



Department of Health



# Endocrine Causes of Hypertension

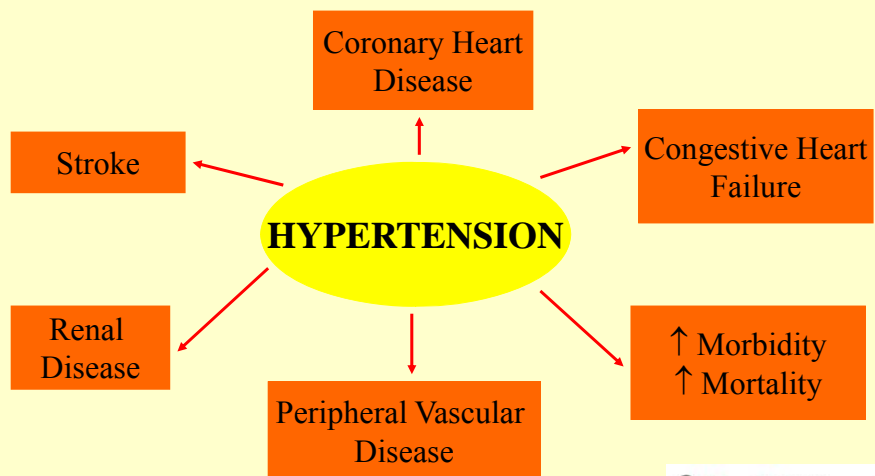
Ee Mun Lim

Chemical Pathologist, QEII  
Endocrinologist, SCGH



## Hypertension:

A Significant Cardiovascular and Renal Disease Risk Factor



Arch Intern Med 1993



## Secondary Hypertension

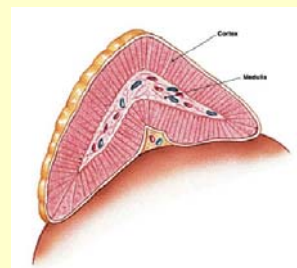
- Potentially curable
- Disease specific treatment
- Other organ effects from underlying disease



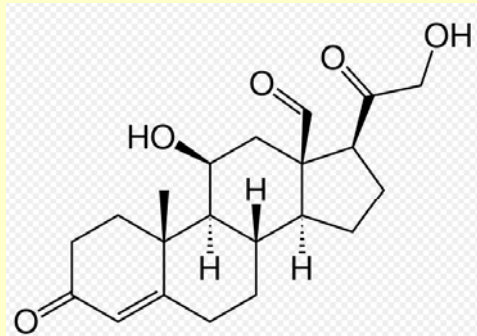
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## Overview

- Causes of Endocrine Hypertension
  - Primary Hyperaldosteronism (PHA)
  - Phaeochromocytoma
  - Cushing's Syndrome
- Strategy for screening



# Primary Hyperaldosteronism (PHA)



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## Excess morbidity and mortality independent of blood pressure

- ↑ carotid intima-media thickness

Bernini et al. *J Hypertens* 2008

- ↑ LV wall thickness, ↓ diastolic function

Tsioufis et al. *Clin Cardiol* 2008

- ↑ risks of stroke, AMI, AF

Milliez et al. *J Am Coll Cardiol* 2005

Born-Frontsberg et al. German Conn's Registry *J Clin Endocrinol Metab* 2009

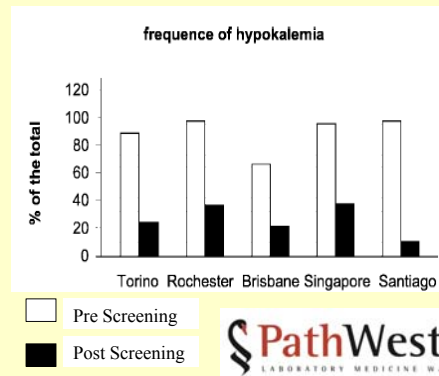
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# Primary Hyperaldosteronism

- Prevalence 5-15% (not 0.1-1%) hypertension

- >50% normokalaemic

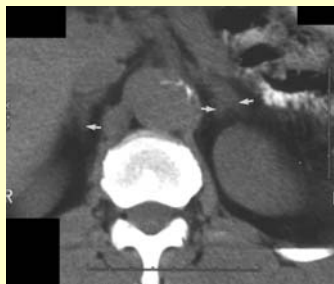
Mulatero et al. *J Clin Endocrinol Metab* 2004;89



- Unilateral adenoma  
- 50% surgical cure



- Bilateral hyperplasia



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## Familial PHA

- Familial hyperaldosteronism Type 1 (Glucocorticoid-remediable aldosteronism)

\* *genetic testing if PHA diagnosed <age 20 and +ve FHx or strokes at young age*

- Familial hyperaldosteronism Type 2 (familial occurrence of aldosterone-producing adenoma or bilateral idiopathic hyperplasia)

- Rare
- Autosomal dominant

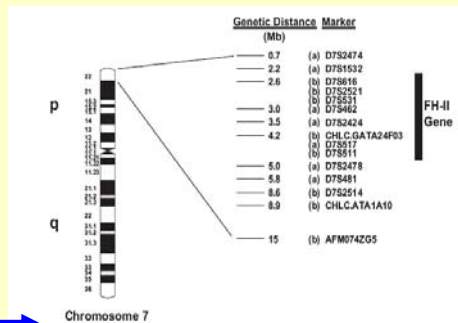


FIG. 1. Ideogram showing the chromosome 7p22 locus demonstrating linkage to FH-II in five affected families (two Australian, one South American, and two Italian). a, Markers previously reported (50) to show linkage to a locus of approximately 5 Mb at 7p22 in a large Australian family (LOD 3.26). b, New markers used to confirm linkage in the large Australian family, demonstrate linkage in the four other families (combined LOD 5.22 for the five families), and refine the region of linkage by 1.8 Mb (3, 4).

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## Endocrine Society Guidelines

### Recommend Case Detection:

- Hypertension and spontaneous or low dose diuretic-induced hypokalaemia
- Severe hypertension (>160/100 mmHg) or drug resistant hypertension
- Hypertension with adrenal incidentaloma
- Hypertension and a family history of early-onset hypertension or cerebrovascular disease at a young age (<40 yo)
- All hypertensive first-degree relatives of patients with primary hyperaldosteronism

Funder et al. *J Clin Endocrinol Metab* 2008;93:3266

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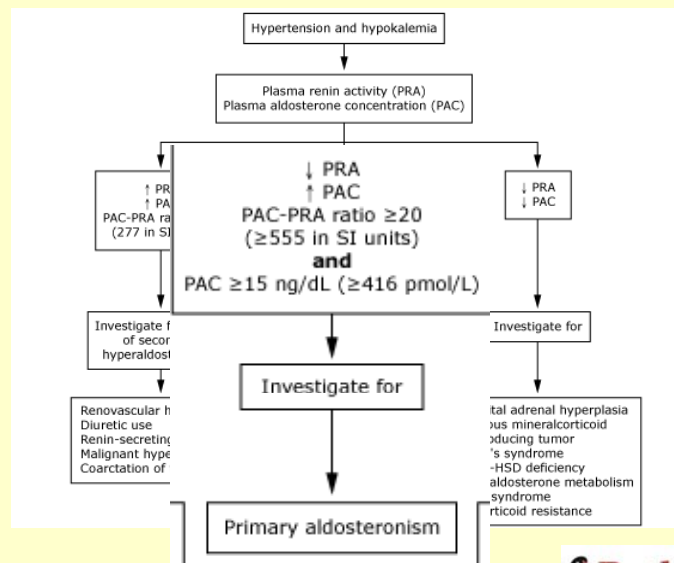
## Biochemical Evaluation

