Chapter 6

Morphology of the Pituitary Gland in Ferrets
(Mustela putorius furo) with Hyperadrenocorticism

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Summary

Pituitary tumors are the cause of hyperadrenocorticism in a variety of species, but the role of the pituitary gland in hyperadrenocorticism in ferrets is not known. In this species, the condition is mediated by the action of excess gonadotropins on the adrenal cortex and is characterized by an excessive secretion of sex steroids.

In this study, the pituitary gland of four healthy control ferrets, both intact and neutered, and ten neutered ferrets with hyperadrenocorticism was examined histologically following staining for adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. Immunohistochemistry revealed that somatotropes, thyrotropes and lactotropes are the most abundant cell types of the pars distalis of the pituitary gland in healthy ferrets. The distribution of corticotropes was similar to that in dogs and humans. In ferrets, similar to dogs, the melanotropic cell is almost the only cell type of the pars intermedia. Gonadotropes were found in the pars distalis of neutered individuals, but not intact, ferrets.

All the ferrets with hyperadrenocorticism had uni- or bilateral tumors of the adrenal gland. In addition, in the pituitary gland of two of these ferrets a tumor was detected. These tumors did not stain for any of the pituitary hormones, and had characteristics of clinically non-functional gonadotrope tumors seen in humans. In some of the other ferrets low pituitary immunoreactivity for gonadotropic hormones was detected, which might be due to the feedback of autonomous steroid secretion by the neoplastic transformation of the adrenal cortex.

It is concluded that the initially high concentrations of gonadotropins, as a result of castration, may initiate hyperactivity of the adrenal cortex. The low incidence of pituitary tumors and the low density of gonadotropin-positive cells in non-affected pituitary tissue in this study, suggest that persistent hyperadrenocorticism is not dependent on persistent gonadotropic stimulation.
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Introduction

Hyperadrenocorticism occurs in several mammalian species, including humans, dogs, and cats. In these species, the glucocorticoid excess leads to a catabolic state characterized by muscle weakness, skin atrophy, and centripetal obesity. The glucocorticoid excess may be due to an adrenocortical tumor or pituitary stimulation of the adrenal cortex. In humans, 60% to 80% of cases of hyperadrenocorticism are pituitary dependent, while in dogs and cats, over 80% of the cases are secondary to a pituitary tumour.

The situation is different in pet ferrets (Mustela putorius furo). In these animals, the changes associated with hyperadrenocorticism are dominated by signs of excessive production of sex steroids, i.e. symmetrical alopecia, vulvar swelling in neutered jills, and recurrence of sexual behavior after neutering. Plasma concentrations of androstenedione, 17α-hydroxyprogesterone, dehydroepiandrosterone sulfate and/or oestradiol are increased, consistent with these signs. In addition, elevated urinary corticoid/creatinine ratios have been reported in ferrets with hyperadrenocorticism.

In most ferrets with hyperadrenocorticism (85%), only one adrenal gland is enlarged and there is no atrophy of the contralateral gland. After unilateral adrenalectomy, the disease may recur in association with enlargement of the contralateral adrenal gland. The histological changes of the adrenal glands range from (nodular) hyperplasia to adenoma and adenocarcinoma.

The characteristics of hyperadrenocorticism in ferrets resemble those of some strains of mice in which nodular adrenocortical hyperplasia and adrenocortical tumors occur after neutering at an early age. It has been suggested that castration also plays a role in the pathogenesis of hyperadrenocorticism in ferrets, and recently the age at neutering was found to be significantly correlated with the age at onset of hyperadrenocorticism. This suggestion, together with the observation that the signs of hyperadrenocorticism initially occur only during the breeding season, that treatment with the gonadotropin-releasing hormone (GnRH)-agonist leuprolide acetate has beneficial effects, and that functional luteinizing hormone (LH) receptors are present in the altered adrenal cortices of ferrets with hyperadrenocorticism has strengthened the hypothesis that hyperadrenocorticism in ferrets is mediated by gonadotropic influence.

