# Hyperadrenocorticism in the Domestic Ferret

*Grant U. Jacobson, DVM[†] and Joanne C. Graham, DVM, MS[††]*

Domestic ferrets *(Mustela putorius furo)* are becoming increasingly common in the United States. They are very popular as household pets and are also used in large numbers as research animals. With the increase in ferret numbers, there has been a corresponding increase in the number and frequency of diseases described.[4] Neoplastic conditions are at the top of the list of problems occurring in ferrets found in the United States. An exceedingly common condition is adrenal disease as a result of adrenocortical hyperplasia, adenoma, or adenocarcinoma. These conditions present as the same clinical syndrome and anyone examining ferrets in a veterinary setting can expect to see many cases of adrenal disease.

The first published account of a tumor in a ferret was by Summers and Thommpson in 1950, and before 1980, only 20 ferret tumors were reported.[2] The low number of reports led several authors to believe that tumors were rare in ferrets.[2] Since that time, it has become clear that the probability for a ferret in the United States to develop a neoplastic condition is quite high.[4] One study described over 50 different neoplasms in ferrets.[2] Currently, adrenocortical tumors are among the most commonly encountered neoplasms found in domestic ferrets living in the United States.[4]

It should be made clear that hyperadrenocorticism in the ferret differs from the condition seen in the dog and therefore cannot be termed Cushing's disease. Clinical signs are different, as are the substances produced by the diseased adrenal gland. Cushing's disease of the dog is characterized by high resting serum cortisol concentrations or abnormal adrenocorticotropic hormone (ACTH) stimulation profiles. These changes are not typically seen in a ferret with adrenal disease, rather the levels of plasma androgens, estradiol, or 17-hydroxyprogesterone may be elevated.[13,16,22]

## Key Facts

- **Clinical Signs:** Classic presentation of bilateral alopecia beginning at the tail and progressing cranially, vulvar enlargement, and possible pruritus.
- **Hormonal Assay:** Plasma androgens, estradiol, or 17-hydroxyprogesterone may be elevated.
- **Diagnosis:** Based primarily on clinical signs, but imaging diagnostics, hormonal assays, and general blood values may be beneficial.
- **Treatment:** Exploratory laparotomy and adrenalectomy treatment of choice. Variable results obtained from medical treatment with mitotane.

### Pathogenesis Theories

The underlying pathogenesis for hyperadrenocorticism in ferrets is not known, but several theories exist attempting to explain why this condition is so common in the United States but is very rare in Great Britain. A prominent theory places blame on early neutering.[16,18] Ferrets in the United States are commonly neutered before 5-6 weeks of age to prevent hyperestrogenism and fatal anemia in the unspayed female, or for increased marketability in the pet trade. Several studies performed using mice have shown that gonadectomy at a very early age can lead to the formation of tumors of the adrenal gland that hypersecrete estrogens or androgens.[5,11,20] During embryological development, ovaries and adrenal glands develop in close anatomic relation.[16] Gonadal cells may be carried with the adrenal glands during migration, and with stimulation due to gona-

[†]Dr. Grant Jacobson is a 1997 graduate of the Iowa State University College of Veterinary Medicine.

[††]Dr. Joanne Graham is an assistant professor in Veterinary Clinical Sciences at the Iowa State University College of Veterinary Medicine.

dectomy, these undifferentiated cells in the adrenal gland may become functionally similar to gonadal tissue.[16,18]

Others consider a genetic predisposition for this condition. Ferrets raised in the United States often are raised in large closed colonies where genetic factors leading to neoplastic conditions may be "recycled" to continuing generations.[4]

In Europe, the majority of ferrets are housed outdoors all year.[4] Long-term effects of keeping ferrets indoors with artificial lighting are not known, but ferret reproductive cycles are very sensitive to photoperiod.[6] It has been observed that hyperadrenocorticism is not common in ferrets that live under natural light conditions.[3]

Dietary considerations have also been theorized as a factor. In this country, ferrets generally eat packaged dry cat and ferret foods. In Europe, many ferrets are still fed whole prey animals, such as rabbits, mice, and rats.[4] Foods today are of a much higher quality than those of the past.[4] With further research into ferret nutritional requirements, this theory may be excluded as a cause of cancer in the future.[4]