- Ensure potassium replete
  - Plasma renin – activity or concentration
  - Serum aldosterone concentration
  - Renin/aldosterone ratio
- 
- Time of day eg: 8am
  - Posture
  - Medications
  - Salt intake

Funder et al. *J Clin Endocrinol Metab* 2008;93:3266



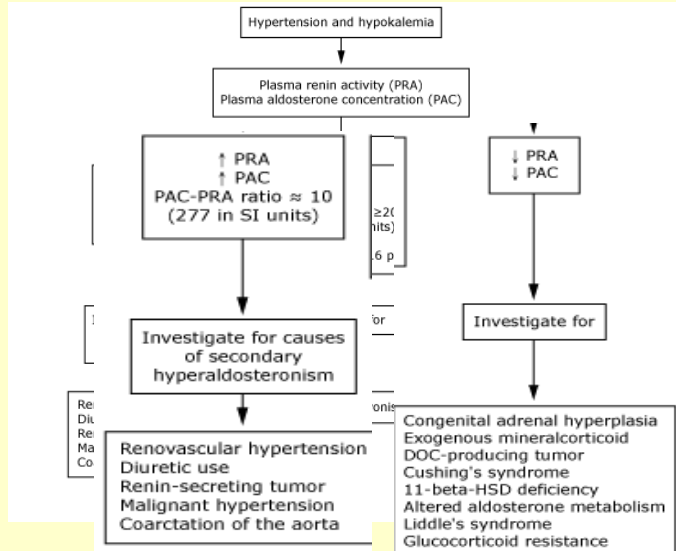
## Interpretation of Aldo Renin



Young W et al. *Trends in Endocrinol Metab* 1994



# Interpretation of Aldo Renin



Young W et al. *Trends in Endocrinol Metab* 1994



# Effects of Anti-Hypertensives

Factor	Effect on aldosterone levels	Effect on renin levels	Effect on ARR
<b>Medications</b>			
<u>β-Adrenergic blockers</u>	↓	↓ ↓	↑ (FP)
Central α-2 agonists (e.g. clonidine and α-methyldopa)	↓	↓ ↓	↑ (FP)
NSAIDs	→ ↑	↑ ↑	↓ (FN)
<u>K<sup>+</sup>-wasting diuretics</u>	→ ↑	↑ ↑	↓ (FN)
<u>K<sup>+</sup>-sparing diuretics</u>	→ ↑	↑ ↑	↓ (FN)
ACE inhibitors	↓	↑ ↑	↓ (FN)
ARBs	↓	↑ ↑	↓ (FN)
Ca <sup>2+</sup> blockers (DHPs)	→ ↓	↑ ↑	↓ (FN) <sup>a</sup>
Renin inhibitors	↓	↓ ↑ <sup>a</sup>	↓ (FN) <sup>a</sup>

ACE, Angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker; DHP, dihydropyridine; FP, false positive; FN, false negative; HT, hypertension; NSAID, nonsteroidal antiinflammatory drug; PHA-2, pseudoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate).

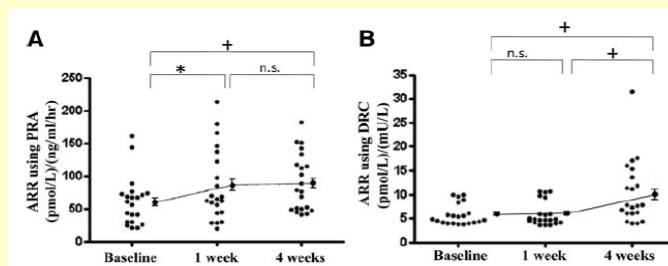
<sup>a</sup> Renin inhibitors lower PRA but raise DRC. This would be expected to result in false-positive ARR levels for renin measured as PRA and false negatives for renin measured as DRC.

Funder et al. *J Clin Endocrinol Metab* 2008;93:3266



## Medications: Summary

- Mineralocorticoid receptor antagonist eg: spironolactone, eplerenone should be avoided and stopped for 6/52
- ACE Inhibitors and AII receptor antagonist unlikely to produce false negatives – autonomous secretion
- Beta-blockers will produce false positives – withdraw for 2 weeks



Ahmed et al. *J Clin Endocrinol Metab* 2010;95:3201

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## Confirmatory Testing

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Oral NaCl Loading             <ul style="list-style-type: none"> <li>- 3/7 Na intake &gt;200 mmol (~6g) daily</li> <li>- 24-hour urine aldosterone excretion</li> </ul> </li> <li>• IV Normal Saline Infusion             <ul style="list-style-type: none"> <li>- Pre and post serum aldosterone</li> </ul> </li> <li>• Fludrocortisone Suppression             <ul style="list-style-type: none"> <li>- 4/7 0.1 mg fludrocort 6hrly (Brisbane)</li> </ul> </li> <li>• Captopril Challenge             <ul style="list-style-type: none"> <li>- Serum aldosterone 1-hr post oral captopril 25-50 mg</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>• Choice of “best” test?</li> <li>• Varying Sensitivity and Specificity</li> <li>• Availability of facilities</li> <li>• Different cut-offs</li> <li>• Search for “ideal” confirmatory test</li> </ul> |
|--|---|

Funder et al. *J Clin Endocrinol Metab* 2008;93:3266

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## Imaging: Subtype Classification

- CT Imaging (MRI)
- Adrenal Vein Sampling (AVS) (+/- under ACTH infusion) if surgery is considered
- Systematic Review:  
Adrenal CT/MRI results did not agree with AVS in 359/950 (37.8%) patients
  - 14.6% inappropriate unilateral adrenalectomy
  - 19.1% could have curative surgery but offered medical therapy
  - 3.9% opposite side

Kempers et al. *Ann Intern Med* 2009;151:329



## Is it easy to diagnose?

48 y.o. man with hypertension.

Difficult to control on atenolol and telmisartan/HCT.

CT imaging by GP revealed left adrenal adenoma.

- “Need to exclude pheochromocytoma, Cushing’s and Conn’s”



## Biochemical Investigations

U&Es:				
Na	144 mmol/L	(134-146)		
K	3.5 mmol/L	(3.4-5.0)		
HCO <sub>3</sub>	28 mmol/L	(22-32)		
Urea	3.7 mmol/L	(3.0-8.0)		
Creat	63 umol/L	(60-110)		
			• Normal plasma metanephrines	
			• Normal 24-hr UFC	
			• Microalbuminuria	
			• P. Renin	<b>2.5</b> mU/L (7-50)
			• S. Aldo	350 pmol/L (80-800)
			• Ratio	<b>140</b> (<50)



## Is it PHA?

Date	K <sup>+</sup> (3.4-5.0 mmol/L)	P. Renin (7-50 mU/L)	S. Aldosterone (80-800 pmol/L)	ARR (<50)
30/06*	3.5	2.5	350	140
25/11**	3.3	3.2	475	148
23/01	3.2	<2.0	195	NC

\* On AII/HCT and Beta-blocker

\*\* Off anti-hypertensives for 2 weeks



## Saline Suppression

1.5 L Normal Saline infused over 2 hours

Pre Aldo	195	pmol/L (80-800)
Post Aldo	238	pmol/L (<240)
K+	3.2	mmol/L (3.4-5.0)

Although serum aldosterone is <240 pmol/L post saline infusion, there was no suppression compared to pre-saline aldosterone of 195 pmol/L. Primary hyperaldosteronism is not excluded. Hypokalaemia (3.2 mmol/L) noted.



