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KCOM Class of 1989

Gonadal Physiology and Disease



No Disclosures



Gonadal Axis

- ↳ Hypothalamic-pituitary-gonadal
- ↳ Feedback mechanisms important
- ↳ Without production of hormone end products, axis should respond

Hypergonadotropic Hypogonadism

- ⌘ Elevated gonadotropins (LH/FSH)
- ⌘ Low gonadal hormones

Hypogonadotropic Hypogonadism

- ⌘ Low or inappropriately normal gonadotropins
- ⌘ Low gonadal hormones

24 Year Old Male

- ♀ Female body habitus
- ♀ Lack of secondary sex characteristics
- ♀ Absent facial hair
- ♀ Infertility
- ♀ Physical exam: small testicles, Tanner I

Laboratory

- ⌘ Elevated LH, FSH, Low testosterone total, free and bioavailable
- ⌘ Normal prolactin
- ⌘ Normal thyroid function
- ⌘ Pituitary is responding appropriately to an end organ hormonal deficiency

Diagnosis

**Hyper-
gonadotropic
Hypogonadism**



Additional Testing

- ↳ Karyotype: check for Klinefelter syndrome
47 XXY

Hypergonadotropic Hypogonadism

- ↳ Germ cell arrest
- ↳ Surgery, chemotherapy
- ↳ Mumps
- ↳ Alcohol
- ↳ Immune
- ↳ Intra-abdominal testicles

14 Year Old Male

- ↳ Lack of secondary sex characteristics
- ↳ Gynecomastia

Laboratory

- ⌘ Low LH, FSH
- ⌘ Low total and low bioavailable (active) testosterone
- ⌘ Normal prolactin
- ⌘ Normal thyroid function

Diagnosis

**Hypo-
gonadotropic
Hypogonadism**



Differential Diagnosis

- ⌘ Delayed puberty
- ⌘ Kallman syndrome: anosmia, deficiency in GnRH
- ⌘ Hyperprolactinemia
- ⌘ Hemochromatosis or infiltrative
- ⌘ Hypopituitarism
- ⌘ Neoplasm (Brain or pituitary)
- ⌘ Anorexia, excess exercise

Treatment

- ⌘ If fertility is in question, will require HCG or GnRH administration
- ⌘ For restoring male hormone levels without fertility: testosterone IM, transdermal patch or gel, including axillary administration
- ⌘ Exogenous Testosterone suppress axis may affect future fertility

Hyperprolactinemia

- ⌘ Hypothyroidism
- ⌘ Pituitary neoplasm
- ⌘ Non-fasting
- ⌘ Medications

- ⌘ TREATMENT: Medical

44 Year Old Male

- ⌘ Breast tenderness, decreased sex drive
- ⌘ Breast enlargement, normal genital exam

Laboratory

- ⌘ Normal estradiol, low free and total testosterone
- ⌘ Normal B-HCG
- ⌘ Normal gonadotropins
- ⌘ High prolactin
- ⌘ Normal thyroid function

Diagnosis

**Hypogonadotropic
Hypogonadism
due to
Hyperprolactinemia**



Treatment

- ↳ Evaluate MRI for pituitary/brain lesion
- ↳ Treatment of pituitary lesion: medical with Cabergoline or Bromocriptine as Dopamine Agonist
- ↳ Rarely require pituitary surgery
- ↳ Visual field testing if large tumor & compressing optic chiasm

Differential Diagnosis

- ⌘ Gynecomastia common in elderly, obese, puberty
- ⌘ High estradiol may represent a testicular or adrenal neoplasm
- ⌘ High HCG suggests testicular or pulmonary neoplasm
- ⌘ Hypothyroidism

Differential Diagnosis

- ⌘ **Hypothyroidism:** promotes increased prolactin, suppression of gonadotropins, low male hormone, infertility, gynecomastia

16 Year Old Female

- ⌘ Lack of secondary sex characteristics
- ⌘ No menses, primary amenorrhea

Laboratory

- ⌘ Low LH, FSH
- ⌘ Low estradiol

Diagnosis

**Hypo-
gonadotropic
Hypogonadism**



Hypogonadotropic Hypogonadism

- ↳ Pituitary tumors
- ↳ Kallman syndrome (anosmia)
- ↳ Anorexia Nervosa
- ↳ Excessive exercise

Additional Findings with similar history but elevated LH & FSH

- ↳ Short stature
- ↳ Prepubertal genital exam
- ↳ These patients have primary amenorrhea with no history of menses
- ↳ Secondary amenorrhea refers to absent menses after menarche

Diagnosis

Hypergonadotropic
Hypogonadism
Turner Syndrome

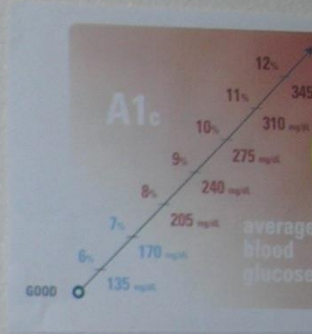


Hypergonadotropic Hypogonadism

- ⌘ Menopause ovarian failure
- ⌘ Surgical removal of ovaries
- ⌘ Turner Syndrome 45 X0

