherapy protocol (Table 3) that closely resembled those published for dogs with lymphosarcoma,<sup>17</sup> and in 2000 Antinoff (personal communication, August 2003) described a COP-L protocol (Table 4) based on recommendations made by oncologists at Gulf Coast Veterinary Specialists in Houston that has been used with success in treating ferret malignant lymphoma. In addition, Brown describes the use of doxorubicin at 1 mg/kg IV q21d for a maximum of five treatments, as single-agent chemotherapy or rescue therapy for patients where disease has recurred after a remission with another protocol.<sup>18</sup>

In 2003, Mayer et al<sup>19</sup> described a novel chemotherapy protocol for ferret lymphoma developed at the Tufts University School of Veterinary Medicine that included drugs given only by oral or SC routes, completely avoiding the need for venipuncture or surgical procedures. Prednisone, L-asparaginase, cyclophosphamide, cytarabine, methotrexate, chlorambucil, and procarbazine are used. The entire protocol extends over a period of 27 weeks, during which 19 treatments are necessary. Blood work (CBC only) is repeated seven times during

**TABLE 2. Protocol Developed by the Oncology Department at the Animal Medical Center in New York City**

| Week | Drug             | Dose          |
|------|------------------|---------------|
| 1    | Vincristine      | 0.07 mg/kg IV |
| 2    | Cyclophosphamide | 10 mg/kg PO   |
| 3    | Vincristine      | 0.07 mg/kg IV |
| 4    | Methotrexate     | 0.5 mg/kg SQ  |
| 5    | Vincristine      | 0.07 mg/kg IV |
| 6    | Cyclophosphamide | 10 mg/kg PO   |
| 7    | Vincristine      | 0.07 mg/kg IV |
| 8    | Methotrexate     | 0.5 mg/kg SQ  |

Induce with L-asparaginase at 400 IU/kg IP given **once only**.

Start on prednisone on the same day at 2 mg/kg divided bid and continue throughout therapy.

Start the weekly protocol 5 days after L-asparaginase administration.

Repeat protocol weeks 1–8 except space out to every 2 weeks instead of weekly.

**TABLE 4. A COP-L Protocol Used by Dr. Natalie Antinoff, Gulf Coast Veterinary Specialists**

| Week    | Drug             | Dose                                   |
|---------|------------------|--|
| -3 days | L-asparaginase   | 400 IU/kg SQ                           |
| 1       | Vincristine      | 0.10 mg/kg IV                          |
|         | Prednisone       | 1 mg/kg PO sid throughout therapy      |
|         | Cyclophosphamide | 10 mg/kg PO 24 hours after vincristine |
| 2       | Vincristine      | 0.10 mg/kg IV                          |
| 3       | Vincristine      | 0.10 mg/kg IV                          |
| 4       | Vincristine      | 0.10 mg/kg IV                          |
|         | Cyclophosphamide | 10 mg/kg 24 hours after vincristine    |
| 7       | Same as week 4   |  |

Continue this protocol every three weeks to maintain remission; if leukopenia (<1,500 cell/ $\mu$ l) is found at 3 week recheck, postpone chemo and recheck CBC in 5–7 days; if interval is prolonged to 4 weeks repeatedly, consider increasing the interval for cyclophosphamide.

**TABLE 3. University of Pennsylvania Chemotherapy Protocol**

| Week | Drug  | Dose           |
|------|---|----------------|
| 1    | Vincristine   | 0.07 mg/kg IV  |
|      | L-asparaginase  | 400 IU/kg IP   |
|      | Prednisone  | 1 mg/kg PO sid |
| 2    | Cyclophosphamide  | 10 mg/kg SQ    |
|      | Prednisone  | 1 mg/kg PO sid |
| 3    | Doxorubicin   | 1 mg/kg IV     |
|      | Prednisone  | 1 mg/kg PO sid |
| 4–6  | Same as weeks 1–3 above, but discontinue L-asparaginase |                |
| 8    | Vincristine   | 0.07 mg/kg IV  |
|      | Prednisone  | 1 mg/kg PO sid |
| 10   | Cyclophosphamide  | 10 mg/kg SQ    |
|      | Prednisone  | 1 mg/kg PO sid |
| 12   | Vincristine   | 0.07 mg/kg IV  |
|      | Prednisone  | 1 mg/kg PO sid |
| 14   | Methotrexate  | 0.5 mg/kg IV   |
|      | Prednisone  | 1 mg/kg PO sid |

Protocol is continued in sequence biweekly after week 14. Prednisone is given daily throughout the protocol.

of the three ferrets have since been euthanized at weeks 6 and 25, respectively, of therapy initiation. For exact details and instructions on how to use the current protocol, please contact the author (joerg.mayer@tufts.edu).

In 1992, Hutson et al<sup>20</sup> reported on the use of two single-agent chemotherapy rescue protocols in combination with orthovoltage radiation therapy in a case of ferret lymphosarcoma after the patient came out of remission with a modified COP protocol. A series of traditional and “salvage” chemotherapeutic and radiation therapies were used for lymphosarcoma diagnosed via biopsy and histopathology in a 2-year-old ferret. The ferret presented with right submandibular lymphadenopathy but was otherwise normal on physical examination. The owner declined diagnostics other than histopathology. Initial chemotherapy consisted of modified COP therapy, vincristine (0.75 mg/m<sup>2</sup>) IV once weekly, cyclophosphamide (200 mg/m<sup>2</sup>) PO 4 consecutive days each week, and prednisone (20 mg/m<sup>2</sup>) PO daily for 2 months then every other day. Sterile cystitis occurred after 2 months, and the cyclophosphamide was discontinued. Attempts at reinstating cyclophosphamide were unsuccessful as cystitis recurred. Clinical remission was observed after 4 weeks and persisted for 6 months, which was gauged by the size of the submandibular lymph node. After a total of 9 months of COP therapy, the last 3 months being progressive disease, the ferret came out of remission and chemotherapy was reinstated using L-asparaginase (400 IU/kg) SC and chlorambucil (1 mg) PO weekly with no

response. Doxorubicin (20 mg/m<sup>2</sup>) IV once and orthovoltage radiation localized to the neoplastic right submandibular lymph node (500 cGy twice weekly) were combined as a salvage procedure. Radiation therapy alone was continued for 5 weeks until the lymph node was no longer palpable. Remission lasted 4 months, at which time IV doxorubicin was administered every 3 weeks at 20 mg/m<sup>2</sup>. Remission was achieved immediately and lasted for 6 months, at which time abdominal ultrasound demonstrated an enlarged liver and mesenteric lymph nodes. A final salvage therapy consisted of weekly high-dose vincristine (2 mg/m<sup>2</sup>) IV, which produced a 3-month remission. At relapse, quality of life was judged to be poor and the ferret was euthanized. Chemotherapeutics and radiation therapy resulted in a 23-month survival time, with a good quality of life from initial diagnosis to euthanasia.

### Other Treatments

Modalities other than chemotherapy have also been tried with some success. C. Orcutt, DVM (oral communication, June 2000) has used half-body irradiation (HBI) to treat stage II malignant lymphoma in a ferret that did not respond to conventional chemotherapy. The ferret's body weight was 300 g, and a dose of 500 cGy was used with each treatment. The first treatment was administered cranial to the diaphragm, and within 1 week affected lymph nodes were nonpalpable. One month later, the second treatment was administered caudal to the diaphragm. Within 48 hours, previously enlarged abdominal lymph nodes were nonpalpable. Sequelae to HBI occurred within 24 hours of each treatment and included depression, anorexia, diarrhea ± melena, as well as elevated BUN and phosphorus levels, all of which resolved within 48 hours of IV fluids and appropriate supportive care. Remission in this case lasted 5 months, at which time another treatment was given caudal to the diaphragm resulting in an additional 7 months of remission.