## Adrenal Vein Sampling (AVS)

SITE	Aldosterone pmol/L	Cortisol nmol/L	Ald/Cor Ratio	Collection Date	Time
Peripheral	263	330	0.8	25/02/09	15:25
Left Adrenal 1	79700	7400	10.8	25/02/09	15:30
Peripheral	407	350	1.1	25/02/09	15:31
Left Adrenal 2	22200	2300	9.7	25/02/09	15:35
Peripheral	377	330	1.1	25/02/09	15:36
Right Adrenal 1	3500	21000	0.2	25/02/09	15:40
Peripheral	335	420	0.8	25/02/09	15:41
Right Adrenal 2	722	480	1.5	25/02/09	15:45
Peripheral	543	440	1.2	25/02/09	15:46
Low IVC	592	510	1.2	25/02/09	16:00
Peripheral	638	480	1.3	25/02/09	16:01

Successful cannulation of both adrenal veins. Lateralisation of aldosterone secretion to left adrenal with associated contralateral suppression of right adrenal. Consistent with unilateral autonomous secretion of aldosterone from the left adrenal gland.

Dr R Maguire



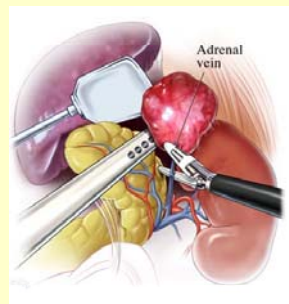
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Successful cannulation of both adrenal veins. Lateralisation of aldosterone secretion to left adrenal with associated contralateral suppression of right adrenal. Consistent with unilateral autonomous secretion of aldosterone from the left adrenal gland.  
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## Surgical Cure



Laparoscopic Adrenalectomy

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## Current and Emerging Treatment Strategies

Subtype	First-line treatment	Second-line treatment
Unilateral <sup>a</sup>	Unilateral laparoscopic adrenalectomy	Spirolactone Eplerenone Amiloride Aldosterone synthase inhibitors
Bilateral (non-GRA) <sup>b</sup>	Spirolactone Eplerenone Amiloride Aldosterone synthase inhibitors	Unilateral laparoscopic adrenalectomy
GRA <sup>c</sup>	Low-dose glucocorticoids	Spirolactone Eplerenone Amiloride Aldosterone synthase inhibitors

Stowasser M. *J Clin Endocrinol Metab* 2009;94:3623

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## Potential Side-Effect from Spirolactone



Gynaecomastia

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## Cost of investigating for PHA

• Screening	Cost(\$A)		Cost(\$A)
Renin and Aldosterone	44.00	Confirmatory Test	>500
U&Es	17.80	CT Abdomen	385.00
	61.80	with contrast	480.05
Repeat x2	123.60	AVS	>1000
Repeat x3	185.40	Adrenalectomy	2510 + 2SD

Up to \$ 8,000

30x  
more expensive



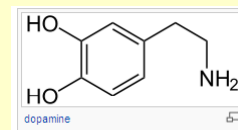
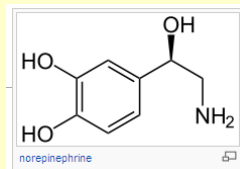
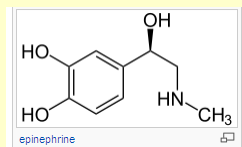
## The Future: Genetics PHA

- **Framingham Offspring Study**
  - ARR and BP development/progression ( $h^2=0.4$ )
- **Linkage analysis**
  - log ARR and Chr 7p21-22 (FH-II)
- **Other candidate genes under Ix**
  - Retinoblastoma-assoc Kruppel-assoc box gene (*RBaK*)
  - Postmeiotic Segregation increased 2 (*PMS2*)
  - Guanine nucleotide-binding protein  $\alpha$ -12 (*GNA12*)
  - Replication protein A3 (*RPA3*)
  - Zinc finger protein 12 (*ZNF12*)
  - Glucocorticoid-induced transcript 1 (*GLCCI1*)

Stowasser M. *J Clin Endocrinol Metab* 2009;94:3623



# Phaeochromocytoma (Pheo) & Paragangliomas (PGL)



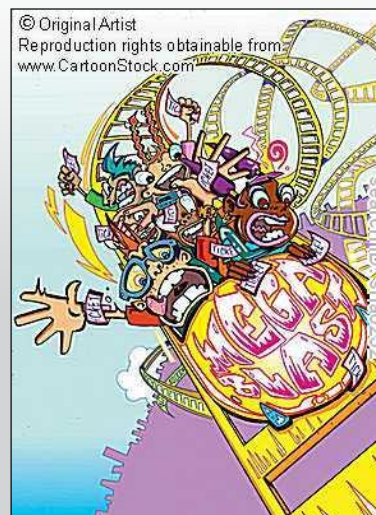
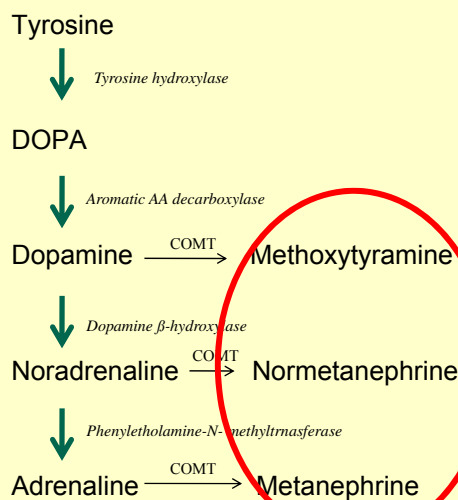
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## Pheo & PGL

- Catecholamine-secreting tumours
- Chromaffin cells of the adrenal medulla and sympathetic ganglia
- Rare, <0.2% of patients with hypertension
- Variable clinical presentation:
  - Paroxysm (sweats, headaches, tachycardia)
  - 5-15% normotensive (adrenal incidentaloma)
  - Non-specific symptoms eg: dyspnoea, panic attacks, etc

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## Symptomatology



## May be Asymptomatic

- Widespread use of CT imaging
- 10-50% patients with “incidentaloma” are asymptomatic

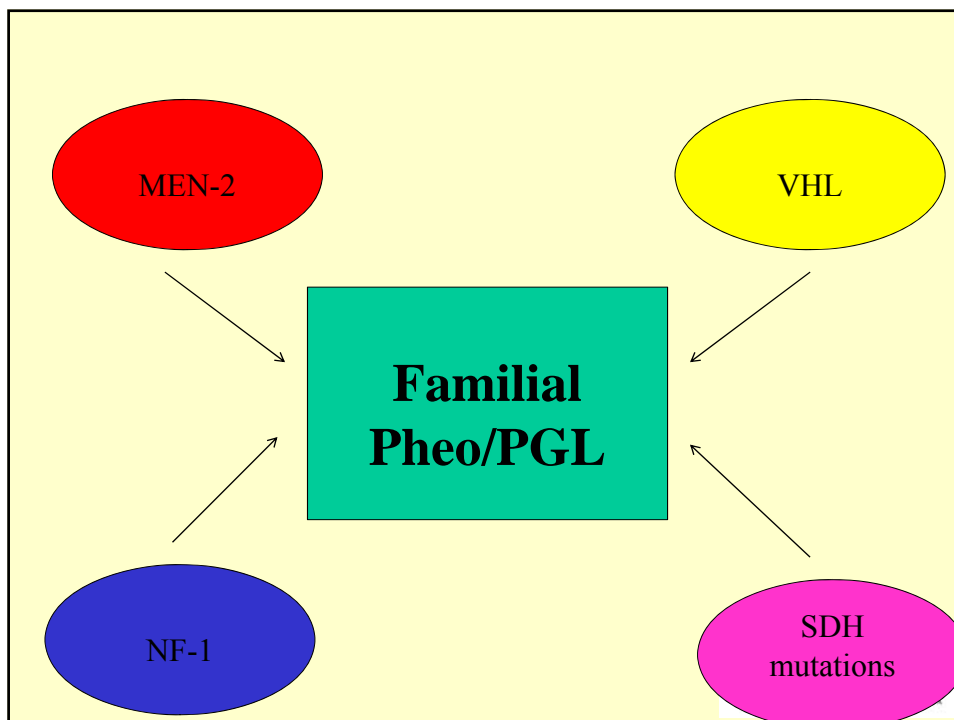
Kudva YC et al. *The Endocrinologist* 1999;9:77  
Baguet JP et al. *Eur J Endocrinol* 2004;150:681  
Motta-Ramirez GA et al. *AJR* 2005;185:684