Secondary Amenorrhea

- ⌘ Polycystic ovarian syndrome: adequate estrogen, excess androgen
- ⌘ Uterine defects and trauma
- ⌘ Pregnancy, profound stress
- ⌘ Systemic illness





Hirsutism

- ⌘ Check DHEAS and Total testosterone:
Neoplasm considered with DHEAS twice normal(adrenal) and Testosterone total > 200 ng/dl (ovarian) or as low as 150 ng/dl
- ⌘ Consider congenital adrenal hyperplasia, Cushing Syndrome, virilizing tumors, PCO

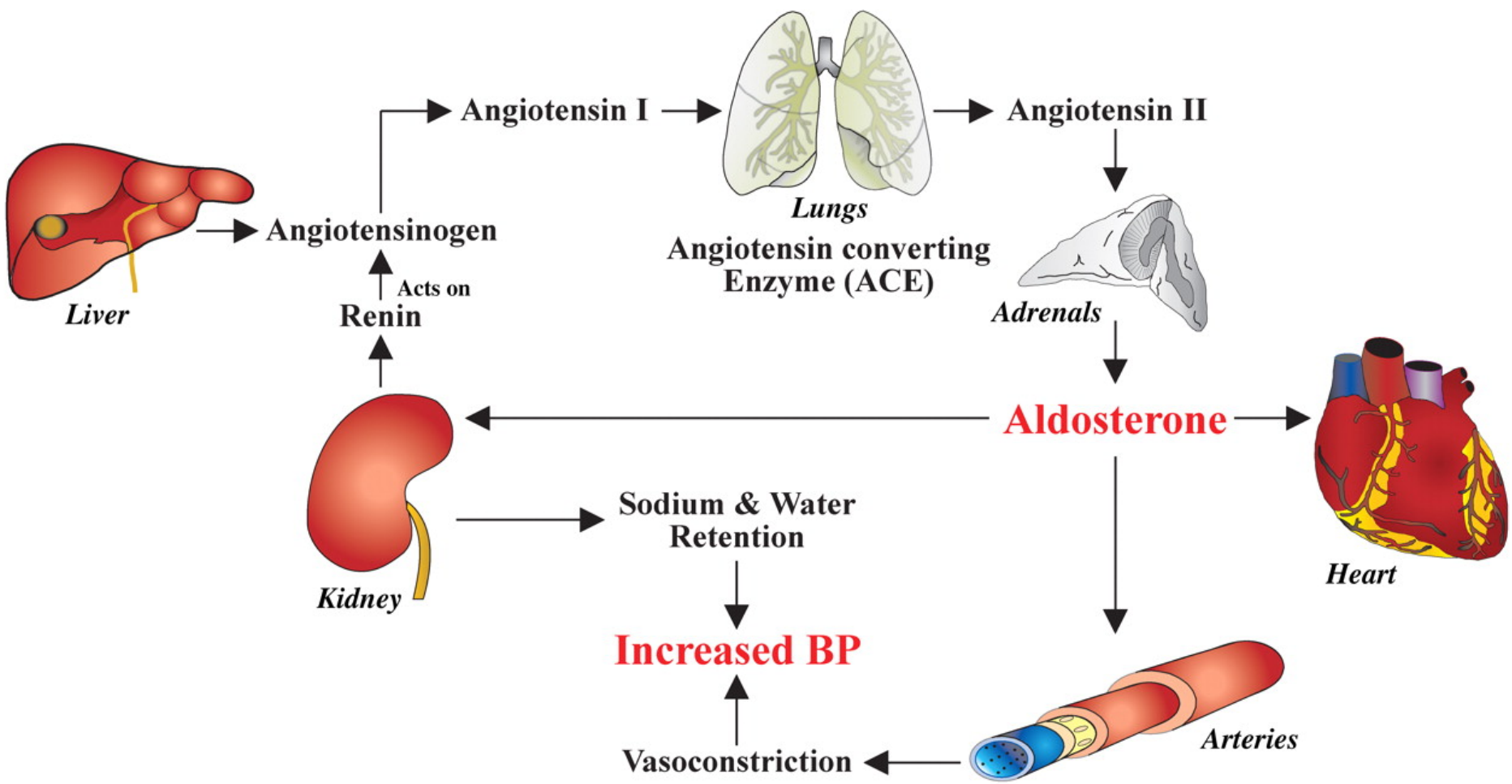


Disease of the Adrenals



Zona Glomerulosa

- ⌘ Mineralocorticoids: aldosterone
- ⌘ Angiotensin II/renin regulation by sympathetic tone; High potassium will stimulate and ACTH
- ⌘ Increase in aldosterone leads to salt and water retention
- ⌘ Increase in Angiotensin II leads to vasoconstriction

