



# FELINE ADRENAL DISEASE

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# FELINE HYPERADRENOCORTICISM

Rare disease in the cat

Middle to old age cats

Mean = 13.4 years

Range 4 - 18 years

Usually associated with:

Diabetes mellitus

72/97 cases female

Cutaneous lesions

74%



# FELINE HYPERADRENOCORTICISM

## Clinical Signs

PU/PD

Polyphagia

Diabetes mellitus

Insulin resistance

## Physical Examination

“Pot-Bellied”

Hepatomegaly

Weight gain

Muscle wasting

Alopecia

Thin skin

Severe ulceration

# FELINE ADRENAL DISEASE





# FELINE HYPERADRENOCORTICISM

## Laboratory Abnormalities

Hyperglycemia

Hypercholesterolemia

Increased SAP (30 %)

Reflects underlying diabetes



# FELINE HYPERADRENOCORTISM

## Laboratory Abnormalities

Stress leukogram is inconsistent

Urine specific gravity  $> 1.020$

UTI's - routine urine cultures



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

ACTH Stimulation

Dexamethasone Suppression

UCCR

Combined Testing



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### ACTH Stimulation

#### Cortrosyn

0.125 mg (1/2 vial) IV or

5 ug/kg IV; freeze remainder

Pre and 60 minute post





# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### Dexamethasone Suppression Testing

Cats are not like dogs

Inconsistent suppression in normal cats  
with 0.01 mg/kg IV DexNaPO<sub>4</sub>

Doses evaluated have ranged from  
0.005 - 1.0 mg/kg



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### Dexamethasone Suppression Testing

Non-adrenal illness

In PDH the most reliable dose is:

0.1 mg/kg IV with pre, 4 and 8  
hour post; 89 % sensitive



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### UCCR

Likely sensitive though poorly specific

Can be used to rule-out HAC

Simple though not easy

Early morning urine sample

# FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Combination Testing

Dexamethsone suppression (0.1 mg/kg; pre, 2 and 4 hours) followed by an ACTH stimulation test (1 and 2 hours).

Limitations related to sample times

No advantage over DST or ACTH alone



# FELINE HYPERADRENOCORTICISM

Endocrinologic Evaluation

Differentiating PDH from AT

HDDES

Abdominal US

Plasma ACTH

CT/MRI



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### Differentiating PDH from AT

#### HDDES

Multiple samples preferred

1.0 mg/kg DexNaPO<sub>4</sub> with a pre, 4  
and 8 hour post



# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

### Differentiating PDH from AT

Abdominal US

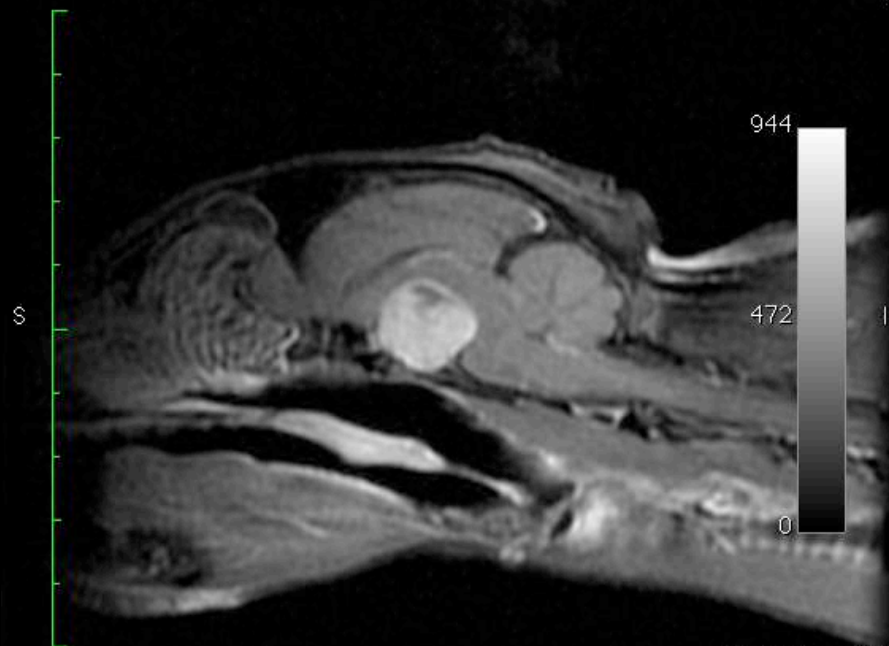
Abdominal radiographs

Adrenal calcification in normal cats

CT or MRI - “silent” lesions

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View size: 565 x 562  
WL: 472 WW: 944

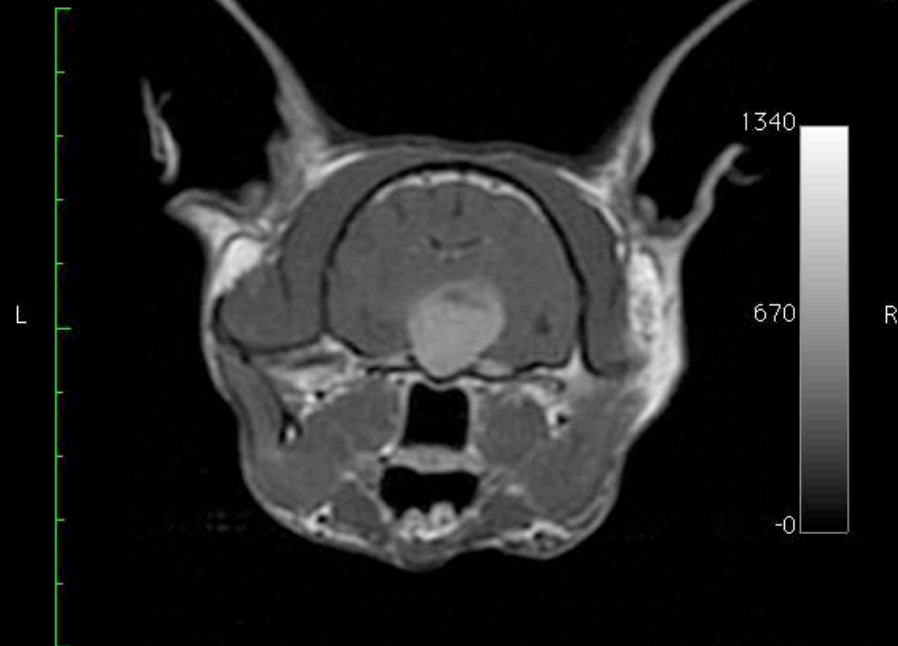
DeSoto,Chairman Meow 4976 ( 13 y , 13 y )  
3 KG Dog Knee- — O-Sag. T1+C-fs SE H 3mm  
1673  
4



