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Phaeochromocytoma Investigations

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Initial Presentation and Case History

45 year old male

July ‘08 (age 39)

- Clinical details – ‘Fatigue, ?cause’
- Initial Ix – FBC, U&E, LFTs, Calcium, TFTs, cholesterol. All normal.

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Jan ’10 (age 40)

- Clinical details – ‘TATT’
- Ix – FBC, Ferritin, TFTs, U&E, Glucose, LFTs, Calcium, Lipids. All normal.
- Testosterone = 9.5 nmol/L (10-30)

- What would you do next?

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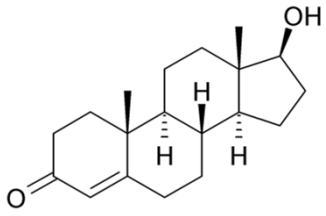
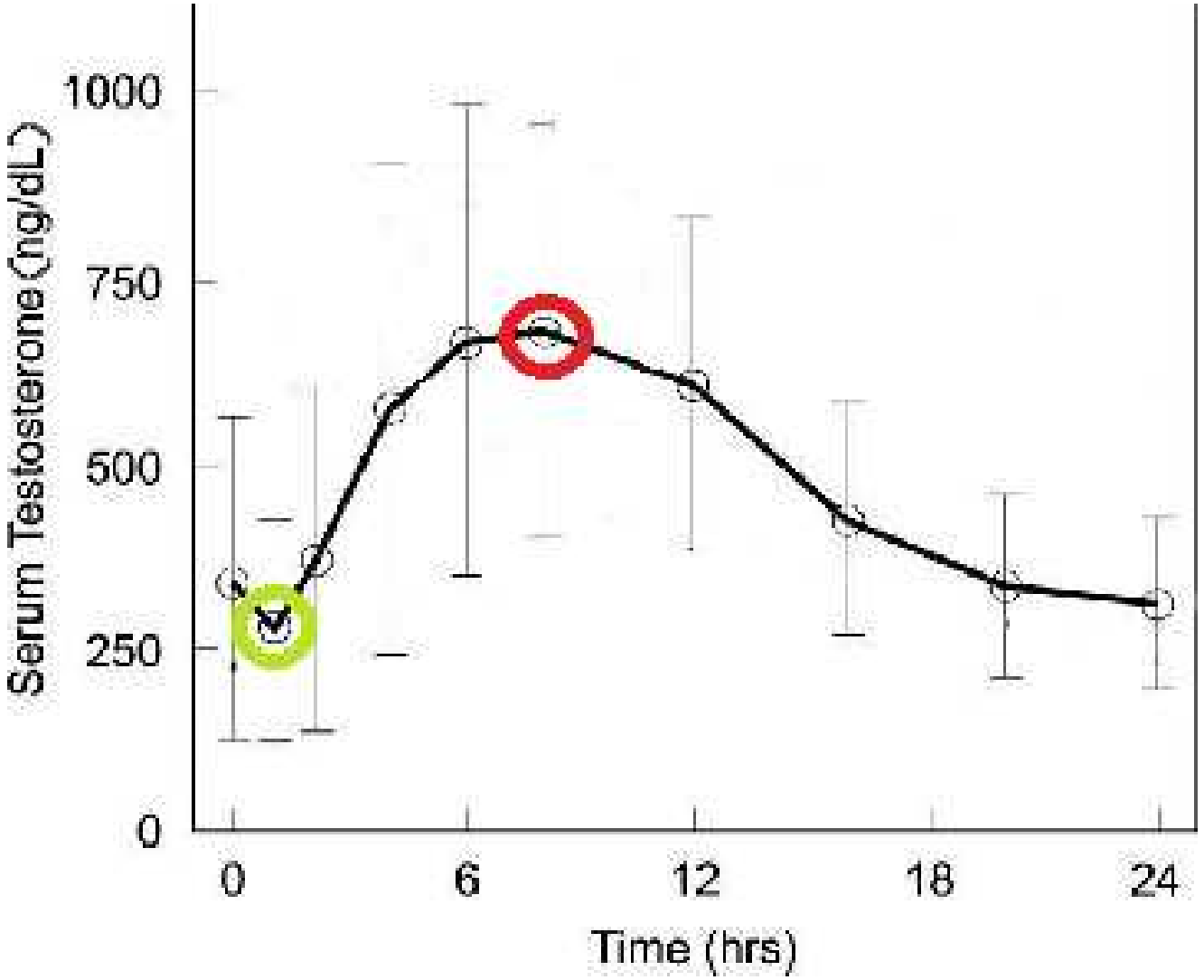