A variety of homeopathic, herbal, and vitamin supplements have also been used in ferrets with malignant lymphoma. Brown<sup>18</sup> reports the use of the chelated, buffered, or ester form of vitamin C (50 to 100 mg/kg PO q12h) as an antioxidant to protect the body from free radicals that are a byproduct of body metabolism. Vitamin C also increases interferon production and stimulates T-effector cell activity. Brown also describes the treatment of a small number of lymphoma ferrets with Pau d'Arco, essiac, and pycnogenol. Clinical response to these remedies has been difficult to assess due to the small number of treated ferrets.

Cutaneous epitheliotropic lymphoma should be treated as a separate entity from systemic lymphoma. Ferrets with this rare form of dermal lymphoma present with varying degrees of pruritus, alopecia, erythema and dermal excoriations, crusts, and ulcerative plaques. Palliative treatment using retinoid (isotretinoin), antibiotics, and oatmeal shampoo therapy versus conventional lymphoma treatment has been reported.<sup>21</sup>

### REFERENCES

1. Li X, Fox JG, Padrid PA: Neoplastic diseases in ferrets: 574 cases (1968–1997). *JAVMA* 212(9):1402–1406, 1998.
2. Erdman SE, Reimann KE, Moore FM, et al: Transmission of a chronic lymphoproliferative syndrome in ferrets. *Lab Invest* 72(5): 539–546, 1995.
3. Williams B: Lymphosarcoma. *Manage Ferret Vet Prof Proc* 2:55–60, 2000.
4. Erdman SE, Brown SA, Kawasaki TA, et al: Clinical and pathologic findings in ferrets with lymphoma: 60 cases (1982–1994). *JAVMA* 208(8):1285–1289, 1996.
5. Erdman S, Li X, Fox JG: Hematopoietic diseases, in Fox JG (ed): *Biology and Diseases of the Ferret*. Baltimore, Williams & Wilkins, 1998, pp 231–246.
6. Coleman LA, Erdman SE, Schrentzel MD, Fox JG: Immunophenotypic characterization of lymphomas from the mediastinum of young ferrets. *AJVR* 59(10):1281–1286, 1998.
7. The Non-Hodgkin's Lymphoma Pathologic Classification Project: National Cancer Institute sponsored study of classification of Non-Hodgkin's lymphomas: Summary and description of a working formulation for clinical usage. *Cancer* 49(10):2112–2135, 1982.
8. Chun R, Garrett L, MacEwen EG: Cancer chemotherapy, in Withrow SJ, MacEwen EG (eds): *Small Animal Clinical Oncology*. Philadelphia, WB Saunders, 2001, pp 92–118.
9. Tehilen GH, Madewell BR: *Veterinary Cancer Medicine*. Philadelphia, Lea & Febiger, 1987.
10. Vail DM, MacEwen EG, Young KM: Hematopoietic tumors, canine lymphoma and lymphoid leukemias, in Withrow SJ, MacEwen EG (eds): *Small Animal Clinical Oncology*. Philadelphia, WB Saunders, 2001, pp 558–590.
11. Rassnick KM, Gould 3<sup>rd</sup> WJ, Flanders JA: Use of a vascular access system for administration of chemotherapeutic agents to a ferret with lymphoma. *JAVMA* 206(4):500–504, 1995.
12. Dugan SJ, Center SA, Randolph JF, Anderson WT: Chemotherapeutic remission of multicentric lymphosarcoma in a ferret (*Mustela putorius furo*). *AAHA* 25:69–74, 1989.
13. Cotter SM: Treatment of lymphoma and leukemia with cyclophosphamide, vincristine, and prednisone: Treatment of dogs. *JAAHA* 19:159–163, 1983.
14. MacEwan EG, Hayes AA, Matus RE, Kurzman I: Evaluation of some prognostic factors for advanced multicentric lymphosarcoma in the dog: 147 cases (1978–1981). *JAVMA* 190(5):564–568, 1987.
15. Brown S: Lymphoma, ferrets. *Proc North Am Vet Conf*:730–732, 1993.
16. Rosenthal K: Ferrets, in *Veterinary Clinics of North America, Exotic Pet Medicine II*. Philadelphia, WB Saunders, 1994, pp 19–20.
17. Matus RE: Chemotherapy of lymphoma and leukemia, in Kirk RW (ed): *Current Veterinary Therapy X*. Philadelphia, WB Saunders, 1989, pp 482–488.
18. Brown SA: Section one: Ferrets, neoplasia, in Hillyer HV, Quisenberry KE (eds): *Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery*. Philadelphia, WB Saunders, 1997, pp 99–114.
19. Mayer J, Payne S, Mateleska J, Moore AS: A novel chemotherapy protocol for lymphoma in ferrets. *Proc Br Vet Zoo Soc Spring Meeting*, Dublin, Ireland, May 9–11, 2003.
20. Hutson CA, Kopit MJ, Walder EJ: Combination doxorubicin and orthovoltage radiation therapy, single-agent doxorubicin, and high-dose vincristine for salvage therapy of ferret lymphosarcoma. *JAAHA* 28:365–369, 1992.
21. Rosenbaum MR, Affolter VK, Osborne AL, Beeber NL: Cutaneous epitheliotropic lymphoma in a ferret. *JAVMA* 209(8):1441–1444, 1996.



## Join Us at the “First Step” Seminar in 2004!

AEMV will once again be offering the “First Step: Basics and Beyond” seminar in conjunction with the International Conference on Exotics (ICE) in 2004. The meeting will provide 4.5 hours of continuing education credit. **For more information, please contact Melissa Kling at [mkn.dvm.uga@att.net](mailto:mkn.dvm.uga@att.net) or 478-757-1600.** It will be posted on the AEMV Web site at [www.aemv.org](http://www.aemv.org), so be sure and check your member’s area often.

### *First Step 2004: Basics and Beyond*

May 5, 2004 • 1–6 pm

The Registry Resort, Naples, Florida

#### **Speakers:**

Peter G. Fisher, DVM—*Basics and Beyond in Ferret Medicine, Small Mammal Surgery*  
Heidi Hoefler, DVM—*Rabbit and Rodent Dentistry, Introduction to Hedgehogs and Chinchillas*  
Susan Kelleher, DVM—*Rabbit Medicine: Abscesses, Respiratory Disease, Gastrointestinal Disease*

## AEMV Annual Business Meeting

The annual AEMV business meeting with officer elections will be held immediately following “First Step: Basics and Beyond” on May 5, 2004 at 6:15 pm at The Registry Resort in Naples, Florida. If you are interested in running for President, Vice President, Secretary, or Treasurer, please let us know. Remember, this is your association, and in order for us to continue moving forward we need more active member participation! If you would like to serve on a committee, write or review articles for the newsletter, help with registration for First Step, or have any comments or suggestions, please let us know.

## First Step 2003 Proceedings

Proceedings from First Step 2003 are now available for members on our Web site. The proceedings, written by Teresa Lightfoot, DVM, cover rabbit, guinea pig, and rodent medicine and surgery. Members can access the proceedings at [www.aemv.org](http://www.aemv.org).

