

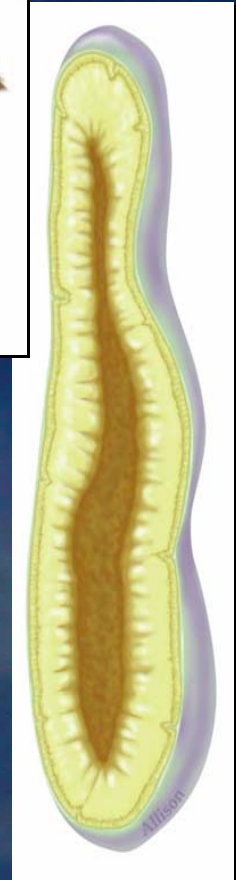
Canine Hypoadrenocorticism - Addison's Disease



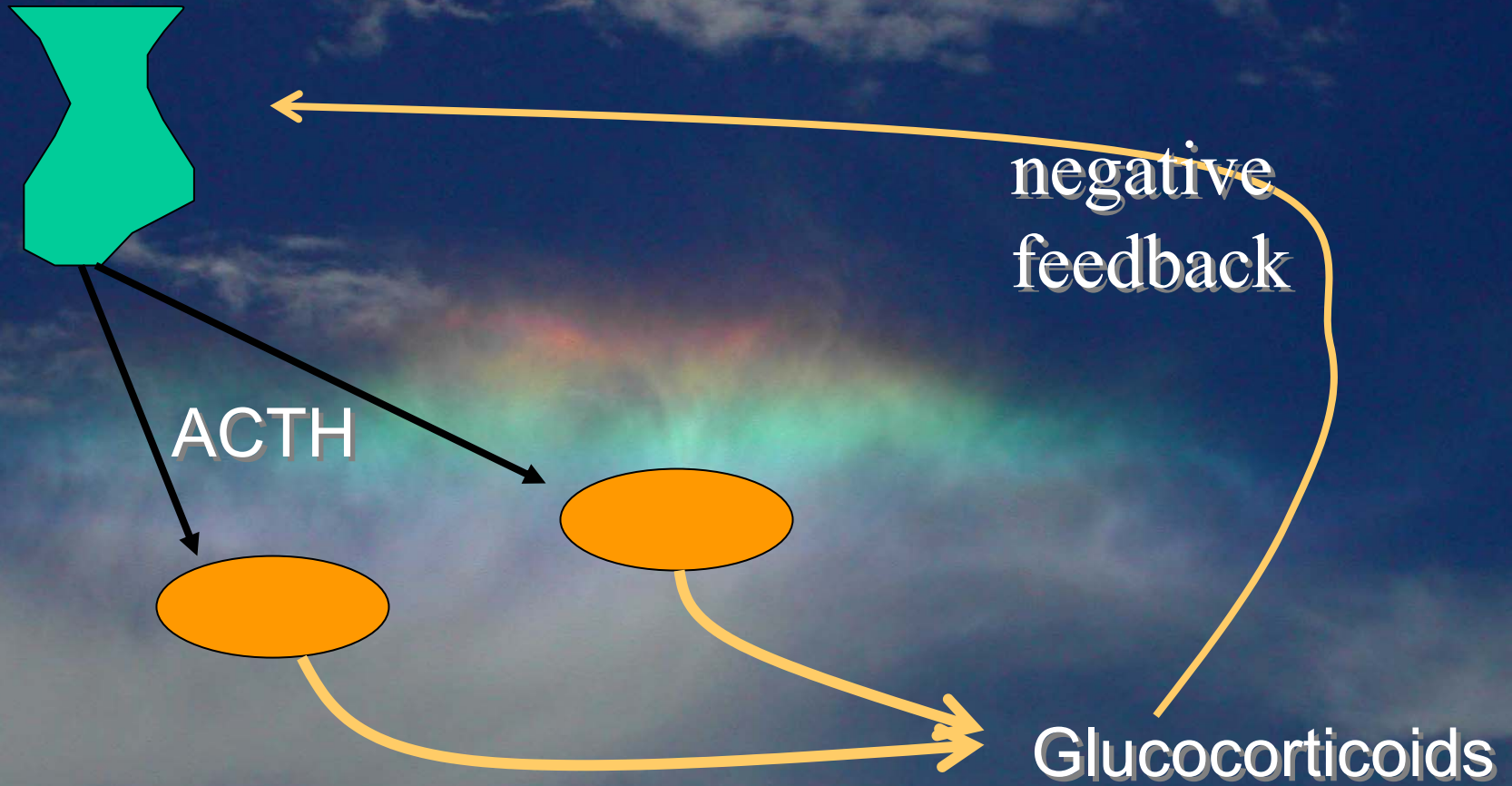
Markus Rick, Med. Vet.
Endocrine Diagnostic Section
Diagnostic Center for Population and Animal
Health Michigan State University
East Lansing, MI 48824, USA

Adrenal Glands

- Both 1g
- Yellow cortex, brown medulla
- Cortex (75%):
 - Z. glomerulosa (25%): mineralocorticoids
 - Z. fasciculata (60%) and Z. reticularis (15%): glucocorticoids, androgens
- Medulla (25%):
 - Catecholamines
- More than 30 different hormones



Glucocorticoids



Glucocorticoids - II

- Cortisol
 - Regulates metabolism by increasing gluconeogenesis
 - Increases vascular reactivity
 - Balances water and electrolytes
 - Has anti-inflammatory activity