Zoom: 220% Angle: 270  
Im: 5/11 (R -> L)  
Uncompressed  
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TE: 13 TR: 600  
FS: 10000  
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Image size: 256 x 256  
View size: 562 x 562  
WL: 670 WW: 1341

DeSoto,Chairman Meow 4976 ( 13 y , 13 y )  
3 KG Dog Knee- — O-Ax T1 SE H 3mm  
1673  
5



Zoom: 220% Angle: 0  
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# FELINE HYPERADRENOCORTICISM

## Endocrinologic Evaluation

Differentiating PDH from AT

Plasma ACTH

Aprotonin tubes

Contact laboratory in advance

Normal or high = PDH

Low values seen in normal cats



# FELINE HYPERADRENOCORTICISM

Disease is uncommon

Dont rely on a single test

No test is 100 % accurate

Multiple modalities

Endocrinologic

Rely on history and PE

Anatomic

Concurrent illness

Treatment and prognosis



# FELINE HYPERADRENOCORTICISM

Functional Adrenal Neoplasia

Approximately 24 % (18/74 cases)

Adenoma = carcinoma

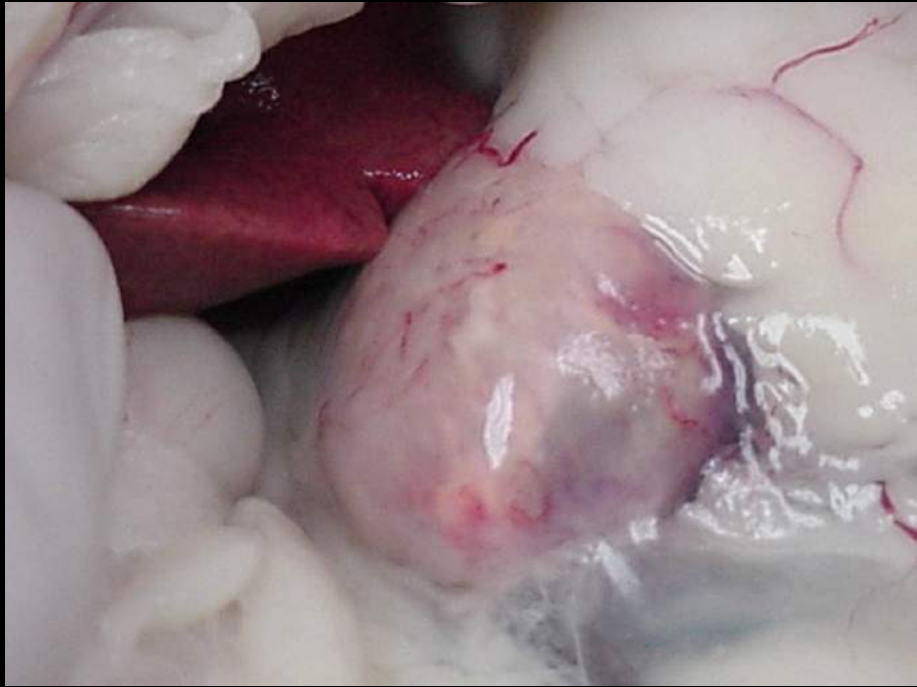
Treatment is surgical correction

Medical therapy prior to surgery

Prognosis

Insufficient data

# FELINE HYPERADRENOCORTICISM





# FELINE HYPERADRENOCORTICISM

## Therapy for Feline PDH

### Medical Therapy

op-DDD (Lysodren)

Metapyrone (Metopirone)

Ketoconazole (Nizoral)

L-Deprenyl (Anipryl)

Trilostane (Vetoryl; Modrenal)\



# FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Ketoconazole (Nizoral)

Oral antifungal agent

Inhibition of cortisol production

15 mg/kg BID

Side-effects

Hepatotoxicity; thrombocytopenia



# FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Metyrapone (Metopirone)

Inhibition of cortisol production

65 mg/ kg BID to TID

Monitor with ACTH stim testing

Questionable long term therapy



# FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

op-DDD (Lysodren)

Similar protocol as in dogs

Supplemental glucocorticoids

Side-effects similar to those in dogs





# FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

L-Deprenyl (Anipryl)

MAO-B inhibitor

Safe in cats at 0.5 to 2.0 mg/kg/day

No data on efficacy in cats with PDH



# FELINE HYPERADRENOCORTICISM

We have recently evaluated the safety and efficacy of trilostane therapy (Vetoryl, Dechra Pharmaceuticals) in 15 cats with PDH. Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within 2 months in 6/9 diabetic cats. Median survival time was 617 days for all cats (range 80-1,278 days).



# FELINE HYPERADRENOCORTICISM

- Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in 1 case. Cause of death occurred as a result of non-adrenal or non-diabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma.



# FELINE HYPERADRENOCORTICISM

Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes. It should be considered first line therapy for cats undergoing medical management of PDH.

Recommended starting dose is 2-3 mg/kg PO once a day

# FELINE HYPERADRENOCORTICISM [



# FELINE HYPERADRENOCORTICISM





# FELINE HYPERADRENOCORTICISM

Therapy for Feline PDH

Surgical Therapy

- Medical therapy prior to surgery

- Bilateral adrenalectomy

  - 3/9 died within 2 months

  - Median survival 5 months

  - Range 1 - 12 + months



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View size: 562 x 562  
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DeSoBo,Chairman Meow 4976 ( 13 y , 13 y )  
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# FELINE HYPOADRENOCORTICISM

Felt to be rare in the cat

Middle-aged cats

Median: 4 yrs

May go unsuspected

Range : 1.5 to 14 years

Incidence of isolated  
glucocorticoid  
deficiency ?