## Meloxicam Approved for Oral Use in Dogs in the United States

Metacam (meloxicam) is an NSAID of the oxicam class that has been used in Europe and Canada for several years for pain management in exotic mammals. Recently approved in the United States for use in dogs, this 1.5 mg/mL oral suspension is manufactured by Boehringer Ingelheim Vetmedica, Inc. and distributed by Merial. Unfortunately, there are no published pharmacokinetic dose rates for most exotics; however, a dosage range of 0.1 to 0.3 mg/kg PO sid has been proposed and used empirically with clinical success in small exotic mammals such as rabbits, guinea pigs, rodents, and ferrets. Anecdotal reports of its long-term use without side effects in these species have been reported.

## Adverse Reaction Reports Redirected

Veterinary teams using the U.S. Pharmacopeia’s Veterinary Practitioners’ Reporting Program (VPRP) will need to change their procedures for reporting adverse reactions. The program, developed by the USP in collaboration with the American Veterinary Medical Association (AVMA) as a way to collect and disseminate data among animal owners, veterinary practitioners, and regulatory agencies, was recently discontinued. Reports should now be made directly to the product manufacturer and to either the FDA Center of Veterinary Medicine for adverse drug experiences (888-FDA-VETS or [www.fda.gov/cvm](http://www.fda.gov/cvm)) or the USDA Center for Veterinary Biologics for issues with vaccines and bacterins (800-752-6255 or [www.aphis.usda.gov/vs/cvb/ic/adverseeventreport.htm](http://www.aphis.usda.gov/vs/cvb/ic/adverseeventreport.htm)).

Keep this in mind when experiencing ferret vaccine reactions. It is important to report all vaccine reactions so the frequency and severity can be documented on a national level. This aids vaccine manufacturers in their endeavor to produce safe and efficacious vaccines. Since the introduction of Merial’s PureVax Ferret Distemper vaccine for protection against canine distemper in ferrets, the incidence of ferret vaccine reactions has markedly decreased.

# Natural History of the Guinea Pig (*Cavia porcellus*)

Jörg Mayer, Dr.MedVet, MSc

Tufts University School of Veterinary Medicine  
North Grafton, Massachusetts

## ORIGIN AND DOMESTICATION

The earliest traceable ancestry of the present day guinea pig dates back to the Miocene Epoch (ca. 23 to 25 million years ago). Grazing animals became established during this time, filling a new ecologic niche as grasses rose on the newly formed landmasses. The domestication of the guinea pig, or “cuy” as it is called in South America, is thought to have begun around 5,000 B.C. in the Andes Mountains. Currently, there are eight recognized species within the genus *Cavia* (*Cavia aperea*, *Cavia tschudii*, *Cavia porcellus*, *Cavia guianae*, *Cavia anolaimae*, *Cavia nana*, *Cavia fulgida*, and *Cavia magna*), which belong to the family Caviidae of the order Rodentia. Some of the oldest documentation of the guinea pig as a food source dates back to 900 B.C.

The origin of the name guinea pig is still not clear. One explanation is that it stems from the English currency, one guinea, the amount an individual would pay to obtain one little piggy. The second explanation is the slight corruption of the name of the South American country of Guiana, from where most of the animals would have been shipped.

In 1758, Linnaeus described the guinea pig for the first time scientifically with the name *Mus porcellus*. Eight years later, Pallas classified the guinea pig as *Cavia cobaya*. Today’s scientific name, *Cavia porcellus*, is an amalgamation of these.

In present-day Andean culture, the guinea pig still plays an important role that could be likened to the role of the chicken in other rural settings; many people own guinea pigs as a food source. The guinea pig was introduced to North America in the late 17<sup>th</sup> century and gained immediate popularity as a pet due to the gentle nature of the animals and their relative ease of case in captivity.

## HABITAT AND BEHAVIOR

Cuys inhabit a large percentage of South America. Wild guinea pigs adapt well to varied climates and may inhabit environments ranging from dry, rocky fields and savannas to damp, swampy forests to mountainous regions of up to 13,000 feet. In the wild, the typical group of guinea pigs is made up of 10 to 12 individuals that live underground in the abandoned burrow systems of other animals. The group consists of only one male, the rest being females living in a harem system. The dominant male animal usually drives out young males. The female animals have a hierarchy of their own, and the dominant females can significantly harass the lower-ranking females. In the wild, females usually produce two litters a year consisting of one to four pups. The females can become pregnant at 90 days of age and every 65 to 75 days after. Estrus usually lasts for 7 to 8 hours and occurs every 13 to 14 days. Any lactating sow feeds nursing piglets. In the wild, the average life span is about 3

years; however, in captivity guinea pigs can live up to 9 years. A few communal projects exist in South America where the cuy is used for meat production and one female can produce 10 pounds of meat per year. In the wild, guinea pigs usually weigh around 1.5 lb; animals used in the breeding program for meat production usually weigh in at around 4.4 lb.

Guinea pigs are very vocal. If youngsters are separated from the group, they will squeal until another animal brings them back. The same squeal can also signal pain or be used as a warning sound. When bonded with humans, this same squeal is frequently used as a begging cry for food. Sexually aroused males and females may create a low rattling noise, which may also serve as a greeting sign of a lower ranking female to a higher one. A rumbling noise is usually used as a warning noise and can be followed by teeth grinding and an actual attack. The happy guinea pig will freely jump up in the air with all four legs, usually referred to as “popcorning,” or may lie down in a completely stretched out position.

## GUINEA PIGS AND MYTHOLOGY

Similar to the rabbit in early Britain, the guinea pig was considered sacred. The Incas used guinea pigs in different rituals, including interpreting its viscera to determine their war strategies. After the Spanish conquistadors conquered most of South America, the church tried to eliminate all religious and social rituals involving guinea pigs. In today’s traditional Andean culture, the cuy still plays an important role in ceremonial practices.

One of the cuy’s most important and interesting roles in Andean culture is its use in traditional medicine. One technique involves rubbing a guinea pig over the naked body of a patient in the form of a “lesion detector.” If the cuy squeals while being rubbed over the body, it is thought that this site is the origin of suffering, and the cuy will absorb the sick spirits. After this “detection,” the cuy is offered a selection of medicinal herbs; the plant the pig chooses is considered the appropriate remedy for the human patient. The cuy is then slaughtered and the intestines used to interpret the state of the patient and the possible cause of the problem. This cuy will not be used for human consumption as it is thought to carry the illness, and is buried in a safe place.

The guinea pig we know as a pleasurable and entertaining household pet has a very interesting past and continues to play an important role in the South American culture.

## SUGGESTED READING

Forstadt MS: *History of the Guinea Pig (Cavia porcellus) in South America*. Available at: <http://cavyhistory.tripod.com>; accessed September 2003.  
Morales E: *The Guinea Pig: Healing, Food, and Ritual in the Andes*. Tucson, University of Arizona Press, 1995.



## Textbook of Rabbit Medicine

By Frances Harcourt-Brown with illustrations by Nigel Harcourt-Brown

Published by Oxford, Butterworth-Heinemann, 2002

ISBN: 0750640022

Hardcover

436 pages

24 illustrations

I cannot remember ever reading a veterinary textbook from cover to cover upon receiving it. However, this is exactly what I did with Frances Harcourt-Brown's *Textbook of Rabbit Medicine*. This new publication represents a major advance in meeting the needs of practitioners seeking comprehensive clinical information on pet rabbits.

