The Work-up and Treatment of Adrenal Nodules

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Outline

- Incidentaloma
- Functional Nodules
  - Cushing's Syndrome
  - Pheochromoctoma
  - Hyperaldosteronism
- Adrenocortical Carcinoma

Incidentaloma

Incidentaloma - Epidemiology

- Autopsy studies – 1.1 - 32% (avg 5.9%)
- Imaging studies:
  - 1,459 patients – 4.3%
  - 61,054 patients – 3.4%

Incidental Adrenal Mass

- Is it functional?

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- Is it malignant?
  (Primary or metastatic)

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  - HTN, weight change, diabetes, appearance change, malignancy, family history

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- Plasma metanephrines or 24 hour urinary catecholamines, metanephrines, and VMA

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- Before FNA – MUST RULE OUT PHEO!

Size

- Masses > 6 cm – Greater >25% Malignant
- Masses < 4 cm Are Generally Monitored
  - Q 6 month imaging x 2
  - Q yr hormonal study x 4
- For Masses Between 4 and 6 cm:

  Criteria other than size should be considered in making the decision to monitor or to proceed to operation.

National Institutes Of Health
Management Of The Clinically Inapparent Adrenal Mass (Incidentaloma) 2002

Adrenal Protocol CT Scans

- Initial HU without contrast:

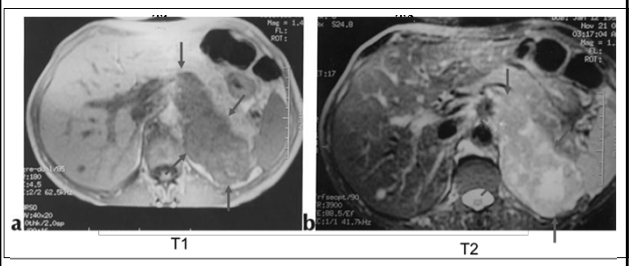
  Adenomas: < 10 HU (lipid rich)
  Malignancies: > 18 HU
  Sensitivity: 73% Specificity: 96%
- Washout 10 – 15 minutes after contrast:

  Adenomas: > 60%
  Sensitivity: 88% Specificity: 96 -100%
- Worrisome features: Irregular, inhomogeneous enhancement, central necrosis, calcification in 30%, local invasion

MRI

- Equally Effective As CT
- Adenomas Are Iso-Intense With The Liver On T2-weighted Images
- Carcinomas Have A Hyper-Intense Signal Compared With The Liver On T2

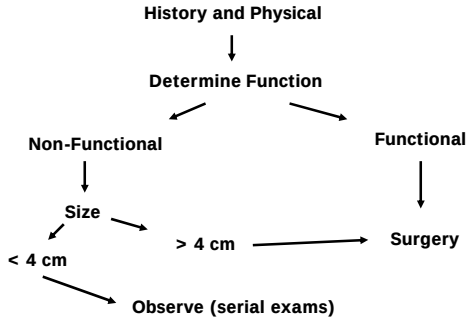
MRI



Fine-Needle Aspiration Biopsy

- FNA is indicated for pts with possible metastatic disease to adrenal or for lymphoma diagnosis
- <u>CANNOT</u> Distinguish A Benign Adrenal Mass From Adrenocortical Carcinoma
- Unnecessary FNA is a common pitfall in working up an adrenal incidentaloma
  - Potentially dangerous
  - Rarely alters management

Evaluation of Incidentaloma



Cushing's Syndrome

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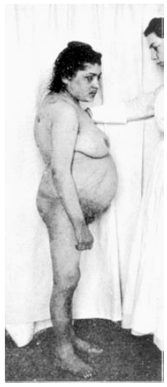
Harvey Cushing

- Born in Cleveland – 1869
- Educated at Yale
- House staff at Johns Hopkins
- Peter Brent Brigham Hospital 1912 – 1932
- Dr. W. T. Bovie develop electrocautery - 1926