Diurnal Variation of Testosterone



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Subsequent Investigations

March ‘10

- Ix – Glucose, TFTs, Prolactin. All Normal
- LH = 5.0 IU/L (1.6 – 9.6)
- FSH = 6.0 IU/L (0 – 6.0)
- Testosterone = 7.9 nmol/L (8.7 – 29.0) (9:30 AM)

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April ‘10

- Testosterone = 5.7 nmol/L (8.7 – 29.0)
- SHBG = 9 nmol/L (15 – 48)
- PSA = 0.7 ug/L

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The patient was diagnosed with hypogonadism and testosterone was replaced with Sustanon (an injectable blend of four esterified testosterone compounds).

March '14
- Δ Diabetes

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March ‘14

GP Requests 24hr Urine Catecholamines

	Sample 1	**Sample 2**
Volume (L)	4.002	4.850
Free Adrenaline (nmol/L) (<100)	68	82
Free Noradrenaline (nmol/L) (<800)	1072	2299

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Referral to endocrinology (April ‘14)

Dexamethasone Suppression Test

- 9am Cortisol (Post-Dex) = 20 nmol/L

Further Ix for Pituitary Adenoma (non-functioning)

- IGF-1 – normal
- TFTs – normal

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April ‘14

Request for 24hr Urine Metanephrines:

	Sample 1
Volume (L)	4.798
Normetadrenaline (umol/24 hrs) (<3.8)	5.6
Metadrenaline (umol/24 hrs) (<2.2)	1.2

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April ‘14

Request for 24hr Urine Metanephrines:

	Sample 1
Volume (L)	4.798
Normetadrenaline (umol/24 hrs) (<3.8)	5.6
Metadrenaline (umol/24 hrs) (<2.2)	1.2

May ‘14

Request for Plasma Metanephrines:

	Sample 1
Normetadrenaline (pmol/L) (120-1180)	1181
Metadrenaline (pmol/L) (80-510)	249

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Phaeochromocytoma

What is it?

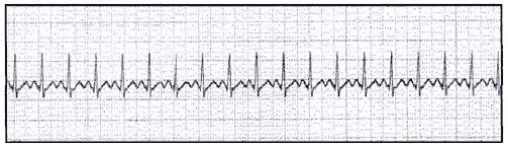
A rare catecholamine producing tumour which may be sporadic, or heriditary.
(MEN2, von Hippel-Lindau disease, neurofibromatosis type 1 and mutations of *SDHD* and *SDHB* genes as familial paraganglioma or carotid body tumours).

What are the classic symptoms of a sporadic phaeocheomocytoma?

Episodic headache, flushing, sweating, tachycardia and hypertension.

What is the incidence of sporadic phaeochromocytoma?

Low, incidence = 0.3 %



Presentation

May be clinically silent, or variable presentations.
PM incidence of 1/200, which may have contributed to death.
Some identified through imaging for unrelated disorders.

To ensure a phaeochromocytoma is not missed, the threshold for biochemical screening should be low, or the sensitivity of the test should be high. This results in the number of false-positive results being higher than true-positive results.