Dr. Harcourt-Brown incorporates her own clinical expertise with the best available clinical evidence and research in her book, making it the best example in exotic pet or laboratory animal medicine of how to practice evidence-based medicine. Her exhaustive reference lists at the end of each chapter are from peer-reviewed English and American journals as well as German, French, Dutch, and other non-English language journals. Diagrams throughout the book are original and are drawn from the author's original dissections. The freshness of this information and its integration into plausible clinical explanations is why I found this book so enjoyable to read.

Six introductory chapters cover biology, diet, husbandry, clinical pathology, drugs, and the rabbit consultation. Digestive physiology includes original drawings on the rabbit's unique gastrointestinal physiology. Dr. Harcourt-Brown has written her nutrition segment exclusively for pet rabbits and for veterinarians like myself, who do not have a strong background in nutrition or its terminology. The chapters on drugs, anesthesia, and analgesia describe traditional as well as recently available pharmaceuticals and their use in rabbits. "Clinical Pathology" comprises clinically applicable information on rabbit hematology and biochemistry. However, the author cautiously states in the first paragraph that she has selected the references from toxicologic studies and diseases of commercial rabbits, and the "infor-

mation available on the hematology and biochemistry of pet rabbits is anecdotal, although it can be helpful and is better than no information at all." The information is extremely helpful.

Eight chapters are dedicated to diseases of a particular organ system, or one subject. The chapter on dental disease, as expected, is extensive, illustrated with numerous original drawings and detailed radiographs. This chapter alone makes the book worth its price. In "Abscesses," Dr. Harcourt-Brown notes that chronic abscesses are common in rabbits and notoriously difficult to cure. She discusses the prognosis for facial abscesses in rabbits realistically, suggesting conservative treatment in long-standing periapical abscesses and in late stages of dental disease with multiple abscesses and extensive pathology of the bones and teeth.

The three final chapters cover surgery, infectious diseases, and necropsy of rabbits. An excellent discussion on *Encephalitozoon cuniculi*, a recently recognized zoonotic disease and increasingly significant disease in pet rabbits, is found in the chapter on infectious diseases. The last chapter on postmortem examination has a clinician-friendly, four-page table that lists common findings for each stage of examination and organ system and catalogues possible causes, which are cross-referenced to the relevant sections of the book.

*Textbook of Rabbit Medicine* is an outstanding book. It is a valuable reference and indispensable textbook for any veterinarian who works with rabbits.

Reviewed by  
**Thomas M. Donnelly, BVSc**  
The Warren Institute  
Ossining, New York

## AEMV OFFICERS AND EDITORS

**President:** Peter G. Fisher, DVM, Pet Care Veterinary Hospital, Virginia Beach, VA; peter.g.fisher@verizon.net

**Managing Editor:** Michael Dutton, DVM, DABVP, Weare Animal Hospital, Weare, NH; mdutton@weareanimalhospital.com

**Vice President:** Heidi Hoefler, DVM, DABVP, West Hills Animal Hospital, Huntington, NY; heidi@heidihoefer.com

**Secretary:** Melissa Kling, DVM, Brantley and Jordan Animal Hospital, Macon, GA; mkn.dvm.uga@worldnet.att.net

**Treasurer:** Jörg Mayer, DrMedVet, MSc, Tufts University, School of Veterinary Medicine, North Grafton, MA; joerg.mayer@tufts.edu

# Bunny Behavior 101: Aggression

Mary E. Cotter, EdD

House Rabbit Society

New York, New York

What behaviors define aggression in rabbits? Lunging, boxing, chasing, grunting, mounting, and nipping/biting (all usually performed with the ears laid flat back) are all displays of rabbit aggression. Here are six common reasons rabbits exhibit aggressive behavior (several are closely related):

## SEXUAL MATURITY

Once a rabbit reaches the age of 4 to 6 months, hormones play a significant role in determining behavior. In males, the most common hormone-driven behavior is mounting; the buck may attempt to mount the caretaker's arm or leg, biting to maintain its grip. The doe, on the other hand, becomes increasingly protective of her territory (see below), as everything in her system prepares her to kindle a litter.

**Solution:** Spaying or neutering can eliminate, or greatly decrease, hormone-driven behaviors in both sexes.

## PROTECTING TERRITORY

Experienced rabbit caretakers have observed that females are often more territorial than males. Even after spaying, some females continue to exhibit cage aggression, boxing, lunging, and nipping at hands that are attempting to perform routine husbandry tasks.

**Solution:** Place one hand on the rabbit's head and exert gentle pressure while removing or replacing bowls, bottles, and litter boxes with the other hand. Do not release pressure on the head until in-cage tasks have been completed and the "working hand" has been removed from the cage. Some rabbits may need this kind of one-hand, in-cage management over the long term, while others may gradually become less aggressive over time.

## DOMINANCE

Individual rabbits vary greatly with respect to dominance. Some extremely dominant rabbits exhibit aggression toward the caretaker (usually lunging and nipping) as well as toward other rabbits (usually mounting, chasing, and nipping) in order to maintain their dominance. In bonded pairs where one rabbit is clearly dominant, it is not unusual for the dominant rabbit to become aggressive when the partner rabbit is receiving attention from (or being handled by) the caretaker.

**Solution:** Avoid situations where the dominant rabbit will be "challenged." With bonded pairs, for example, stroke the dominant rabbit first, or stroke both rabbits simultaneously. With some pairs, when access to the submissive rabbit is

needed, it may be helpful to follow this sequence: 1) remove the dominant rabbit from the cage or pen; 2) remove the submissive rabbit (for medication, etc.); 3) return the submissive rabbit to the cage; 4) return the dominant rabbit to the cage.

## PAIN

A rabbit in pain can exhibit a broad spectrum of responses, ranging from withdrawal and hunching to sudden irritability and aggression. In my experience, well-localized pain is more likely to result in aggression than more global, systemic pain, but this varies with the individual rabbit.

**Solution:** If aggression occurs suddenly in a rabbit that is normally not aggressive, a thorough physical examination may be indicated.

## POOR CLOSE VISION

Although rabbits have excellent distance vision, the placement of their eyes makes it difficult for them to see objects directly in front of them at close range. They will often lunge and box at fast-moving objects approaching them from the front (such as hands entering their cages to provide food or water).

**Solution:** Approach the rabbit from the side, pausing briefly a foot or so from the rabbit's face before attempting to touch it.

## POOR HANDLING

When picked up or handled in ways that cause fear, discomfort, or stress, many rabbits develop a repertoire of behaviors (including lunging, boxing, grunting, and nipping) aimed at keeping hands at a distance. I have known two rabbits that actually learned to hold their mouths wide open in readiness as they saw humans approach.

**Solution:** Control the rabbit's head as described above (see "Protecting Territory") and work toward developing alternative ways of lifting and handling the rabbit. Support the front quarters with one hand under the thorax (rather than the abdomen) while using the other hand to support the entire hindquarters.

## SUMMARY

When dealing with aggressive behavior, it is usually counterproductive to try to "discipline" a rabbit, since this can exacerbate the problem rather than resolve it. Patience and a calm approach are much more likely to yield satisfactory results.

# Guidelines for Authors

We invite readers to submit manuscripts of quality research, case reports, and reviews to *Exotic Mammal Medicine & Surgery*.

**In My Experience (IME):** Brief clinical experiences regarding unusual or novel aspects of exotic mammal care.

**Case Reports:** Reports of clinical cases with detailed introduction, history, laboratory data, diagnosis, therapy, and results. Cases should be informative to veterinarians and advance the medicine of exotic mammals. Discussion should emphasize important points in the care of the case and should identify the new information imparted by the case report.