Given that the pituitary derived gonadotropic hormones play a role in the pathogenesis of hyperadrenocorticism in ferrets, it is of interest to know whether the disease in ferrets is associated with morphological changes in the pituitary. Previous reports indicate that there are no macroscopically visible changes in the pituitary glands of ferrets with hyperadrenocorticism, or neoplastic diseases. Here, we report on the pituitary histology of ten ferrets with hyperadrenocorticism and four control ferrets.
Materials and Methods

Healthy ferrets

Four healthy ferrets (two 1-year-old intact males, two 2-year-old neutered females) were euthanased during the breeding season, after which routine post-mortem examinations were performed within four hours of death. No histological abnormalities were found in the adrenal glands of these ferrets.

Table 1. Physical and histopathological data of ten neutered ferrets with hyperadrenocorticism

<table>
<thead>
<tr>
<th>Ferret</th>
<th>sex</th>
<th>age (year)</th>
<th>alopecia</th>
<th>miscellaneous surgery</th>
<th>histology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>left adrenal</td>
</tr>
<tr>
<td>1</td>
<td>m</td>
<td>6</td>
<td>yes</td>
<td>Increased libido</td>
<td>hyperplasia</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>4</td>
<td>no</td>
<td></td>
<td>carcinoma</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>5</td>
<td>yes</td>
<td></td>
<td>hyperplasia</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>7</td>
<td>yes</td>
<td></td>
<td>carcinoma</td>
</tr>
<tr>
<td>5</td>
<td>m</td>
<td>5</td>
<td>yes</td>
<td></td>
<td>adenoma</td>
</tr>
<tr>
<td>6</td>
<td>m</td>
<td>3</td>
<td>no</td>
<td></td>
<td>carcinoma</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>5</td>
<td>yes</td>
<td></td>
<td>adenoma</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>6</td>
<td>no enlarged prostate</td>
<td>yes</td>
<td>carcinoma</td>
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<tr>
<td>9</td>
<td>m</td>
<td>5</td>
<td>yes</td>
<td></td>
<td>hyperplasia</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>5</td>
<td>no</td>
<td></td>
<td>hyperplasia</td>
</tr>
</tbody>
</table>

* NAF = no abnormalities found

Clinical Cases

Ten (9 male, 1 female) neutered ferrets (age 4 – 7.5 years; median 5 years) were presented with signs of hyperadrenocorticism. At first presentation the following findings were observed. Six ferrets had alopecia. The female ferret had a slightly swollen vulva. One male ferret had an increased libido and another male had stranguria due to an enlarged prostate (Table 1). Mean urinary corticoid/creatinine (C/C) ratios (n=8) in two consecutive morning urines ranged from 3.2 to 86.5 x 10^-6 (reference < 1.66 x 10^-6)10. In two other ferrets only one urine sample was collected (Table 2); these C/C ratios also exceeded the reference range. Immediately after collection of the basal urine samples, a high-dose dexamethasone suppression test 29 was performed in six ferrets by oral administration of dexamethasone (0.1 mg/kg; 3 times at 8-hour intervals). The urinary C/C ratios after dexamethasone administration were compared to the mean urinary C/C ratios of the previous 2 days. The mean percentage change after dexamethasone administration in the six ferrets was 107.6% (range 11.5 – 276.3%).

Plasma concentrations of adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), androstenedione and 17α-hydroxyprogesterone are
summarized in Table 2. Concentrations of androstenedione and 17α-hydroxyprogesterone exceeded the reference range in all cases (n=7) in which these hormones were measured.

Table 2. Laboratory data of ten neutered ferrets with hyperadrenocorticism

<table>
<thead>
<tr>
<th>Ferret</th>
<th>Urine (C/C x 10⁶)</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 1*</td>
<td>day 2</td>
</tr>
<tr>
<td>1</td>
<td>5.2</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.6</td>
<td>4.6</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>7.7</td>
<td>6.1</td>
</tr>
<tr>
<td>7</td>
<td>23</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>3.8</td>
<td>2.5</td>
</tr>
<tr>
<td>9</td>
<td>4.6</td>
<td>4.7</td>
</tr>
<tr>
<td>10</td>
<td>2.9</td>
<td>3.8</td>
</tr>
<tr>
<td>reference</td>
<td>&lt; 1.66</td>
<td>&lt; 1.66</td>
</tr>
</tbody>
</table>