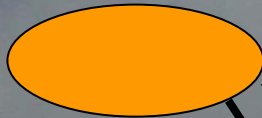
Aldosterone



ACTH- necessary to maintain baseline

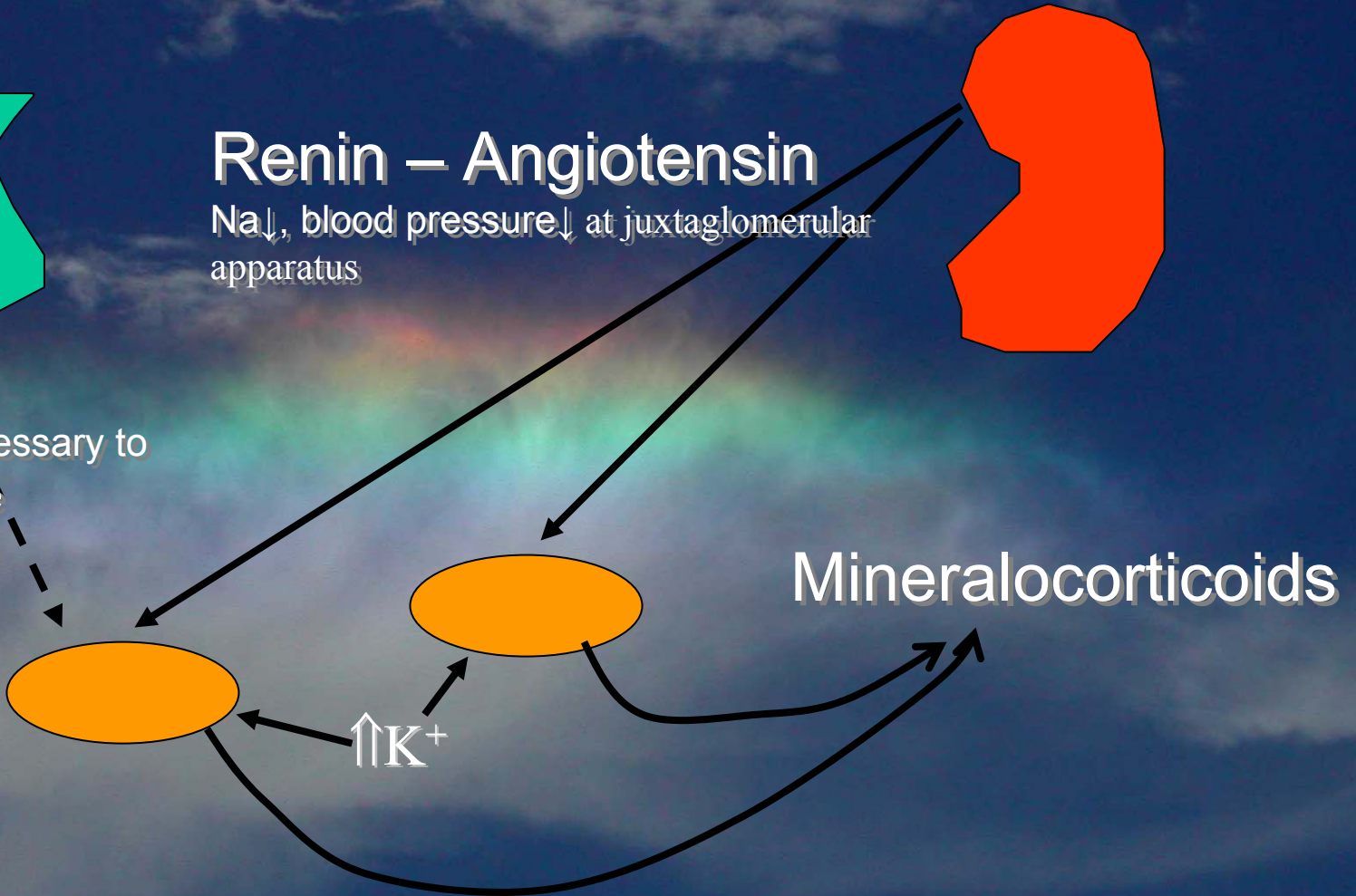
Renin – Angiotensin

Na↓, blood pressure↓ at juxtaglomerular apparatus



Mineralocorticoids

↑K⁺



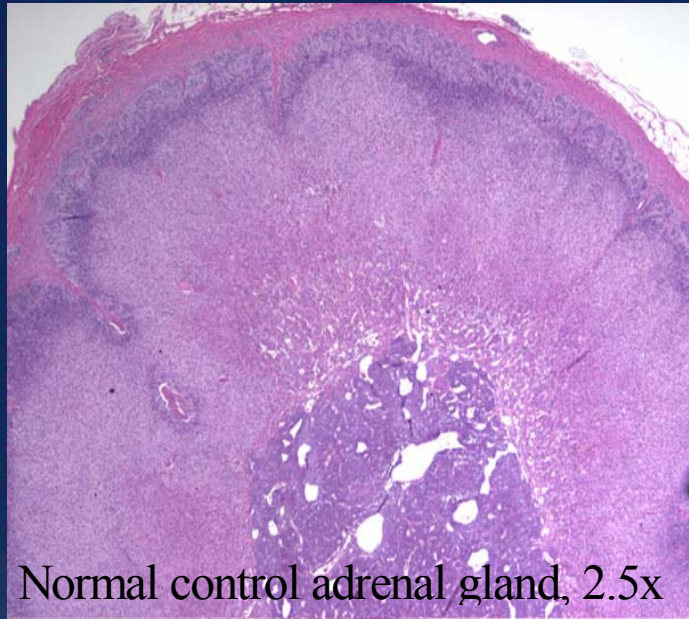
Aldosterone - II

- Induces renal resorption of Na, Cl, H₂O
- Releases K through intestines, salivary glands and kidneys
- Overall it corrects hypotension and changes K against Na and therefore corrects the hyperkalemia and hyponatremia

