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## Melatonin Implants: An Option for Use in the Treatment of Adrenal Disease in Ferrets

**Jerry Murray, DVM**  
*Animal Clinic of Farmers Branch  
Dallas, Texas*

Peer-Reviewed Article

Adrenal gland disease (hyperadrenocorticism) is very common in middle-aged to older neutered ferrets. It is different from human, canine, equine, and feline hyperadrenocorticism (Cushing's disease) because in ferrets the adrenal sex hormones and the adrenal androgens are overproduced instead of cortisol.<sup>1</sup> Common clinical signs may include alopecia, vulvar enlargement in females, pruritus, return of sexual or aggressive behavior, and a noticeable increase in musky odor (Figure 1). Additional clinical signs may include prostatic hyperplasia, prostatic cysts, prostatic abscesses, prostatitis, estrogen-induced bone marrow toxicity, mammary gland hyperplasia, cystitis, muscle atrophy, and lethargy. Clinical manifestation of signs may vary depending on which sex hormone is elevated, and clinical signs do not always correlate with the size of the adrenal gland or degree of adrenal gland pathology. In some ferrets, seasonal shedding with minor alopecia may be a normal physiologic occurrence and should not be confused with evidence of adrenal disease. Diagnostics are needed to definitively confirm the presence of adrenal disease. These include the sex hormone serum panel (the University of Tennessee has the only validated test for use on ferrets), ultrasonography or laparotomy to assess the glands, and biopsy with histopathology.

The current theory on pathogenesis of ferret adrenal disease is that lack of negative gonadal hormonal feedback on hypothalamic gonadotropin-releasing hormone (GnRH) as a result of neutering leads to persistently elevated gonadotropic luteinizing hormone (LH), which may induce hyperplastic and/or neoplastic adrenocor-

tical enlargement via functional LH receptors.<sup>2</sup> LH binds with these LH receptors, causing the adrenal gland to overproduce one or more of the following sex hormones and androgens: estradiol, androstenedione, 17 $\alpha$ -hydroxyprogesterone, and dehydroepiandrosterone sulfate.<sup>1,2</sup> This results in the physical and behavioral changes dominated by features consistent with excessive production of these sex hormones and androgens.

Medical therapy of ferret adrenal disease may be the preferred treatment option in geriatric ferrets, in ferrets in which concurrent illness makes them high-risk anesthetic and surgery patients, when owners decline surgery, or in cases in which the adrenal glands cannot be removed surgically because of their size or location. Because of the association of adrenal disease with persistently elevated circulating LH levels and the effects of those elevated levels on adrenal LH-receptor function, drugs capable of lowering LH should suppress the overproduction of adrenal gland sex steroids and thereby control the subsequent associated clinical signs seen in ferrets with adrenal disease.<sup>3</sup> Melatonin appears to be a suitable agent for medical therapy in affected ferrets. In fact, recent work at the University of Wisconsin has shown that daily oral administration of melatonin can help control the clinical signs associated with adrenal gland disease.<sup>4</sup>

### HOW MELATONIN WORKS

Melatonin is the primary hormone produced by the pineal gland. Melatonin is directly and indirectly involved in activating (in the spring/summer) and terminating (in the fall/winter) the



**Figure 1.** Ferret with clinical signs of adrenal gland disease. Generalized alopecia, weight loss, muscle atrophy, and a swollen vulva are common with chronic cases.

ferret's natural breeding season. As day length decreases in the fall, higher levels of melatonin are released during the dark hours. When ferrets are exposed to the dark for more than 12 hours/day, the pineal gland maintains a high circulating melatonin concentration that in turn suppresses release of GnRH and subsequently inhibits the release of pituitary LH and follicle-stimulating hormone.<sup>5,6</sup> This suppresses the breeding season and causes the ferret to put on its winter haircoat and increase body fat.

Supplemental melatonin is available in oral tablets (1 and 3 mg), a liquid solution (2.5 mg/ml), and an injectable implant approved by the FDA for use in the mink and fox industries to promote growth of the thick winter haircoat.<sup>7</sup> Previous work in the 1970s and 1980s using injectable melatonin on intact ferrets proved that melatonin could bring a ferret out of estrus.<sup>8</sup>

### THE PILOT STUDY

In conjunction with James H. Johnson, DVM, MS, DACZM (Clinical Assistant Professor, College of Veterinary Medicine, Texas A&M University), I completed a clinical study on the treatment of ferret adrenal disease using the male mink melatonin implant (5.4 mg, Prime-X melatonin implants, Neo Dynamics, LLP, Lake Delton, WI). This depot product releases melatonin over a 3- to 4-month period. It was speculated that a constant-release melatonin implant (Figure 2) might work as well as or better than a once-daily tablet and eliminate the owner compliance problems associated with administration at a specified time (7 to 8 hours after sunrise). Because no documented blood levels using this product in mink or ferrets have been published and because of the expense associated with commercial blood assays, blood melatonin levels were not measured.

Neutered pet ferrets (38 males and 32 females) showing clinical signs consistent with adrenal gland disease were given the male mink melatonin implant subcutaneously in the intrascapular region. Clinical signs were then monitored



**Figure 2.** The male mink melatonin implants and the implanter. The implants are about the size of a piece of rice.



**Figure 3.** Male adrenal ferret after receiving the melatonin implant. Note the thick winter pelage and the fat pad on the lateral neck.

subjectively. Swollen vulvas returned to normal in 1 to 2 weeks. Alopecia resolved and thick “winter coats” grew within 6 to 8 weeks after implant administration. Several owners commented that this was the ferret’s “best coat ever.” Most of the ferrets became more active, experienced an increase in appetite, and gained weight, all of which reflect melatonin’s effect on “winter weight.” Several ferrets developed large fat pads on the lateral aspect of their necks (Figure 3). Pruritus usually resolved in 1 to 3 weeks. Most of the ferrets were followed for only 3 to 4 months, so there are no data on time to recurrence of clinical signs. There was no noticeable enlargement of the adrenal glands based on abdominal palpation, but ultrasonographic measurements were not performed during this study. The only side effect noted was lethargy, which was seen in practically all ferrets during the first 3 to 5 days after implantation. Of the 70 animals receiving implants, only one female ferret, which had a large right adrenal carcinoma and concurrent lymphoma, did not respond well to the melatonin implant.

Adrenal hormones were monitored in only one ferret in this study. The level of  $17\alpha$ -hydroxyprogesterone in this neutered male ferret decreased from 0.27 to 0.0 nmol/L (100% decrease), and androstenedione decreased from 14.0

to 6.6 nmol/L (51% decrease). However, estradiol level in this ferret increased from 159.0 to 187.6 pmol/L (18% increase). In the Wisconsin oral melatonin study,<sup>4</sup> estradiol, 17 $\alpha$ -hydroxyprogesterone, dehydroepiandrosterone sulfate, and prolactin were decreased after 4 months. It is interesting to note that a reduction of androstenedione was not seen with oral melatonin but was seen in one ferret with the implant.<sup>4</sup> Since hormone levels increased after 8 months in the oral melatonin study,<sup>4</sup> additional pre- and postimplant adrenal hormone panels need to be performed to monitor the long-term effectiveness of the mink melatonin implants.