* C/C = corticoid/creatinine ratio; C/C day 3 = corticoid creatinine ratio after dexamethasone suppression; androstenedione = androstenedione; 17-OH-prog = 17α-hydroxyprogesterone

Within four weeks after first presentation six ferrets underwent a laparotomy. Of these ferrets, one had left, three had right, and two had bilateral adrenal involvement. In three ferrets the adrenal glands were left in place because of either the extent of attachment of the gland to the wall of the vena cava or the presence of bilateral tumors. One ferret died immediately after surgery, and in two ferrets signs recurred after left adrenalectomy.

Post-mortem examinations were performed within 4 hours of death. Histology revealed adenoma (n=2) and adenocarcinoma (n=1) in the surgically removed adrenal glands, and hyperplasia (n=2) and adenoma (n=1) in the contralateral adrenal glands. The other seven ferrets all had bilateral adrenocortical involvement at post-mortem examination (Table 1).

**Pituitary gland collection and tissue preparation**

The entire head of one of the healthy female ferrets was fixed in 4% phosphate-buffered formalin. After 24 hours of fixation the skull was placed in a Na-EDTA solution (10%, pH = 7) for 2 weeks, to soften the bone before sectioning in a midsaggital plane. In this manner slides were obtained of the pituitary gland within the fossa hypophysis of the os basisphenoidal.

In the other three healthy ferrets and seven ferrets with hyperadrenocorticism the sphenoid bone (os basisphenoidale) was cut around the pituitary gland. The brain including the pituitary gland and sphenoid bone was removed, and the pituitary gland was carefully dissected from under the dorsum sellae and its posterior clinoid processes. Sections were cut in a midsaggital plane. Consecutive sections were cut of the pituitary gland of one of the healthy ferrets to investigate the distribution of corticotropes throughout the pituitary.
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gland. In the three remaining ferrets with hyperadrenocorticism the skull was opened dorsally and the brain was lifted so that the pituitary gland came out of the pituitary fossa. The pituitary glands in these ferrets were cut in a horizontal plane.

All tissues were fixed in 4% phosphate-buffered formalin for at least 24 hours and then embedded in paraffin wax. Sections (4 µm) were cut and stained with hematoxylin and eosin (HE). Multiple consecutive sections were stained with periodic acid-Schiff (PAS) or were used for immunohistochemistry of pituitary hormones.

Immunohistochemistry

Immunohistochemical staining of pituitary sections was performed with a monoclonal mouse antibody to synthetic ACTH1-24, a polyclonal rabbit antibody to synthetic α-MSH [PU060-UP, Biogenex Laboratories, San Remo, Ca, USA], a polyclonal rabbit antibody to porcine thyroid-stimulating hormone (TSH) [Biogenesis, Poole, England], a polyclonal rabbit antibody to porcine prolactin (PRL), a polyclonal rabbit antibody to porcine growth hormone (GH), a polyclonal rabbit antibody to human LH [DAKO, N 1543, ITK Diagnostics, Uithoorn, The Netherlands], and a polyclonal rabbit antibody to human follicle-stimulating hormone (FSH) [DAKO, N 1539, ITK Diagnostics, Uithoorn, The Netherlands]. Because of strong cross-reaction between the ACTH1-24 and α-MSH antibodies, two additional ACTH antibodies were used to stain the pituitary glands of two ferrets (a polyclonal rabbit antibody to human ACTH18-39 (hACTH) [Sigma-Aldrich Chemie bv., Zwijndrecht, The Netherlands] and a polyclonal rabbit antibody to synthetic carp ACTH10-23 (cACTH) [KLH-cys-GKPVGRKRPIKVV, Eurogentec, Seraing, Belgium]. One of these two ferrets, a 5-year-old neutered male, was euthanased during the breeding season because of an insulinoma. The adrenal glands of this ferret did not show any abnormalities on histological examination. The pituitary gland of the other ferret was from one of the clinical cases (ferret 10).