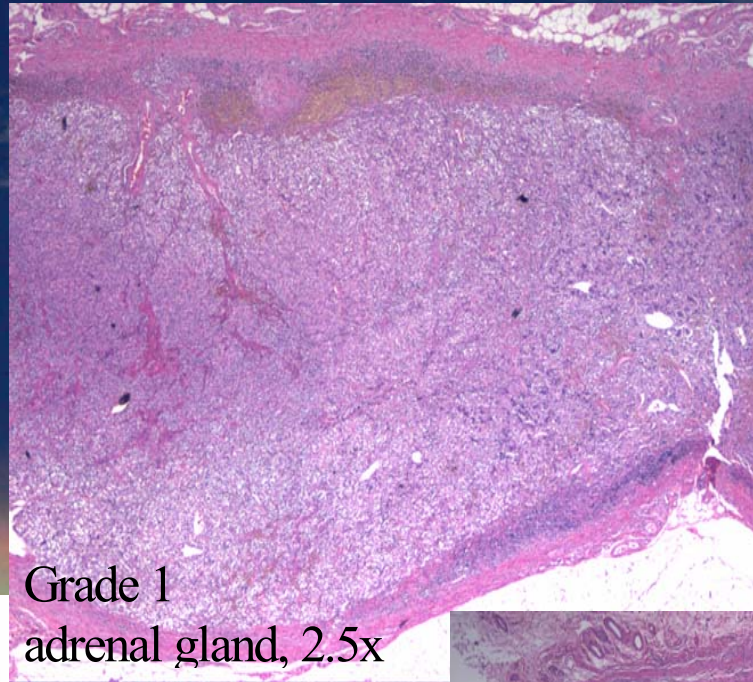
Primary Addison's Disease

- Gluco- and mineralocorticoid insufficiency is present
- Primary disease affects the adrenal gland
- Common reasons:
 - Idiopathic (atrophy or destruction of adrenal cortices (>85%)), in man 70-90% are immune mediated
 - Autoimmune etiology is not proven in dogs yet, but is suspected
 - Iatrogenic (chemotherapeutical destruction, adrenalectomy)
 - Rare: hemorrhage/ thrombosis, infarction, infiltration
 - In man also: tuberculosis, AIDS