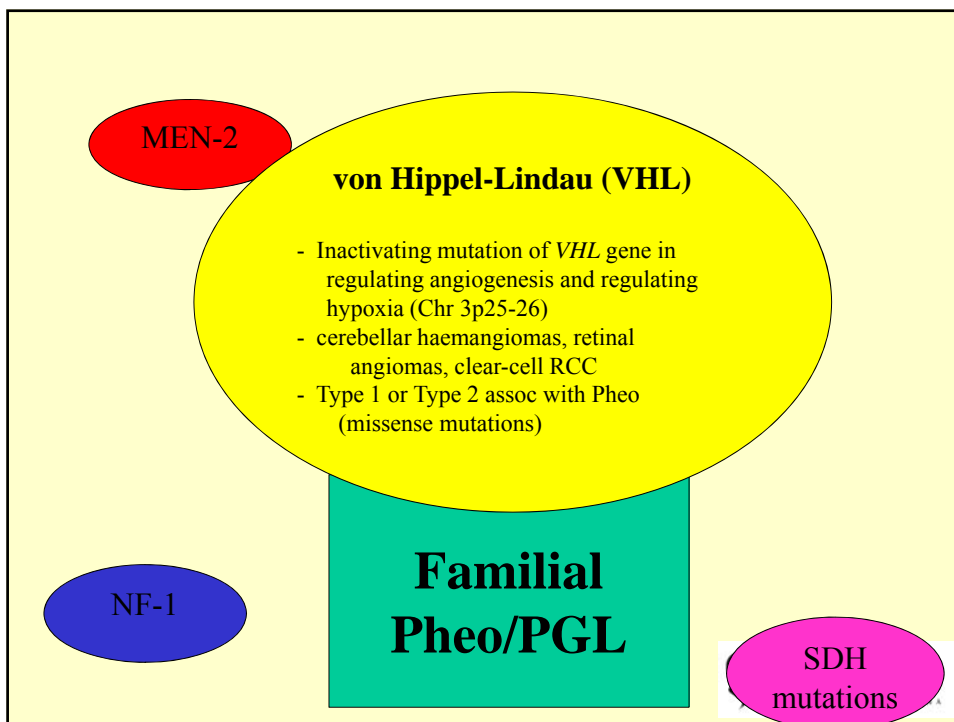
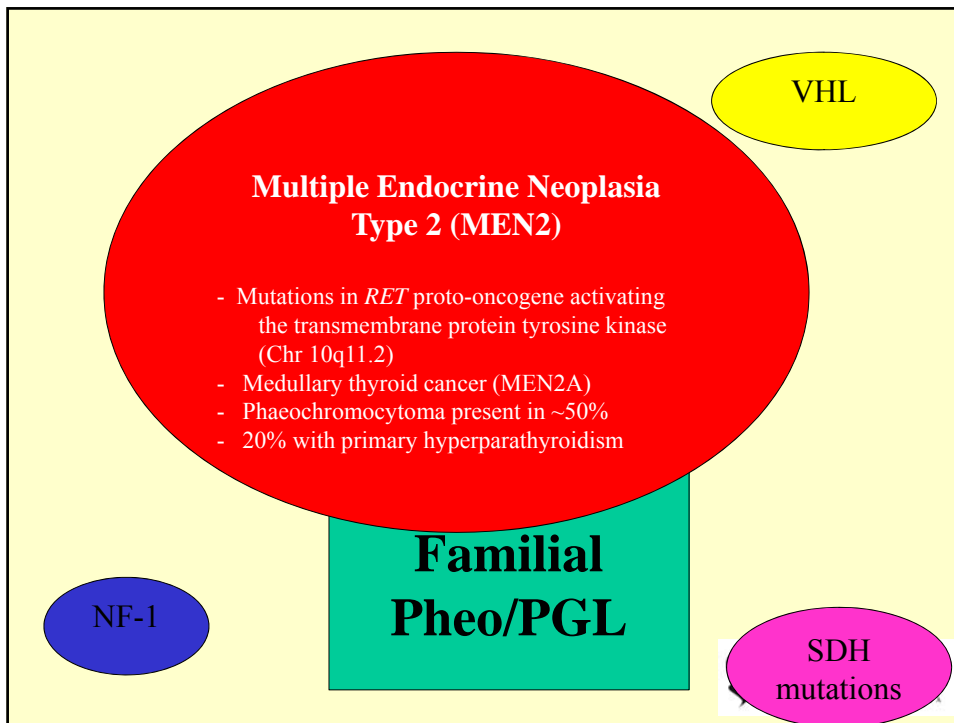
- Incidental finding at autopsy

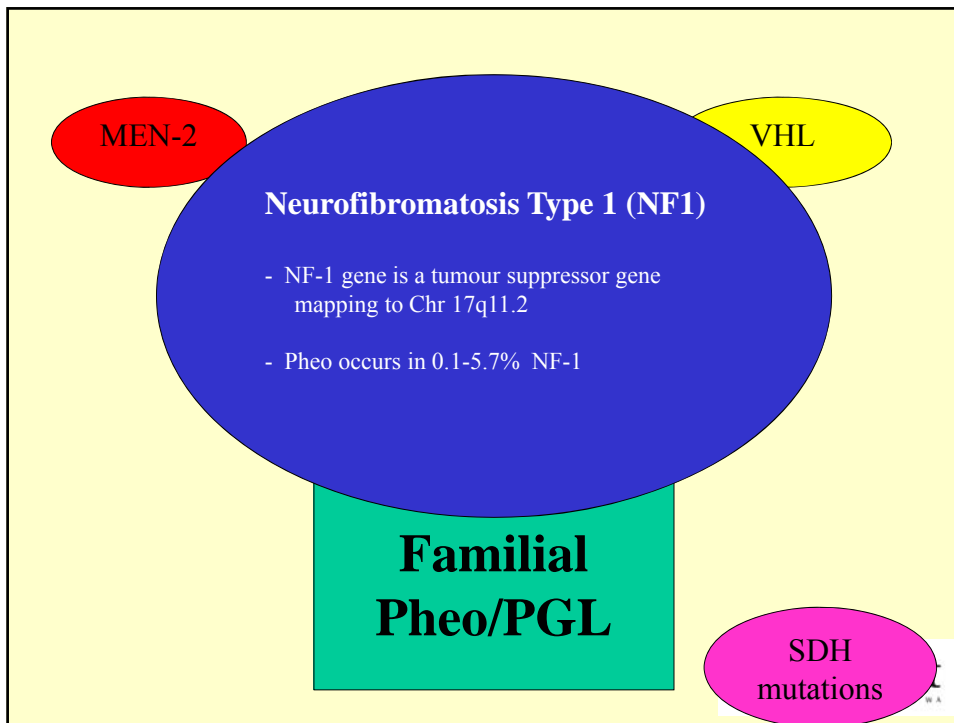


## Familial Pheo/PGL

- **Multiple Endocrine Neoplasia type 2 (MEN2)**
  - Mutations in *RET* proto-oncogene activating the transmembrane protein tyrosine kinase (Chr 10q11.2)
  - Medullary thyroid cancer (MEN2A)
  - Pheochromocytoma present in ~50%
  - 20% with primary hyperparathyroidism
- **von Hippel-Lindau (VHL)**
  - Inactivating mutation of *VHL* gene in regulating angiogenesis and regulating hypoxia (Chr 3p25-26)
  - cerebellar haemangiomas, retinal angiomas, clear-cell RCC
  - Type 1 or Type 2 assoc with PC (missense mutations)
- **Neurofibromatosis Type 1 (NF1)**
  - NF-1 gene is a tumour suppressor gene mapping to Chr 17q11.2
  - PC occurs in 0.1-5.7%