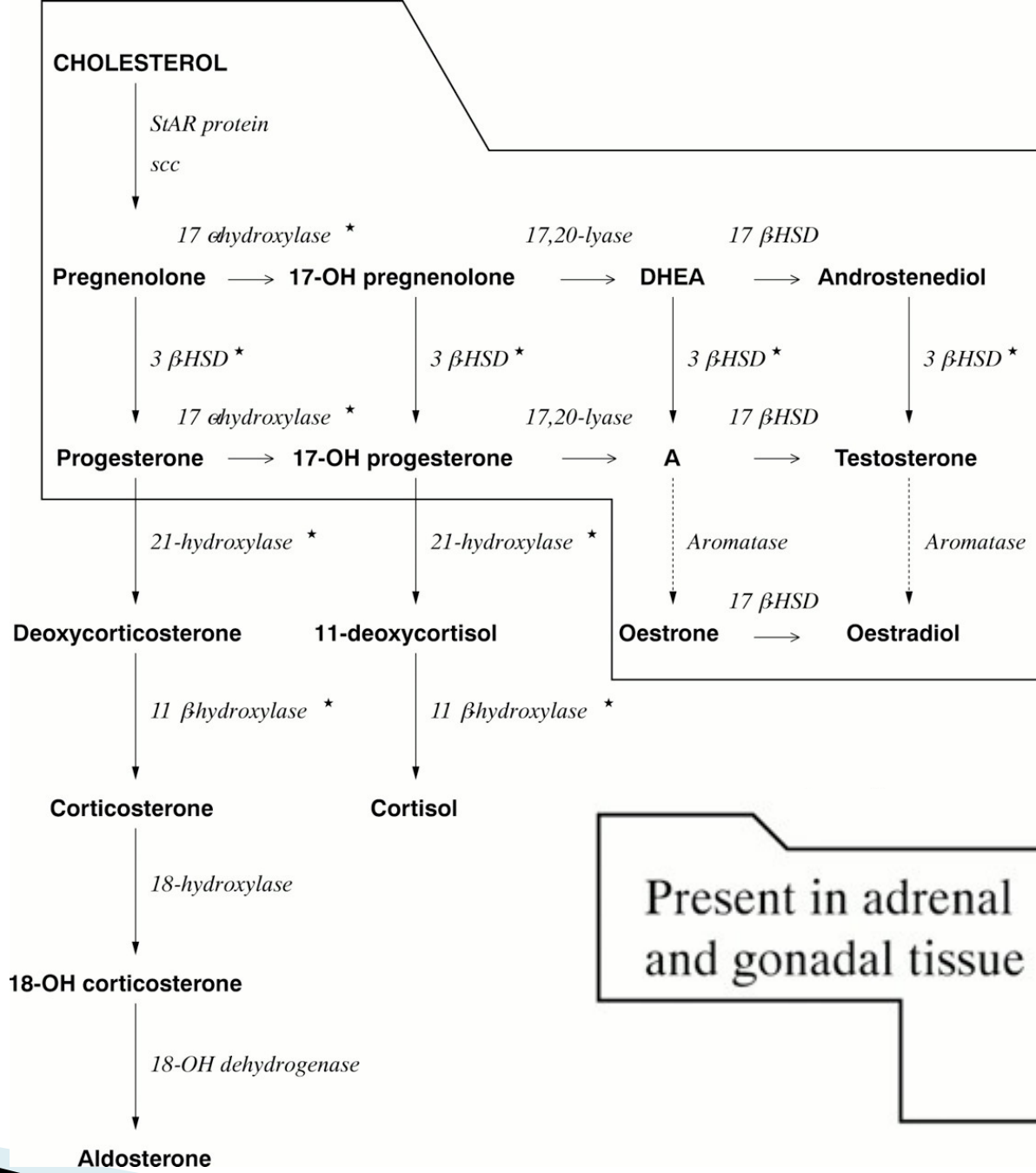


Zona Fasciculata and Reticularis

- ↳ Glucocorticoids: Cortisol
- ↳ Androgen: DHEAS
- ↳ Regulated by ACTH

Steroid Production Pathway (steroidogenesis)

- ↳ Baseline substrate = cholesterol
- ↳ Precursors: DHEAS
17-OH progesterone
- ↳ End products: estradiol, cortisol,
aldosterone



20 year old female

- ⌘ Weight loss, easy tanning, nausea, vomiting, abdominal pain, weakness, dizzy
- ⌘ BP=70/30, tan, confusion







Laboratory

- ⌘ Hyponatremia
- ⌘ Hyperkalemia
- ⌘ Hypoglycemia
- ⌘ Elevated Bun & Cr
- ⌘ Vitiligo

- ⌘ Deficiency of all steroids



Diagnosis

Primary Adrenal Insufficiency

Laboratory

- ⌘ AM cortisol, ACTH
 - ⌘ Cosyntropin (ACTH) stimulation IV or IM
Baseline, 30 min and 60 minute values for cortisol
 - ⌘ If Aldosterone drawn with Cosyntropin stimulation, response blunted
- **Cortisol Goal > 18 micrograms/dl with Cosyntropin Stimulation, assuming a normal baseline cortisol