### SAFETY

Ferrets with adrenal gland disease appeared to benefit clinically from the melatonin implants. These implants appeared to be safe, although no blood analysis or histopathology was done during this study. No overt clinical adverse reactions were seen. Implant toxicity studies were performed in mink before the implant received FDA approval. Ten mink kits (8 to 10 weeks old) were injected with 10 implants each (containing 7.82 mg for a total dose of 78.2 mg melatonin). This represented an average dose of 80.6 mg/kg for the five male kits and 123.9 mg/kg for the five female kits. After 5 months, there were no signs of toxicity on gross or histopathologic examination of the adrenal, kidney, heart, liver, brain, spleen, ovaries, testes, thyroid, or thymus.<sup>9</sup> Body weight records from this study showed that the treated males gained an average of 324 g more than untreated male controls.

A second study was performed in which adult minks received 10 implants each (containing 10 mg for a total dose of 100 mg melatonin). Again, there were no signs of toxicity or adverse reactions related to the melatonin implants.<sup>10</sup> Summary data from the numerous clinical field trials involving 13,619 male kits, 11,623 female kits, 5,847 female adults, and 25 male adults (a total of 31,114 mink) showed no signs of toxicity or adverse reactions related to the melatonin implants.

Similarly, in a dose-determination study conducted at the University of Saskatchewan, 15 male ferrets were given a single melatonin implant containing 2.7 mg (half the dose of the mink implant used in this study) with no adverse reactions.<sup>9</sup> In a study conducted in New Zealand, thirteen 3-month-old ferret kits received an 8-mg melatonin implant in late summer. They then received a second implant at the same time the following year. No adverse reactions were reported during this 16-month study.<sup>11</sup>

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Pharmacokinetic work performed on the domestic ferret showed elution within 30% to 33% in each of the first 3 months, with only a small amount of melatonin residually eluted up to 273 days after implantation.<sup>9</sup> Toxicity studies were not performed in ferrets.

### DISCUSSION

Further long-term studies with the melatonin implants, including repeated implantation, are needed. Future studies should include long-term monthly adrenal hormone panels with monthly adrenal gland ultrasonographic measurements. In addition, specific testing for melatonin receptors on ferret adrenal glands, prostate, and bone marrow needs to be performed. Melatonin receptors have been found on avian, primate, ovine, rabbit, and rodent adrenal glands.<sup>12-19</sup> In birds, melatonin directly and indirectly downregulates adrenal activity.<sup>12</sup> In primates, melatonin inhibits corticotropin-stimulated cortisol production.<sup>13</sup> In sheep, melatonin did not increase 17,20-desmolase, 11 $\beta$ -hydroxyandrostenedione, or 11-ketoandrostenedione.<sup>14</sup> In rabbits, melatonin inhibited the adrenal cortex and reduced the nuclear volume as well as the cellular activity. In the zona reticularis, the nuclear volume was reduced by almost half during the short days of the winter when melatonin was increased.<sup>15</sup> The zona reticularis is the zone believed to make adrenal sex hormones and the adrenal androgens.



**Figure 4.** Large right adrenal gland and liver lobes. Untreated adrenal tumors can become large, space-occupying masses, but melatonin may help prevent this.

Even more extensive research has been done with rodent adrenal glands. In hamsters, melatonin decreased the size of both the zona reticularis and the zona fasciculata. This study also showed melatonin to decrease the secretion of adrenal androgens.<sup>16</sup> A study in mice showed that melatonin significantly decreased the mean mitotic activity rate of the adrenal cortex in both male and female mice.<sup>17</sup> In a similar study, melatonin suppressed the proliferogenic effect of pinealectomy on rat adrenocortical cells.<sup>18</sup> In a rat study, melatonin caused a notable atrophy of zona fasciculata cells and lowered the plasma level of corticosterone. Melatonin also enhanced the intracellular catabolism of corticosterone, which depressed the growth and the steroidogenic capacity of rat adrenocortical cells.<sup>19</sup> These four rodent studies and the previous rabbit study suggest that melatonin receptors may be directly involved in the inhibitory control of adrenocortical cell proliferation. If ferret adrenal glands have melatonin receptors and melatonin inhibits adrenal cell proliferation, it may be speculated that melatonin could prevent a hyperplastic or neoplastic adrenal gland from enlarging (Figure 4). No enlargement was seen in the Wisconsin oral study via ultrasonographic measurements over 12 months, and no palpable enlargement was detected on deep abdominal palpation during this implant study.<sup>4</sup>

There are also melatonin receptors (mt1) on human and rat prostates.<sup>20–28</sup> Melatonin inhibits proliferation of both androgen-sensitive and some hormone-independent prostatic cancer cells along with benign hyperplastic cells.<sup>20–28</sup> In addition to decreasing cancer cell growth, melatonin can also induce cellular differentiation of the cancer cells.<sup>24</sup> In benign prostatic hyperplasia, melatonin receptors are present on the glandular epithelial cells, and these receptors can be responsible for a reduction in cell growth and viability.<sup>27</sup> In a rat prostate study, melatonin reduced the volume of prostatic stroma and epithelium and the height of the epithelium.<sup>28</sup> If similar receptors exist in male ferrets, then melatonin may help with the treatment of adrenal-associated prostatic problems by lowering circulating androgen levels and directly through the antiproliferative effects of the melatonin receptors on the prostate. A reduction in prostatic size was seen in the Wisconsin oral melatonin study.<sup>4</sup>

Melatonin is also important in the bone marrow. Recent

studies in mice, rats, and humans have shown very high levels of melatonin in the bone marrow.<sup>29–32</sup> The bone marrow synthesizes melatonin, and the melatonin level in the bone marrow is generally two to three times that in the bloodstream. Melatonin helps to protect bone marrow cells from oxidative damage and stimulates hematopoiesis.<sup>29–32</sup> Melatonin also helps to stimulate platelet generation. In a human study, nightly administration of 20 mg of melatonin orally for 7 days normalized the platelet count in nine of 12 (75%) cancer patients. It also prevented platelet decline during chemotherapy with epirubicin in these patients.<sup>33</sup> From these data, one can speculate that melatonin may be helpful in preventing the estradiol-induced thrombocytopenia and potentially the moderate to severe anemia seen in some ferrets with chronic, untreated adrenal disease and elevated estradiol levels.