Male = female

Mix breed cats



# FELINE HYPOADRENOCORTICISM

## Historical Findings

Lethargy

Anorexia

Weight loss

Vomiting

Episodic signs; waxing and waning

Response to fluids; glucocorticoids



# FELINE HYPOADRENOCORTICISM

## Physical Examination Findings

Depression

Weakness

Mild to severe  
dehydration

Hypothermia

50 % presented in shock

Duration of signs

Median: 14 days

Range: 5 – 10 days

# FELINE HYPOADRENOCORTICISM

## Laboratory Abnormalities

Similar to dogs

Hyponatremia

Na/K ratio less than 24

Hyperkalemia

Azotemia

BUN: 31 - 80

Creatinine: 1.6 - 6.0

PO<sub>4</sub>: 6.1 - 9.1

Hypercalcemia in 1 cat



# FELINE HYPOADRENOCORTICISM

## Diagnosis

### ACTH Stimulation Test

Cortrosyn

5 ug/kg IV

Pre and 60 minute post



# FELINE HYPOADRENOCORTICISM

## Mineralocorticoid Replacement Therapy

Fludrocortisone acetate (Florinef)

0.1 to 0.2 mg BID

Desoxycorticosterone pivalate (DOCP)

2.2 units/kg IM or SQ



# FELINE HYPOADRENOCORTICISM

## Glucocorticoid Replacement Therapy

Prednisone

1.25 – 2.5 mg/day

Methyprednisolone acetate

10 mg once a month

# Feline Hyperaldosteronism

Incidence ?

Clinical Signs

Increased awareness

Weakness

Lethargy

Geriatric disease

Cervical ventroflexion

Anorexia

Multiple endocrine  
neoplasia (MEN)



# Feline Hyperaldosteronism

About 40 cases of presumed or confirmed feline primary hyperaldosteronism have been reported. Affected cats were presented at a median age of 13 years (mean 12.4 years; range 5–20 years; n=34). In the remaining cases the age was not specified).

There has been no apparent sex predilection and the breeds have included domestic shorthair, domestic longhair, British shorthair, and Siamese, Burmese, Burmilla, Tonkinese and Persian.