## Typical History and Clinical Findings Upon Presentation

The most common presenting complaint in affected animals is bilaterally symmetric alopecia that begins on the tail and slowly progresses cranially. In spayed females, vulvar enlargement with or without mucoid discharge may be a sign of the disease.[10,12,16] Male ferrets may have a history of dysuria and/or urinary blockage due to hyperplastic or cystic changes in the prostate, which may have cells that are hormonally responsive.[16,21] Female ferrets suffering from this condition are presented more frequently than are male ferrets.[10,16] Only one case of an intact female with hyperadrenocorticism has been reported.[19] The uneven relationship of female to male cases may be linked to the concern owners have for a ferret with a swollen vulva. Many owners are aware that hyperestrogenism, found in intact females or those with ovarian remnants, is a condition that can kill ferrets, and that a swollen vulva and alopecia are seen in that condition. These owners are likely to consult a veterinarian immediately if such signs are seen. Other owners may be more likely to simply live with a hairless male ferret than to seek medical attention.

Kathleen Mullin, ISU

**Adrenal disease is an exceedingly common condition in the domestic ferret. It is often a result of adrenocortical hyperplasia, adenoma, or adenocarcinoma.**

Affected ferrets are often pruritic with erythematous skin in the pruritic areas.[10,16] Owners often report that signs first occurred the previous year, resolved without treatment, then recurred with greater severity the next spring and failed to resolve at that point.[10,18] One should be aware that seasonal alopecia of the tail is observed in some normal ferrets, and the hair will typically regrow in a few weeks.

Early literature described clinical signs similar to those seen in cats and dogs.[7] Currently, this is recognized to not be the case, as signs normally associated with Cushing's disease, such as calcinosis cutis, polyuria/polydipsia, polyphagia, muscle weakness, lethargy, or increased panting are rarely seen in ferrets.[18]

Physical palpation may reveal enlarged adrenal glands. The right adrenal gland is more cranial and beneath a liver lobe, therefore the left adrenal gland is more easily identified than the right and may be found engulfed in a large fat pad cranial to the left kidney.[16] The spleen may also be palpably enlarged. This is a common finding in the older ferret and may be coincidental.[16] Authors of one report of a ferret with adrenocortical carcinoma attempted to link concurrent hyperplasia of the mammary gland with endogenous hormone stimulation by the adrenal gland mass.[14] It is often the case that a ferret suffering from adrenal disease may also have other conditions related to or unrelated to the underlying disease. These should not be missed on examination.

Kathleen Mullin, ISU

**Hyperadrenocorticism has been observed more commonly in ferrets housed under artificial lighting conditions, leading some to believe that an altered photoperiod may influence disease.**

### Establishing a Diagnosis

Diagnosis of hyperadrenocorticism is based largely on clinical signs. The primary differential diagnosis in a spayed ferret with the classical alopecia pattern and swollen vulva without other sign of illness should be adrenal disease.[4,16,19,22] Further diagnostic imaging, steroid hormone assays, and surgical confirmation will establish a final diagnosis.

Radiographs are seldom useful. Whole body radiographs may or may not reveal a visibly enlarged adrenal gland, but other conditions such as splenomegaly or heart enlargement may be detected.[15] Even if no abnormalities are found, hyperadrenocorticism cannot be ruled out.

Abdominal ultrasound may be useful in detecting adrenal disease. Ultrasonographically, adrenal glands appear as small, flattened, triangular masses of moderate echogenicity. The normal size of a ferret's adrenal gland is less than 2 mm.[10] Unilateral enlargement of the adrenal glands is indicative of adrenal gland hyperplasia or neoplasia.[1] Prognosis may also be determined by examining the caudal vena cava for signs of extension of the adrenal gland tumor into the lumen or the tissues around the vein.[1] Morphologic abnormalities of the spleen, lymph nodes, or pancreas (insulinomas) may also be evaluated with ultrasound.[1,16] Often, ultrasound will fail to provide a diagnosis of adrenal disease, but it is probably the better choice when compared to radiographs. Computed tomography[16] and magnetic resonance imaging[15] are other diagnostic imaging procedures that can show adrenal gland abnormalities, but these are rarely performed in practice.