Specificity of the antibodies

The specificity of the ACTH1-24, PRL, GH, and TSH antibody reactions was previously determined by staining of Western blots containing canine pituitary proteins. The ACTH1-24 antibody cross-reacted with α-MSH. The GH antibody was highly specific, whereas the prolactin antibody showed considerable cross-reaction with other proteins. The TSH antibody reacted specifically with protein fragments with molecular weights of 23 and 27 kDa. The 27-kDa fragment corresponds with the molecular weight of TSH. According to the manufacturer’s information, the LH and FSH antibodies show 10% cross-reaction with each other.
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Figure 1. Midsagittal section of the pituitary gland of a 2-year-old neutered female ferret within the *fossa hypophysis* (FH) of the *os basisphenoidale* (OB). As an artifact the *pars distalis adenohypophysis* (PD) is pressed against the *pars intermedia adenohypophysis* (PI). Due to the artifact the *cavum hypophysis* (CH) is obscured (see figure 2). (D: dorsum sellae; I: *infundibulum neurohypophysis*; LN: *lobus nervosus neurohypophysis*; M: mammillary body; ME: median eminence; T: *tuberculum sellae*; TV: third ventricle; V: venous sinus connecting cavernous sinuses). Hematoxylin and Eosin. Bar is 0.5 mm.

**Results**

*Healthy ferrets*

By observing a sagittal section of the entire hypothalamo-pituitary system of a ferret it is clear that the *dorsum sellae* extends dorsally over the *lobus nervosus neurohypophysis* of the pituitary gland (Fig 1), which makes it difficult to lift the pituitary gland out of its fossa without rupturing the pituitary stalk. There is almost no *pars tuberalis adenohypophysis* in ferrets. At most there are only a few cell layers. This thin layer did not show immunoreactivity against any of the pituitary hormones. When the pituitary gland was taken from the *fossa hypophysis*, the *infundibulum neurohypophysis* retracted, giving it a curved appearance (Fig 2).

Most of the ACTH$_{1-24}$/α-MSH positive cells of the *pars distalis adenohypophysis* were in the anterior and mid-ventral portion of the pituitary gland. The number of ACTH$_{1-24}$
positive cells diminished with lateralization of consecutive sections. All of the cells in the pars intermedia adenohypophysis stained positive with these two antibodies (Color section; Fig 1). Cells in the pars intermedia adenohypophysis did not react with the hACTH antibody, whereas cells in the pars distalis adenohypophysis reacted with the hACTH (Color section; Fig 2) and cACTH antibodies (not shown). Only at high magnification a few cells staining with the cACTH antibody were seen in the pars intermedia adenohypophysis (not shown).

By estimation, 30% to 40% of cells stained for PRL, another 30% to 40% of cells stained for TSH, and another 30% to 40% of cells stained for GH. The cells were diffusely scattered throughout the pars distalis adenohypophysis (Color section; Fig 1 and 3). At high magnification of the pars intermedia adenohypophysis a few cells were observed which stained positive for PRL and GH (not shown).

The number of cells staining positive for LH and FSH varied greatly. In the two healthy neutered ferrets approximately 15% to 20% of all cells were immunopositive (Color section; Fig 1), whereas in the other two (intact, 1-year-old, male) ferrets only a few cells were positive. In the pars intermedia adenohypophysis of the neutered jills, a small...
number of cells stained positive for LH and FSH at the junction of the pituitary stalk and the lobus nervosus neurohypophysis (Color section; Fig 4).

Clinical cases

Two pituitary glands had evidence of neoplasia and 8 had no abnormalities. The pituitary neoplasias in the two 5-year-old male neutered ferrets (No 3 and 10) were round chromophobic, PAS-negative adenohypophyseal adenomas. These neoplasias were not surrounded by a capsule and contained mainly poorly differentiated cells with a low cytoplasm-to-nucleus ratio. Some normal pituitary cells were seen between the adenomatous cells. There was no necrosis and few mitotic figures were seen.

On immunohistochemical examination of the pars distalis adenohypophysis, in 5 of the 8 non-tumorous pituitaries only a few cells were positive for ACTH₁-2₄ (number 1, 6, 7, 8 and 9), while in the other three the number of cells positive for ACTH₁-2₄ was similar to that in the healthy ferrets. In three ferrets the number of cells positive for LH and FSH were similar to those in the neutered control ferrets. In five ferrets (numbers 1, 3, 4, 6 and 7) only a few cells were positive for these hormones. The distribution of the cells staining positive for other hormones did not differ from that in the healthy ferrets.