# Feline Hyperaldosteronism

## Physical Examination

Usually non-specific

Muscle weakness

Look for concurrent  
illness

Heart disease

Hyperthyroidism

## Laboratory Findings

Hypokalemia

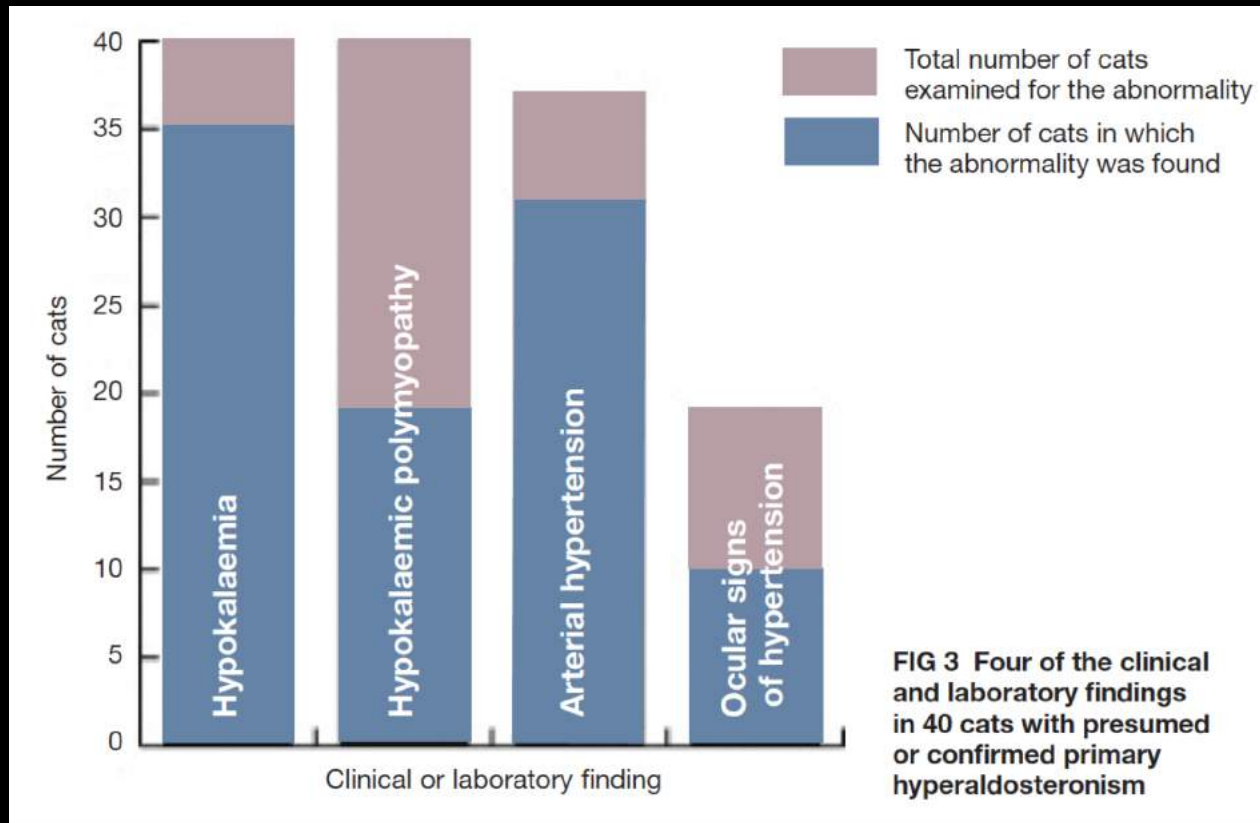
Can be severe

Sodium usually normal

Increased CPK

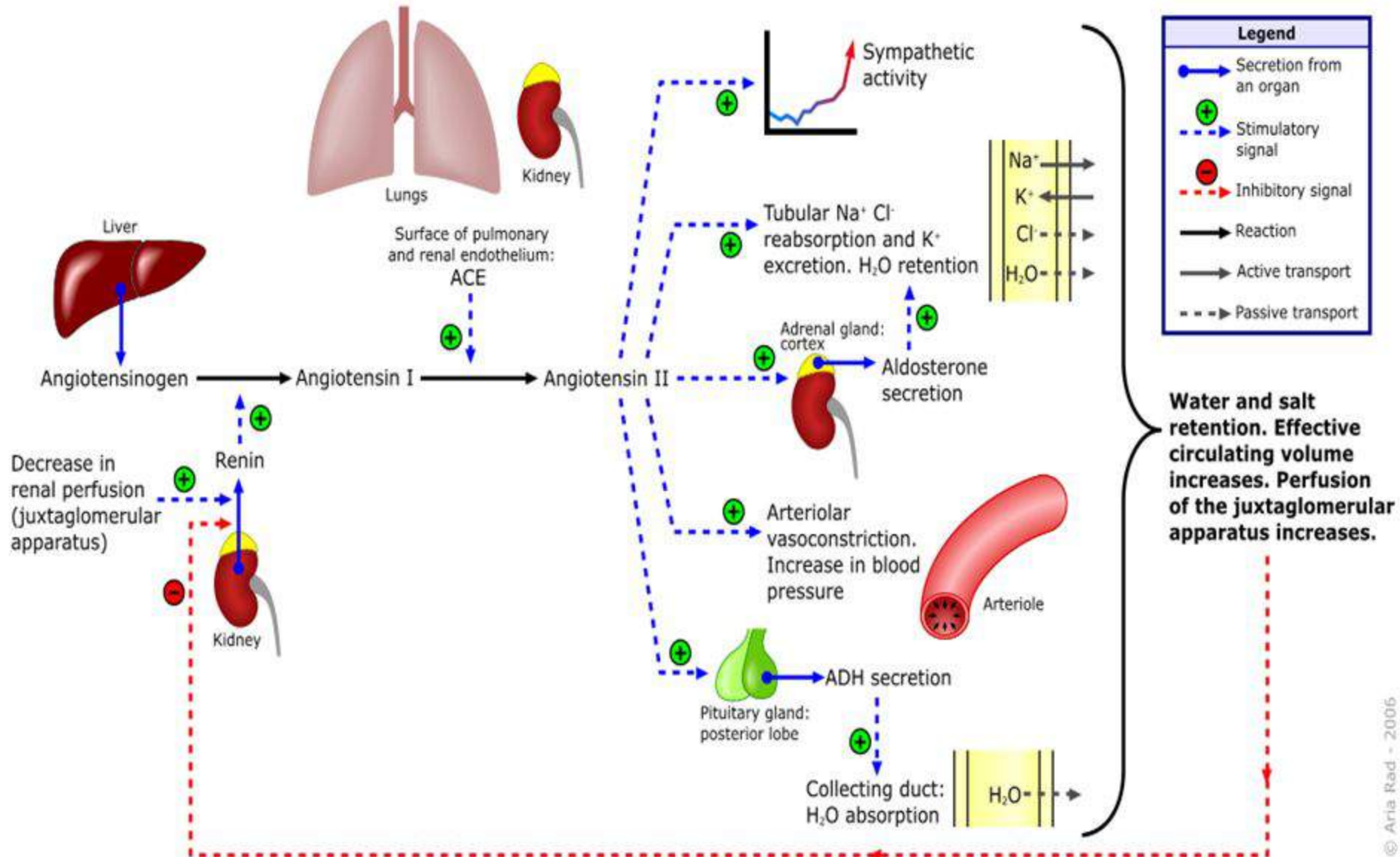
Hypertension

# Feline Hyperaldosteronism



# Renin-Angiotensin-Aldosterone System(RAAS)

## : systemic effect of Ang II



# Feline Hyperaldosteronism

Primary Hyperaldosteronism:

“Conn’s syndrome”

Underlying Cause:

Adenoma

Carcinoma

Bilateral adrenal hyperplasia (idiopathic)

High aldosterone, low to normal renin

Subtype of Primary Aldosteronism	Genetic Variant	Encoded Protein	Brief Description
FH Type I	<i>CYP11B1/CYP11B2</i> hybrid gene	<i>CYP11B2</i>	Ectopic expression in ZF; regulated by ACTH
FH Type II	<i>CLCN2</i> mutations	CIC-2	Chloride voltage-gated channel 2
FH Type III	<i>KCNJ5</i> mutations	GIRK4	Potassium Voltage-Gated Channel Subfamily J Member 5
FH Type IV	<i>CACNA1H</i> mutations	Cav3.2	Calcium Voltage-Gated Channel Subunit $\alpha$ 1H



Gene	Encoded Protein and Description	Reference Tissue	Ref.
<b>Upregulated Genes</b>			
<i>CYP11B2</i>	Aldosterone synthase- steroid hydroxylase cytochrome P450 enzyme with 11 $\beta$ -hydroxylase, 18-hydroxylase and 18-oxidase activities	AAC; NLA	[34,39–41]
<b>Calcium Signaling</b>			
<i>VSNL1</i>	Visinin-like 1, calcium sensor protein of visinin/recoverin subfamily	NLA	[59]
<i>CALN1</i>	Calneuron 1, calcium-binding protein with high similarity to calmodulin family	NLA	[41,67]
<i>CALM2</i>	Calmodulin 2, calcium-binding protein of calmodulin family.	Adjacent ZG	[42]
<i>PCP4</i>	Purkinje cell protein 4, regulates calmodulin activity by modulating calcium binding by calmodulin	NFA	[68]
<b>Nuclear receptor Transcription Factors</b>			
<i>NR4A1</i>	Nuclear receptor subfamily 4 group A member 1; steroid-thyroid hormone-retinoid receptor superfamily.	WT-KCNJ5-APAs	[56]
<i>NR4A2</i>	Nuclear receptor subfamily 4 group A member 2; steroid-thyroid hormone-retinoid receptor superfamily.	WT-KCNJ5-APAs	[56]
<i>NR5A1</i>	Nuclear receptor subfamily 5 group A member 1 (SF1); transcriptional activator of sex determination.	AAC	[39]
<i>NR0B1</i>	Nuclear receptor subfamily 0 group B member 1 (DAX1); functions in proper formation of adult adrenal gland formation.	AAC	[39]
<b>G-protein-coupled Receptors</b>			
<i>LHCGR</i>	Luteinizing hormone/choriogonadotropin receptor	NLA	[60]
<i>GNRHR</i>	Gonadotropin releasing hormone receptor	NLA	[60]
<i>HTR4</i>	5-hydroxytryptamine receptor 4	NLA; NFA	[60,64]
<i>PTGER1</i>	Prostaglandin E receptor 1	NFA	[64]
<i>MC2R</i>	Melanocortin 2 receptor	NLA	[60]
<i>AGTR1</i>	Angiotensin II receptor type I	NLA	[60]
<b>Others</b>			
<i>NEFM</i>	Medium neurofilament protein- biomarker of neuronal damage	KCNJ5-mut APAs; ZF-like APAs	[62,63]
<i>TDGF1</i>	Teratocarcinoma-derived growth factor 1- signaling protein that functions in development and tumor growth	NLA	[41]
<i>NPNT</i>	Nephronectin, a secreted matrix protein	NLA	[72]
<b>Downregulated Genes</b>			
<i>GSTA1</i>	Glutathione S-transferase alpha 1- member of a family of enzymes that protect cells from reactive oxygen species	WT-KCNJ5-APAs; NLA	[69]
<i>SFPR2</i>	Secreted frizzled related protein 2- agonist of Wnt signaling	NLA	[72]

AAC: adjacent adrenal cortex; APAs: aldosterone-producing adenomas; *KCNJ5*-mut APAs: APAs with *KCNJ5* mutations; NFA: non-functioning adrenocortical adenomas; NLA: normal adrenals; WT-KCNJ5 APAs: APAs with wild type *KCNJ5* gene; ZF: *zona fasciculata*; ZG: *zona glomerulosa*.