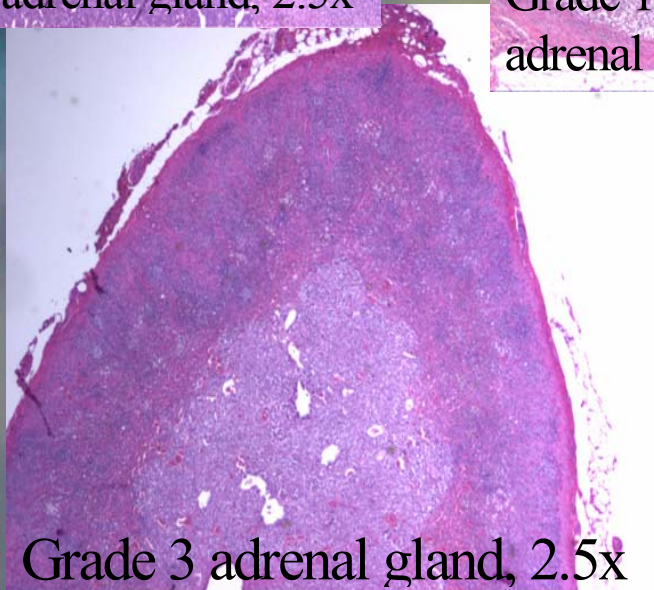
Primary Addison's Disease - II



Normal control adrenal gland, 2.5x



Grade 1 adrenal gland, 2.5x

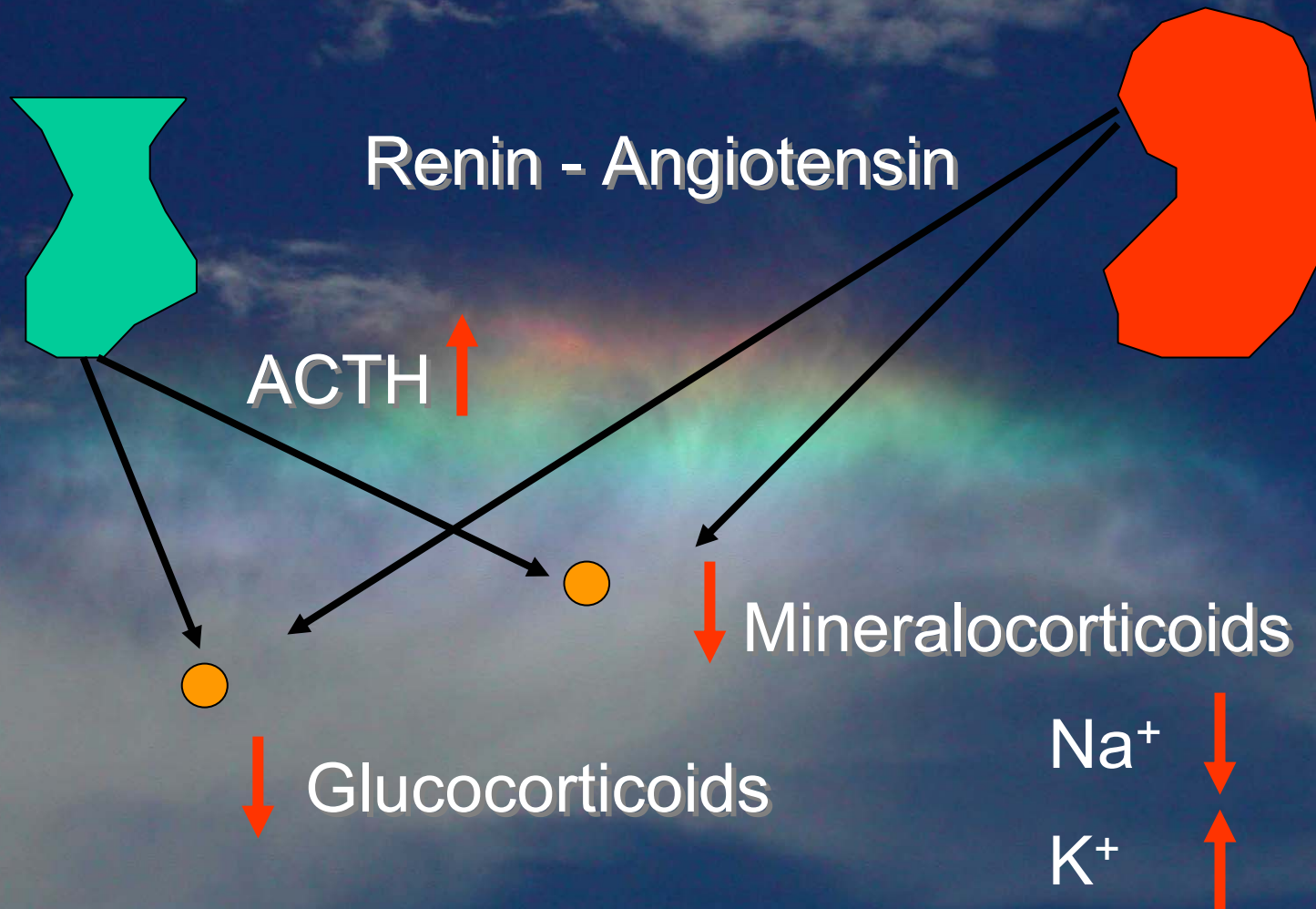


Grade 3 adrenal gland, 2.5x



No inflammation, cortex collapsed

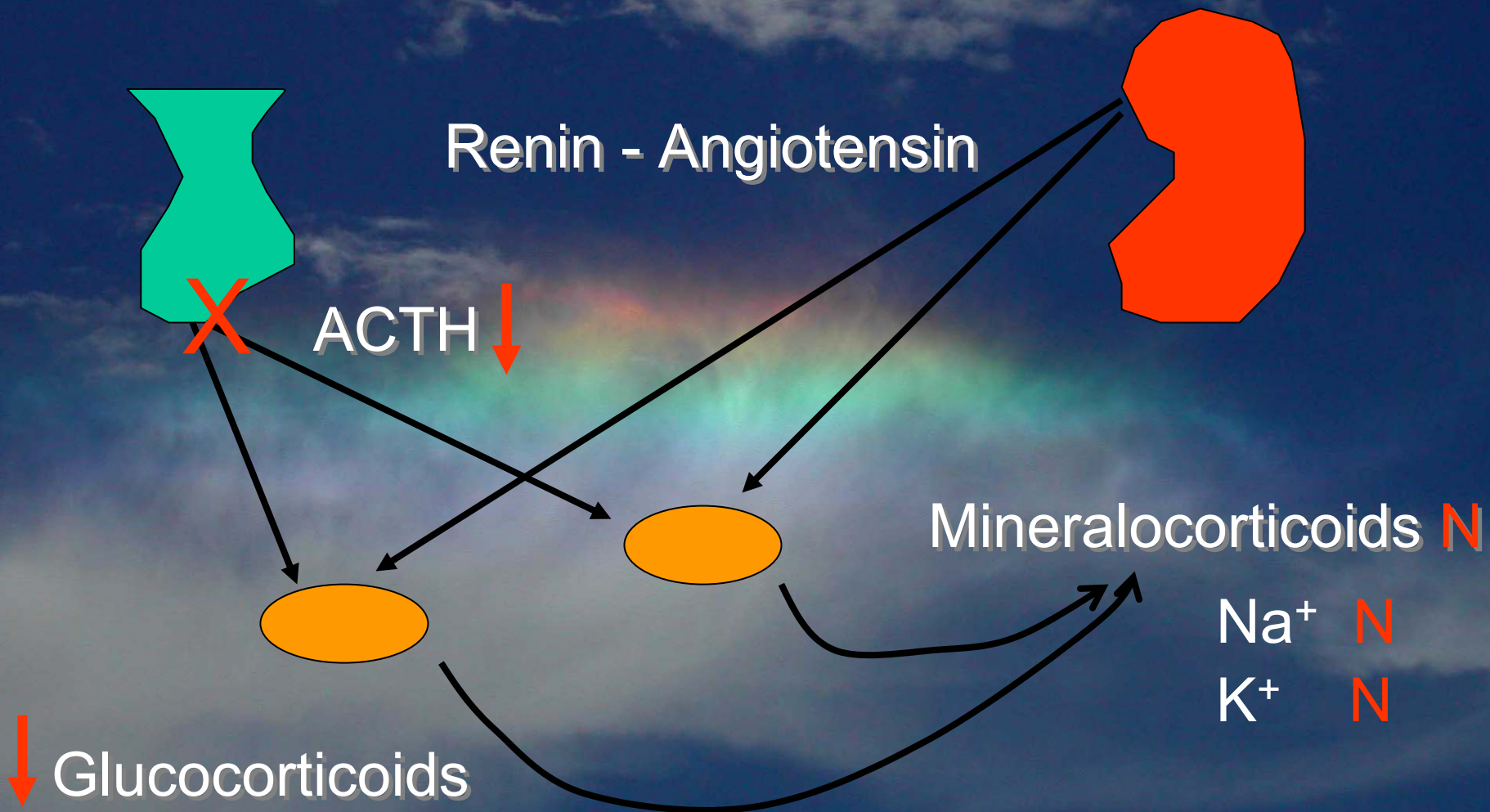
Primary (Adrenal)



Secondary Addison's Disease

- Is not well defined in the literature
- Glucocorticoid insufficiency only
- Secondary disease affects pituitary or hypothalamus, but not the adrenal gland
- Theoretical reasons:
 - ACTH (or CRH) insufficiency
 - Tumors of pituitary gland or hypothalamus
 - Suppression of ACTH due to drug treatment