In the adenomas immunohistochemical staining for ACTH₁-2₄, α-MSH, TSH, GH, PRL, LH, and FSH was negative. Positive staining of some normal cells associated with the adenomas was observed. The cells of the non-affected part of the adenohypophysis stained positive for ACTH, α-MSH, TSH, GH, and PRL in ferret 3 (Color section; Fig 5) and positive for TSH, GH, LH, FSH, and PRL in ferret 10. In ferret 3 only a few LH- and FSH-positive cells were found while in ferret 10 very few ACTH- and α-MSH-positive cells were found in the surrounding tissue.

Discussion

As in other species, the cells of the ferret adenohypophysis are classified according to their specific secretory products: somatotropes (secreting GH), lactotropes (secreting PRL), thyrotropes (secreting TSH), gonadotropes (secreting LH and FSH), corticotropes (secreting ACTH) and melanotropes (secreting α-MSH).

Immunopositivity for ACTH was predominantly located in the anterior and ventral region of the pars distalis adenohypophysis, as has been described in humans and dogs.⁷,¹⁷,³⁸ Previous studies of ferrets did not describe the distribution of the cells in the pituitary gland.²⁰,²¹ The intense staining of the pars intermedia adenohypophysis for ACTH, as found with the antibody to ACTH₁-2₄, must be attributed to cross-reaction with α-MSH, as has previously been reported for dogs with the same antibody.¹⁵ With the cACTH₁₀-₂₃ antibody a few immuno-positive cells in the pars intermedia adenohypophysis were detected, but with the hACTH₁₈-₃₉ antibody positive cells were not found in the pars intermedia adenohypophysis. Thus in ferrets, as in dogs,¹⁵,²⁷ the most abundant cell type of the pars intermedia adenohypophysis is the melanotrope. The staining with the cACTH₁₀-₂₃ antibody and the observations of Mohanty et al. indicate that some corticotropic cells exist in the pars intermedia adenohypophysis.²⁰,²¹ Although Mohanty and co-workers attributed
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due to cross-reaction with α-MSH, this is not possible with the cACTH_{10-23} antibody, since these two hormone fragments do not have similar epitopes.

Mohanty et al. reported on the occurrence of corticotropes and gonadotropes in the pars tuberalis adenohypophysis.20,21 However, comparison of their pictures with our sections of the pituitary gland within the sella turcica suggests that the area they described as pars tuberalis adenohypophysis may either be a transitional zone or the pars intermedia adenohypophysis. In this region, we not only found gonadotropes but also thyrotropes and somatotropes. By contrast, Mohanty et al. found somatotropes to be confined to the pars distalis adenohypophysis.21

In the present study, gonadotropes were well represented in the pars distalis adenohypophysis in the neutered ferrets whereas only a few gonadotropes were detected in the pituitary glands of the intact male ferrets. This is in agreement with observations in rats, in which castration leads to a 2-fold increase in the number of gonadotropes within 6 months due to loss of feedback by sex steroids.12 Although Mohanty et al. detected gonadotropes in the pars distalis adenohypophysis of male ferrets, they did not specify whether the animals were castrated.21

In four of the neutered ferrets with hyperadrenocorticism the number of gonadotropes was similar to that found in the neutered healthy ferrets. In the other 6 ferrets only a few gonadotropes were found. A possible explanation for the low number of gonadotropes in some of these ferrets may be that hormones by adrenal tumors, such as oestradiol,31 exert a negative feedback on the gonadotropes.

In the pituitary glands of 5 of 8 ferrets with hyperadrenocorticism, only a few corticotropes were found. In healthy humans corticotropes are mainly distributed in the anteriomedian part of the anterior lobe.38 In the pituitary gland of a healthy neutered ferret, we examined multiple consecutive sections and found that the number of corticotropes diminished with lateralization of the sections. Thus sections with only low numbers of corticotropes may not have been taken from the median part of the pituitary gland. Another explanation, however, is that the adrenocortical neoplasia in some ferrets may have produced an excess of cortisol, which suppressed the ACTH synthesis in corticotrophs.19 Although Rosenthal et al. have reported that hypercortisolism is unusual in hyperadrenocortical ferrets,31,32 they also found elevated plasma cortisol concentrations in some cases.31 The fact that hyperadrenocorticism in ferrets seems to be independent of ACTH and α-MSH33 makes the first explanation the more plausible.