Etiology

- ⌘ 80 % Autoimmune/Idiopathic
- ⌘ 20 % Tuberculosis
- ⌘ Other: Vascular, infectious, AIDS, trauma, mets, meds, congenital adrenal hyperplasia

Autoimmune Etiology

- ⌘ Addison Disease, adrenalitis
- ⌘ May be associated with other autoimmune conditions, as in Hashimoto or vitiligo

50 year old female

- Similar symptoms to index patient: low to low normal BP, fatigue weakness
- No change in skin color
- COPD

Laboratory

- ⌘ Low sodium
- ⌘ Normal potassium, which suggests normal aldosterone production
- ⌘ Low ACTH or inappropriately normal when the end organ value is low
- ⌘ Be careful with the timing of the stimulation test and blood draw for ACTH

Additional History

- ⌘ History of long term steroid use IV and oral treatment
- ⌘ Recent change in pharmacy
- ⌘ Prednisone not renewed
- ⌘ Presents with fever and lung infiltrate

Diagnosis

Secondary Adrenal Insufficiency

Etiology

- ↳ Steroid dependent
- ↳ Tumor, infection, radiation, surgery, trauma involving hypothalamic region or pituitary

Physical findings in AI

- ← Generalized abdominal tenderness
- ← Fever
- ← Postural hypotension
- ← Look for precipitating infection
- ← Careful with consideration for surgical abdomen
- ← Surgery could precipitate adrenal crisis if adequate steroids are not on board

Adrenal Insufficiency

- ← Electrolyte imbalance: Hyponatremia, Hyperkalemia in primary adrenal insufficiency
- ← Hypotension and medical crisis
- ← Hyponatremia without hyperkalemia in secondary adrenal insufficiency, less likely to result in adrenal crisis

Electrolyte imbalance in AI

- ← 85 to 90 % of patients have hyponatremia
- ← Mineralocorticoid deficiency results in sodium loss and volume depletion and increased Vasopressin secretion due to loss of cortisol
- ← Hyperkalemia in 60 to 65 % of patients
- ← Rare hypercalcemia

Imaging

- ⌘ Consider CT of the adrenals for primary adrenal insufficiency ———small adrenals
- ⌘ MRI of the brain for secondary adrenal insufficiency unless the cause is evident

Treatment at diagnosis in Crisis

- ⌘ IV hydrocortisone 100 mg q 6-8 hrs wean as tolerated to daily oral dose of 25 mg daily/divided
- ⌘ Saline and glucose
- ⌘ Supportive and correcting precipitating factors
- ⌘ Primary adrenal insufficiency: Florinef as aldosterone replacement
- ⌘ If steroids < 30 days in general medical treatment, do not necessarily need to

Crisis Intervention

- ⌘ Surgery
- ⌘ Acute illness
- ⌘ Additional steroids IV and/or PO
- ⌘ Home illness: short course of double dose steroids
- ⌘ Observe sodium, potassium and BP; Pt can follow BP at home for crisis intervention

25 Year Old Female

- ⌘ Weight gain, hirsutism, diabetes, osteoporosis
- ⌘ Centripetal obesity, striae, acne, hypertension, capillary fragility, amenorrhea