**International Seminars in Surgical Oncology** BioMed Central

Case report **Open Access**

**Concomitant composite adrenal pheochromocytoma, multiple gastric stromal tumours and pseudohermaphroditism in a patient with von Recklinghausen's disease**

Dean Lisewski<sup>1</sup>, Simon Ryan<sup>\*1</sup>, Ee Mun Lim<sup>2</sup>, Felicity Frost<sup>2</sup> and Hieu Nguyen<sup>1</sup>

**Figure 1A:** Neurofibroma of the clitoris.



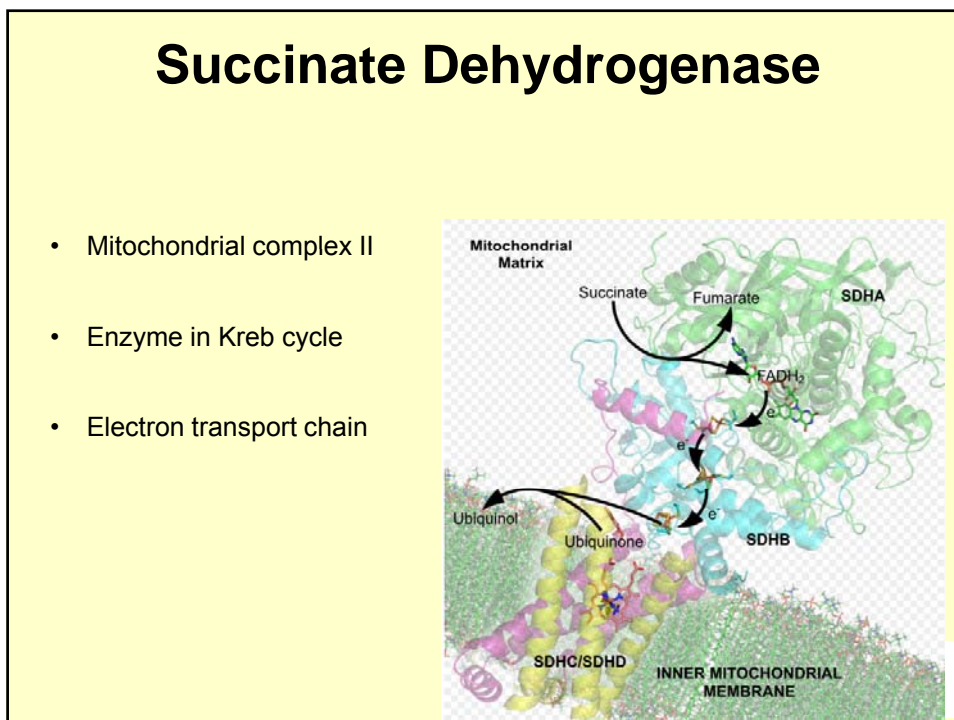
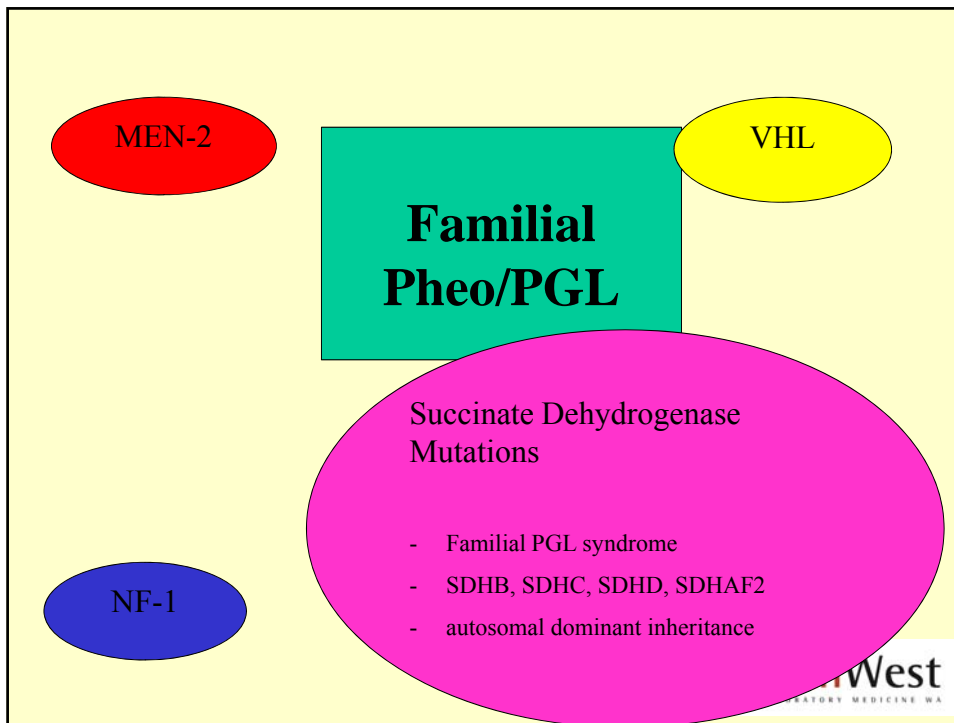
**Figure 1B:** Clitoromegaly.



**Figure 4**



Composite adrenal tumour with pheochromocytoma (left lower) merging with ganglioneuroma (upper right) (H&E, original magnification  $\times 250$ ).

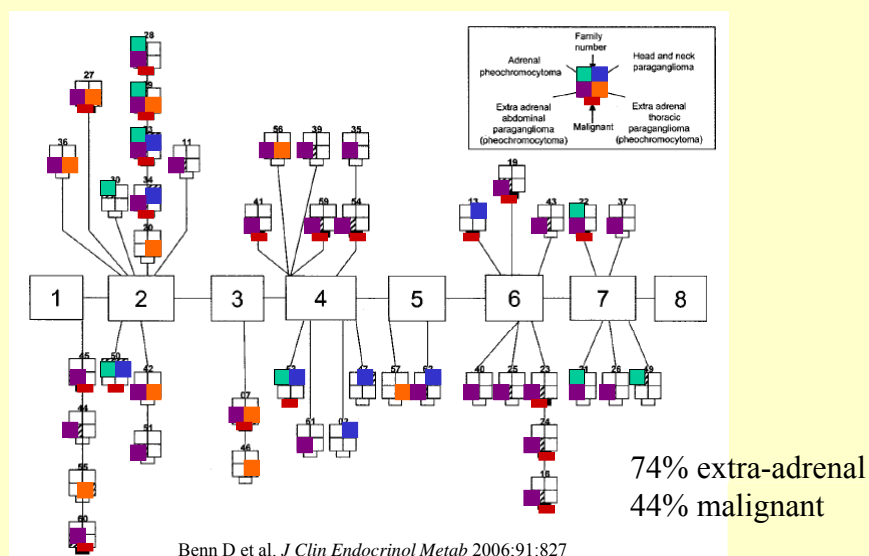


# SDHB

- Increased risk of malignancy
- catecholamine secreting PGL of thorax, abdomen, pelvis+/- pheo
- Renal cancer in 14%
- Early development of disease (mean age 34 yrs)
- 45% die within 5 years of diagnosis