**Original/Review/Roundtable Articles:** In-depth articles or discussions focusing on a specific disease or topic.

**Behavior/Care/Nutrition:** In-depth articles or discussion focusing on the unique behavior, care, and/or nutrition of an exotic species.

**Article Review:** A brief synopsis of current literature or publications pertaining to exotic mammals. The article to be reviewed must be previously approved by the Board.

**Natural History:** A brief synopsis of the natural habitat, behavior, and history of a particular exotic mammal species. Photographs highlighting breed differences if applicable would be appropriate in this type of article.

## Manuscript Submission

Three copies of each manuscript must be submitted to *Exotic Mammal Medicine & Surgery*. Please mail to Michael Dutton, Managing Editor, Association of Exotic Mammal Veterinarians, P.O. Box 396, Weare, NH 03281.

- Manuscripts, including references, photos, and figure legends, must be typewritten and double-spaced in 12-point Arial with 1-inch margins and left justification. The manuscript must also be submitted on standard 1.44 MB disk or CD-ROM in Microsoft Word format or ASCII format.
- Manuscripts must be submitted with a separate cover letter that includes the primary author name(s), additional author name(s), and address of each author. Please indicate who the contact person is for the manuscript and include his/her telephone number, fax number, and email address.
- A separate title page should include the title, the author's full name(s) and academic degrees, affiliations (hospital, institution), and complete address for all those listed.
- An abstract is required for all submissions excluding IME and article reviews. The abstract should cover key points.
- A list of six key words should precede all submitted articles. Key words should include species name, genus name, and common name.
- All measurements should be metric. Biochemical values should be listed in Systeme International units with conventional units in parentheses, or on the next line if they are in a table. Temperature should be in Celsius with Fahrenheit in parenthesis.
- Drugs and other products should be listed by generic or chemical name followed by, in parentheses, trade name, con-

centration, manufacturer, city, state, and country. Dosages of all drugs should be given in mg/kg or mL/kg. Route of administration (abbreviated), frequency of dosing (abbreviated and use hours such as q8h, not sid, tid, bid), and duration of treatment should be included.

- References should be cited by author and year and placed as endnotes at the end of the article. For references with more than four authors, citations need only include the first three authors followed by *et al.* Journal titles should be abbreviated in a consistent manner. The style for a chapter or article in the book is: author of the chapter or article, name of the chapter or article, the word 'In:', the editor of the book followed by (ed), the name of the publication, ', publisher, city of publisher, state of publisher, year of publication, ', pages referenced. An example is: Evans HE, An NQ: Anatomy of the ferret, in Fox JG (ed): *Biology and Diseases of the Ferret*, ed 2. Baltimore, Williams & Wilkins, 1998, pp 159-173.
- Black and white pictures are preferable to color, either should be submitted as three sets of 4 × 6 inch glossy prints or scanned at 300 dpi and saved as TIFF files and sent via email, standard 1.44 MB disk, or CD-ROM. Photographs should be labeled with author's name, figure number, and the topside indicated on the back of the picture. Drawings should be in black India ink. Glossy black and white photographs or scanned files of the original drawings are preferred. Short legends must be provided for each picture and should be submitted on a separate page.
- Guidelines for digital art are:
  - Line drawings and the like at 1200 dpi.
  - Halftones at 300 dpi.
  - Combination art at 600 dpi.To ensure sufficient resolution, files should be saved at approximately 4" × 3" as a TIFF format on the PC or Mac platform. Please save on a standard 1.44 MB disk or CD-ROM. You must supply a hard copy of each image for matching and quality control purposes. The hard copy should include author's name, figure number, and topside.
- All manuscripts are submitted with the understanding that all authors have seen the article. We reserve the right to reject any manuscript. Submitted manuscripts are subject to anonymous peer review. Authors are expected to respond to reviewers' comments and make revisions within 14 days. Revised manuscripts are sent out to review again. Manuscripts that pass peer review are accepted for publication if the author has addressed all questions and concerns raised by review.
- Acknowledgements should be limited to persons who have contributed materially to the content.
- Manuscripts that are published become the property of the Association of Exotic Mammal Veterinarians and Veterinary Learning Systems. The electronic rights for the manuscript become the property of the Association of Exotic Mammal Veterinarians and the manuscript will be placed on our Web site.

# Selected Abstracts on Exotic Mammal Medicine and Surgery

## Response to Novel Objects and Foraging Tasks by Common Marmoset (*Callithrix jacchus*) Female Pairs

Majolo B, Buchanan-Smith HM, Bell J: *Lab Anim* 32(3):32–38, 2003.

### ABSTRACT

The common marmoset (*Callithrix jacchus*) is frequently kept in laboratory and zoo collections, and as a result has been the focus of numerous environmental enrichment studies. In the wild, common marmosets usually live in family units composed of a breeding pair, adult offspring, and sometimes other individuals. In captivity, however, they are often kept in same-sex pairs, where the rate of female–female aggression is especially high. Enrichment devices are intended to improve the well-being of common marmosets by reducing social tension; however, those containing highly palatable food can potentially increase aggression between cage mates (especially female pairs) as the monkeys attempt to monopolize the objects.

This study analyzed the response of common marmoset female pairs to artificial enrichment devices by measuring the response to novel objects versus foraging tasks; whether the size, shape, aural responsiveness, and vertical position within the enclosure made a difference; and whether the monkey's age made a difference. The study also sought to determine if allo-grooming and aggressive stress-related behaviors are affected by the presence of enrichment devices. The study utilized 32 common marmoset female pairs, each composed of an older monkey housed with a younger, usually unrelated, monkey.

The monkeys were presented with three different novel objects: a cup filled with plastic test tubes, a plastic drink bottle full of cloth strips with a hole in the side for access, and a string of film canisters, each with a marble in it. With raisins hidden inside, these same objects were used to evaluate foraging tasks in a separate experiment. The study found that the monkeys explored foraging tasks sooner and spent more time exploring them than the objects that were simply novel.

The relative position of the objects in the cage appeared to be more important than the size, shape, or aural responsiveness of the object. Objects placed high or in the middle of the cage received more attention than objects placed on the cage floor, which was not surprising because common marmosets in the wild occupy the lower strata of the canopy and rarely go to the ground. While the latency to explore and eat was not significantly different between older and younger monkeys, the younger marmosets were found to explore objects for a longer time than the older ones. This finding supports previous studies indicating that older monkeys lose interest in novel objects earlier than their younger counterparts.

The presence of these devices had no effect on allo-grooming, which was rarely observed. The rates of aggressive behaviors were not affected by the introduction of enrichment devices, regardless of which device was introduced. The rate of scratching (a reliable indicator of stress in common marmosets) was reduced during object presentation, and the decrease was more significant with foraging tasks than for novel devices.

### COMMENTARY

*Common marmosets are a familiar nonhuman primate species in exotic animal practice. Primate owners must be educated on how to reduce the stress level of captive nonhuman primates in order to reduce stress-related illnesses and to speed recovery from disease. For common marmosets, and probably all monkeys, the stress of captivity is reduced when group composition is as similar to the natural social structure as possible. Instruct owners to watch for scratching as an indicator of the level of stress in common marmosets. Where it is feasible, clients should avoid housing female common marmoset pairs alone. Swings, perches, tunnels, hammocks, infant-safe toys, mirrors, noisemakers, and water-play toys are staples in primate enrichment. Enrichment devices should be rotated often so the novelty does not wear off. Whenever possible, foraging should also be encouraged. Hiding treats in an object can encourage foraging, as this provides a greater diversion. There are a multitude of homemade busy boxes and foraging devices that can be constructed, limited only by the imagination. They are available commercially as well. For best results, instruct clients to place items somewhere in the top half of the enclosure. In order to prevent obesity, use low-calorie foods or provide part of the daily ration for foraging.*

### CORRECTION

In Vol. 1 No. 1 of *Exotic Mammal Medicine and Surgery*, the publication year stated in the reference Munday JS, Stedman NL, Richey LJ: Histology and immunohistochemistry of seven ferret vaccination-site fibrosarcomas. *Vet Pathol* 40(4):288–293 should have been 2003, not 2002. We regret the error.