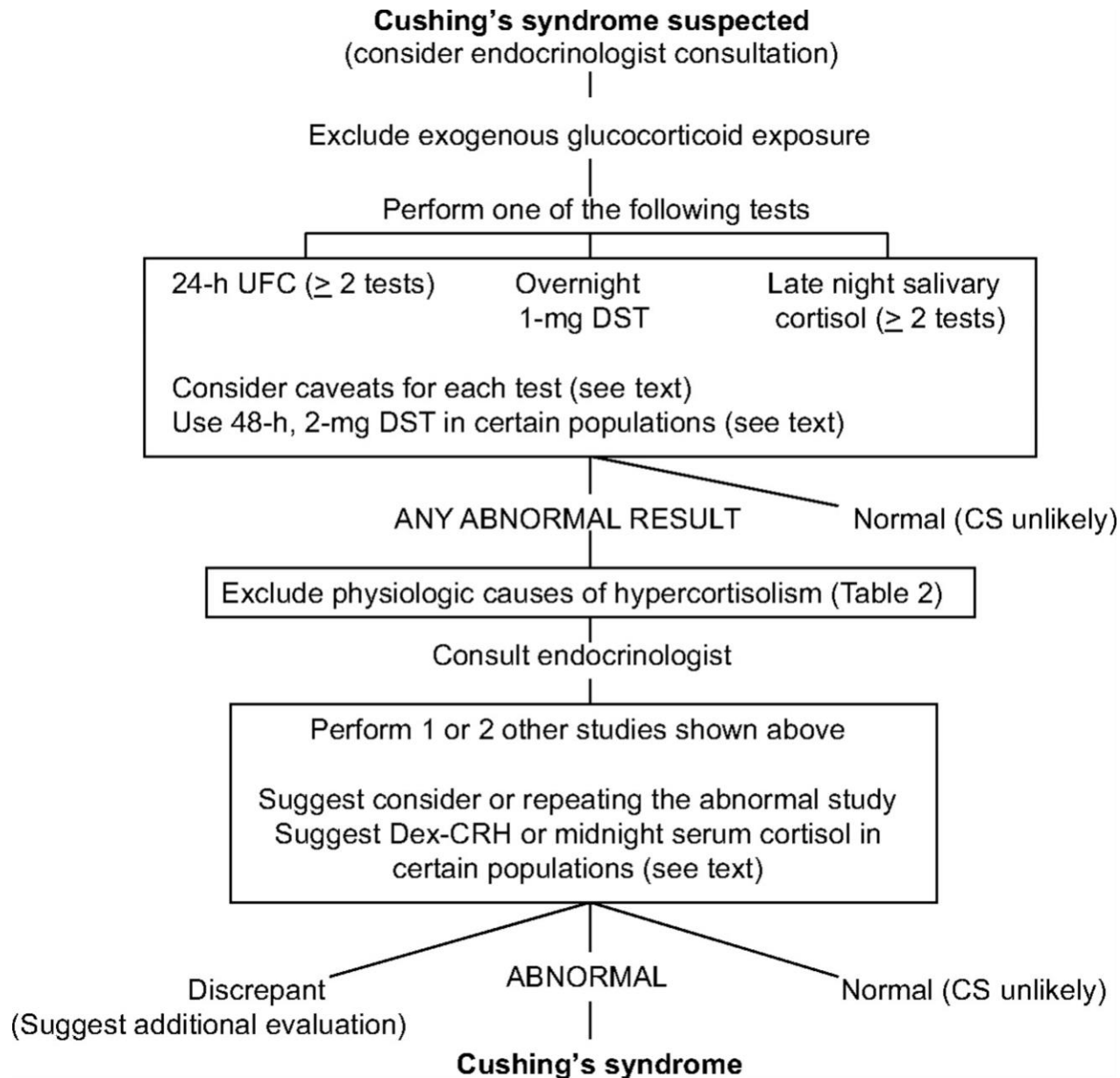




Diagnosis

**Cushing
Syndrome**





Laboratory

- ⌘ 1 mg overnight dexamethasone suppression testing; 1 mg Dex 11 pm with 8 am cortisol next day---may identify subtle with normal urine free cortisol---goal suppression < 1.8
- ⌘ 24 hour urine free cortisol
- ⌘ Late night salivary cortisol
- ⌘ Hypokalemia, hyperglycemia
- ⌘ Some false positives

Pregnancy Striae





Differential Diagnosis

- ⌘ Cushing disease: Cushing syndrome due to pituitary adenoma/high ACTH---dependent
- ⌘ ACTH Independent vs ACTH Dependent
- ⌘ Exogenous steroids
- ⌘ Adrenal adenoma or hyperplasia
- ⌘ Ectopic: lung tumor





Differential Diagnosis

- ⌘ Cushing disease and ectopic have higher ACTH >>>> ACTH Dependent
- ⌘ Adrenal disease is ACTH independent
- ⌘ Clarification required with additional dexamethasone testing including urinary testing

Imaging

- ⌘ Cushing disease: MRI of the pituitary
- ⌘ Cushing syndrome: CT or MRI of (adenoma vs hyperplasia) adrenals
- ⌘ Ectopic: localize source

Treatment

- ⌘ Pituitary: surgery, radiation, anti-adrenal drugs
- ⌘ Ectopic: surgery, drugs
- ⌘ Adrenal: surgery, drugs

Adrenal Carcinoma

- ⌘ Metastatic at diagnosis
- ⌘ Presents with weight loss
- ⌘ Rapid onset
- ⌘ Typical excessive activity of steroidogenesis pathway, not typical insufficiency

35 Year Old female

- ⌘ Hypertension
- ⌘ Hypokalemia
- ⌘ Thin
- ⌘ Metabolic alkalosis

Diagnosis

**Hyper-
aldosteronism**



Hyperaldosteronism

- ↳ Biochemical work-up first
- ↳ Low renin/high aldosterone is primary
- ↳ High renin/high aldosterone is secondary
- ↳ Elevated 24 hour urine aldosterone on high sodium diet and off diuretics
- ↳ Saline Suppression Testing

Hyperaldosteronism

- ⌘ Adrenal adenoma (Conn Syndrome) “APA”
Aldosterone Producing Adenoma
- ⌘ Idiopathic Hyperaldosteronism “IHA” with
bilateral disease

Secondary Hyperaldosteronism

- ↳ Sodium restriction
- ↳ Renal disease
- ↳ High Potassium intake
- ↳ Pregnancy
- ↳ Diuretics

Localization testing

- ↳ Cat Scan
- ↳ Nuclear imaging with Iodocholesterol
- ↳ **Adrenal venous sampling—Gold Standard**