Melatonin receptors are present on human mammary gland cancer cells, and melatonin may inhibit mammary cancer in multiple ways.<sup>34–40</sup> At physiologic concentrations, melatonin inhibits the proliferation of cancer cells, acts as a differentiating agent, and lowers their invasive and metastatic potential. It can actually induce apoptotic cell death in some cancer cells.<sup>36</sup> Melatonin also downregulates the expression of estrogen receptor  $\alpha$  and inhibits the binding of the estradiol–estrogen receptor complex to the estrogen-response element in the cancer cell DNA.<sup>35,37,39</sup> Melatonin also reduces linoleic acid uptake by the cancer cells. Linoleic acid is metabolized to a potent mitogen inside the cancer cell, which can stimulate tumors to grow up to seven times faster.<sup>38</sup> Very recently it has been reported that melatonin also modulates aromatase activity in breast cancer cells. By reducing aromatase activity, melatonin reduces the local estrogen biosynthesis, even when aromatase activity is stimulated by cAMP or cortisol. Melatonin downregulates aromatase activity at the transcriptional level.<sup>40</sup> If melatonin receptors are present on ferret mammary gland tissue, these actions could decrease mammary gland hyperplasia or neoplasia secondary to estradiol stimulation from adrenal gland disease. Furthermore, if the estrogen receptors in the bone marrow and vulva are downregulated by melatonin and if aromatase activity were inhibited by melatonin in other cells such as the bone marrow and vulva (and estrogen levels could be lowered at these local levels), then this would be very beneficial in ferrets with estrogen-induced anemia and/or thrombocytopenia and in those with vulvar enlargement. Note: A reduction in vulvar size was seen in both the Wisconsin oral study and in this implant study.<sup>4</sup>

Melatonin may also provide ferrets with adrenal disease additional benefits as an antioxidant, appetite stimulant, and bone-density protector. Melatonin is an efficient antioxidant and a highly efficient free-radical scavenger; it also increases glutathione peroxidase activity. In addition, melatonin increases antigen presentation and expression of major histocompatibility complex class II molecules, increases the production of interleukin-1 and -2, and decreases insulin-like growth factor-1.<sup>41,42</sup> Theoretically, this increased pro-

duction of immunomodulators may reduce susceptibility to viral and bacterial infections in ferrets. Increased interleukin-2 and lower insulin-like growth factor-1 levels in some species have been shown to have antineoplastic effects.<sup>42</sup> Melatonin is also an appetite stimulant.<sup>43-45</sup> Most ferrets in this study had a noticeable increase in appetite with weight gain, and male mink kits also gained more weight (324 g on average) than untreated control kits in the toxicity study.<sup>9</sup> This increase in appetite can help some ferrets that may have lost weight from chronic adrenal gland disease gain weight (i.e., their “winter weight”). It has recently been suggested that ferrets with adrenal gland disease may have a lower bone density.<sup>46</sup> Recent reports indicate that high levels of follicle-stimulating hormone in humans may lower bone density.<sup>47,48</sup> Recent research has also showed that melatonin can increase bone mass; thus, if ferrets actually have a lower bone density as a result of elevations in follicle-stimulating hormone (several studies currently in progress), melatonin may increase their bone mass.<sup>49,50</sup> There have been no documented clinical manifestations of decreased bone density or increased bone pathology in ferrets with elevated sex steroids from adrenal disease.

Since this pilot study was completed, I have used roughly 150 melatonin implants. In general, the response is faster when the implant is administered during the fall and winter than during the spring and summer. Some of the ferrets had a new haircoat in as little as 2 weeks after implantation during the fall or winter. Even ferrets with chronic adrenal disease and generalized alopecia over the majority of the body (Figure 1) have responded well. In my experience, the implants can be safely used in combination with other human medications frequently used to treat adrenal gland disease and its secondary complications.<sup>3</sup> It can be used with leuprolide acetate depot (Lupron Depot, TAP Pharmaceutical Products, Lake Forest, IL) and finasteride (Propecia or Proscar, Merck) or bicalutamide (Casodex, AstraZeneca) to treat prostatic cases. It can also be used with leuprolide acetate, anastrozole (Arimidex, AstraZeneca), and epoetin alfa (Epogen or Procrit, Amgen) to treat cases of estrogen-induced anemia, or it can be used with just leuprolide acetate and anastrozole to treat cases of estrogen-induced thrombocytopenia and/or mammary gland hyperplasia.

## SUMMARY

Ferrets with presumed adrenal gland disease showed a decrease in clinical signs following implants of melatonin. The implants were deemed safe and were very easy to administer. Most ferrets were merely distracted with a treat, such as Nutri-Cal (CSI Chemical Corporation, Bondurant, IA) or FerreTone (Eight in One Pet Products, Hauppauge, NY), as the implant was injected under the skin in the intrascapular region. Melatonin may be helpful in preventing an adrenal tumor from enlarging: The Wisconsin study showed no increase in the size of the adrenals by ultrasonographic measurements over 12 months, and I did not palpate

any tumor enlargement during my study. Based on my experience and the University of Wisconsin study, melatonin may also be useful in treating an enlarged prostate gland; based on my experience and the mechanisms of action, there are no contraindications against combining the implants with leuprolide acetate depot and finasteride or bicalutamide. Melatonin may also be useful in treating estrogen-induced anemia, thrombocytopenia, and mammary gland hyperplasia. There are no known contraindications for concurrent usage with leuprolide acetate depot, anastrozole, and epoetin alfa to treat estrogen-induced anemia. Similarly, it can be safely combined with leuprolide acetate depot and anastrozole to treat estrogen-induced thrombocytopenia and/or mammary gland hyperplasia.

The antioxidant properties and appetite stimulation might be clinically beneficial for ferrets with adrenal disease. These properties may also be useful for ferrets undergoing chemotherapy for other concurrent neoplasms. In addition, melatonin may help decrease the bone marrow suppression and increase the intracellular concentrations of doxorubicin by inhibiting doxorubicin efflux from the cancer cells.<sup>51,52</sup> Melatonin may even help to increase bone density. In conclusion, the melatonin implants marketed for male mink are an inexpensive treatment option that can be used alone or in combination with other therapies for ferret adrenal disease.

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# Melatonin Study with Four Intact Adult Male Ferrets and Two Female Ferrets with Adrenal Disease

*Cathy A. Johnson-Delaney, DVM, DABVP (Avian)*

*Washington Ferret Rescue & Shelter  
Bothell, Washington*

In January 2004, a short study was undertaken to look at the effects of melatonin implants in intact adult male ferrets in the season of reproductive activity. Although there was not a statistical number of ferrets involved, we wanted to see if the implants could suppress sex steroidogenesis. These ferrets had been monitored for 2 years as part of the control group of intact animals in the ferret adrenal disease study that I conducted in collaboration with Jack Oliver, BS, MS, DVM, PhD, of the University of Tennessee. These ferrets had shown complete suppression of sex steroidogenesis in previous breeding seasons using leuprolide acetate 30-day depot (Lupron Depot 7.5 mg, TAP Pharmaceutical Products, Lake Forest, IL).

Jerry Murray, DVM, provided the implants, which were the commercial implants (5.4 mg melatonin) used in the mink industry to promote coat growth for pelting. Four intact adult male ferrets were sedated using ketamine and acepromazine for the purpose of collecting baseline blood samples for hormone panels to be analyzed at the University of Tennessee. Three males (Crais, Husky, and Bubba) received the melatonin implants, and one (Nick) received an AVID microchip as the placebo, which was placed in the subcutaneous intrascapular region in the same place as the melatonin implants (using the same gauge needle). Blood for hormone panel analysis was collected from all ferrets at 30, 60, and 90 days after implantation. In addition, observations of testicle size and behavior were made (for future publication). The results (Table 1) have not been analyzed statistically but illustrate that the implants did not seem to suppress sex steroid production. Production in the control male decreased as expected throughout the study as the season progressed. Based on these results, it would be difficult for me to recommend the use of the implant alone to suppress sex steroid production associated with adrenal disease during the peak hormone season, at least in male ferrets.

No change was noted in the males' appetites or sexual behavior during the study. However, the three that received the implants were judged to be less active than usual based on their activity in playgroups.