Harvey Cushing

- 1912 described Minnie G.
  - Multiglandular disease



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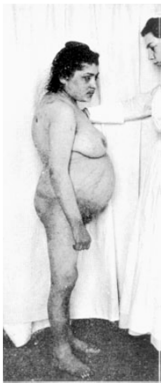
  - Pituitary Basophilism



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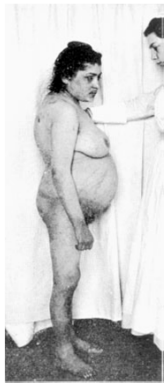
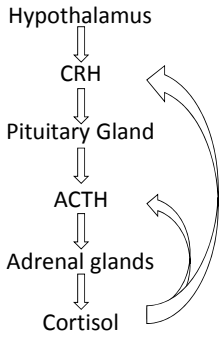
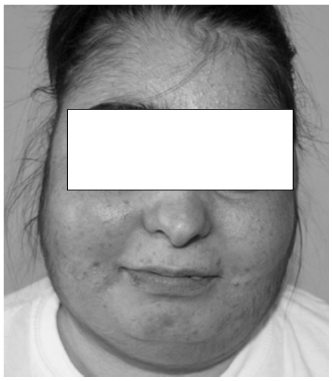
- **1912 described Minnie G.**
  - **Multiglandular disease**
- **1932 reports on 12 patients**
  - **Pituitary Basophilism**
- **Bishop and Close named the disease "Cushing's syndrome"**



Hypothalamus – Pituitary – Adrenal Axis



Clinical Manifestations



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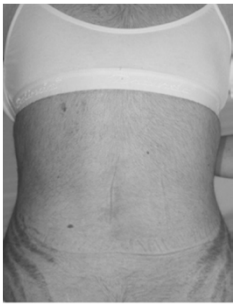

Cushing's Syndrome - Etiology

- ACTH dependent – 90%
  - Pituitary (Cushing's disease) or ectopic
- ACTH independent – 10%
  - Adrenal

Cushing's Syndrome - Diagnosis

- Establish abnormal cortisol production
  - 24 hour urine for free cortisol and creatinine
  - Low-dose dexamethasone test – 1 mg at 11pm, measure cortisol at 8 am (nl < 5 ug/dl)
  - Midnight salivary cortisol– correlates well with serum cortisol, lowest levels at midnight

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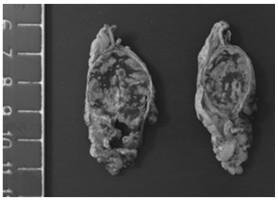
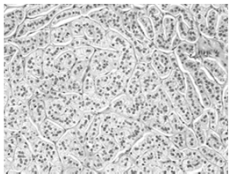
- Next establish cause ⇒ Serum ACTH
  - if > 15 then ACTH dependent (pituitary, ectopic)
  - if < 5 ACTH independent (adrenal)

Cushing's Syndrome - Treatment

- ACTH Dependent
  - Treat cause
  - Rarely bilateral adrenalectomies
- ACTH Independent
  - Laparoscopic/Robotic adrenalectomy
  - Exogenous steroids for several months to a year for HPA axis recovery





Subclinical Cushing's Syndrome

- 20% develop overt clinical Cushing over time
- At risk for post-operative Addison's
  - 40 – 100%
- Associated with increased incidence of:
  - HTN, Obesity, DM, Cardiovascular dz, Decreased bone density (controversial)
- Surgery Improves
  - Weight 55 – 100%
  - HTN 57 – 100%
  - Glucose control 50 – 100%

Pheochromocytoma

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- Hallmark is hypertension
  - Paroxysmal HTN - 30%
  - Sustained HTN – 50%
  - No HTN – 20%

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- Previously reported 80% mortality in patients with unsuspected pheochromocytomas who undergo surgery or anesthesia

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- 24 hour urinary catecholamines – epinephrine, norepinephrine, metanephrine, VMA
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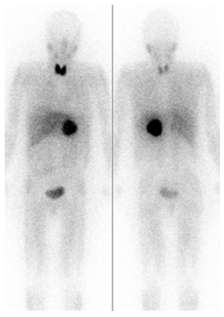
Must be done prior to FNA of any adrenal mass!