# Feline Hyperaldosteronism

Secondary Hyperaldosteronism:

Characterized by:

High aldosterone, normal to high renin

Caused by:

Congestive heart failure

Renal failure

GI disease

Hepatic disorders



# Feline Hyperaldosteronism

Leads to:

- 1) Increased potassium excretion in urine
- 2) Increased sodium reabsorption
- 3) Increased renal tubular bicarbonate transport/loss of hydrogen ions in urine

Clinical Signs:

Profound muscle weakness

Blindness (retinal detachment secondary to hypertension)

# Feline Hyperaldosteronism

## Diagnosis:

Plasma aldosterone levels (Michigan State)  
6x normal

Plasma renin activity  
Low to normal

Diagnostic imaging (AUS, CT)

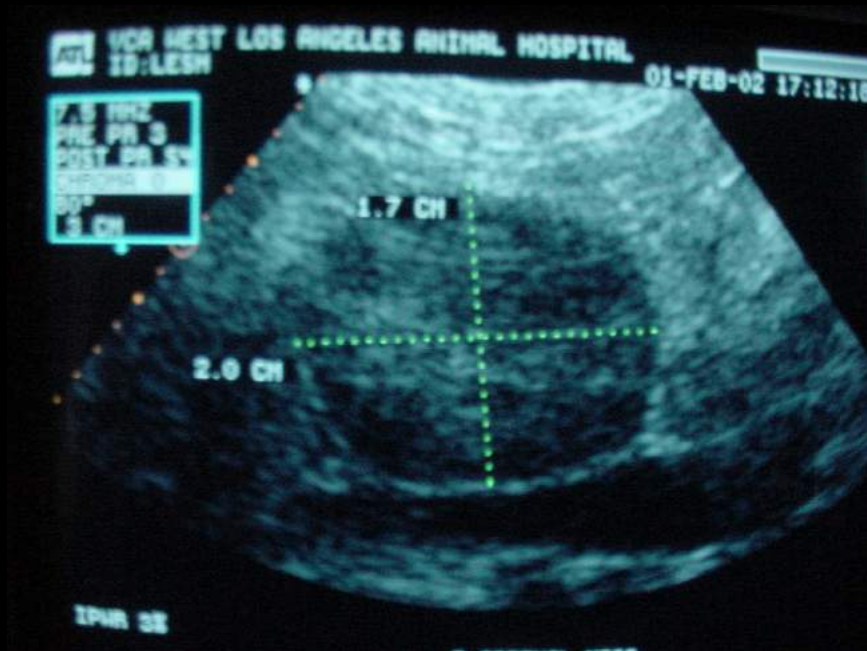
## Evaluation of the Oral Fludrocortisone Suppression Test for Diagnosing Primary Hyperaldosteronism in Cats. J Vet Intern Med 2013; 27:1493–1499

The urinary aldosterone-to-creatinine ratio (UACR) was determined in morning urine before, during, and after 4 days of oral fludrocortisone administration in a dose of 0.05 mg/kg q12h. Arterial blood pressure and plasma potassium concentration were measured before and after fludrocortisone administration.

Results: A basal UACR above 46.5, the upper limit of the reference range, was found in 3 cats with PHA. All PHA cats had basal UACRs  $>7.5$ . In all non-PHA cats with a basal UACR  $>7.5$  fludrocortisone administration induced  $>50\%$  suppression. In contrast, fludrocortisone administration resulted in  $<50\%$  suppression in 6 of the 9 PHA cats. arterial hypertension.

Conclusions and Clinical Importance: Measuring the UACR before and after 4 days of administering fludrocortisone is a practical method of confirming most cases of PHA in cats, and of substantiating the absence of PHA in cats having an ARR within the reference range.

# Feline Hyperaldosteronism



# Feline Hyperaldosteronism



CT/e  
Ex: 77

P

Animal Imaging  
Cockrum, Alice  
2000 Apr 10 F 4698

C: ISOVUE 300 11CC  
Se: 6/4  
Im: 15/48  
Ax: H55.0

Acc:  
2008 Dec 29  
Acq Tm: 12:13:32.929780

Mag: 1.6x

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512 x 512  
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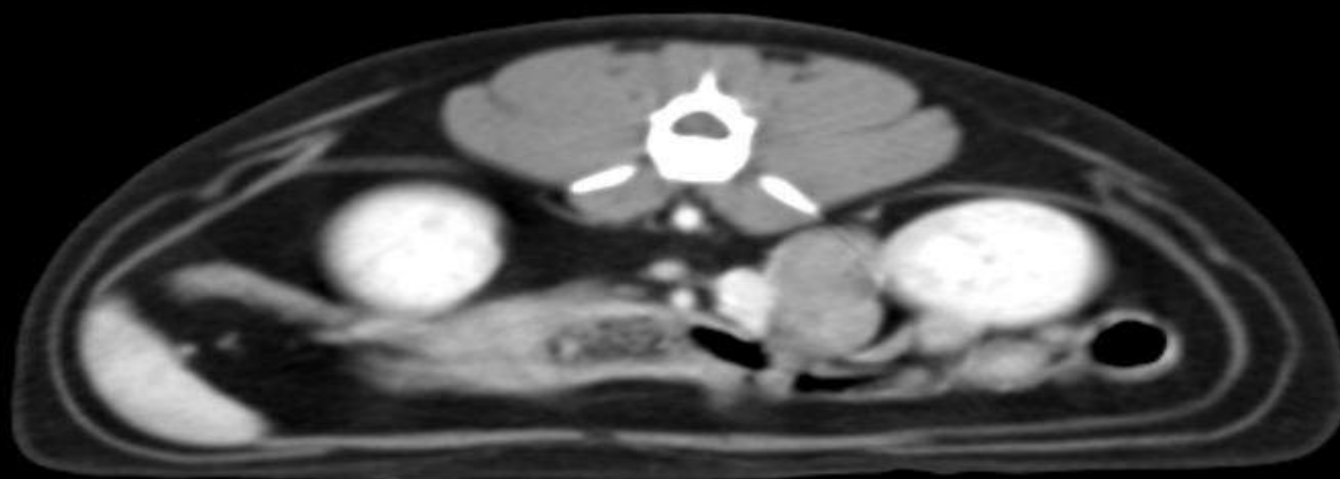
120.0 kV  
80.0 mA  
5.0 mm/0.0:1Tilt: 0.0  
1.5 s