A fourth implant was placed in one of the two remaining female ferrets in the Lupron versus adrenalectomy study. A microchip was used as the placebo in the "control" ferret (Bonnie). These females had been stable on Lupron for more than 2 years, and both had adrenals that appeared just slightly enlarged on ultrasonography performed shortly before implantation. The melatonin implant appeared to be similarly effective as monthly administration of Lupron. However, this is not a statistical number for efficacy determination, and no second

implant was inserted at 90 days nor was the study continued. This was because of the side effects in this 560-g female: She became so lethargic within 2 weeks of implantation that she needed to be roused daily to eat. This was not her normal behavior, and no physical or medical reason for the lethargy could be found. Her activity level gradually increased during the study period and was deemed normal by the end of April. Lupron therapy was resumed in May, and this ferret remains stable hormonally with normal daily activity and behavior to date. This leads me to put a note of caution on using the implant in ferrets weighing less than 600 g, as the dosage may be too high. Based on other species, extreme lethargy is one of the signs of melatonin overdose. Comparisons between the two female ferrets with adrenal disease appear in Table 2.

Given the data from this extremely small number of trials, I would not want to use melatonin alone to control sex steroid production in ferrets diagnosed with adrenal disease on the basis of hormone panels, ultrasonography, and/or surgery with biopsy or excision. It may have some effect as an adjunctive therapy. In mink, implants are more effective when placed in the fall to effect seasonal coat change. An in-depth study of the implants in both intact ferrets and ferrets with adrenal disease through an entire year with hormone panels and adrenal size measured monthly may provide better information regarding whether efficacy improves during certain seasons.

According to FDA information, the pharmacokinetic work on the implants was done in domestic ferrets. It was found that the implant elutes around 30% of its dosage in the first 3 months but that some melatonin is still being eluted up to 273 days. Data published by the FDA do not discuss toxicity because the implant was designed to be a one-time injection: Mink are pelted following use of the implant when coat growth is optimal. In mink, repeated implants have a diminishing effect on coat change because a refractory period is reached; this may also be related to the time of year in which melatonin is administered. I could not find information about blood levels of melatonin persisting in ferrets past the 90-day mark, but theoretically, if additional implants were placed every 90 days, it may be possible to reach a toxic level. Furthermore, ferrets may become refractive to the effects of melatonin as a result of time of year, immunologic response to exogenous material of the implant, or the stage of adrenal disease.

Additional controlled studies using the commercial implants are warranted, although anecdotally they do promote hair growth and seem to control clinical symptoms. Outward cessation of some clinical signs should not be used as a full clinical measurement of control of the disease pro-

**TABLE 1. Hormone Levels in Four Intact Adult Male Ferrets Following Placement of a Melatonin Implant**

<i>Hormone</i>	<i>Day</i>			
	<i>1: Baseline<sup>a</sup> (1/10/2004)</i>	<i>30 (2/14/2004)</i>	<i>60 (3/15/2004)</i>	<i>90 (4/10/2004)</i>
<b>GROUPED BY FERRET</b>				
<b>Nick (Control)</b>				
Estradiol (pmol/L)	162	194	241	220
17-OH progesterone (nmol/L)	6.18	8.12	17.6	1.48
Androstenedione (nmol/L)	400.3	1,146.8	377.3	98.4
<b>Crais</b>				
Estradiol (pmol/L)	188	213	227	183
17-OH progesterone (nmol/L)	5.51	12.67	3.33	2.58
Androstenedione (nmol/L)	1,108.4	859.6	265.6	212.5
<b>Husky</b>				
Estradiol (pmol/L)	96	140	197	242
17-OH progesterone (nmol/L)	3.09	3.73	2.12	10.12
Androstenedione (nmol/L)	512.3	441.5	140.6	338.9
<b>Bubba</b>				
Estradiol (pmol/L)	158	159	175	182
17-OH progesterone (nmol/L)	6.73	4.06	2.42	3.18
Androstenedione (nmol/L)	568.5	79.9	75	328.8
<b>GROUPED BY HORMONE</b>				
<b>Estradiol (pmol/L)</b>				
Nick (Control)	162	194	241	220
Crais	188	213	227	183
Husky	98	140	197	242
Bubba	158	159	175	182
<b>17-OH Progesterone (nmol/L)</b>				
Nick (Control)	6.18	8.12	17.6	1.48
Crais	5.51	12.67	3.33	2.58
Husky	3.09	3.73	2.12	10.12
Bubba	6.73	4.06	2.42	3.18
<b>Androstenedione (nmol/L)</b>				
Nick (Control)	400.3	1,146.8	377.3	98.4
Crais	1,108.4	859.6	265.6	212.5
Husky	512.3	441.5	140.6	338.9
Bubba	568.5	79.9	75	328.8

<sup>a</sup>Implants placed after baseline blood samples were collected.

gression. Practitioners need to continue to monitor hormones, adrenal size and mass growth, metastasis, and prostate health regardless of modalities used in the treatment of adrenal disease. While the melatonin implants may be useful adjuncts to other therapies, I would not use them

without appropriate monitoring and diagnostics and possibly additional medications.

Another major reason to use melatonin has been cost. However, I do not see the cost factor to be a significant reason to choose the implants as a sole treatment. In addition,

**TABLE 2. Hormone Levels in Two Female Ferrets with Adrenal Disease Following Placement of a Melatonin Implant versus Lupron Depot 7.5 mg**

<i>Hormone<sup>a</sup></i>	<i>Day</i>			
	<i>1: Baseline<sup>b</sup> (1/10/2004)</i>	<i>2 (2/14/2004)</i>	<i>3 (3/15/2004)</i>	<i>4 (4/10/2004)</i>
<b>Zoe</b>				
Estradiol (pmol/L)	189	213	223	193
Progesterone (nmol/L)	0.82	0.48	0.27	0.12
Androstenedione (nmol/L)	10.5	5.2	5.6	3.14
<b>Bonnie</b>				
Estradiol (pmol/L)	220	173	219	206
Progesterone (nmol/L)	1.82	0.64	1.39	0.67
Androstenedione (nmol/L)	33.2	8.4	15	8.4

<sup>a</sup>Zoe received the implant; Bonnie continued receiving 100 µg of Lupron monthly.

<sup>b</sup>Implant placed after baseline blood samples were collected.

I am opposed to putting ferrets with adrenal disease on any therapy in which one does not see the ferret for 3 months. Because their condition changes rapidly and many are geriatric, other problems frequently occur during that time.

I was recently sent samples and information on the commercially available implant, Ferretonin (Melatek, Fort Collins, CO). This is a 5.4-mg implant in a single implant device. Cost to practitioners of this implant is \$19.95 each plus shipping. The estimated total cost of a single implant is approximately \$23. Compared with Lupron for a ferret receiving 100 µg/month, the implant is more expensive (based on my cost of \$5.50/100 µg of the 7.5-mg Lupron purchased through Rx-Counter.com). So my cost for 3 months would be \$16.50. For ferrets receiving 200 µg of Lupron monthly, my cost for 3 months' therapy is \$33. I do not see this as a significant cost advantage or savings for the owners.

Management of adrenal disease should be tailored to the best therapy for the individual ferret and should be based on diagnostics, examination, and evaluation of the quality of life that can be provided. Melatonin implants may be just one of a number of treatments to reduce hormone production. However, until it is possible to control the tumor suppressor gene problem most likely at the root of the disease and deal with the role that neutering or spaying (particularly if disease develops before puberty) plays in onset and severity of the disease, practitioners should do what is best for the individual ferret. Our goal is a full life span of 5 to 7 years with a good quality of life. Management packages should be worked out to be feasible and affordable to owners for the duration of the ferret's life.