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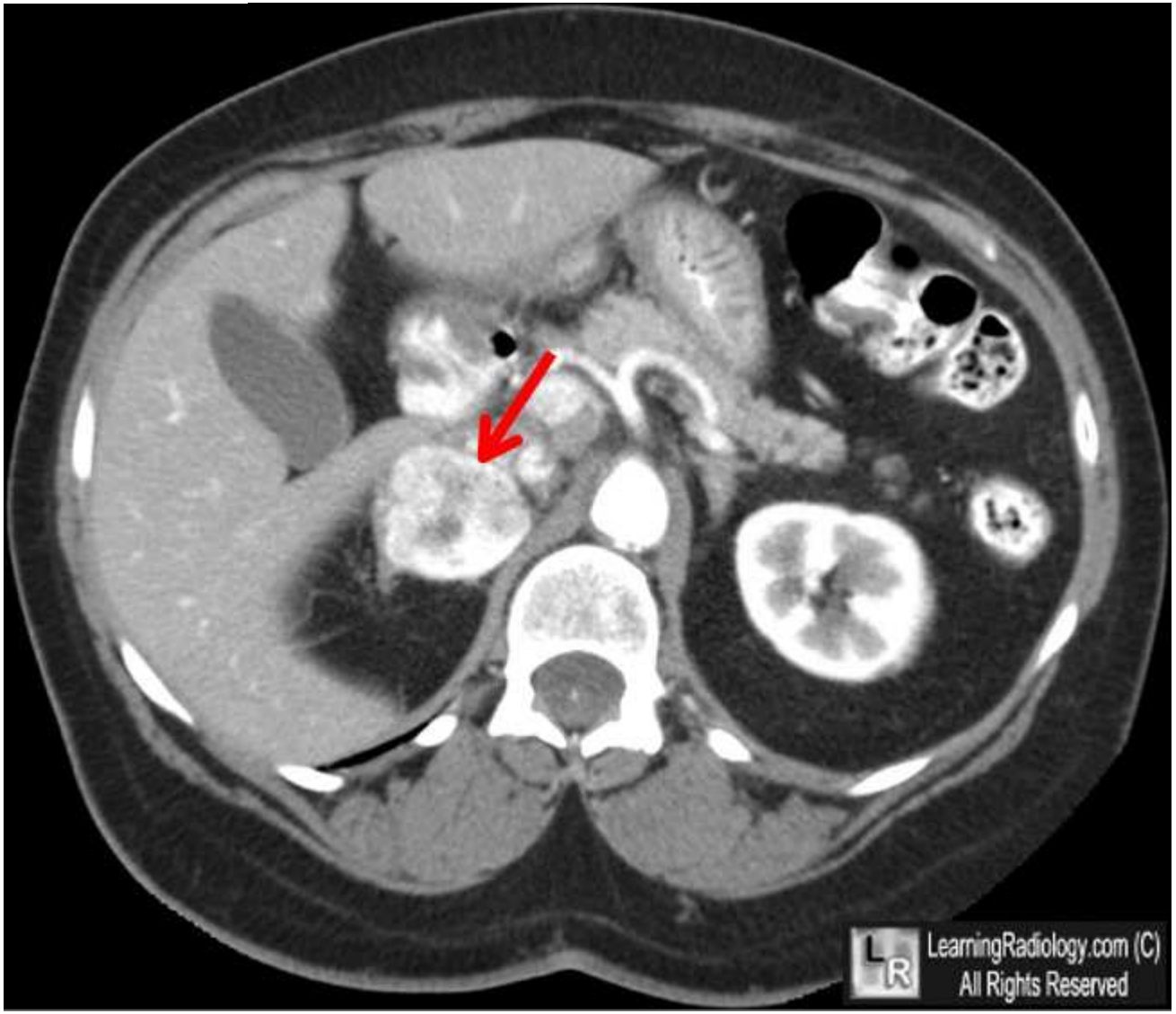