Hematology is of limited value when evaluating a ferret for adrenal disease. A complete blood count is generally normal. Anemia, pancytopenia, or both may be found on rare occasions in ferrets with estrogen-induced bone marrow toxicity.[16,19] The biochemistry panel may show an occasional elevation in alanine transaminase.[16] Glucose values may be useful in ruling out insulinoma, a common neoplasm that often occurs concurrently with adrenal disease.

Attempts at various hormonal assays for diagnosis have been made. The ACTH stimulation test may be a useful test in the diagnosis of canine Cushing's disease, but it is not helpful in ferrets.[17,22] Cortisol and corticosterone secretion stimulation have been reported in normal ferrets following ACTH administration, as cortisol appears to be the predominant circulating glucocorticoid in ferrets.[17] It has been shown, however, that secretion of corticosterone is normal in ferrets with adrenocortical disease.[9,16,19] Therefore, ACTH stimulation testing is not a reliable method of detecting ferret hyperadrenocorticism. Dexamethasone suppression tests do not appear to be useful in diagnosis for similar reasons.[9,16]

The urinary cortisol to creatinine ratio (UC:CR) has also been evaluated in a recent study as a test for adrenal disease.[8] The authors reported that UC:CR values are significantly higher in ferrets with adrenal gland tumors when compared to clinically normal ferrets.[8] Contrary to previous reports, they suggest that cortisol is produced in excessive amounts in ferrets with adrenal tumors.[8] As cortisol levels may fluctuate through the day, and thus fall into normal reference ranges, mean cortisol excretion in the urine may be increased over a period of time as the bladder is filling.[8] It should be noted that ferrets with diseases other than hyperadrenocorticism were not included in the study, nor were serum and urine values of other hormones, such as estradiol. Until additional research is conducted on the use of the cortisol to creatinine ratio, such a test may be of limited value.

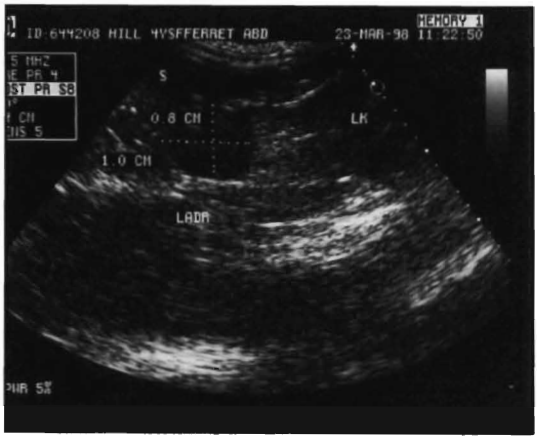
The measurement of other plasma steroids may be the most reliable means of diagnosing adrenal gland disease. Sex hormone-producing cells are thought to be involved, therefore measurement of the hormones they

produce may be diagnostic. Dehydropiandrosterone sulfate, androstenedione, 17-hydroxyprogesterone, and estradiol may be significantly elevated in the diseased ferret.[13,16,19,22] In a female, an elevation of only estradiol does not confirm or rule out hyperestrogenism.[16] For differentiation, an injection of human chorionic gonadotropin (hCG) (100 IU, IM) may be given and repeated in 7-10 days.[16] If the ferret is intact or if an ovarian remnant is present, the vulva should decrease in size following administration.[16] A ferret adrenal panel, which includes several adrenal hormones, is available through the Endocrinology Department, University of Tennessee, Knoxville.[16]

Definitive diagnosis is gained through exploratory laparotomy. Enlarged adrenal glands may be observed, and the presence or absence of ovarian tissue can be evaluated in this way. Examination for other abnormalities such as splenic enlargement or pancreatic insulinomas may be performed at the time of surgery. Histopathologic examination may then be performed on removed adrenal tissue. Typical histopathologic results are adrenocortical hyperplasia, adrenocortical adenoma, and adrenocortical carcinoma.[16] Should a client not wish to pursue other diagnostic measures, surgical exploratory without ultrasound and hormonal assays is an acceptable practice, however, as with any surgery, a preoperative work-up should be performed to determine the general health status of the ferret.