A number of therapies used in the treatment of adrenal disease were discussed in the January 2004 *Seminars in Avian and Exotic Pet Medicine*. Pharmaceutical studies need to be conducted on the potential toxicities of repeated implants.



## NEWS YOU CAN USE

### ABVP Board Certification Progress Report

The AEMV recently completed another step toward creation of the American Board of Veterinary Practitioners—Small Exotic Mammal board specialty. All 20 candidates submitted for inclusion in a formal formation committee were accepted by ABVP in January 2005. The committee will soon begin work on creating testing standards, selecting references from which to draw examination material, and ultimately drafting examination questions themselves. The process is still expected to take 3 to 5 years and will require a substantial financial commitment as well.

Please check the AEMV Web site, [www.aemv.org](http://www.aemv.org), for more information on this exciting opportunity for exotic mammal practitioners. We extend a special thanks to Michael Dutton, DVM, DABVP, for his work on this project and for agreeing to serve as committee chairperson.

### Congratulations

AEMV member Dr. James Carpenter was awarded the Emil Dolensek Award at the annual AAZV meeting in September 2004. This award was in appreciation for exceptional contributions to the conservation, care, and understanding of zoo and free-ranging wildlife. On behalf of AEMV, we extend our congratulations to Jim for this prestigious award.

# Selected Abstracts on Exotic Mammal Medicine and Surgery

## SPECIAL FOCUS: RAT-BITE FEVER

### Fatal Rat-Bite Fever—Florida and Washington, 2003

CDC: *MMWR Morb Mortal Wkly Rep* 53(51 & 52):1198–1202, 2005.

#### ABSTRACT

Rat-bite fever (RBF) is a rare, systemic illness caused by infection with *Streptobacillus moniliformis* and is associated with a fatality rate of 7% to 10% among untreated patients. *S. moniliformis* is commonly found in the nasal and oropharyngeal flora of rats. Human exposure and infection can result from a bite or scratch wound from an infected or colonized rat, ingestion of food or water contaminated with infected rat excrement, or handling an infected rat. This report summa-

rizes the clinical course and exposure history of two rapidly fatal cases of RBF. In both cases, previously healthy individuals died following a several-day history of fever, headache, myalgia, rash, profound weakness, and gastrointestinal upset characterized by abdominal pain, nausea, and diarrhea.

One patient, a 52-year-old woman, died within 12 hours of hospital admission after failing to respond to treatment for a suspected gram-negative sepsis. Blood culture demonstrated growth of gram-negative filamentous bacteria that were later identified by the Centers for Disease Control and Prevention as *S. moniliformis*. The second patient, a 19-year-old female, was dead on arrival; clusters of filamentous bacteria were identified in sections of liver and kidney and identified as *S. moniliformis* via gene sequencing from extracted organism DNA.

### Epidemiology, Clinical Findings, Diagnosis, Treatment, and Prevention and Reporting of Rat-Bite Fever (RBF) Caused by *Streptobacillus moniliformis*<sup>a</sup>

#### Epidemiology and Ecology

- Zoonotic disease caused by infection with *S. moniliformis*, a fastidious gram-negative bacillus.
- *Spirillum minus* also causes RBF outside the United States.
- *S. moniliformis* is part of the normal respiratory flora of rats. Other rodents might also be reservoirs.
- Transmitted to humans by contact with infected rats or by ingestion of rat excreta. Person-to-person transmission has not been reported.
- Incubation period: 2–10 days.
- Cases are rare, but disease incidence is not well characterized.

#### Clinical Findings

- Initial symptoms are nonspecific and include fever, chills, myalgias, arthralgias, headache, and vomiting.
- Patients can have a maculopapular rash on the extremities or septic arthritis 2–4 days after fever onset.
- Severe manifestations can include endocarditis, myocarditis, meningitis, pneumonia, sepsis, and death.

#### Diagnosis

- Blood or synovial fluid culture, collected in tubes without sodium polyanethol sulfonate (SPS). Inoculate into media supplemented with 20% solution of sterile normal

rabbit serum and incubate in humid environment with 5%–10% CO<sub>2</sub> at 98.6°F (37°C). Hold cultures ≥5 days.

- Pleomorphic bacilli in Gram-, Wright-, or silver-stained blood smears or tissues support diagnosis.
- For assistance, contact a state public health laboratory or CDC Meningitis and Special Pathogens Branch, telephone 404-639-3158.

#### Treatment

- Intravenous penicillin, 1.2 million units/day for 5–7 days, followed by oral penicillin or ampicillin 500 mg four times a day for 7 days if improvement is observed.
- Oral tetracycline 500 mg four times a day or intramuscular streptomycin 7.5 mg/kg twice daily are alternatives.

#### Prevention and Reporting

- Wear protective gloves, practice regular hand washing, and avoid hand-to-mouth contact when handling rats or cleaning rat cages.
- Adults should closely supervise children aged <5 years to prevent bites and hand-to-mouth contact.
- If bitten by a rat, promptly clean and disinfect the wound.
- Efficacy of antimicrobial prophylaxis is unknown.
- Not a notifiable disease; however, unexplained deaths and critical illnesses or rare diseases of public health importance might be reportable in certain states.

<sup>a</sup>From: CDC: Fatal rat-bite fever—Florida and Washington, 2003. *MMWR Morb Mortal Wkly Rep* 53(51 & 52):1198–1202, 2005.

Both patients had a history of exposure to pet rats. The first patient worked in a pet shop and was bitten on her right index finger by a store rat 2 days before the onset of symptoms and 4 days before arriving at the hospital. Immediately after being bitten, this patient had self-treated the wound by using antiseptic ointment. The second patient worked as a dog groomer and owned nine pet rats. One of these rats had recently been diagnosed with respiratory signs at a veterinary hospital. This patient had no known animal bites during the 2 weeks preceding her death.

**COMMENTARY**

*Although rare in the United States, all veterinarians, hospital staff, and clientele who come in contact with pet rats should be familiar with RBF. Despite its name, approximately 30% of patients with RBF do not report having been bitten or scratched by a rat. Initial symptoms may be nonspecific, and*

*patients can have severe disease before onset of the typical symptoms of septic arthritis and maculopapular rash. Because of the high prevalence of colonization and asymptomatic infection with *S. moniliformis* among rodents, testing and treating rats are not practical. Disease prevention should therefore focus on risk reduction among individuals with frequent exposure to rats. They should wear gloves, wash hands regularly, and avoid hand-to-mouth contact when handling rats or cleaning cages. If bitten by a rat, the victim should promptly clean and disinfect the wound; immediate medical attention (with reported exposure history) should be sought if subsequent illness develops. The disease is more common in children; therefore, adults should closely supervise young children to prevent bites and hand-to-mouth contact.*

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

**SPECIAL FOCUS: ZONONOSES**

**Zoonoses of Occupational Health  
 Importance in Contemporary Laboratory  
 Animal Research**

Hankenson FC, Johnston NA, Weigler BJ, Di Giacomo RF: *Comp Med* 53(6):569-601, 2003.