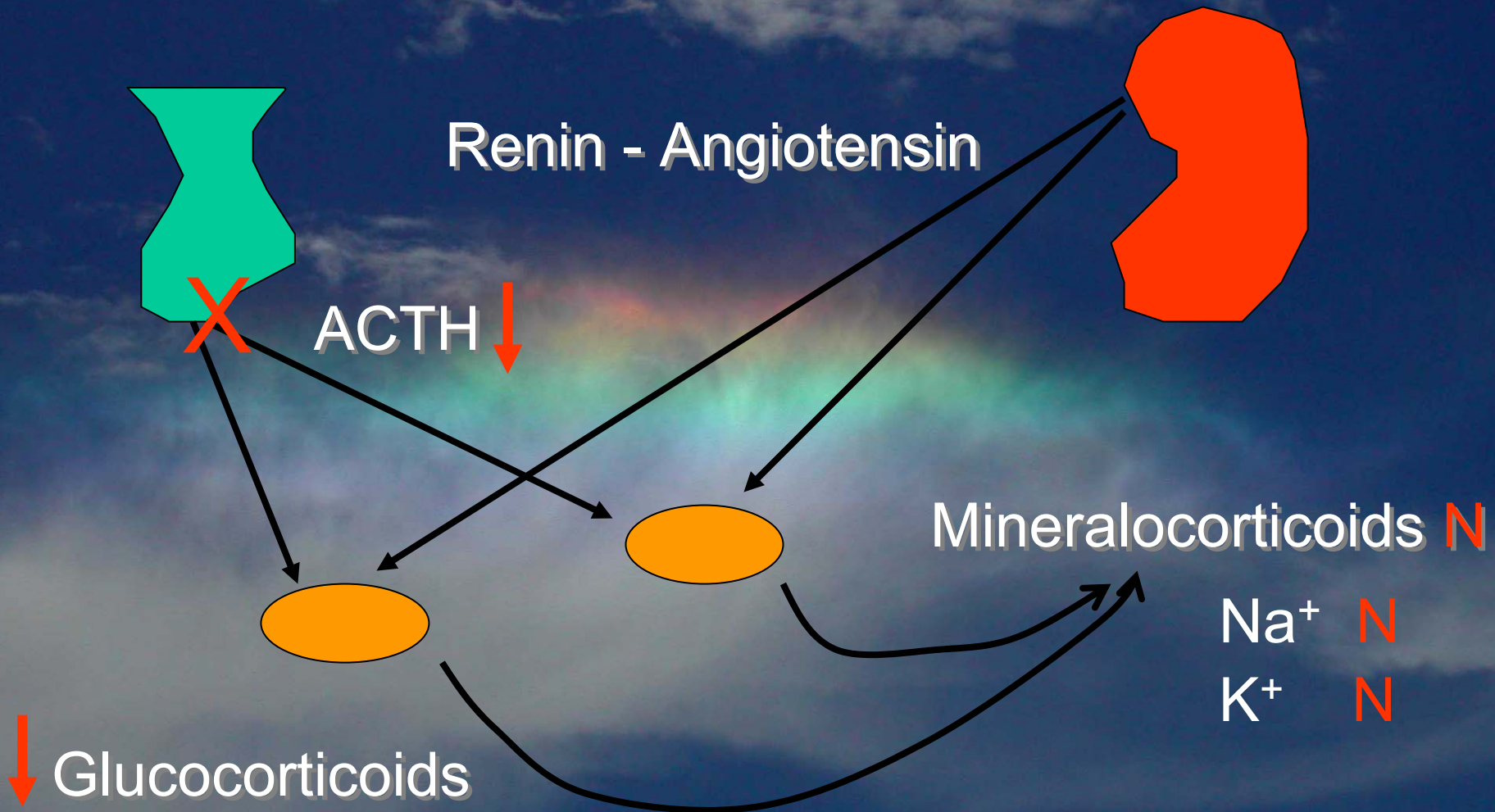
Secondary (Pituitary Or Hypothalamus)



Exogenous Glucocorticoids

- Only glucocorticoid insufficiency present
- Reasons:
 - Potent glucocorticoids cause suppression of ACTH and atrophy of the zona fasciculata and reticularis
 - Others with mineralocorticoid activity might also cause atrophy of the zona glomerulosa as well (not well documented)

Exogenous Glucocorticoids



Hypoadrenocorticism

- Incidence: 0.13-0.6 cases/ 1000 dogs
- Prevalence (natural): 0.6-2.8 cases/ 1000 dogs
- Prevalence (natural and iatrogenic): 0.6-3.1
- Young to middle aged: 2-7 years (median: 4 years; range **2 months** to 14 years)
- 70% females
- Castrated males are at higher risk than intact males; females controversial

Breed Predisposition

- Breeds at higher risk include:
 - Bearded Collie
 - Standard Poodle
 - West Highland White Terrier
 - Portuguese Water Dog
 - Leonberger
 - Great Dane
 - Airedale Terrier
 - Basset Hound
 - Wheaten Terrier
 - Rottweiler

Who is affected? - II

- In these breeds, always consider Addison's disease as a possibility
- Consider testing animals with unexplained vomiting, diarrhea or other signs that resolve with fluid and/or glucocorticoid treatment
- Clinicians at MSU almost test all Portuguese Water Dogs

Clinical Findings

- Clinical signs may be vague and nonspecific and compatible with:
 - Primary GI disease
 - Primary renal failure
 - Neuromuscular disease
 - *Trichuris vulpis* infestation (Whipworms)
 - Sepsis

Clinical Findings - II

- Most commonly found:
 - Depression, lethargy
 - Weakness
 - Weight loss
 - Anorexia
 - Emesis
 - If acute:
 - Dehydration
 - Diarrhea and vomiting (also chronic)

Clinical Findings - III

- May be present:
 - Melena
 - Hematemesis
 - Polyuria/ Polydipsia
 - If acute:
 - Bradycardia
 - Weak pulse
 - Slow capillary refill

Clinical Findings - IV

- Less often reported:
 - Shaking/ tremors
 - Alopecia
 - Megaesophagus (1%), reversible
 - If acute:
 - Hypothermia
 - Painful/ sensitive abdomen

Hematology

- Mild to severe monochromic, normocytic anemia (20-30%)
- Eosinophilia (20%)
- Lymphocytosis (10%)

Chemistry

- Hyperkalemia (90%)
- ↑ BUN (86%)
- Decrease of sodium:potassium ratio (normal 27-40:1) (90%, recent published: 65%)
- Hyponatremia (83%)
- ↑ Creatinine (68%)
- Hypochloremia (46%)
- Hypercalcemia (30%)
- Hypoglycemia (20%)