## Treatment

The preferred treatment for hyperadrenocorticism is exploratory laparotomy and adrenalectomy.[10,12,15,16,18] Ventral mid-line celiotomy allows best exposure of both adrenal glands, as well as the rest of the abdominal contents.[12] Initially, the surgeon should identify and palpate both adrenal glands. Other structures such as liver, lymph nodes, pancreas, and kidneys should be examined during exploration. The left adrenal gland will generally be found to be unilaterally affected, but about 10% of ferrets with hyperadrenocorticism have disease of both glands.[18] A unilateral adrenalectomy is recommended when only one gland is affected. Removing the right adrenal gland is difficult due to the intimate association with the caudal vena cava.[10] If both glands are diseased, a bilateral surgical procedure should be considered. The gland with the greatest degree of abnormality should be removed completely and a subtotal adrenalectomy of the other gland should be performed.[10,16,18] Post-surgically, an injection of sodium dexamethasone phosphate (4 mg/kg, IV) may be needed in a ferret that appears lethargic following unilateral or bilateral adrenal biopsy.[16] Maintenance and replacement fluids may be given as needed, and the ferret may be fed six to twelve hours after surgery.



Elizabeth Riedesel, ISU

**This ultrasound image demonstrates a 0.8 x 1.0 cm mass adjacent to the left adrenal gland of a ferret with clinical signs of hyperadrenocorticism. This mass was found to be an ovarian remnant at surgery, illustrating how ultrasound may fail to provide a diagnosis of adrenal disease.**

Following surgical treatment, most ferrets recover well. One can expect the clinical signs in most ferrets to resolve within 1-2 months, with vulvar swelling decreasing in a matter of days and hair returning within months.[12,16,18,19] Rarely, recurrence of the adrenal tumor due to metastasis, or less rarely, the re-appearance of a tumor in the adrenal gland may occur.[16]

Attempts to medically manage a ferret with an adrenal tumor may be made. Should surgery not be an option due to surgical risk or monetary considerations, or if incomplete removal of bilateral adrenal tumors is obtained, protocols for medical treatment with mitotane have been described. Mitotane (o,p-DDD) is most effective in dogs for the treatment of pituitary-dependent hyperadrenocorticism, which is not recognized in the domestic ferret.[16,19] Because of this, treatment with mitotane is unreliable in ferrets. Often, if resolution of clinical signs occurs, they recur when treatment is discontinued.[15,16,19] One report

described a five month temporary resolution of clinical signs in a ferret receiving mitotane.[15] Mitotane is administered 50 mg PO SID for 1 week, followed by a maintenance dosage of 50 mg every 3 days.[16] The ferret should be carefully monitored for resolution of clinical signs. Because all adrenal hormones, including cortisol, should be depressed with treatment, an ACTH stimulation test may be used to determine whether the loading dose is effective after a week of treatment, but is not a monitor for tracking the long term effectiveness of treatment.[16] Other medical treatments such as ketoconazole are not considered to be effective in the treatment of ferret hyperadrenocorticism.[16,19]

## Summary

Adrenal disease in the domestic ferret is a very common condition. The classic presentation of bilateral alopecia beginning at the tail and progressing cranially, vulvar enlargement, and possibly pruritus in an otherwise normal appearing ferret should not be missed. Such classic signs should not cause a clinician to overlook other concurrent problems. Imaging diagnostics, hormonal assays, and general blood values may be useful in establishing a diagnosis. Exploratory laparotomy remains the definitive means of diagnosis and treatment. With surgical excision of the diseased gland, a good prognosis for recovery can be expected. When medical means of treatment (mitotane) are used, results are variable at best. Unless a pathogenesis can be identified in the future that leads to elimination of the disease, adrenal tumors of the ferret will remain a common condition that should concern any veterinarian working with ferrets.◆