**ABSTRACT**

Laboratory animal workers are potentially exposed to zoonotic disease on a regular basis because a wide range of species they work with are capable of carrying diseases that infect humans. Zoonotic diseases of macaques, pigs, dogs, rabbits, mice, rats, sheep, goats, cats, ferrets, and pigeons are discussed in this article. An alphabetical listing of information on a wide range of diseases, from amebiasis to lymphocytic choriomeningitis to yellow fever, is presented in some detail. Each discussion includes the following information presented in a reference format: agent, laboratory animal reservoir, disease, detection, control, mode of transmission, communicability, human occurrences, clinical syndromes, incubation period, diagnosis, prevention, and treatment.

**COMMENTARY**

*Small mammal veterinarians provide care for many of the same species that are handled by laboratory workers. The main areas of overlap are ferrets, gerbils, guinea pigs, hamsters, mice, rabbits, and rats. The format of the article makes it very useful as a quick reference guide to the more than 30 zoonotic diseases covered. The following are identified diseases of most relevance to veterinarians who see exotic mammals:*

- **Ferrets:** *Campylobacteriosis, cryptosporidiosis, ectoparasitism, rabies*

- **Gerbils:** *Ectoparasitism, leptospirosis*
- **Guinea pigs:** *Balantidiasis, chlamydiosis, dermatophytosis, ectoparasitism, lymphocytic choriomeningitis, salmonellosis*
- **Hamsters:** *Campylobacteriosis, ectoparasitism, lymphocytic choriomeningitis, leptospirosis*
- **Mice:** *Ectoparasitism, hantaviral disease, leptospirosis, lymphocytic choriomeningitis, rat-bite fever, salmonellosis*
- **Rabbits:** *Dermatophytosis, ectoparasitism, pasteurellosis, salmonellosis*
- **Rats:** *Ectoparasitism, hantaviral disease, leptospirosis, lymphocytic choriomeningitis, rat-bite fever, salmonellosis*

*The multiple occurrences of ectoparasitism and dermatophytosis on the above list underscore the importance of obtaining a diagnosis when presented with an exotic mammal with dermatologic disease. Skin scrapings and fungal culture (DTM) should always be performed as part of a minimum database. Although disease in humans is usually transient, it can be severely pruritic and irritating and may lead to secondary pyoderma.*

*Clients should be educated on potential zoonoses with emphasis on the importance of proper hygiene when handling sick, or even healthy-appearing, small mammals. Diseases such as salmonellosis, leptospirosis, and campylobacteriosis can be present in the absence of clinical signs. Wild rodents can track in lymphocytic choriomeningitis and expose pet mammals while at the original breeding facility, during shipping, in the pet store, or at the owner's home.*

**Jeffrey A. Mills, DVM**  
 Banfield the Pet Hospital  
 Louisville, Kentucky

**Brief Report: Tularemia Associated with a Hamster Bite—Colorado, 2004**

CDC: *MMWR Morb Mortal Wkly Rep* 53(51 & 52):1202–1205, 2005.

**ABSTRACT**

In April 2004, the Colorado Department of Public Health and Environment was notified of a 3-year-old boy diagnosed with tularemia associated with a hamster bite. The boy was exposed to six hamsters during a 5-week period; all the hamsters subsequently died of “wet tail disease.” One hamster bit the child on the left ring finger shortly before it died. Seven days later, the child had fever, malaise, painful left axillary lymphadenopathy, and skin sloughing at the bite site. After initial treatment failure, excisional biopsy and tissue culture of the left axillary lymph node yielded a type B *Francisella tularensis* isolate. No other risk exposure factors for tularemia were identified. The patient improved after treatment with ciprofloxacin.

The pet store where the hamsters were purchased reported an unusual number of hamster deaths during the time of the suspect hamsters’ purchase. None were available for necropsy. One cat kept at the store as a pet had a positive serologic test for *F. tularensis*. It was theorized that infected wild rodents had infested the store and spread the infection to the hamsters by urinating and defecating through metal screens covering the hamster cages. The infected cat might have had a subclinical illness after catching or eating an infected wild rodent.

**COMMENTARY**

*F. tularensis* is a gram-negative coccobacillus and the causative agent of rabbit fever or tularemia. It is primarily a pathogen of wild rodents and lagomorphs, and the domestic cat may serve as a reservoir for this microbe as a result of its possible contact with infected wildlife. Although associated with hamster-hunting in Russia, tularemia is unusual in captive rodents and has not been associated previously with pet hamsters in the United States. *F. tularensis* can be transmitted by aerosolization, direct contact, or ectoparasites (ticks and fleas). Affected individuals may develop pneumonia, cutaneous lesions, or meningitis.

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

**Hedgehog Zoonoses**

Riley PY, Chomel BB: *Emerg Infect Dis* 11(1):1–5, 2005.

**ABSTRACT**

A review of known and potential zoonotic diseases that can be carried and transmitted by pet or rescued wild-caught hedgehogs is presented. *Erinaceus europaeus*, the European hedgehog, and *Atelerix albiventris*, the African pygmy

hedgehog, are commonly seen as pets. Importation of hedgehogs from Africa to the United States has been prohibited since 1991 because of the risk of transmission of foot-and-mouth disease (FMD).

Salmonellosis is the most significant bacterial zoonoses from hedgehogs; 28% of hedgehogs are asymptomatic carriers. Multiple cases of salmonellosis in humans have been linked to hedgehogs. *Yersinia pseudotuberculosis*, *Mycobacterium marinum*, and *Yersinia pestis* have been reported in hedgehogs. Antibodies against *Coxiella burnetii*, *Chlamydia*, and *Toxoplasma gondii* have been found in European hedgehogs.

*Trichophyton mentagrophytes* var *erinacei* is the most common dermatophyte transmitted to humans from hedgehogs, although *Microsporum* spp have also been found in hedgehogs. *Candida albicans* has been isolated from hedgehogs, so zoonotic transmission is possible.

Research suggests that hedgehogs may serve as a reservoir for viruses within the family *Bunyaviridae*, but the role of hedgehogs as hosts still needs to be documented. Hedgehogs serve as hosts and reservoirs for tickborne encephalitis virus. While hedgehogs may be susceptible to infection from Crimean–Congo hemorrhagic fever (CCHF), viremia levels vary among species of hedgehogs. Because hedgehogs act as hosts to immature stages of tick species from which CCHF has been isolated, hedgehogs may be a potential source of infection. Paramyxovirus commonly occurs in hedgehogs; if the virus crosses species barriers, infection could be possible in humans. Herpesvirus infection has been reported in hedgehogs; in one case, human herpes simplex virus was cultured from a dead hedgehog. Although the source was not confirmed, it is possible the hedgehog was infected from contact with the human owners. A case of rabies was reported in a hedgehog in Budapest; postexposure prophylaxis was given to the family exposed to the hedgehog. Although FMD is not zoonotic, European and African hedgehogs are susceptible to the FMD virus. Identical strains of FMD virus from cattle have been found in hedgehogs trapped from infected premises during an outbreak of FMD. The cycle of infection of FMD between cattle and hedgehogs has been demonstrated.

*Cryptosporidium* spp were the cause of death in a captive African hedgehog. Although the protozoan was not identified to species, zoonotic potential should be kept in mind.