Dan Johnson, DVM  
Raleigh, North Carolina

## Analgesic Efficacy of Orally Administered Buprenorphine in Rats

Martin LBE, Thompson AC, Martin T, Kristal MB: *Comp Med* 51(1):43–48, 2001.

### ABSTRACT

Buprenorphine is a commonly used analgesic in lab animal medicine. Buprenorphine prepared in food or water may be preferred to parenteral administration due to decreased animal stress and required technical skill. Buprenorphine mixed in flavored gelatin at a dose of 0.5 mg/kg has become a widely accepted postoperative analgesic. This study sought to quantify the analgesic efficacy of orally administered buprenorphine in rats and compare it with an established parenteral dose of 0.05 mg/kg SC. The hot-water tail-flick method was chosen to determine pain threshold. Buprenorphine for injection was prepared at a concentration of 0.05 mg/mL. For oral administration, buprenorphine hydrochloride powder (RBI/Sigma, Natick, MA) was mixed with sterile, deionized water (vehicle) to make a stock solution of 5.0 mg/mL. Experimental doses were obtained by making serial dilutions of the stock solution. To prepare the medicated gelatin, buprenorphine was added at a concentration of 0.125 mg/mL of gelatin after cooling to 55°C. Gelatin solutions were poured into plastic 2-mL ice cube trays and refrigerated until firm. Cubes were fed at a rate of 2 mL gelatin/kg body weight. Raspberry- and beef-flavored gelatin was used based on previous reports of acceptance, and both flavors were enthusiastically accepted by the rats prior to testing.

In this study, rats were fed concentrations of 0.5 mg/kg (0.125 mg/mL), 1 mg/kg (0.25 mg/mL), 2.5 mg/kg (0.625 mg/mL), 5 mg/kg (1.25 mg/mL), and 10 mg/kg (2.5 mg/mL). All strengths were fed in 2-mL gelatin cubes. It was found that rats would not readily consume gelatin with concentrations of 1 mg/kg (0.25 mg/mL). Buprenorphine is alkaline and bitter, thus accounting for the decrease in palatability. To achieve doses >1.0 mg/kg would necessitate increasing the volume of gelatin consumption beyond practical applications. As a result, all rats in this study received their dose of oral buprenorphine via orogastric infusion.

The next part of the study measured pain threshold to the various dosages of oral buprenorphine. The results clearly indicated that ingestion of 0.5 mg/kg in flavored gelatin did not induce an increase in pain threshold and was not an effective analgesic at this dose or route of administration. Instead, an oral dose of 5 mg/kg was necessary to increase the pain threshold appreciably and induce analgesia comparable to the standard dose of injectable buprenorphine.

A study of the duration of analgesia followed, and the results indicated that oral buprenorphine at dosages of 5 and 10 mg/kg induced a detectable increase in tail-flick latency (pain threshold), comparable to SC administration of buprenorphine, for >4 hours and <8 hours. In the same study, SC buprenorphine at the standard dose resulted in an analgesic

duration of 2 to 4 hours.

It should be noted that SC buprenorphine has previously been reported to provide approximately 4 to 8 hours of analgesia, and the authors speculated that the magnitude and duration of action of both oral and injectable buprenorphine may vary with a number of factors, including method of pain assessment, clinical setting, and strain or gender of rat tested.

Further research will be necessary to determine whether a sufficiently palatable vehicle exists that will encourage rodents to consume adequate buprenorphine to induce analgesia.

### COMMENTARY

*Buprenorphine is a commonly used parenteral analgesic in exotic small mammals. As well, buprenorphine mixed in flavored gelatin at a dose of 0.5 mg/kg has been widely accepted as an effective oral postoperative analgesic. This paper suggests that dosages of 5 to 10 mg/kg of oral buprenorphine are necessary in providing adequate analgesia to rats and that a palatable vehicle for administration of these concentrations of oral buprenorphine needs to be investigated. Studies need to be performed to determine if orally administered and injectable buprenorphine are absorbed in the intestinal tract of rodents, thereby providing adequate analgesia.*

Melissa A. Kling, DVM  
Brantley and Jordan Animal Hospital  
Macon, Georgia

## Effects of Some Dietary Phytoestrogens in Animal Studies: Review of a Confusing Landscape

Yang CZ, Bittner GD: *Lab Anim* 31(9):43–48, 2002.

### ABSTRACT

Dietary phytoestrogens are derived from plants and exhibit estrogenic or antiestrogenic effects due to their structural and/or functional similarity to estrogen. Isoflavonoids and lignans are the most common dietary phytoestrogens. Soy has been a universal dietary ingredient for years in both animal and human diets and is one of the principal contributors of phytoestrogens. Commercial lab animal diets have a broad range of isoflavone concentrations due to the varying amounts of soybeans used in the diets and unpredictable isoflavone content of the soybeans.

Recently, scientists recognized dietary phytoestrogens as a confounding factor in an endocrine study. Phytoestrogens in soy or other foodstuffs have also been incriminated in altering female reproductive and developmental factors and affecting mammary and prostatic tumor development and growth in lab animals. In addition, phytoestrogens may result in lower blood cholesterol levels. As a result, some scientists are contemplating the elimination of soy from all lab animal diets. Several significant experimental design complexities

involving phytoestrogens exist, and there have been no rigorously controlled scientific studies examining their effects; consequently, optimal levels of dietary phytoestrogens have not been established. Environmental influences such as mycoestrogens and bisphenol A, a plasticizer used in cage and plastic food bowl composition, can also potentially affect data that have been attributed to phytoestrogens and soy.

In summary, research studies on the effects of soy and/or phytoestrogens in mammals have generated contradictory and inconsistent results. This underscores the importance of using commercial suppliers that pay critical attention to ingredient quality and monitor batch-to-batch consistency. Although it may be valuable to eliminate soy and phytoestrogens from the diet in some studies (in particular estrogen-sensitive systems in developing mammals), the elimination of soy in the diets for all biologic and toxicologic studies is not warranted at this time. More meticulously controlled and precise research on the role of phytoestrogens and other environmental estrogens is needed.

**COMMENTARY**

*Rodents fed commercially available lab animal diets, rabbits fed alfalfa-based diets, and ferrets fed diets high in soy protein are all examples of diets that may contain phytoestrogens. Practitioners that see exotic mammals should be aware of*

*the potential long-term effects of dietary phytoestrogens, including development of mammary tumors in rats and vulvar swelling in rabbits. The influence of phytoestrogens on the overall health of pet small mammals seems to be limited, and further studies of true significance are needed before changes in dietary recommendations can be made.*

*Melissa A. Kling, DVM  
Brantley and Jordan Animal Hospital  
Macon, Georgia*

**Pathophysiological and Functional Aspects of the Megacolon-Syndrome of Homozygous Spotted Rabbits**

Bodeker E, Turck O, Loven E, et al: *Zentralbl Veterinarmed* 42(9):549-559, 1995.