Right adrenal mass, left adrenal is normal

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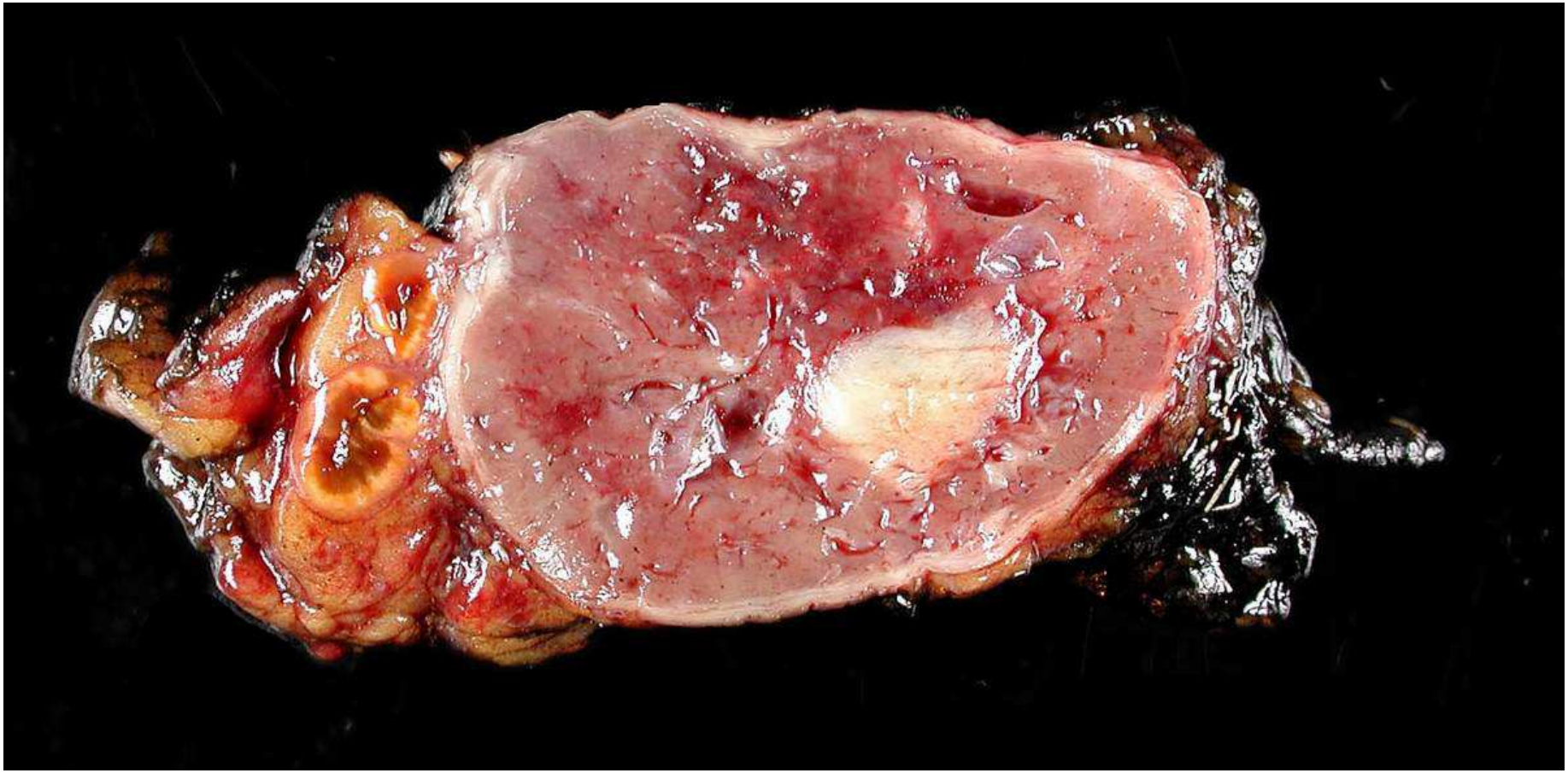