Adrenal Venous Sampling Summary

RE: Male

DOB: 1942

	Aldosterone (ng/dL)	Cortisol (ug/dL)
Basal:		
Right adrenal vein	1	4.3
Left adrenal vein	221	10.2
Peripheral Arm	12	12.3
POST ACTH:		
Right adrenal vein	4	108.1
Left adrenal vein	16430	>150
Peripheral Vena Cava	71	14.4
Peripheral Femoral Vein	46	18.9

Treatment

- ⌘ Aldosterone producing adenoma: surgery; takes 6 months for final HTN results, may have underlying essential HTN but hypokalemia should resolve; Spironolactone in patients with poor surgical risk
- ⌘ Bilateral adrenal disease: restrict sodium, spironolactone use, no surgery

40 Year Old Male

- ⌘ Hypertension unresponsive to meds
- ⌘ Normal electrolytes
- ⌘ Thin
- ⌘ Headache, palpitations

Diagnosis

Pheochromocytoma



Laboratory

- ⌘ Check 24 hour urine fractionated catecholamines, fractionated metanephrines, VMA
- ⌘ 24 hour urine testing off meds if possible
- ⌘ Some endocrinologists recommend serum catecholamine/metanephrine testing

Imaging

- ⌘ MRI or CT: MRI may help with difference in signal intensity T1/T2---bright signal in pheo
- ⌘ MIBG (Metalogobenzylguanidine) nuclear imaging tracer concentrates in catecholamine producing cells

Treatment

- ⌘ Alpha blockers preferred
- ⌘ Avoid Beta Blockers, which can precipitate a pheo crisis without alpha blockade on board
- ⌘ Avoid adrenal biopsy of a lesion that is not yet evaluated for pheochromocytoma