**COMMENTARY**

*Risk of disease transmission is most significant for individuals rescuing and rehabilitating wild-caught hedgehogs or adopting them as pets. Hedgehog owners and veterinarians should keep zoonotic disease in mind when handling hedgehogs. Proper hygiene and increased awareness around young, elderly, or immunocompromised individuals will help prevent illness.*

**Jennifer Graham, DVM, DABVP (Avian)**  
 Veterinary Specialty Center of Seattle  
 Lynnwood, Washington

**Tuberculosis**

Kaneene JB, Thoen CO: *JAVMA* 224(5):685–691, 2004.

**ABSTRACT**

Tuberculosis refers to a group of diseases caused by *Mycobacterium* spp, including *M. tuberculosis*, *M. bovis*, and *M. africanum*. Signs of the disease in humans include both pulmonary and extrapulmonary infections. The main zoonotic source for humans is *M. bovis* infection from unpasteurized dairy products and contact with infected cattle. Immunocompromised humans are also susceptible to *M. avium*. Mycobacteria are aerobic, nonmotile, non-spore-forming, acid-fast bacilli. Nonhuman primates, swine, cats, dogs, and lab animals such as guinea pigs and rabbits are susceptible to *M. bovis*. Transmission through biting has been documented in New Zealand black-footed ferrets. The principal clinical sign of tuberculosis is emaciation. Other signs include enlarged lymph nodes, weakness, anorexia, and fever.

**COMMENTARY**

*Although mycobacteriosis is not common in small exotic mammal practice, the susceptibility of these species requires practitioners to consider this potentially zoonotic illness, especially in patients exhibiting signs of nonspecific wasting, fever, peripheral lymphadenopathy, or apparent infection that does not respond to common first-line antibiotics.*

*Jeffrey A. Mills, DVM  
Banfield the Pet Hospital  
Louisville, Kentucky*

**Rabies in Two Privately Owned Domestic Rabbits**

Karp BE, Ball NE, Scott CR, Walcott JB: *JAVMA* 215(12):1824–1827, 1999.

**ABSTRACT**

Two privately owned domestic rabbits (*Oryctolagus cuniculus*) in Maryland were found to be infected with the raccoon variant of the rabies virus in 1998. Both rabbits had an acute onset of anorexia and paralysis or paresis of the left forelimb; one also developed head tremors and a head tilt. One of the rabbits became ill 25 days after being attacked by a raccoon (*Procyon lotor*) and was euthanized 3 days after onset of illness. The other rabbit, which was housed in an outdoor hutch, died 4 days after onset of clinical signs; the source of infection in that rabbit remains unknown. Currently, there is not a rabies vaccine approved for use in rabbits; thus, the only way to prevent the infection in rabbits is to prevent exposure. Veterinarians in rabies-enzootic areas should be familiar with the clinical signs of rabies in rabbits and should caution rabbit owners about the need to protect their pets from contact with wildlife.

**COMMENTARY**

*Exotic animal veterinarians may not be accustomed to considering the possibility of rabies in small exotic herbivores. These two cases illustrate naturally occurring rabies in two rabbits. Experimentally, most mammals are susceptible to rabies, but cases of naturally occurring rabies in rabbits are rare: 30 cases were reported to the Centers for Disease Control and Prevention between 1971 and 1997. As the signs of rabies in these two rabbits and in other reported cases can be vague and nonspecific, veterinarians should not neglect this disease as a possibility, especially in rabbits housed outdoors with potential contact with wildlife.*

*Angela Lennox, DVM, DABVP (Avian)  
Avian and Exotic Animal Clinic of Indianapolis  
Indianapolis, Indiana*

**Utilizing Natural Behavior to Treat Chinchilla Ringworm**

Badman J, Schenone S, DeNardo D, et al: *Tech Talk News! Lab Anim Sci Tech* 9(5):3, 2004.

**ABSTRACT**

This clinical brief discusses the incorporation of natural dusting behavior in chinchillas to treat an outbreak of dermatophytosis in a small group of laboratory animals. Three of 12 animals exhibited alopecia with crusty red lesions on the face, back, and tail. The clinical signs were noted several weeks after the chinchillas were purchased from a commercial vendor. All animals were housed singly in stainless steel cages. The lesions fluoresced under a Wood's lamp, and skin scrapings were negative. No samples were obtained for fungal culture. Standard treatment for ringworm includes oral and topical administration of antifungal therapeutics. To decrease stress associated with administration of oral medication and to ensure eradication of the infection, topical treatment using the natural dusting behavior of chinchillas was instituted.

Two percent miconazole nitrate powder (Lotrimin Antifungal Powder, Schering-Plough) was added at a rate of 1 teaspoon per an equal amount of chinchilla dust (Chin Dust Bath, Kaytee Products, Chilton, WI). The mixture was placed in a dusting pan in each cage 10 minutes/day for 17 days. The three animals with lesions also received 2% miconazole nitrate cream (Conofite, Fougere & Co, Melville, NY) to the affected areas twice daily. The animals in this group experienced a decrease in appetite after 2 days and became lethargic on the third day. These side effects were attributed to either a toxic reaction to the cream and/or stress due to frequent handling. The cream was withdrawn from the treatment protocol, but the medicated dust baths continued. After 17 days, new hair growth was noted and skin lesions had resolved on the affected animals. The nonsymptomatic animals never developed alopecia or skin lesions.

This method of treatment effectively eradicated a transmittable infection, minimized stress on the animals, and required very little effort by the caretakers.

## COMMENTARY

*Dermatophytosis caused by Trichophyton mentagrophytes is a relatively common skin disease in chinchillas. It is important that the disease be diagnosed and treated appropriately because of its zoonotic potential and contagious nature. This paper presented a novel method to treat ringworm that could eas-*

*ily apply to pet chinchillas. This technique would promote the incorporation of other natural animal behaviors when dealing with analogous situations. Care must be taken to limit the exposure of pet owners to medicated dust bath. As some chinchillas are known to dust bathe vigorously, owners must avoid inhalation, ingestion, and ocular exposure. Individuals known to be sensitive to this product should avoid skin contact as well.*

**Melissa A. Kling, DVM**

Secretary, AEMV  
Brantley and Jordan Animal Hospital  
Macon, Georgia

## SPECIAL FOCUS: RABBIT HEALTH

### Conjunctival Flora Observed in 70 Healthy Domestic Rabbits (*Oryctolagus cuniculus*)

Cooper SC, McLellan GJ, Rycroft AN: *Vet Rec* 149(8):232–235, 2001.

#### ABSTRACT

Conjunctival swabs were taken from both eyes of 70 healthy domestic rabbits and cultured to determine the microbial population. Bacteria were recovered from 83% of the specimens. DNase-negative *Staphylococcus* spp (57%) were the most commonly recovered organisms, followed by *Micrococcus* spp (25%) and *Bacillus* spp (19%). Other organisms isolated included *Stomatococcus* spp (8%), *Neisseria* spp (8%), *Pasteurella* spp (6%), *Corynebacterium* spp (6%), *Streptococcus* spp (6%), and *Moraxella* spp (4%). Other bacteria were isolated less frequently. Statistical analysis showed that there appeared to be no significant differences in bacterial isolation rates from different breeds of rabbit. Significantly more of the swabs taken from young rabbits yielded cultivable bacteria than did those taken from rabbits older than 12 months of age.