Lin:DCM / Lin:DCM / Id:ID

W:400 L:40

A

DFOV: 22.4 x 22.4cm





# Feline Hyperaldosteronism

## Treatment

Unilateral adenoma or adenocarcinoma without evidence of metastasis → adrenalectomy

## Medical management

Spironolactone 2-4 mg/kg/day po

Potassium supplementation

+/- Amlodipine for hypertension



# Feline Hyperaldosteronism

Primary (non-tumorous) hyperaldosteronism

Progressive renal disease

Normal abdominal US vs mild adrenomegaly

Hypertension

Hypokalemia

Elevated aldosterone levels

Suppressed renin levels





# Feline Hyperaldosteronism

Non-tumorous hyperaldosteronism (hyperplasia)

Renin-angiotensin-aldosterone system implicated in progressive renal sclerosis

Aldosterone promotes thrombosis and fibrosis

Systemic arterial hypertension and fibroproliferative destruction of kidney

# Feline Hyperaldosteronism

Hypokalemic paroxysmal flaccid paresis, retinal detachment with hemorrhages.

Normal BUN and creatinine but later increased

8 cats azotemic at first examination

Adrenal hyperplasia based on histopathology of 3 of the cats.  
Histopathology of cats at necropsy – interstitial fibrosis, glomerular sclerosis