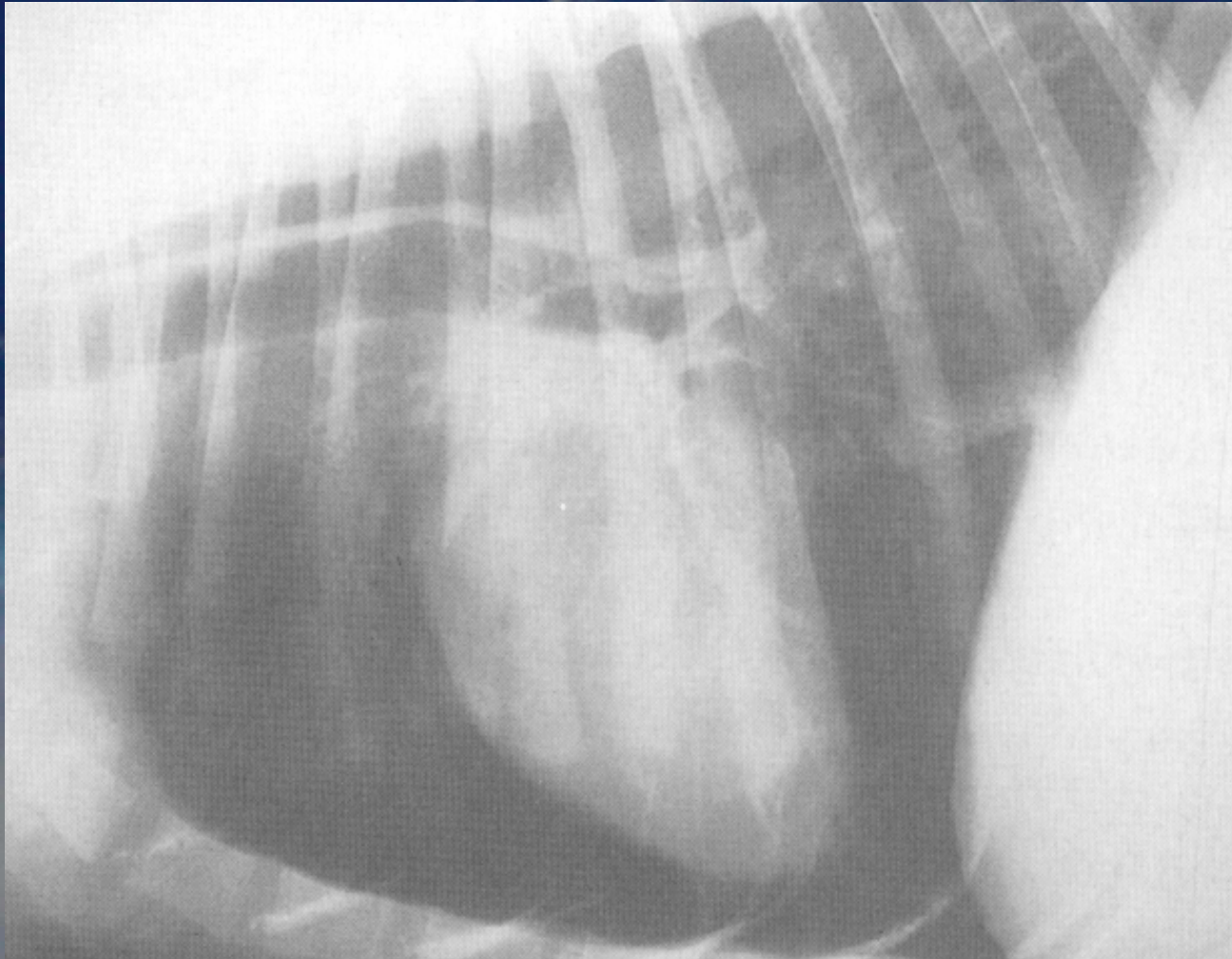
Chemistry - II

- Don't use a normal Na/K ratio to
RULE OUT Addison's

Imaging

- More to rule out other causes:
 - Ultrasound might be useful to define cortical atrophy but requires high skills and good equipment, more helpful in Cushing's
 - Radiographs are less useful, but sometimes you see signs related to hypovolemia/ decreased tissue perfusion including microcardia, narrowed caudal vena cava, descending aorta and hypoperfusion of the lungs

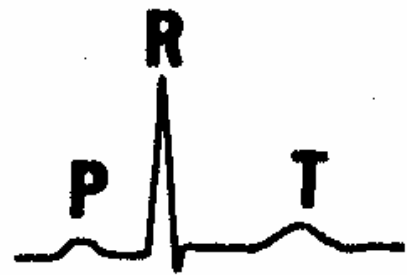
Imaging - II



Others

- Urinalysis:
 - Pre-renal azotemia: well-concentrated urine
 - Renal azotemia: low specific gravity (<1.018)
 - Helpful to differentiate between renal failure and Addison's disease
- Blood pressure
 - Hypotension in approximately 90% (not enough data yet!)
- Electrocardiogram
 - Changes due to hyperkalemia
 - First: mild changes (tall peaked T-wave)
 - Severe: cardiac arrest

Others - II



NORMAL



HYPERKALEMIA (EARLY)



HYPERKALEMIA (LATE)

Endocrinology

- ACTH response test
- Most reliable and consistent test available
 - Sample pre- and 1 hour post
 - 250 μ g/dog (or 5 to 10 μ g/kg i.v.) cosyntropin (Cortrosyn[®])
 - Sample pre- and 2 hours post
 - 2.2 IU/kg ACTH gel i.m. (compounded or Acthar Gel[®])
- Measure cortisol and/or aldosterone