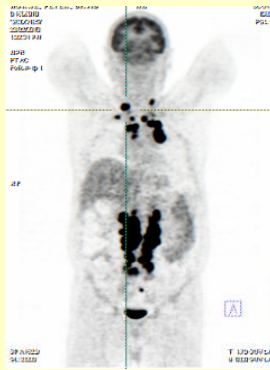


# SDHB Mutation

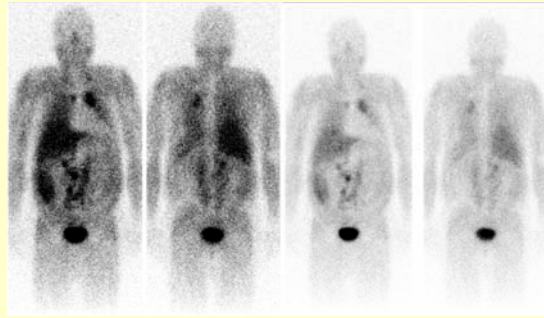


53 y.o. man with SDHB mutation  
 Diagnosed in 1995  
 Known metastatic disease since 2003

FDG-PET



MIBG

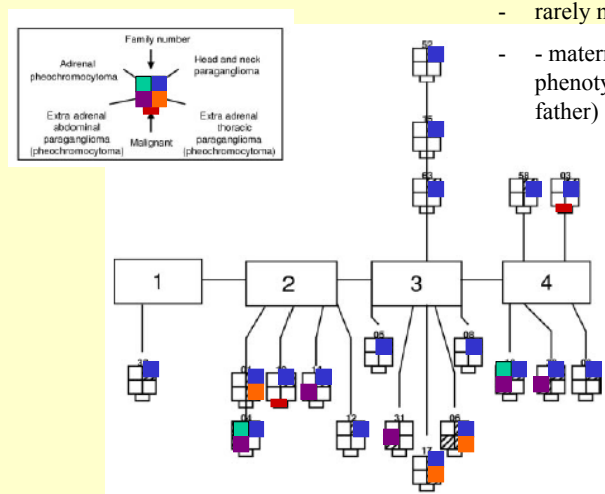


Plasma nor-metadrenaline (free)	<b>65850</b>	pmol/L	(< 660)
Plasma metadrenaline (free)	270	pmol/L	(< 300)
Chromagranin A	<b>400</b>	U/L	(<18)



## SDHD Mutation

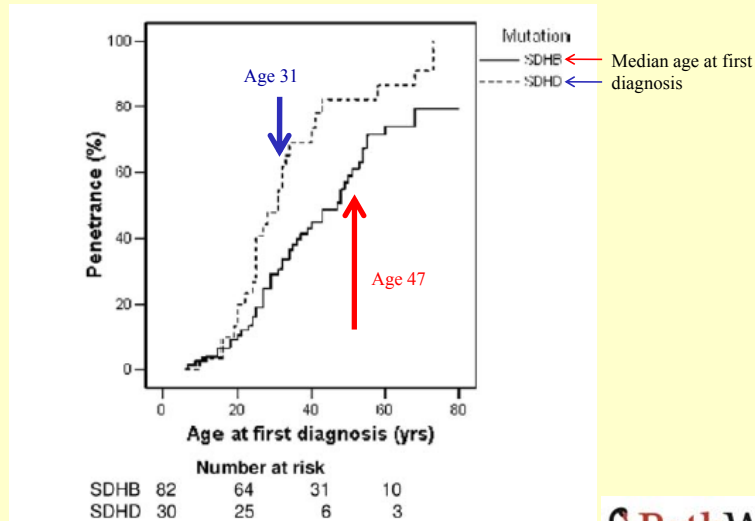
- head and neck
- rarely malignant and rarely functional
- - maternally imprinted (disease phenotype if mutation inherited from father)



Benn D et al. *J Clin Endocrinol Metab* 2006;91:827



## Age-related Penetrance for SDH Mutation Carriers



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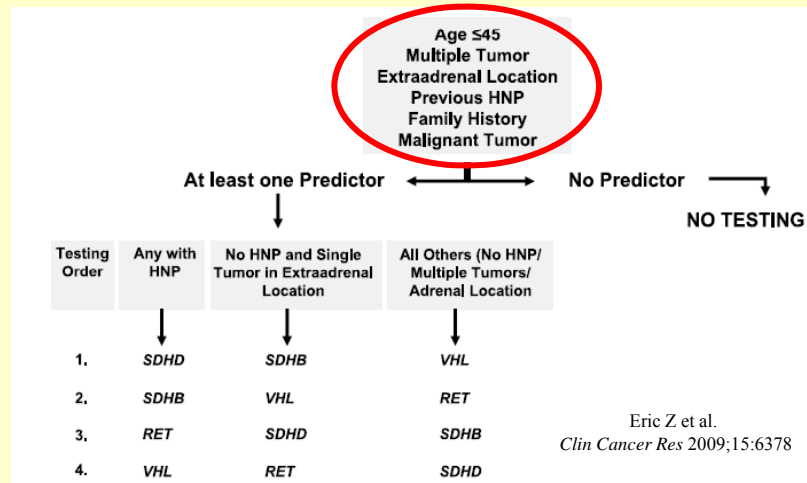
## Other SDH Mutations

- **SDHC**
  - usually biochemically silent head and neck PGL
  - very rare
  
- **SDHAF2** (chromosome 11q13.1)
  - complete loss of flavin-adenine dinucleotide (FAD) cofactor
  - Maternally imprinted
  - Dutch and Spanish kindreds
  - Parasympathetic PGL of head and neck
  - Not associated with pheo

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## Genetic Algorithm: Sporadic Pheo

- After age 50: 5-10% familial



## Biochemical Investigations:

### 24-hr Urine Tests

- Catecholamines and dopamine
- Metanephrines – total or fractionated
- Dopamine – in children with neuroblastomas

### Plasma

- Catecholamines
- Total metanephrines
- Free fractionated metanephrines
- Methoxytyramine

### Plasma/Serum Chromagranin A (CgA)

## Which Investigation?

- Regional, institutional and international differences
- No consensus on “best” test
- Methodology depends on expertise and equipment  
eg: HPLC, LCMSMS
- Patient Preparation  
eg: Plasma Metanephrines – overnight fast, indwelling cannula, supine
- Interfering Medications  
eg: tricyclic antidepressants, decongestants, ethanol, caffeine, etc
- Different cut-offs and “equivocal range”
- Varying sensitivity and specificity



## Sensitivities & Specificities

Sensitivity

Specificity

Specificity of plasma metanephrines of 82-85% in a rare tumour

→ more false-positives than true-positives.

\* Lenders et al. *JAMA* 2002;287:1427

# Kudva et al. *J Clin Endocrinol Metab* 2003;88:4533



## The Debate

???