## References

1. Ackermann J, Carpenter JW, Godshalk CP, et al. Ultrasonographic detection of adrenal gland tumors in two ferrets. *J Am Vet Med Assoc* 1994;205:1001-1003.
2. Beach JE, Greenwood B. Spontaneous neoplasia in the ferret. *J Comp Path* 1993;108:133-147.
3. Bell JA. Common tumors in ferrets: treatment options. *Proceedings:6th Annual WEZAM Exotics Conference*. Madison 1997;11-21.
4. Brown SA. Neoplasia. In: Hillyer EV, Quesenberry KE, Eds. *Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery*. Philadelphia:WB Saunders 1997;99-114.
5. Fekete E, Wooley G, Little CC. Histological changes following ovariectomy in mice: dba high tumor strain. *J Exp Med* 1941;74:1-8.
6. Fox JG. Reproduction, breeding, and growth. In: Fox JG, Ed. *Biology and Diseases of the Ferret*. Philadelphia:Lea & Febiger 1988;174-183.
7. Goad MEP, Fox JG. Neoplasia in ferrets. In: Fox JG, Ed. *Biology and Diseases of the Ferret*. Philadelphia:Lea & Febiger 1988;274-288.
8. Gould WJ, Reimers TJ, Bell JA, et al. Evaluation of urinary cortisol:creatinine ratios for the diagnosis of hyperadrenocorticism associated with adrenal gland tumors in ferrets. *J Am Vet Med Assoc* 1995;206:42-46.
9. Heard DJ, Collins B, Chen DL, et al. Thyroid and adrenal function tests in adult male ferrets. *Am J Vet Res* 1990;51:32-35.
10. Kolmstetter CM, Carpenter JW, Morrisey JK. Diagnosing and treating endocrine diseases in ferrets. *Vet Med* 1996;91:1104-1110.
11. Krishna Murthy AS, Brezak MA, Baez AG. Postcastrational adrenal tumors in two strains of mice: morphologic, histochemical, and chromatographic studies. *J Natl Cancer Inst* 1970;45:1211-1222.
12. Lawrence HJ, Gould WJ, Flanders JA, et al. Unilateral adrenalectomy as a treatment for adrenocortical tumors in ferrets: five cases (1990-1992). *J Am Vet Med Assoc* 1993;203:267-270.
13. Lipman NS, Marini RP, Murphy JC, et al. Estradiol-17ß-secreting adrenocortical tumor in a ferret. *J Am Vet Med Assoc* 1993;203:1552-1555.
14. Mor N, Qualls CW, Hoover JP. Concurrent mammary gland hyperplasia and adrenocortical carcinoma in a domestic ferret. *J Am Vet Med Assoc* 1992;201:1911-1912.
15. Neuwirth L, Isaza R, Bellah J, et al. Adrenal neoplasia in seven ferrets. *Vet Rad Ultra* 1993;34:340-346.
16. Rosenthal KL. Endocrine Diseases: Part II. In: Hillyer EV, Quesenberry KE, Eds. *Ferrets, Rabbits, and Rodents: Clinical Medicine and Surgery*. Philadelphia:WB Saunders 1997;91-98.
17. Rosenthal KL, Peterson ME, Quesenberry KE, et al. Evaluation of plasma cortisol and corticosterone responses to synthetic adrenocorticotropic hormone administration in ferrets. *Am J Vet Res* 1993;54:29-31.
18. Rosenthal KL. Ferrets. *Vet Clin North Amer (Sm An Pract)* 1994;24:1-23.
19. Rosenthal KL, Peterson ME, Quesenberry KE, et al. Hyperadrenocorticism associated with adrenocortical tumor or nodular hyperplasia of the adrenal gland in ferrets: 50 cases (1987-1991). *J Am Vet Med Assoc* 1993;203:271-275.
20. Rosenthal KL, Peterson ME. Stranguria in a castrated male ferret (clinical case conference). *J Am Vet Med Assoc* 1996;209:62-64.
21. Sharawy MM, Liebelt AG, Dirksen TR, et al. Fine structural study of postcastrational adrenocortical carcinomas in female CE-mice. *Anat Rec* 1980;198:125-133.
22. Wagner RA, Dorn DP. Evaluation of serum estradiol concentrations in alopecic ferrets with adrenal gland tumors. *J Am Vet Med Assoc* 1994;205:703-707.