Incomplete renin suppression

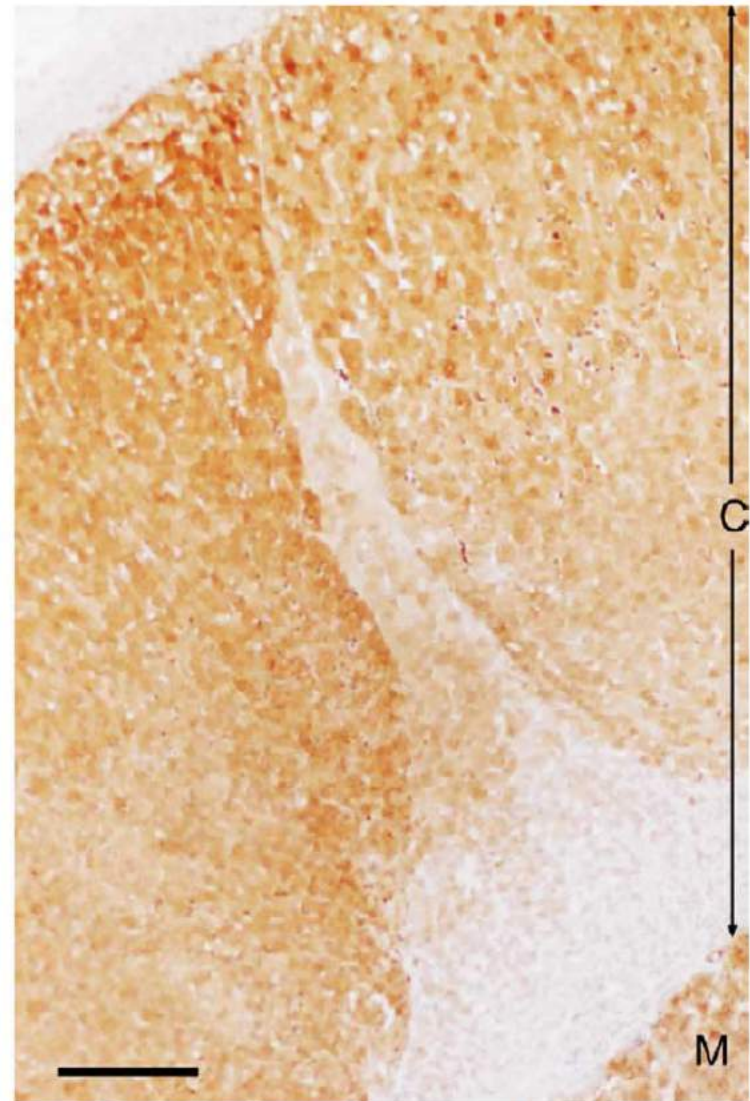
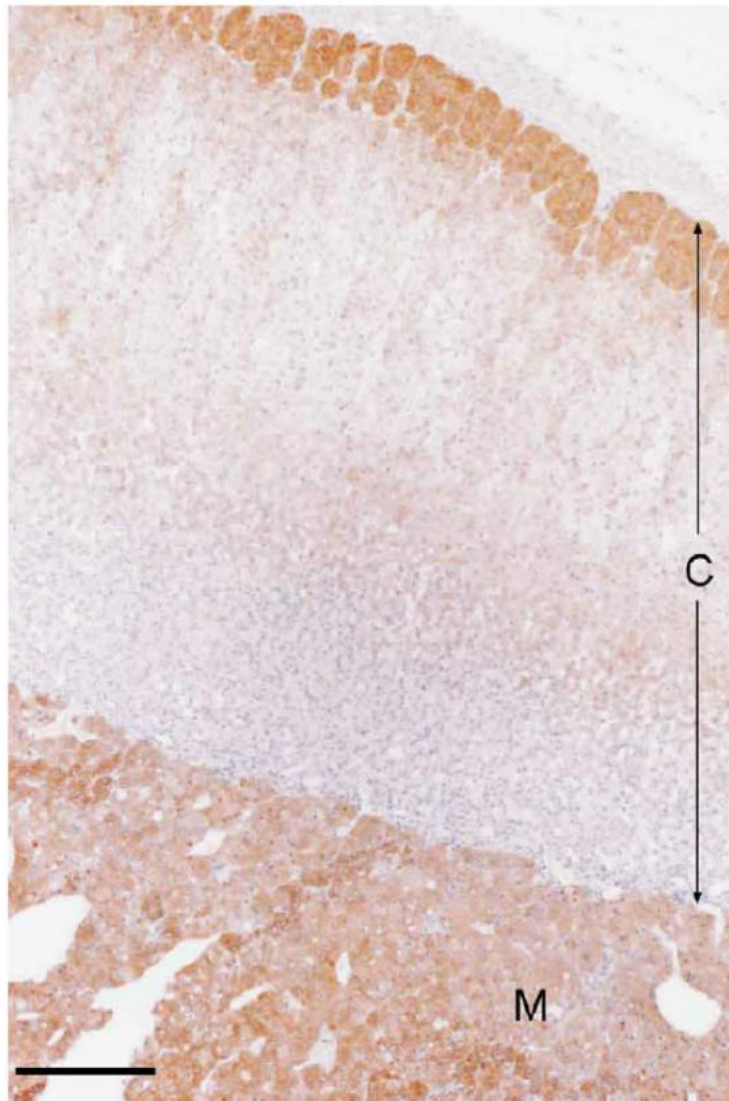
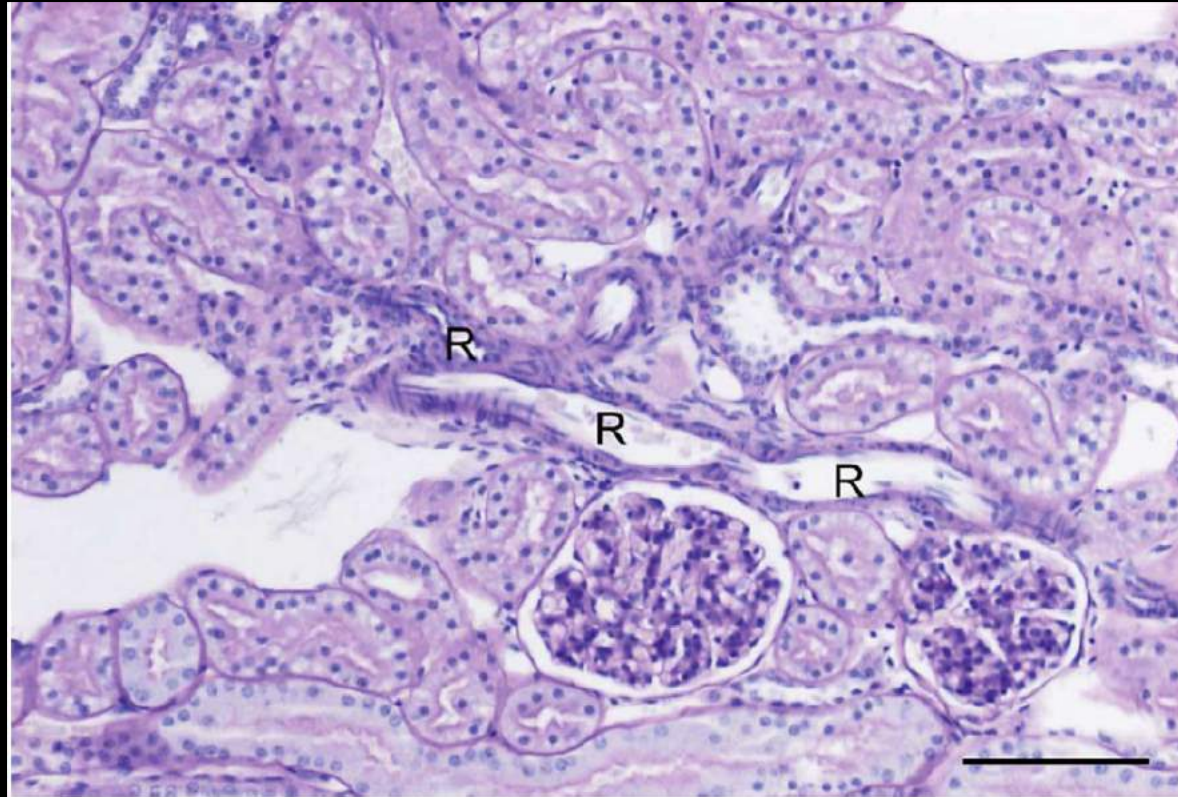
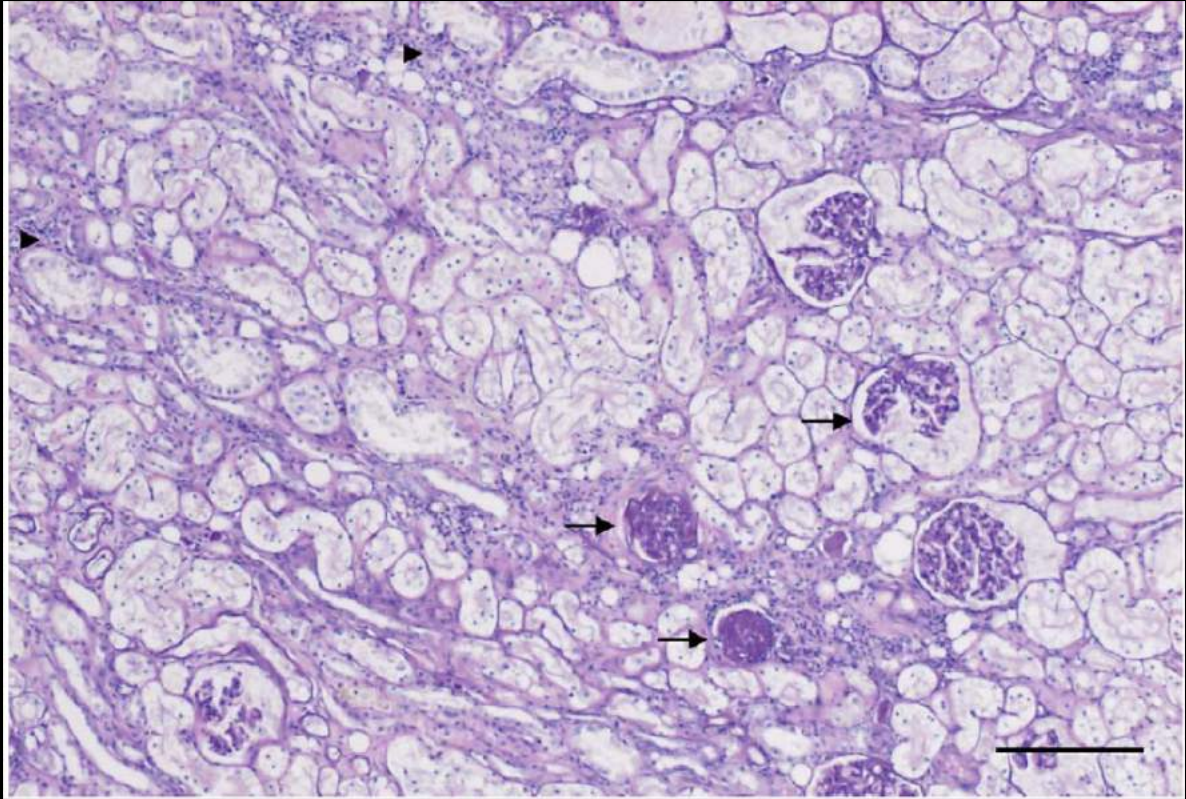