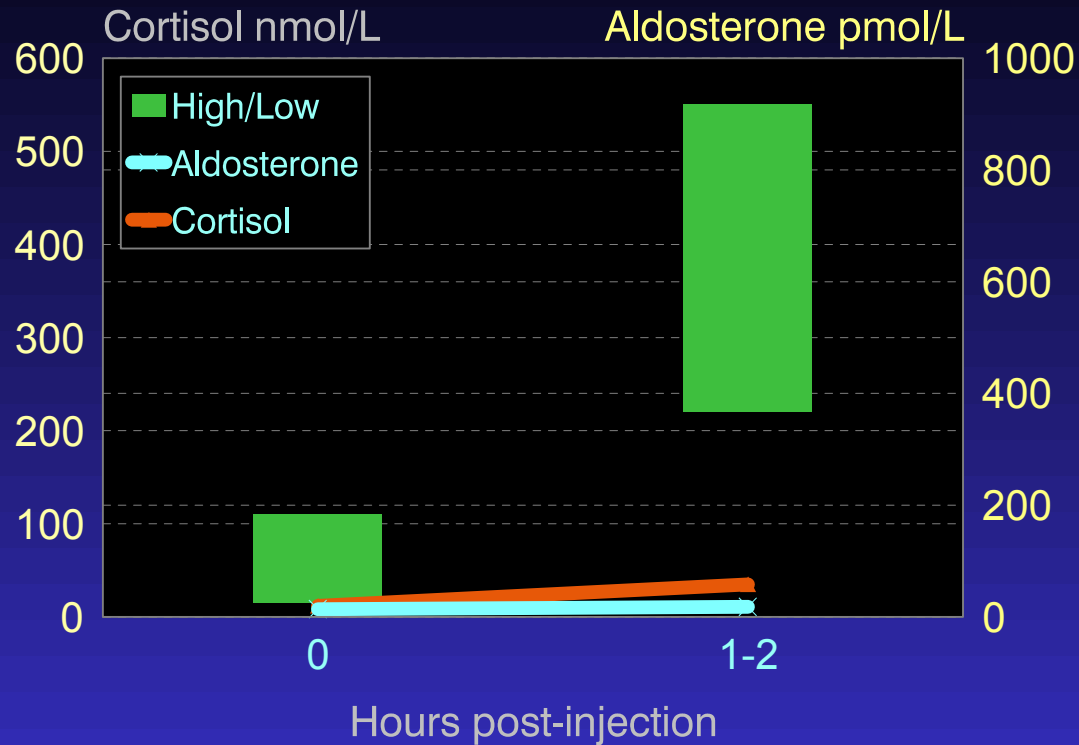
Endocrinology - II

- Perform ACTH response test prior to glucocorticoid treatment! (**Pred and hydrocortisone show cross-reaction in the assay and might cause spurious results**)
- If emergency requires immediate glucocorticoid treatment, use Dexamethasone
- Endogenous (plasma) ACTH: primary/secondary in pre-treatment samples

Endocrinology - III

ACTH/Cortrosyn Response Test

Primary (adrenal) Addison's hypoadrenocorticism

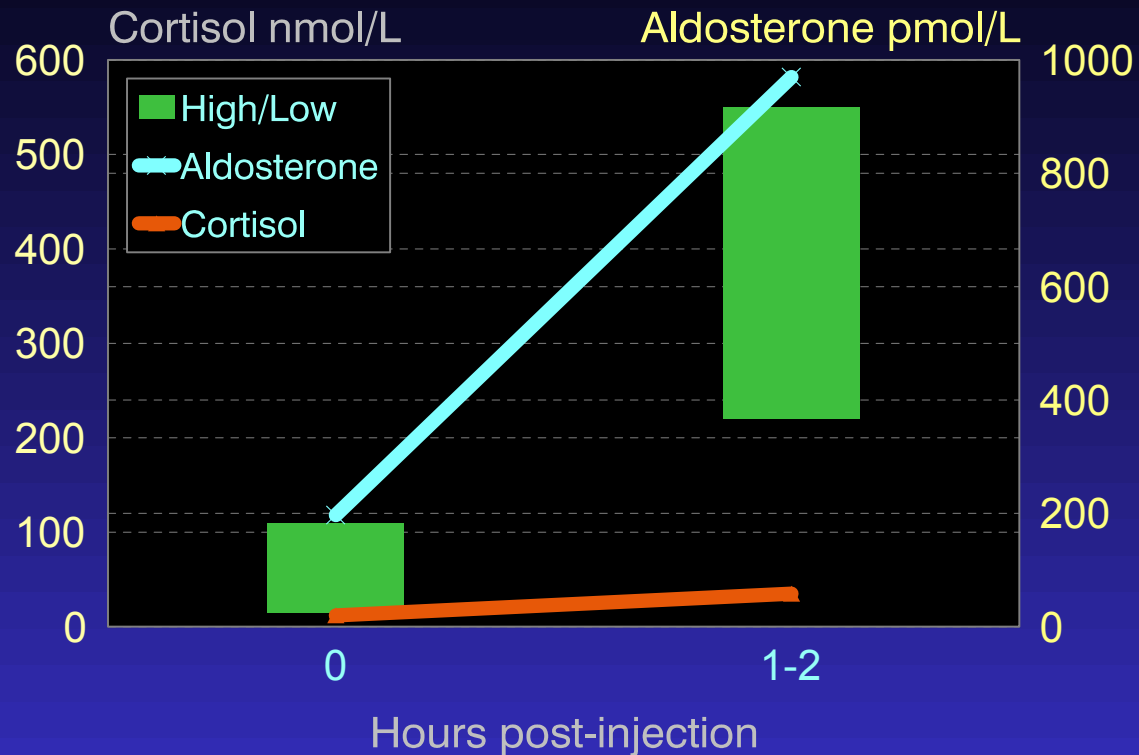


Endogenous ACTH concentration HIGH; (shaded is cortisol ref ranges)