**ABSTRACT**

This study showed that megacolon-syndrome is a hereditary disease of homozygous spotted rabbits (English spot or white spot), resulting in a decreased ability to absorb sodium across the wall of the cecum. This decreased sodium resorption results in reduced dry matter content of ingesta and increased ash within the cecum. A resulting characteristic of this disease is significantly more liquified ingesta in the cecum and distal colon. The study also looked at dry matter content of the intestinal tract and found a decreased proportion of dry matter within the wall of the large intestine (especially the cecum). Interestingly, homozygous spotted rabbits in this study also had a lower pH in the proximal duodenum (ingesta leaving the stomach is more acidic in these rabbits), hypertrophic adrenal glands, and decreased T<sub>3</sub> levels. The authors suggested that reduced blood levels of triiodothyronine in these rabbits resulted in myxedema of the large intestine gut wall, thus reducing dry matter content. The small intestine of homozygous rabbits, when compared to heterozygous rabbits, was shorter and the gut wall had an increased proportion of dry matter content, the cause of which remains unclear. Obstipation of the cecum is a characteristic end-stage form of the megacolon-syndrome and can be influenced by the sex and genetic background of the rabbit as well as environmental factors.

Overall body weight at slaughter and absolute weight of the carcass

Sixth Annual  
*International Conference on Exotics*  
**ICE 2004**  
Naples, Florida



— The Registry Resort —  
**May 6-8, 2004**  
Visit us online at  
[www.exoticdvm.com/icehome.htm](http://www.exoticdvm.com/icehome.htm)  
800-946-4782 or 561-641-6745

were decreased in homozygous spotted rabbits when compared to heterozygous spotted rabbits. However, the weight of the gut was markedly higher in homozygous rabbits. The authors proposed that this disparity was the result of increased catabolic metabolism brought about by this disease and the resulting lysis of muscle protein and fat tissue.

Unlike megacolon in other species (human, horse, mice), megacolon in homozygous spotted rabbits does not seem to be the result of a lack of ganglia in the myenteric and submucosal plexus of the distal colon.

## COMMENTARY

*If an unthrifty spotted rabbit presents to a veterinary practitioner with weight loss, chronic diarrhea, and repeated bouts of ileus, megacolon-syndrome should be on the differential diagnosis. Homozygous spotted rabbits may be termed "white spot," "Chaplins," or "Charlies" by rabbit breeders. These rabbits are not shown because of the lack of normal spotting patterns and are often sold into the pet trade. Most breeders cull homozygous English spotted rabbits and have commented on the fact that they are usually poor-doers. It is possible that a similar condition could exist in other breeds of rabbits. A prominent Lop breeder commented that Lop "Charlies" are more susceptible to enteritis in her experience. Further research may be helpful in determining successful treatment of this condition. Megacolon conditions in other species of animals, such as humans and cats, traditionally involve protracted and involved extensive supportive care and surgery.*

Jennifer Graham, DVM, DABVP (Avian)  
Animal Emergency and Referral Center  
Lynnwood, Washington

## Periodontal Bacteria in Rabbit Mandibular and Maxillary Abscesses

Tyrrell KL, Citron DM, Jenkins JR, Goldstein EJ: *J Clin Microbiol* 40(3):1044-1047, 2002.

### ABSTRACT

Odontogenic abscesses are common in rabbits; however, treatment is often difficult or unsuccessful. The abscessed material is usually caseous and surrounded by a capsule, thus drainage is difficult and antibiotics have difficulty penetrating the site of infection. Conventional treatment usually involves antibiotic therapy and surgical excision. Complete removal of the nidus of infection may be difficult; therefore, recurrence with fistulation, osteomyelitis, and retrobulbar involvement is common.

Odontogenic abscesses from 12 rabbits were excised and cultured aerobically and anaerobically. The samples were taken percutaneously in order to avoid contamination with normal gingival flora. Two samples were taken from each animal: one from the center of the excised abscess and one

from the capsular margin or surrounding bone.

All samples yielded potentially pathogenic bacteria that were consistent with organisms cultured from human periodontal disease, including anaerobes *Fusobacterium nucleatum*, *Prevotella heparinolytica*, *Peptostreptococcus micros*, *Actinomyces israelii*, and *Arcanobacterium haemolyticum*, and aerobes *Streptococcus intermedius* and *Streptococcus* spp.

Susceptibility testing was performed on all potential pathogens and demonstrated 100% susceptibility to clindamycin and chloramphenicol; 96% to penicillin, ceftriaxone, and cefazolin; 86% to azithromycin and tetracycline; 54% to metronidazole and ciprofloxacin; and 7% to trimethoprim-sulfamethoxazole. The authors suggest that when culture and sensitivity results are not available, the clinician should carefully consider these susceptibility results as well as those from similar studies in humans and other mammals.

## COMMENTARY

*Notable findings in this study include the absence of Pasteurella multocida and the marginal sensitivity of cultured organisms to fluoroquinolones and trimethoprim-sulfamethoxazole. These facts need to be considered when formulating a treatment plan. Also, it should be noted that oral administration of some of the antibiotics investigated, specifically beta-lactams and clindamycin, can cause a fatal intestinal enterotoxemia in rabbits. As a result, new methods for the parenteral administration of clindamycin, ceftiofur, and penicillins, including the use of antibiotic-impregnated polymethylmethacrylate (AIPMMA) beads, are being investigated.*

*Also of interest was the finding that in approximately one-half of the cultured abscesses the purulent center yielded a greater variety or quantity of bacterium than cultures of the abscess margin or wall. Abscess centers have previously been reported to be poor sources of culture material.*

Jeffrey A. Mills, DVM  
Smith Animal Clinic  
Ramsey, Indiana

## Prevention of Rat Mammary Carcinoma Utilizing Leuprolide as an Equivalent to Oophorectomy

Jett EA, Lerner MA, Lightfoot SA, et al: *Breast Cancer Res Treatment* 58:131-136, 1999.

### ABSTRACT

This report summarizes a research project comparing the effects of leuprolide acetate (Lupron, TAP Pharmaceuticals, Deerfield, IL) with oophorectomy on reducing the incidence of mammary tumors in laboratory rats with induced carcinomas. Leuprolide acetate is a gonadotropin-releasing hormone analogue, which in humans results in down-regulation of luteinizing hormone and follicle-stimulating hormone. 7,12-Dimethylbenzanthracene (DMBA) is

a compound shown to reliably induce carcinoma formation in intact virgin female rats. Rats given DMBA were divided into eight groups, including a no additional treatment control group. Other groups received Lupron only given 2 weeks prior to and 2 weeks after administration of DMBA; Lupron given 4 weeks prior to and 4 weeks after administration of DMBA; Lupron given 2 weeks prior to DMBA and 6 weeks after administration of DMBA; Lupron given 2 weeks prior to and continued every 4 weeks thereafter until the end of the experiment; and Lupron given 2 weeks prior and 6 weeks after administration of DMBA with the addition of bromocriptine, a dopamine agonist. The two remaining groups were oophorectomized 4 weeks and 2 weeks prior to administration of DMBA. Both surgical groups of rats then received estrogen replacement therapy until the end of the experiment. All rats receiving Lupron were given SC injections of the 30-day depot form, which releases 100 µg/kg/day.