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ORTAL VENOUS

512 x 512

Series: 3

SCT ABDOMEN WI



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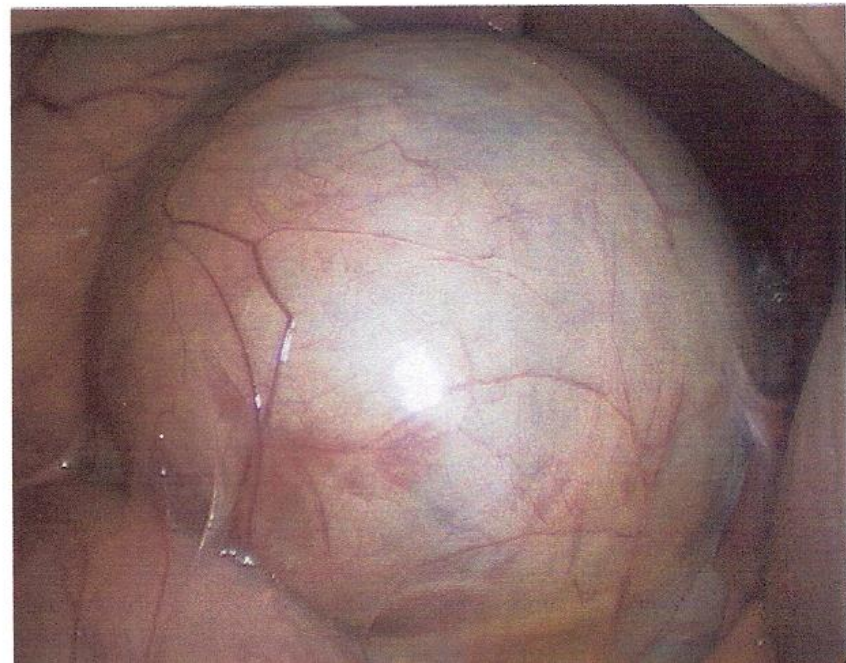
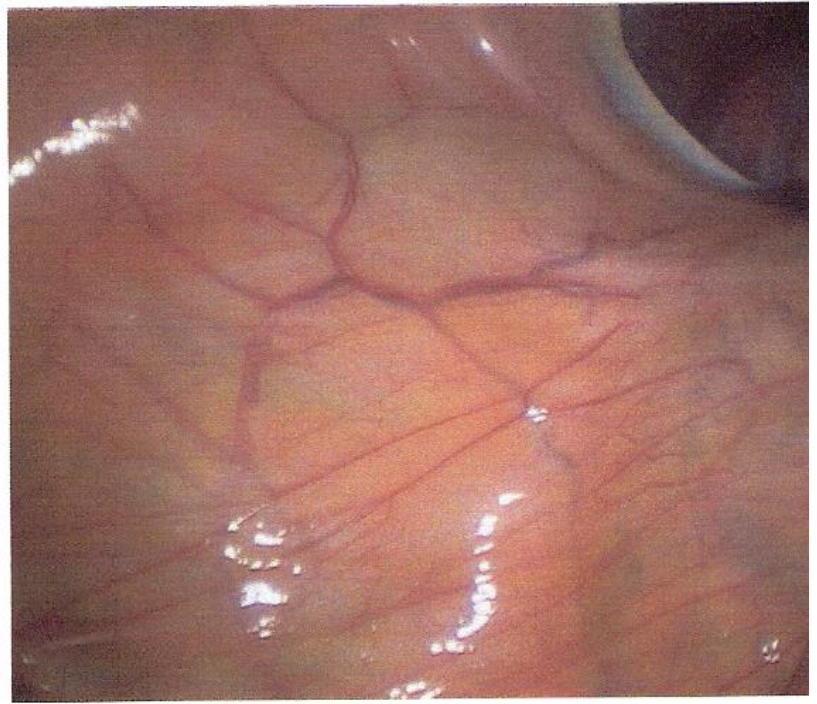
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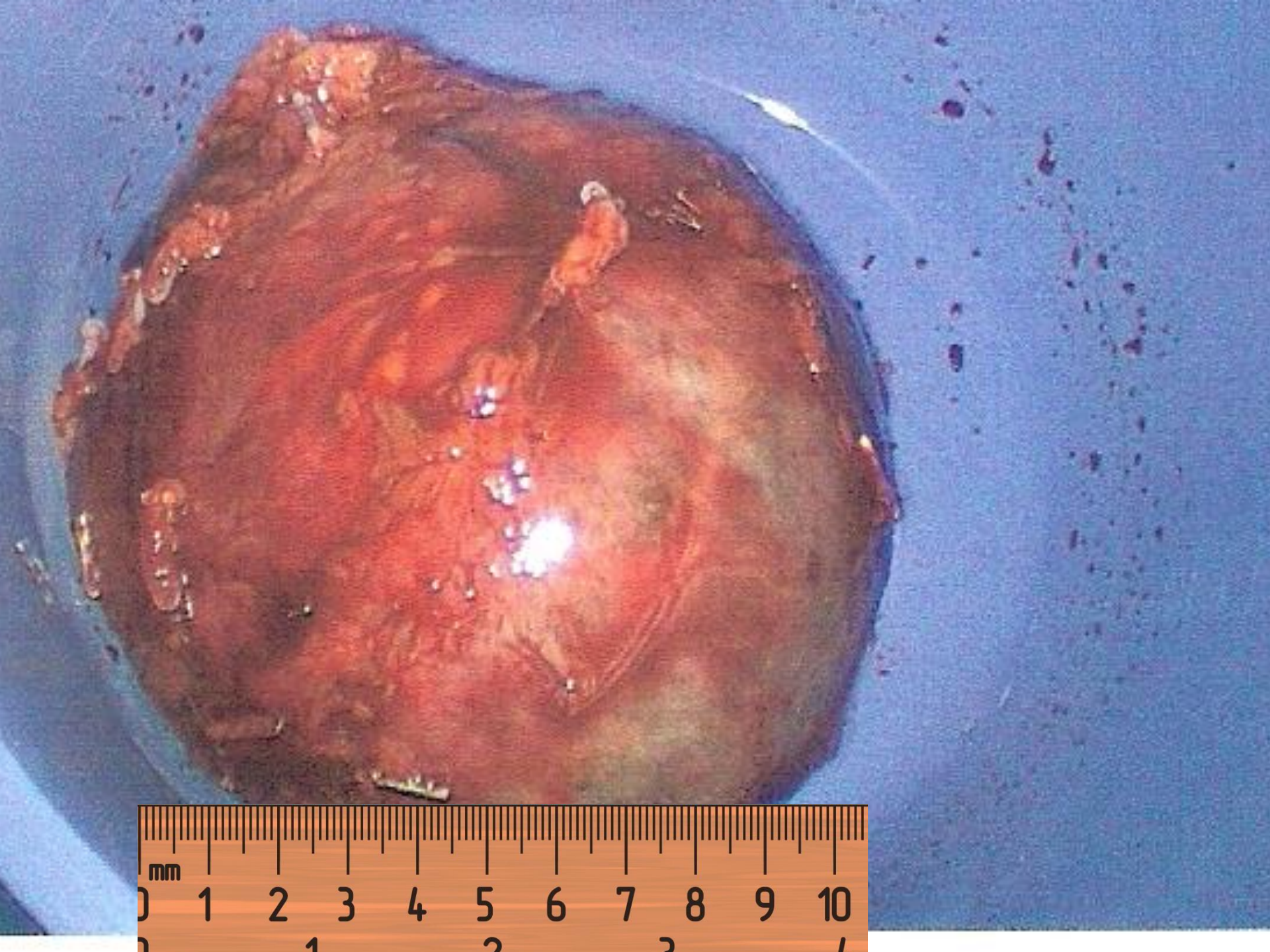
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ORTAL VENOUS