Endocrinology - IV

ACTH/Cortrosyn Response Test

Secondary (pituitary) Addison's hypoadrenocorticism

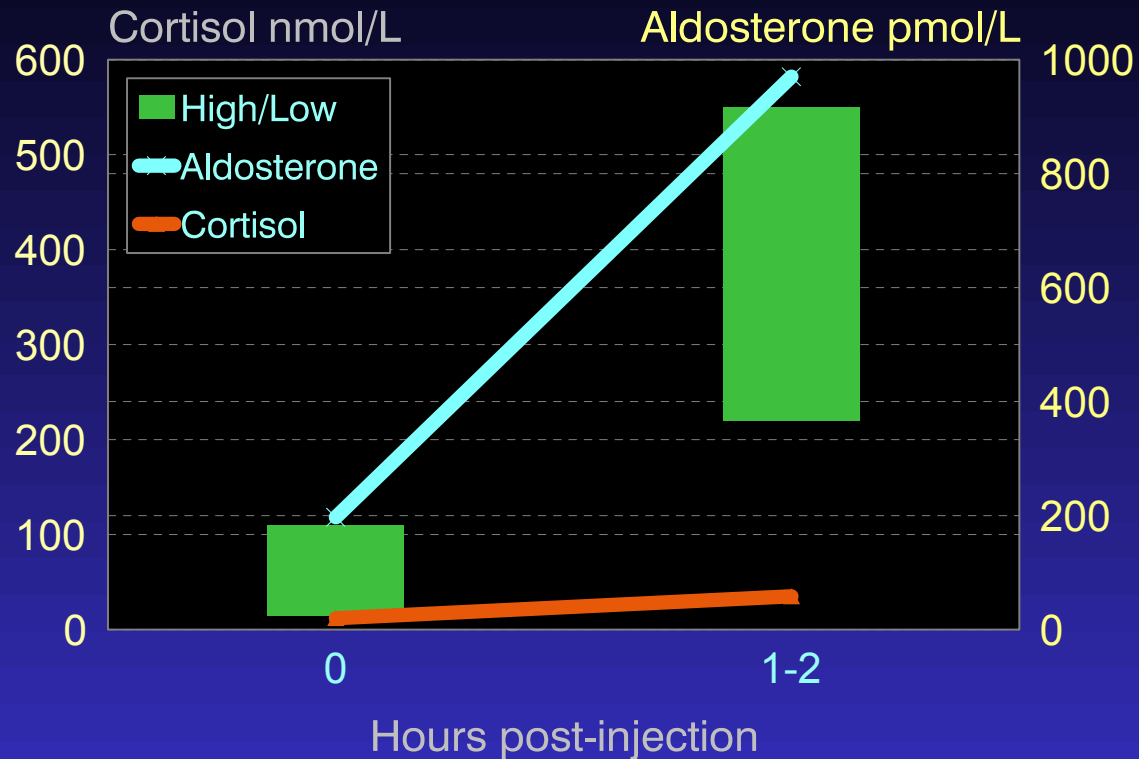


Endogenous ACTH concentration LOW; (shaded is cortisol ref ranges)

Endocrinology - V

ACTH/Cortrosyn Response Test

Chronic exogenous glucocorticoid therapy



Endogenous ACTH concentration LOW; (shaded is cortisol ref ranges)

Endocrinology - VI

- Measurement of Aldosterone is a helpful tool to confirm Addison's in a dog pre-treated with steroids
- A single dose of dexamethasone does effect plasma cortisol baseline (0.1mg/kg)
- Post-ACTH plasma cortisol concentrations are suppressed on days 1 to 3 after administration of 5mg/kg (33% compared with the control dogs)

Endocrinology - VII

- Prolonged and excessive use of topical, parental or oral steroids may result in adrenal suppression
- Another remark: **Crossreaction between cortisol and other corticosteroids (apart from dexamethasone) can result in spurious cortisol measurements**

Acute

- Obtain diagnostic samples
- Restore intravascular volume
- Provide glucocorticoids
- Check correction of Na/K ratio
- Treat life threatening cardiac arrhythmias

Acute - II

- Intravenous fluids
 - Normal saline (0.9%)
 - 20 - 40 ml/kg/hr for first 1- 2 hours (40 - 80 ml/kg/hr if very severe)
 - Maintenance dose 2 - 3 ml/kg/hr thereafter
 - Glucose solution as necessary
 - Bicarbonate ONLY if blood pH is lower than 7.1
- **Goal: reduction of serum potassium concentration, restoration of renal perfusion, correction of acidosis**

Acute - III

- Glucocorticoids
 - Hydrocortisone 5-10mg/kg i.v. every 6hrs or 0.625mg/kg/hr (up to 50mg/kg)
 - Glucocorticoid and mineralocorticoid activity
 - Short acting
 - Methyl prednisolone sodium 1 - 2 mg/kg i.v.
 - Glucocorticoid and weak mineralocorticoid activity
 - Intermediate acting

Acute - IV

- If unable to perform diagnostic cortisol test, use dexamethasone in meantime
 - Dexamethasone 0.5 - 2.0 mg/kg i.v.
 - Dexamethasone SP 0.5 - 2.0 mg/kg i.v.
 - Very high glucocorticoid activity (8 times more potent than Pred)
 - No mineralocorticoid activity
 - Long acting
- As animal is stable, gradually reduce dose over next 3-5 days

Chronic

- Mineralocorticoids
 - Desoxycorticosterone pivalate (Percorten V[®])
 - 2.2 mg/kg i.m. every 25 days (1.7mg/kg – 2.2mg/kg)
 - No glucocorticoid activity
 - Reassess after 12 days: Na low and/or K high: increase by 10%
 - Reassess after 25 days: Na low and/or K high: decrease by 5%

Chronic - II

- Fludrocortisone acetate (Florinef[®])
 - 15 μ g/kg/d per os SID
 - Recheck 1-2 times/year
 - Dosage too high: hypokalemia
 - High glucocorticoid effect
 - If side effects occur: decrease glucocorticoids, decrease salt uptake or change to DOCP

Chronic - III

- Dr. Deb Greco, Michigan Veterinary Conference 2004:
 - Use high end of Percorten V[®] dose range to increase dosing interval \Rightarrow cost-effective??
 - Hydrocortisone might be used in dogs with normal electrolytes but low aldosterone levels

Chronic - IV

- Glucocorticoids
 - Goal: As little as possible...depending on clinical signs
 - With DOCP (no glucocorticoid activity): best choice prednisolone or prednisone 0.2 mg/kg/d
 - Required by 50% dogs treated with Florinef[®]
- Client education: stress!

Miscellaneous

- Prognosis: good, but life-long treatment necessary
- Cats: very rare
 - First case described in 1983
 - Since then only about 15 more cases reported
 - Everything similar except no diarrhea!
- Research project at MSU:
 - **“Preclinical Detection of Hypoadrenocorticism (Addison’s Disease) in Dogs: Development and Evaluation of Laboratory Techniques for the Diagnosis of Immune-Mediated Canine Adrenal Disease”**

ACTH Stimulation

- Henry Schein (1-800-872-4346) sells Cortrosyn[®] to veterinarians for \$510/10 vials which equals \$1.02/kg (5 μ g/kg)
- Butler does sell Cortrosyn[®] by the vial
- Acthar Gel[®] (Questcor Pharmaceuticals) costs \$876 per 400IU which equals \$4.80/kg (2.2IU/kg)

ACTH Stimulation - II

- Cortrosyn[®] can be aliquoted upon reconstitution and can be stored in the refrigerator for several weeks or in the freezer for at least 6 months
- Veterinarians are diluting the vial with 4ml saline to create approximately 50 μ g/ml (slightly underestimated) which they freeze in syringes
- If you then use 5 μ g/kg i.v., one syringe is good for 10kg
- Our experience shows that compounded ACTH gels may not have sufficient potency

Mineralocorticoid Supplementation

- Percorten V[®] costs \$96 per vial of 100mg (4ml). 2.2mg/kg every 25 days and 0.2mg/kg Pred per day equals 9c/d/kg
- Florinef[®] (generic) costs \$69 per 100 tablets (0.1mg). 0.02mg/kg/day equals 14c/d/kg