#### COMMENTARY

*Because of their prominent, laterally placed eyes, rabbits often present with trauma-related corneal abrasions or ulcers. Conjunctivitis and chronic epiphora are also sequelae to rabbit dental disease. Knowledge of the rabbit's normal fauna can aid in antibiotic choice. If ocular injury or infections arise, Gram stain can be used to dictate preliminary antibiotic choice, with adjustments made based on results of a culture and sensitivity testing. These culture results differ slightly from those of a previous study reported in "Corneal Diseases of Rabbits" by Stacey E. Andrew, DVM, in the May 2002 Veterinary Clinics of North America Exotic Animal Practice. The bacterial isolates mentioned in Dr. Andrew's study included Bacillus subtilis (56%), Staphylococcus (43%), and Streptococcus viridans (7%), as well as lower numbers of Pasteurella, Bordatella, and Moraxella spp.*

**Jeffrey A. Mills, DVM**  
Banfield the Pet Hospital  
Louisville, Kentucky

### Diseases and Outcomes in Rabbits with High BUN Levels

Saito K, Hasegawa A: *J Vet Med Sci* 65(5):625–628, 2003.

#### ABSTRACT

One hundred ninety rabbits seen at animal hospitals in Saitama and Tokyo, Japan, from 1998 to 2001 with blood urea nitrogen (BUN) values greater than 27 mg/dl were analyzed regarding their underlying and/or complicating diseases and outcomes. Gastrointestinal disorder (54 cases) was the most common disease, followed by overgrowth of molar teeth and liver disturbance. The total mortality was 48.9% within 3 months, with cases having complications such as liver disturbance or bacterial infection showing the highest mortality. Cases with higher BUN values demonstrated even higher mortality, although mortality varied depending on the complications. Therefore, the prognosis of rabbit cases with high BUN values should be evaluated based on findings from blood chemistry together with the seriousness of the underlying and/or complicating disease.

#### COMMENTARY

*This article illustrates an interesting clinical correlation of elevated BUN with general clinical disease and mortality in pet rabbits. A number of underlying disease conditions were diagnosed in rabbits with elevated BUN. What would have been of great interest, however, would have been correlation of elevated BUN with evaluation of the kidney via biopsy or at necropsy. Examination of creatinine and urine specific gravity levels would have also been useful. It is probable that many of these cases of elevated BUN reflected dehydration, a common feature of many diseases in rabbits.*

**Angela Lennox, DVM, DABVP (Avian)**  
Avian and Exotic Animal Clinic of Indianapolis  
Indianapolis, Indiana

Dear Editor,

We read with interest the article by Dr. Finkler titled, "A Nutritional Approach to the Prevention of Insulinomas in Ferrets" (Vol. 2.2, December 2004). However, we are gravely concerned that mere speculation with little supportive data may be misinterpreted as sound pathophysiologic understanding of insulinomas in ferrets. While the author correctly assesses that ferrets are indeed strict carnivores and therefore possess particularities to their digestive physiology with respect to carbohydrate and protein digestion, no scientific data supporting a pathologic relationship between carbohydrate ingestion and development of a neoplastic condition are presented. The author attempts to rationalize some of his speculations by invoking comparisons to another domestic carnivore, the cat. The author asserts that, as in the cat, excess carbohydrates may be responsible for hyperinsulinemia and subsequent abnormal  $\beta$  cell dysfunction in ferrets. But unlike the cat, this  $\beta$  cell dysfunction leads first to hypertrophy and then neoplastic transformation. While this may be an interesting hypothesis, there are currently no studies that have (1) demonstrated a hyperinsulinemic or "preinsulinoma" condition in ferrets, (2) related such a condition to the diet, (3) documented  $\beta$  cell hypertrophy either as part of or a precursor condition to insulinomas in ferrets or any other species, or (4) any epidemiologic data identifying diet as a risk factor for the development of insulinomas in ferrets or any other species.

While we do not object to the notion that the "ideal" diet composition for optimal health in ferrets is not known and probably not available commercially, a considerable amount of research is needed before "preventative" measures can be recommended. First, a better understanding of the pathogenesis of insulinomas in ferrets is needed. This must go beyond case series and retrospective studies. The pathobiology and cellular behavior of neoplastic  $\beta$  cells in ferrets must be better characterized. Second, while recognizing that strict carnivores such as cats and ferrets do not possess a "dietary requirement" for carbohydrates, this does not necessarily mean that carbohydrates are toxic to either species. To suggest that excess carbohydrate consumption is the cause of diabetes mellitus in cats and insulinomas in ferrets

should be supported by some data other than mere speculation. While the provision of carbohydrates to animals that do not have a dietary requirement is a source of lively debate, no study has actually linked the consumption of carbohydrates to the development of diabetes mellitus in cats or people. Obesity, however, is perhaps the single most important predictor of development of diabetes mellitus in both cats and people and has been demonstrated.

A better understanding of dietary needs in ferrets is definitely warranted and may indeed demonstrate that higher protein and fat in lieu of carbohydrates may be better. However, it should be emphasized that diets high in protein and fat are very high in calories and may worsen the problem of obesity, which may in itself be more "pathologic" than "high-carbohydrate diets," although it is recognized that this may not always occur because of the satiety effect of high-protein, high-fat, low-carbohydrate diets.

In summary, we feel that a dietary protocol designed to reduce the occurrence of insulinomas in ferrets is premature given the current lack of understanding of the pathophysiology of insulinomas. Furthermore, we feel that it is perhaps more appropriate to encourage scientific investigations to elucidate the actual risk factors for development of insulinomas in ferrets, the heritability pattern of the disease, the actual cellular events that lead to neoplastic transformation, and what role diet plays in such events. Further scientific investigations of dietary requirements, digestibility of nutrients, and nutrient handling are warranted as well.

Respectfully,

Daniel L. Chan, DVM, DACVECC, ACVN Board-Eligible  
Clinical Nutrition Service  
Foster Hospital for Small Animals

Jörg Mayer, DrMedVet, MSc  
Clinical Assistant Professor  
Head of Exotics Service

Tufts University School of Veterinary Medicine  
North Grafton, Massachusetts

*(continues on back page)*

## AEMV OFFICERS AND EDITORS

**President:** Angela Lennox, DVM, DABVP (Avian), Avian and Exotic Animal Clinic of Indianapolis, Indianapolis, IN; birddr@aol.com

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**Letters** (continued from p. 15)

**Author's Response**

I appreciate the thoughtful comments of Drs. Chan and Mayer regarding this topic. They raise many valid points, which illustrate how little we know about the pathophysiology of insulinoma formation in ferrets. As stated in the article, my nutritional strategy is based on a hypothesis (which, by definition, is speculative) and the exact etiology is unknown.

I fully agree with their suggestions for further scientific investigation of risk factors, heritability analysis, etc. With

the current lack of such information, and while witnessing a near-epidemic prevalence of insulinomas in pet ferrets, I feel compelled to offer my clients an educated guess as to one possible preventive strategy. At best, the proposed dietary strategy may help; at worse, it is unlikely to do harm. If offering this strategy is "premature," then so be it.

**Mark R. Finkler, DVM**  
*Roanoke Animal Hospital*  
*Roanoke, Virginia*



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

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