**Plasma Free  
Metanephrines**

Urine Fractionated  
Metanephrines

### High Pre-Test Probability:

Hyperadrenergic spells  
Resistant hypertension  
Familial syndrome  
Family history  
Adrenal mass  
Pressor response during anaesthetic and surgery  
Onset of hypertension at a young age  
Idiopathic cardiomyopathy

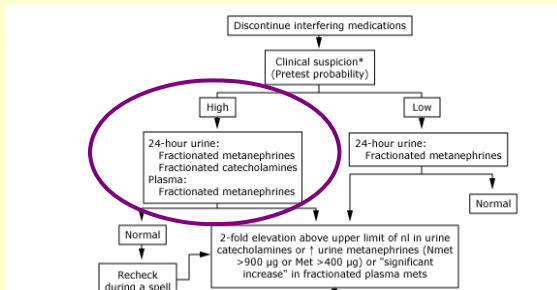
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## Improving Diagnostic Specificity of Plasma Metanephrines

- Supine venipuncture
- Fasting
- Withdrawal of interfering medications  
Eg: tricyclic antidepressants, reboxetine, beta-blockers
- Higher diagnostic cut-offs (>4x ULN)
- Additional testing with urine metanephrines
- Combining with Chromagranin A
- Consider clonidine suppression test

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## Evaluation of Pheochromocytoma



### High Pre-Test Probability:

Hyperadrenergic spells  
Resistant hypertension  
Familial syndrome  
Family history  
Adrenal mass  
Pressor response during anaesthetic and surgery  
Onset of hypertension at a young age  
Idiopathic cardiomyopathy

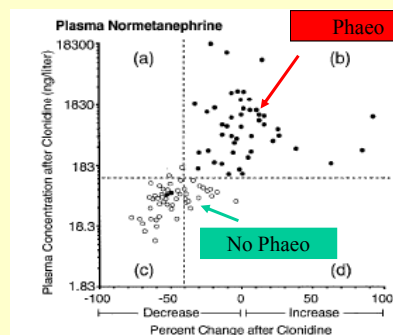
VMA: vanilylmandelic acid; CT: computed tomography; MRI: magnetic resonance imaging; I231-MIBG: I231-meta-iodobenzylguanidine.  
\* Clinical suspicion is triggered by paroxysmal symptoms (especially hypertension); hypertension that is intermittent, unusually labile, or resistant to treatment; family history of pheochromocytoma or associated conditions; or an incidentally discovered adrenal mass.  
Modified and reprinted with permission from Young, WF Jr. Pheochromocytoma: 1926-1993. In: Trends in Endocrinology and Metabolism vol 4, Elsevier Science, Inc 1993. p 122.

Surgical resection

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## Clonidine Suppression Test

- Equivocal plasma metanephrines (N and <4x ULN)
- Overnight fast
- A fall in plasma normetadrenaline into the normal range or by at least 50% of baseline values is considered a normal response 3 hours post 0.3mg clonidine.



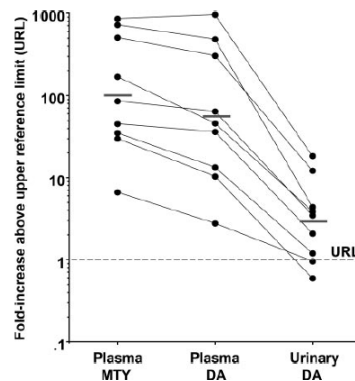
Eisenhofer G et al.  
*J Clin Endocrinol Metab* 2003;88:2656

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## Plasma Methoxytyramine

- Dopamine secreting pheo/PGL
- Extremely rare
- Maybe normotensive with normal plasma mets

FIG. 3. Relative increases of plasma concentrations of free methoxytyramine (MTY), compared with plasma concentrations and 24-h urinary outputs of dopamine (DA) above the upper reference limits (URL) in nine patients with dopamine-producing paragangliomas. Results for each of the nine patients for each of the three biochemical tests are linked. Mean values (geometric means) are shown by gray bars. Note the logarithmic scale.



Eisenhofer G et al. *J Clin Endocrinol Metab* 2005;90:2

## Chromagranin A

- Member of chromagranins or secretogranins
- Present in secretory granules in neuroendocrine cells (eg: pheo, carcinoid)
- Combining with plasma metanephrine  
Sensitivity 87% and specificity 73-89%  
*Grebe S. J Clin Endocrinol Metab* 2008;93:91
- CgA alone has sensitivity of 70% (SDHB) and 54% (SDHD) if plasma or urine metanephrines n/a  
*Pacak K, ESA* 2010

## False Positives of Elevated CgA

- Proton-pump inhibitor
- Renal impairment
- Liver disease
- Inflammatory bowel disease



## Imaging

2-fold elevation of urine cats  
or  
urine Nmet >900 ug or Met >400 ug  
or  
“significant increase” in fractionated plasma mets

Adrenal CT (MRI)

MIBG Scan  
18-FDA or FDG PET  
?Whole body MRI/CT

Consider Genetic Testing

VMA: vanillylmandelic acid; CT: computed tomography; MRI: magnetic resonance imaging; 123I-MIBG: 123I-meta-iodobenzylguanidine.  
\* Clinical suspicion is triggered by paroxysmal symptoms (especially hypertension); hypertension that is intermittent, unusually labile, or resistant to treatment; family history of pheochromocytoma or associated conditions; or an incidentally discovered adrenal mass.  
Modified and reprinted with permission from Young, WF Jr. Pheochromocytoma: 1926-1993. In: Trends in Endocrinology and Metabolism vol 4, Elsevier Science, Inc 1993. p 122.



## Imaging

- CT/MRI (specificity 90%)
- MIBG (sensitivity 67-86%)
- PET eg: FDA, FDOPA, FDG (sensitivity 67-93%)
- Octreotide Scan (sensitivity <50%)

Paccac K. *Trends Endocrinol Metab* 2005



## Personal Experience

- 24-hr Urinary Catecholamines
  - not sensitive, false negative
  - not be used in familial syndromes and adrenal incidentaloma
  - \* should be used in conjunction with **Urinary Metanephrines**
- Plasma Free Fractionated Metanephrines
  - Sensitive
  - Good Negative Predictive Value
  - False positives and “equivocal range”
  - Consider clonidine suppression test for “equivocal” results



## Cushing's Syndrome (CS)



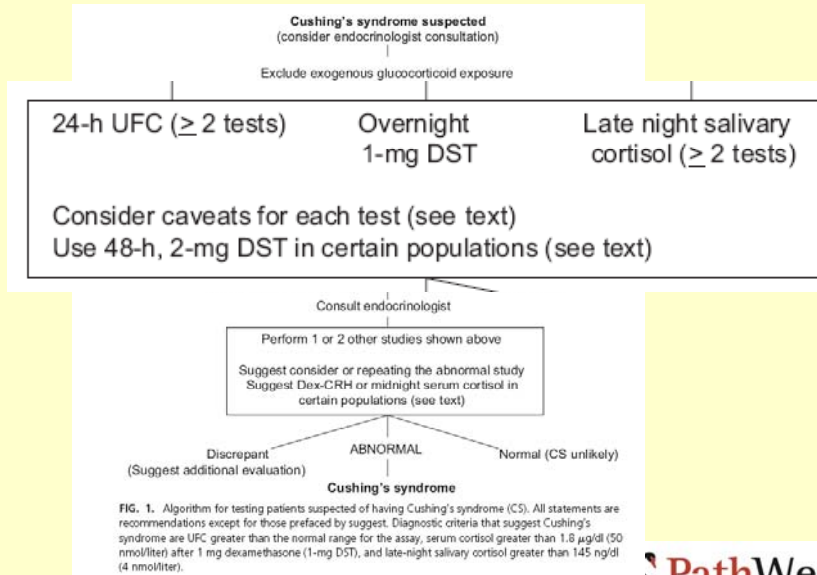
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## Etiology

<b>Diagnosis</b>	<b>% Patients</b>
<b>ACTH-Dependent CS</b>	
Cushing's disease (Pituitary)	68
Ectopic ACTH	12
Ectopic CRH	<1
<b>ACTH-Independent CS</b>	
Adrenal Adenoma	10
Adrenal Carcinoma	8
Micro- or Macro-nodular Hyperplasia	<1
<b>Pseudo CS</b>	
Major Depressive	<1
Alcoholism	<1

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## 2008 Endocrine Society Practice Guidelines



Nieman L et al. *J Clin Endocrinol Metab* 2008;93:1526



## Hypercortisolism in the absence of CS

**TABLE 2.** Conditions associated with hypercortisolism in the absence of Cushing's syndrome<sup>a</sup>

Conditions
Some clinical features of Cushing's syndrome may be present
Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing's syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not urine cortisol)

59 y.o. builder  
Worsening hypertension.  
Acute anxiety.