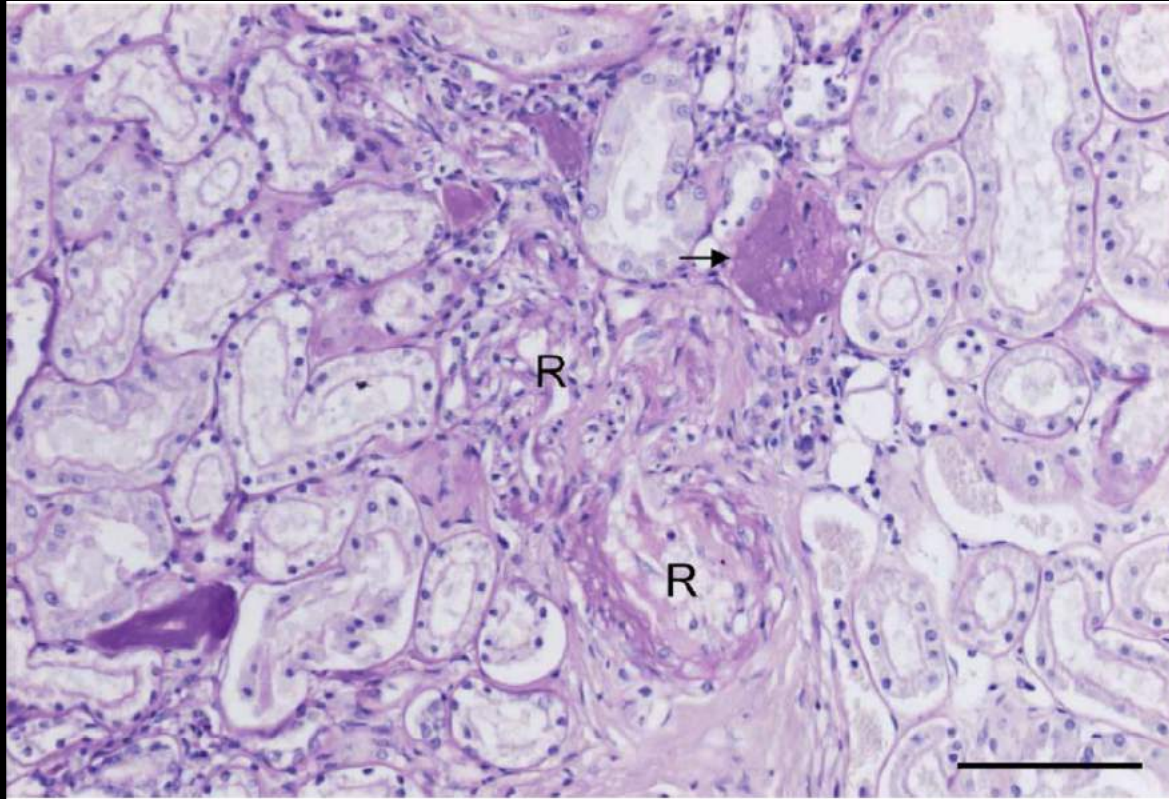
Fig. 4. Two adrenal glands stained with neuron-specific enolase (NSE, bar = 200  $\mu$ m). In the healthy control cat (left), the staining of the cortex (C) is confined to the zona glomerulosa with some vague staining of the outer parts of the zona fasciculata. In the cat 2 with primary hyperaldosteronism (right), the cortex mainly consists of multiple hyperplastic nodules, staining positively for NSE. In both sections, there is similar staining of the adrenal medulla (M). Bar = 200  $\mu$ m.













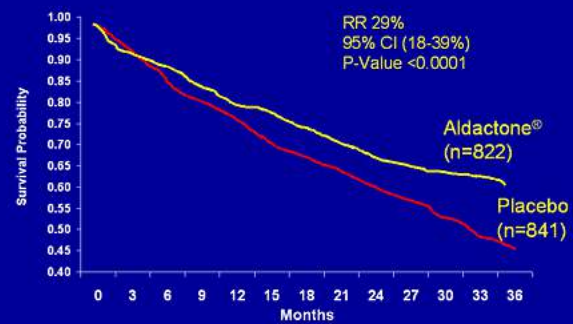
# Feline Hyperaldosteronism

Incidence likely much more common than reported

Screen older cats with hypokalemia and/or hypertension

Studies on spironolactone in cats with hyperaldosteronism to prevent ongoing renal injury

RALES: Aldactone® vs. Placebo  
All Cause Mortality





# FELINE PRIMARY HYPERALDOSTERONISM



## ANNALS OF INTERNAL MEDICINE

VOLUME 44

JANUARY, 1956

NUMBER 1

### PRIMARY ALDOSTERONISM, A NEW CLINICAL ENTITY\*†

By JEROME W. CONN, M.D., F.A.C.P., and LAWRENCE H. LOUIS, ScD.,  
*Ann Arbor, Michigan*

ALDOSTERONE, the newly discovered normal adrenal secretory product,<sup>1,2</sup> has attracted the attention of a great many clinical investigators because of its apparent rôle in the pathogenesis of a number of clinical disorders. This extremely potent sodium-retaining corticoid has been found to be present in excessive amounts in the urine of edematous nephrotics,<sup>3,4</sup> cardiacs with congestive failure,<sup>5, 19</sup> patients with decompensated hepatic cirrhosis<sup>11-13</sup> and women with eclampsia.<sup>14-18</sup> All of these conditions manifest marked edema, but it is obvious that the *primary* difficulty in each condition is *not* due to increased activity of a sodium-retaining steroid. It seems reasonable to assume that in the course of the development of each of these conditions a metabolic event occurs which is common to them and which triggers the production of excessive quantities of aldosterone. We would therefore classify such conditions as being associated with *secondary aldosteronism*.

*Primary aldosteronism*, by which we mean that the disease originates in the adrenal gland, is *not* associated with edema, and in its pure state manifests itself in the form of an interesting complex of symptoms and a fascinating disturbance of electrolyte metabolism.

The data to be presented have been obtained in the course of an extensive metabolic balance study upon a *single patient*. The investigation extends from April, 1954, to April, 1955, and includes 227 days of rigid metabolic control. It appears to establish the existence of a new clinical syndrome, which we have named "primary aldosteronism."<sup>10, 14</sup> The data afford a reasonable explanation for the abnormality of electrolyte metabolism which

\* Presented at the Thirty-sixth Annual Session of the American College of Physicians, Philadelphia, Pennsylvania, April 27, 1955.

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

† This study has been supported in part by a grant from the Research and Development Board, Office of the Surgeon General, U. S. Army.