Pheochromocytoma - Imaging

- CT scan
- MRI
- MIBG scan



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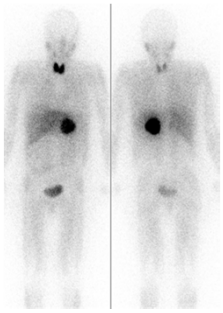

CT most cost-effective, MRI more sensitive, and MIBG more specific

MIBG indications

- Risk for multiple tumors, extra-adrenal tumors, metastases
- Young pts and those with syndromes
- Persistent/recurrent malignant disease
- Overall Sensitivity 87%, Specificity 100%
  - Sensitivity higher for malignant pheo and familial pheo as opposed to sporadic

Pheochromocytoma - Preoperative Preparation

- Alpha-blockade (FIRST)
  - Doxazosin 2mg QHS
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  - Titrate up to orthostatic tachycardia or hypotension

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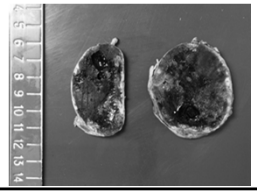

Treatment: Laparoscopic/ Robotic adrenalectomy

Treatment of Malignant Pheochromocytoma

- Incidence of malignancy may be closer to 30-50% than 10%
- Resect localized recurrences or mets
- Painful bony mets respond to well to radiotherapy
- Chemo:
  - Standard chemo regimens have limited efficacy
- Iodine-131 MIBG therapy:
  - In pts whose tumors are imaged by MIBG
  - Reported response rate of 60%

Hyperaldosteronism

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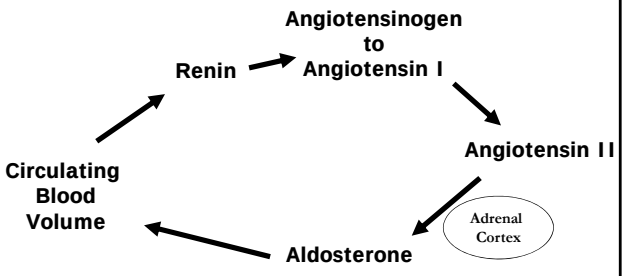
Hyperaldosteronism



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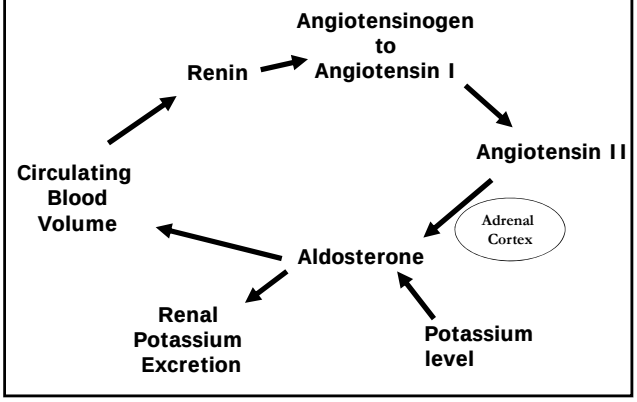

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- **<u>Previously</u> experts thought**
  - **<1% of HTN patients**
  - **hypokalemia *sin qua non***
- **<u>Currently</u>**
  - **5 – 10% of HTN patients**
  - **Only 10 – 40% hypokalemia**

Primary Hyperaldosteronism - Etiology

- **Aldosterone-producing adenoma (APA or Conn's syndrome)**
  - **Typically small: <2 cm**
  - **Corrected by surgery**

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  - **Typically small: <2 cm**
  - **Corrected by surgery**
- **Idiopathic hyperaldosteronism (IAH)**
  - **Bilateral adrenal hyperplasia or nodules**
  - **Not cured by surgery**
  - **Life long medical treatment – spironolactone, eplerenone**