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SCT ABDOMEN WI



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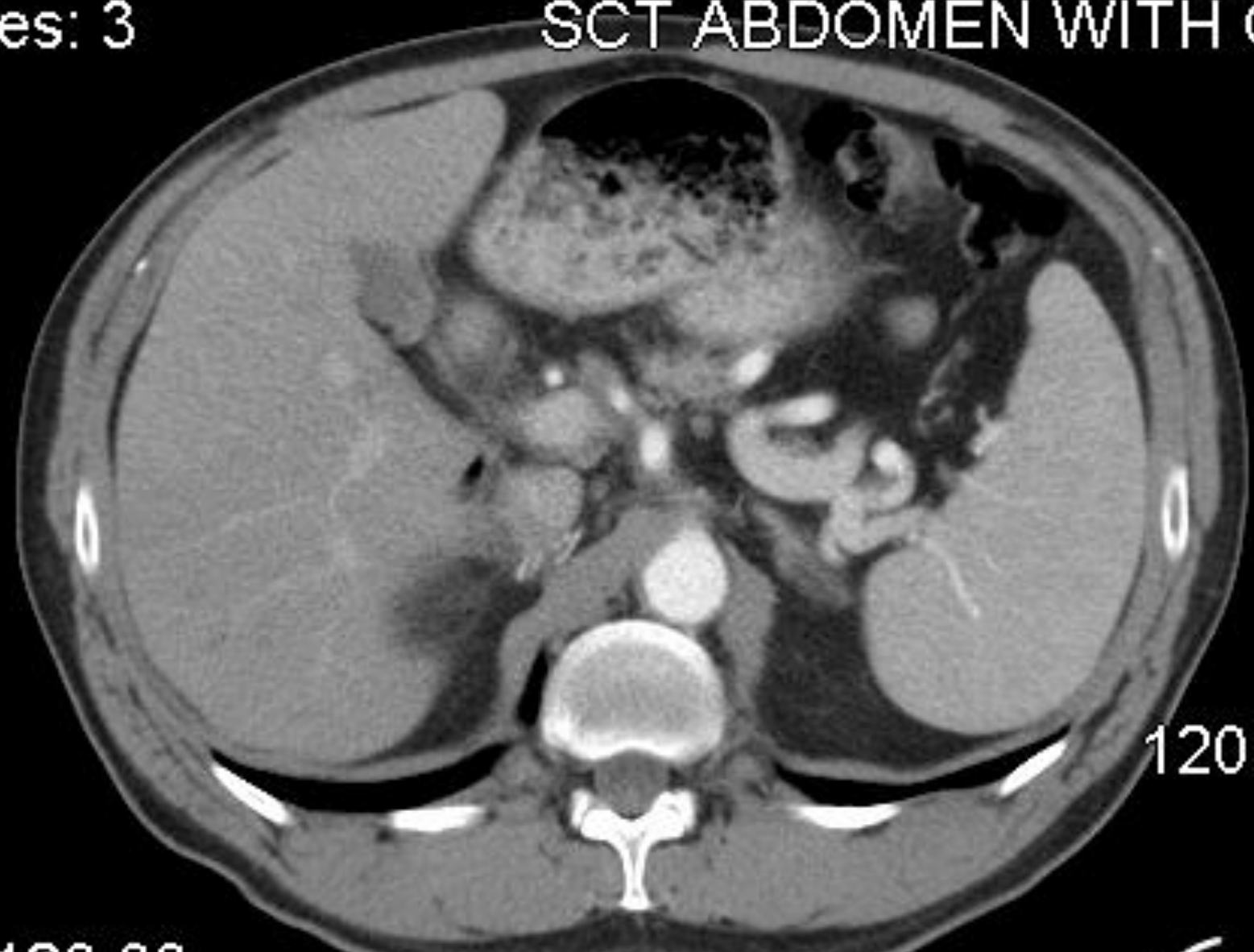
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Pos 182.0

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W 400

L 50

V Sc 2/2/6





W 400

W 400

Incidental Adrenal Adenoma

- ⌘ Benign adenomas common
- ⌘ Avoid imaging until biochemical diagnosis
- ⌘ Evaluation important with coexisting HTN, hypokalemia, hirsutism

Adrenal Incidentaloma

- ⌘ Lesions discovered “inadvertently in the course of diagnostic testing or treatment for other clinical conditions that are not related to the suspicion of adrenal disease”

Prevalence

- ↳ In autopsy series 2.1 %
- ↳ More identified with better imaging
- ↳ Prevalence of 4.3 % in patients with a previous diagnosis of cancer
- ↳ Higher with aging at 7 % in 70 +
- ↳ More lesions in women—related to who is being tested

Causes

- ⌘ Pathology: Cancer patients $\frac{3}{4}$ mets, No history of cancer $\frac{2}{3}$ benign
- ⌘ 70 % non-functioning in patients without endocrine symptoms
- ⌘ 5-10 %-----Cushing Syndrome, subclinical

Natural History of lesion size

- 25 % of lesions larger than 6 cm represent adrenal cancer
- Up to 25 % of adrenal lesions may grow 1 cm, but the significance of size change is not known
- Adrenal Cancer rapid growth “doubling time”

Natural History of function

- ⌘ Up to 20 % may develop a functional component
- ⌘ Development of function more common in larger neoplasms (3 cm)---this evidence can depend on study follow-up length and methods
- ⌘ Less than 3 cm neoplasms rarely change in function

Adrenal Incidentaloma Diagnosis

- ⌘ Function
- ⌘ Surgical resection vs non-surgical treatment
- ⌘ Malignant vs benign