In the present study, blood samples for hormone measurements were collected when the animals were first presented. Since the time between first presentation and post-mortem examination ranged from several weeks to over 3 years, it is not possible to correlate the in vivo data with the number of corticotropes or gonadotropes found at post-mortem examination. Disease progression may have led to changes in the secretory pattern of adrenocortical hormones, which would affect the activity and distribution of pituitary gonadotropes and corticotropes.

In dogs, somatotropes account for 50% or more of the adenohypophyseal cells, with the other cell types each representing 5% to 15% of the cells.27 The results of the present study confirm an earlier report that somatotropes are an abundant cell type in the ferret adenohypophysis.21
Up to 40% of the adenohypophyseal cells of healthy ferrets stained positively for prolactin. In cows, multihormonal cells have been found containing both GH and PRL, but this has not been found in ferrets. The cross-reaction of the PRL antibody with small protein fragments might explain the high number of positive cells found in the present study. Cells staining positive for TSH also comprised up to 40% of the adenohypophyseal cells of ferrets. This percentage may also be an overestimation since the TSH antibody stained proteins of different molecular weights (23, 27 and 28 kDa).

Among the ten ferrets with hyperadrenocorticism, there were two with a pituitary tumor, which are the first ever described in ferrets. This is in contrast to the situation in humans, dogs and cats, in which there is general agreement that pituitary-dependent hyperadrenocorticism is secondary to a tumor originating from corticotropes or melanotrophs. The present pituitary tumors were immunonegative for all hormones tested.

The classification of pituitary tumors in man is based on morphology, immunohistochemistry, and ultrastructure. Generally, tumors can be stained with an antibody raised against the hormone produced, i.e., the hormone of the cell of origin, the exception being the gonadotrope adenomas, which stain poorly or not at all for their respective hormones. These adenomas are usually chromophobic, have poorly developed cytoplasm, and are PAS negative. The pituitary tumors described in this study meet this description and can be categorized as gonadotrope adenomas. In vitro studies have revealed that gonadotrope adenomas may secrete gonadotropic hormones or their alpha-subunits. In the ferrets of this study, tumor development may have been initiated by the lack of negative gonadal feedback on hypothalamic GnRH as a result of neutering. This is in line with the hypothesis that persistent stimulation of the adrenal cortices by gonadotropic hormones plays a role in the pathogenesis of hyperadrenocorticism in ferrets. Persistent stimulation may lead to adrenocortical hyperplasia and finally to autonomous hypersecretion due to tumor formation. The negative feedback action of adrenal androgens, produced by an autonomously hyperfunctioning adrenal tumor, might explain why at the time of necropsy very few LH- and FSH-positive cells were found in the non-tumorous part of the adenohypophysis in one of these ferrets.

Pituitary adenomas have been found at autopsy in approximately 11% (1.5 to 26.7%) of human beings not suspected of having pituitary disease while alive. In the cases in which immunohistochemistry was performed for prolactin, approximately 40% of these tumors stained positively. No information was given on the immunohistochemistry of other hormones. The large number of pituitary tumors found in seemingly healthy humans suggests an alternative explanation for our findings, namely, that the pituitary adenomas found in the two ferrets reported here were not related to the adrenal disease and was an incidental finding.

In conclusion, our observations suggest that hyperadrenocorticism in ferrets is unlikely to be the result of persistent stimulation of the adrenal cortex as a result of a pituitary lesion. Instead, the decreased numbers of corticotropes and gonadotropes in the adenohypophysis seem to be a consequence, rather than a cause, of the adrenocortical hyperplasia and tumors. The non-staining pituitary adenomas found in two of the ten ferrets
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with hyperadrenocorticism may be related to the disease, but may also be incidental findings unrelated to hyperadrenocorticism.

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