Rats were euthanized and necropsied 16 weeks after administration of DMBA. All control rats developed tumors. No tumors developed in animals that were oophorectomized or given Lupron 4 weeks prior to DMBA, or in the rats given Lupron throughout the length of the experiment. Occasional tumors developed in rats that were oophorectomized or given Lupron 2 weeks prior to administration of DMBA. The authors concluded that chemical oophorectomy with leuprolide is as effective as surgical oophorectomy in inhibiting tumors induced by DMBA.

### COMMENTARY

*This report is of great interest to practitioners seeking to prevent development of all too common mammary tumors in pet rats. Before the results of this experiment can be extrapolated to pet rats in practice, it must be understood that not all rat mammary tumors are carcinomas and may not respond exactly like this particular laboratory model with DMBA-induced carcinoma. According to Drury Reavill, DVM, histopathology of rat mammary tumors submitted by private practitioners are more frequently fibroadenomas. Out of 75 submissions, Dr. Reavill found 84% to be fibroadenomas, with the rest a mixture of hyperplasia, adenoma, and only 3 of 75 (4%) being carcinomas.<sup>1</sup> This experiment also does not address the issue of whether or not oophorectomy (or ovariectomy) and/or Lupron will prevent recurrence in older rats that have undergone surgical removal of established neoplasms. The success of this experiment does suggest a potential therapeutic option that warrants further exploration.*

Angela M. Lennox, DVM  
Avian and Exotic Animal Clinic of Indianapolis  
Indianapolis, Indiana

<sup>1</sup>Reavill D. Zoo/Exotic Pathology Service. Citrus Heights, CA. Personal communication.

## Temporary Tube Cystostomy as a Treatment for Urinary Obstruction Secondary to Adrenal Disease in Four Ferrets

Nolte DM, Carberry CA, Gannon KM, Boren FC: *JAAHA* 38(6): 527-532, 2002.

### ABSTRACT

Based on clinical signs, clinical pathology, radiology, and ultrasonography, four castrated male ferrets were diagnosed with adrenal disease with secondary urinary obstruction. All four ferrets demonstrated unproductive stranguria with large- to moderate-sized, turgid, nonexpressible urinary bladders. Hyperplasia or cystic change in the periprostatic tissue, secondary to adrenal-associated elevated androgen levels, can cause urethral compression and complete urethral obstruction.

Treatment for a ferret with this condition involves adrenalectomy and urinary diversion. The options available for managing urethral obstruction include cystocentesis, urethral catheterization, urethrotomy followed by catheterization, or placement of a cystostomy catheter. Urinary catheters can be difficult to place and have a high complication rate of blockage or self-induced removal. As a result, the authors chose to place cystostomy catheters at the time of surgical adrenalectomy in four ferrets with a history of preoperative urinary obstruction, nonexpressible bladders, and prostatomegaly, prostatic cysts, or periurethral swelling identified at surgery. During exploratory celiotomy, a 5- or 8-French Foley catheter was passed through a ventral abdominal paramedian incision and then into the bladder lumen, where it was secured with a purse-string suture. The catheter was inflated with saline and then used to bring the bladder in close apposition to the body wall where it was secured. A light abdominal wrap or body stockinet was applied along with an Elizabethan collar. The cystostomy tube was drained every 2 hours for the first few days postoperatively, then every 4 to 6 hours until normal voiding was attained. Voluntary urination resumed in a median 60 hours (range, 6 to 120 hours). Cystostomy catheters were pulled when it was assured that the ferrets were urinating on their own without difficulty. Complications included mild incisional swelling in one ferret and orally induced catheter damage in two ferrets.

### COMMENTARY

*Increased androgen blood levels, secondary to adrenal disease, may periodically result in prostatic hyperplasia or periprostatic cysts in male ferrets. Complete urinary obstruction may result, and the tube cystostomy offers veterinarians another choice (versus urethral catheterization or urethrostomy) for temporary urinary diversion until androgen levels are controlled with appropriate treatment of adrenal disease. Ferrets have a strong inclination for chewing on soft rubber products, and the Foley catheter used in this procedure is no*

*exception. As a result, physical prevention via body bandage wraps that incorporate the catheter and careful monitoring for self-induced catheter trauma are essential.*

*Peter G. Fisher, DVM  
Pet Care Veterinary Hospital  
Virginia Beach, Virginia*

## Echocardiographic Examination of Healthy White New Zealand Rabbits in the Awake State and the Anesthetized State

Breithardt A: Veterinary dissertation at the Ludwig-Maximilians University, Munich, Germany, 2001.

### ABSTRACT

The aim of this study was to establish normal values for echocardiography in rabbits. The study was performed with 20 New Zealand whites. The animals were examined twice, once awake and once anesthetized. The anesthetic agent was a ketamine-xylazine mixture given IM. The weight of the animals was between 2.45 kg and 3.35 kg with a mean of 2.92 kg. The study used standard techniques in order to assess physical characteristics of the heart as well as extensive approaches for the assessment of the hemodynamics presented in the publication.

The measured physical parameters, which are the most important measurements for the clinician, are summarized in the following table. Please note that only four values were statistically significantly different in the two different states of examinations (marked with a star). Unfortunately, the paper did not give measurements for the aorta or the left atrium, which are commonly used parameters in the echocardiologic exam. In a healthy rabbit, one can probably assume that the value for the aorta

and the diameter of the left ventricular outflow tract should not differ significantly.

|                   | <i>Awake</i>  | <i>Anesthetized</i> |
|-------------------|---------------|---------------------|
| TrPD (cm)         | 0.514 ± 0.077 | 0.534 ± 0.105       |
| LVOTD (cm)        | 0.723 ± 0.065 | 0.714 ± 0.064       |
| RVD-d (cm)        | 0.545 ± 0.144 | 0.466 ± 0.110       |
| IVS-d (cm)        | 0.217 ± 0.056 | 0.199 ± 0.033       |
| IVS-s (cm)        | 0.357 ± 0.038 | 0.336 ± 0.066       |
| LVPW-d (cm)       | 0.274 ± 0.041 | 0.267 ± 0.047       |
| LVPW-s (cm)*      | 0.503 ± 0.046 | 0.473 ± 0.060       |
| LVD-d (cm)        | 1.540 ± 0.091 | 1.480 ± 0.081       |
| LVD-s (cm)*       | 1.009 ± 0.091 | 1.074 ± 0.089       |
| FS (%)*           | 34.5 ± 4.9    | 28.5 ± 3.8          |
| Heart rate (bpm)* | 234 ± 26      | 198 ± 37            |

TrPD = Truncus pulmonalis diameter; LVOTD = Diameter of the left ventricular outflow tract; RVD-d = End diastolic diameter of the right ventricle; IVS-d = Intraventricular septum at end diastole; IVS-s = Intraventricular septum at end systole; LVPW-d = Left ventricular posterior wall at end diastole; LVPW-s = Left ventricular posterior wall at end systole; LVD-d = End diastolic diameter of the left ventricle; LVD-s = End systolic diameter of the left ventricle; FS (%) = fraction shortening.

### COMMENTARY

*Scientific publications on rabbit echocardiology are rare. The confirmation of cardiac pathology is difficult due to the lack of established and published basic parameters. The values in this publication can help guide the experienced cardiologist to a tentative diagnosis when examining the rabbit heart. More data is needed in this interesting and popular field.*

*Jörg Mayer, DrMedVet, MSc  
Tufts University School of Veterinary Medicine  
North Grafton, Massachusetts*



P.O. Box 396  
Weare, NH 03281-0396

PRSR STD  
U.S. POSTAGE  
PAID  
BENSALEM, PA  
PERMIT #118