Primary Hyperaldosteronism - Diagnosis

- **Aldosterone – Renin ratio (ARR)**
  - **Hyperaldo if ARR is greater than 20 (nl <10) especially if aldo level > 15**
  - **Ideally blood drawn mid morning**
  - **Stop spironolactone, eplerenone, amiloride, and triamterene for 4 weeks**
- **Saline Suppression test**
  - **Infuse 2 liters saline over 4 hours – normally aldo should drop to <5**
  - **(>10 consistent with hyperaldo)**

Adenoma vs. Hyperplasia

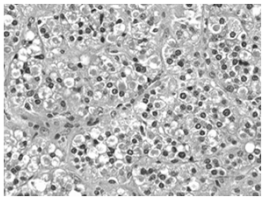
- Very High PAC/PRA → Adenoma
- Measure morning 18-hydrocycorticosterone
- Typically level > 100 for APA

Adrenal Vein Sampling

- Gold-standard distinguishing APA and IAH
- Challenging procedure: cannulating right adrenal vein difficult (directly off IVC)
  - Successful 75 – 95% depending on experience
- Consider for all pts age > 40, equivocal CT findings or equivocal diagnosis
- Measure aldosterone and cortisol simultaneously to confirm placement and dilution (phrenic and renal on left), also use ACTH (cosyntropin) infusion
- Typical APA aldo/cort ratio >3 – 4 times higher than contralateral side

Primary Hyperaldosteronism - Treatment

- Laparoscopic/Robotic adrenalectomy
- Results
  - Hypokalemia resolves
  - Hypertension improves



Adrenocorticol Carcinoma

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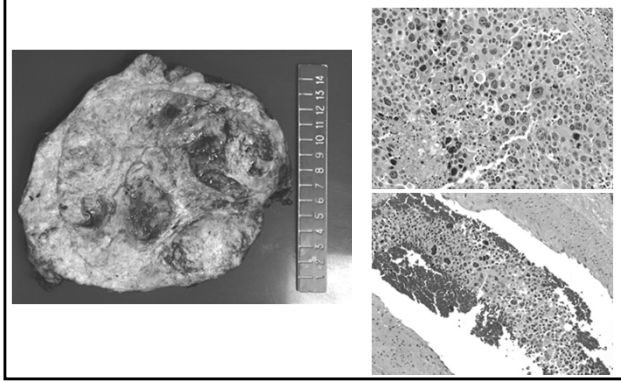
Adrenocortical Carcinoma

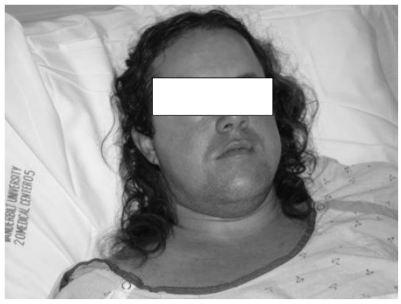
- Multiple or mixed hormone secretion is highly suspicious for malignancy
- Measure DHEA-sulfate and total testosterone
- Most sporadic, but can be familial
  - Li-Fraumeni, Carney Complex, Beckwith-Wiedemann, FAP, MEN1
  - Consider TP53 testing in all patients

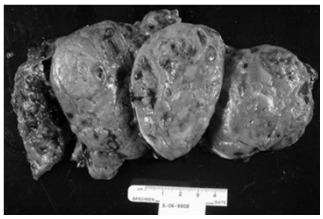
Adrenocortical Carcinoma



Adrenocortical Carcinoma - Treatment

- Surgical Resection – <u>OPEN</u>
- Metastatic work-up preoperatively
- Mitotane 15 – 22% response rate
- Combination cytotoxic chemotherapy
- Consider radiotherapy locally





Adrenocortical Carcinoma - Prognosis

- **Depends on Stage and Complete Resection**
  - **< 50% ACC localized to adrenal only**
  - **Overall, 22% 5-yr survival for resected**
  - **<10% 1-year survival for Stage IV disease**
- **About 2/3 develop recurrence within 2 years**