Serum cortisol **605** nmol/L (150-600)

Overnight 1mg Dex:  
Serum cortisol **288** nmol/L (<50)

Late night salivary cortisol  
3 and 5 nmol/L (<9)

Nieman L et al. *J Clin Endocrinol Metab* 2008;93:1526



## 24-Hour UFC

- Integrated index of free plasma cortisol
- Not affected by CBG (patient on oestrogen)
- Up to 3 urine collections (cyclical CS)
- Urine Creatinine to verify adequacy of collection (eGFR <30ml/min → false -ve)
- **Advantages:**
  - Simple
- **Disadvantages:**
  - Problems with urine collection
  - Poor Specificity (urine metabolites)
  - Varying reference interval between labs:
    - \* immunoassay eg: RIA, Immunometric
    - \* HPLC
    - \* LCMSMS



## Overnight Low Dose DST

- 1mg dex at 2300-2400
- Fasting plasma cortisol 0800-0900
- Not for pregnant women or on estrogens
- **Normal Suppression “Cut-offs”**
  - In the past: <138 nmol/L
  - Now: <50 nmol/L
  - (↑↑ sensitivity, ↓ specificity, more false +ve)
- **False Positives:**
  - ↑ **CBG** eg: estrogen, pregnancy
  - ↓ **Dex absorption**
  - **Drugs enhancing hepatic Dex metabolism**
    - eg: barbiturates, phenytoin, carbamazepine
  - **PseudoCushing’s State**
    - eg: depression, alcoholism, chronic anxiety
  - **Acute medical or psychiatric illness**
- \* **Some healthy individuals may fail to suppress**

Nieman L et al. *J Clin Endocrinol Metab* 2008;93:1526



## Late-Night Salivary Cortisol



- Commonly used in USA (ELISA or LCMSMS)
- Easy to use
- 2 separate collections between 2300-2400
- Sample is stable at room temperature
- Sensitivity and specificity vary between 92-100%
- Accuracy of test similar to 24-hr UFC
- Further validation on gender, age and co-existing medical condition (and shift workers!)

Nieman L et al. *J Clin Endocrinol Metab* 2008;93:1526



## Dexamethasone Suppression Test

### 2-day Low Dose DST

#### Instructions:

(1) It is important that you take the **dexamethasone** tablets at the exact specified times:

**9am, 3pm, 9pm, and 3am**

- (2) Be reminded to set your alarm clock at 3am for the overnight dose.  
 (3) Attend PathWest before 9am every morning to have a blood test for serum cortisol before you take the 9am dexamethasone tablet.  
 (4) 24-hour urine collection for cortisol should be performed before starting Dexamethasone (Sunday). Bring the urine collection to PathWest on Monday when you have your first (baseline) blood test before 9am. Continue 24-hour urine collection from 8.30-8.30 am during the dexamethasone suppression test.

Date	Day	Dexamethasone		Done (Tick ✓)	
		Time	Dose (µg)		
	Sun	Commence 24hr urine collection eg: 8am-8am			
	Mon	Bring urine collection. Baseline blood test for cortisol and ACTH before 9am. Pick up urine bottle to continue urine collection.			
		9am	0.5		
		3pm	0.5		
		9pm	0.5		
	(Tues)	3am	0.5		
	Tues	Bring urine collection. Blood test for cortisol before 9am. Pick up urine bottle to continue urine collection.			
		9am	0.5		
		3pm	0.5		
		9pm	0.5		
	(Weds)	3am	0.5		
	Weds	Bring urine collection. Blood test for cortisol before 9am. Pick up urine bottle for urine collection.			
		9am	2		
		3pm	2		
		9pm	2		
	(Thurs)	3am	2		
	Thurs	Bring urine collection. Blood test for cortisol before 9am. Pick up urine bottle for urine collection.			
		9am	2		
		3pm	2		
		9pm	2		
	(Fri)	3am	2		
	Fri	Bring urine collection. Final blood test for cortisol before or at 9am.			

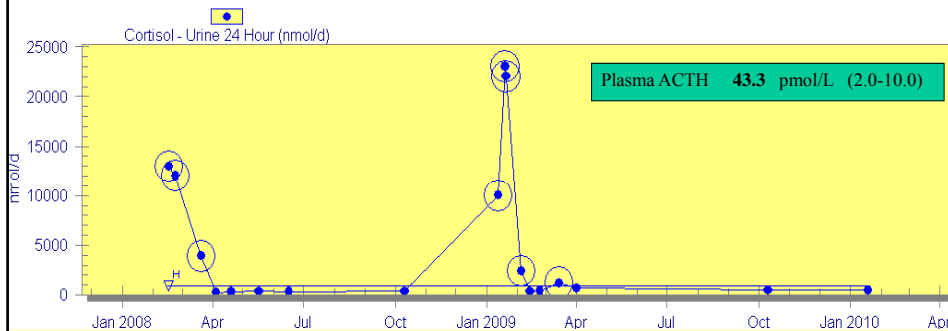
Please contact Dr E M Lim on (08) 9346 1054 if you have any queries or concerns.

## Beware of Cyclical CS!

67 y.o. Woman

Na	148	mmol/L	(134-146)
K	2.0	mmol/L	(3.4-5.0)
HCO <sub>3</sub>	40	mmol/L	(22-32)
Urea	5.7	mmol/L	(3.0-8.0)
Creat	68	umol/L	(45-90)

Cortisol - Urine 24 Hour



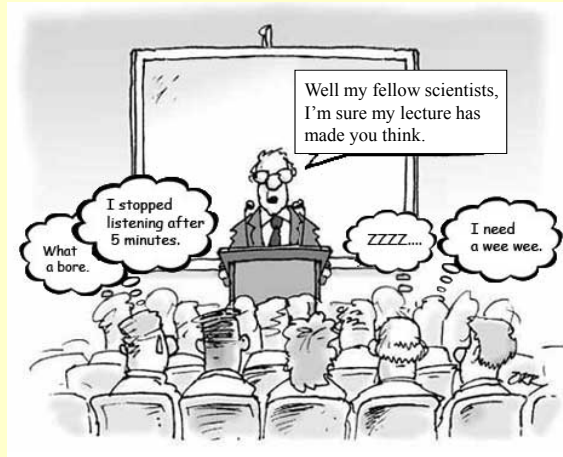
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## Take Home Messages

- Secondary endocrine hypertension is worth screening for in selected population
- It may not be easy to diagnose
- Interaction between the laboratory and clinician is important
  - Screening and dynamic testing

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# Thank You



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