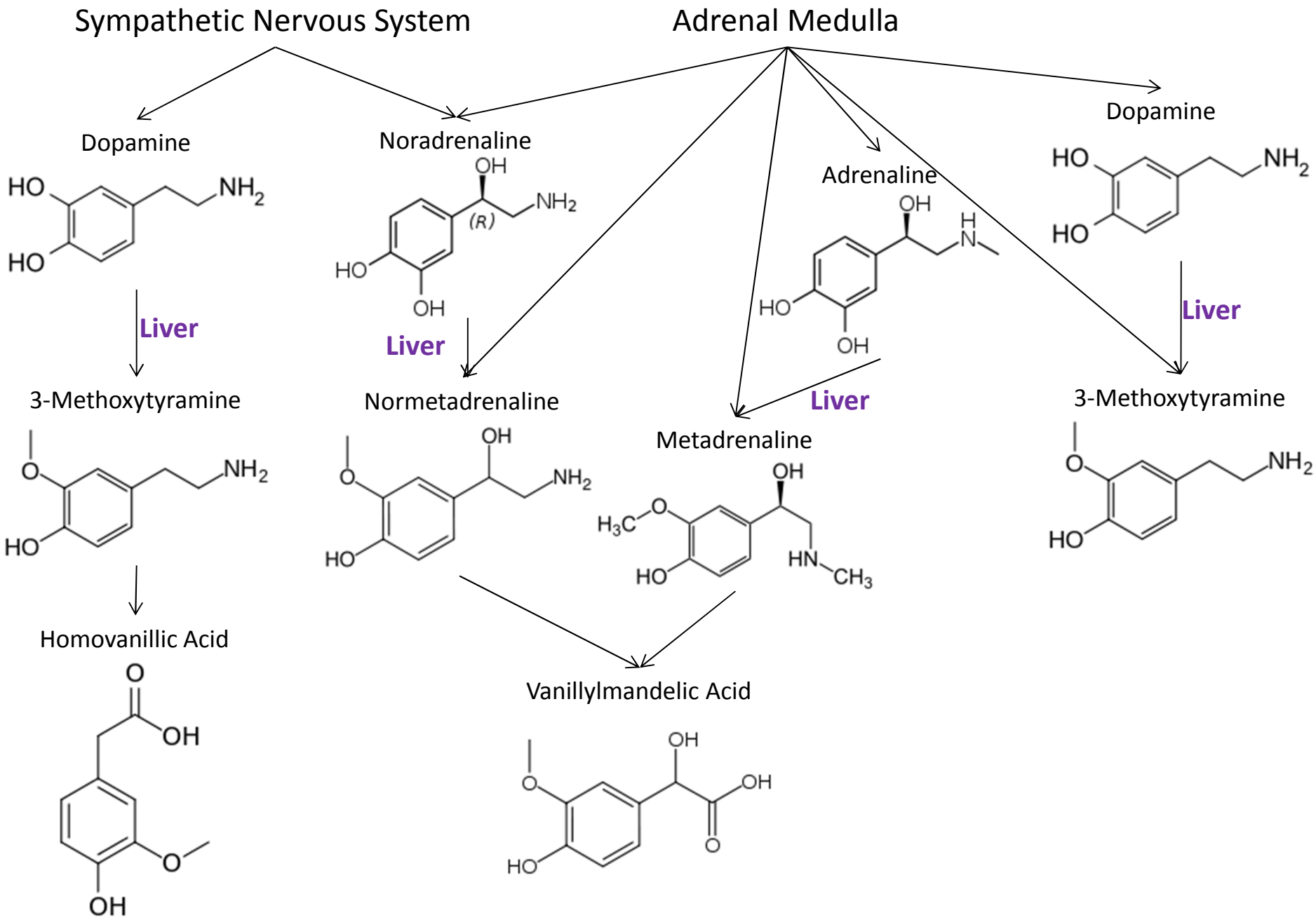


Origins of Catecholamines and Metadrenalines



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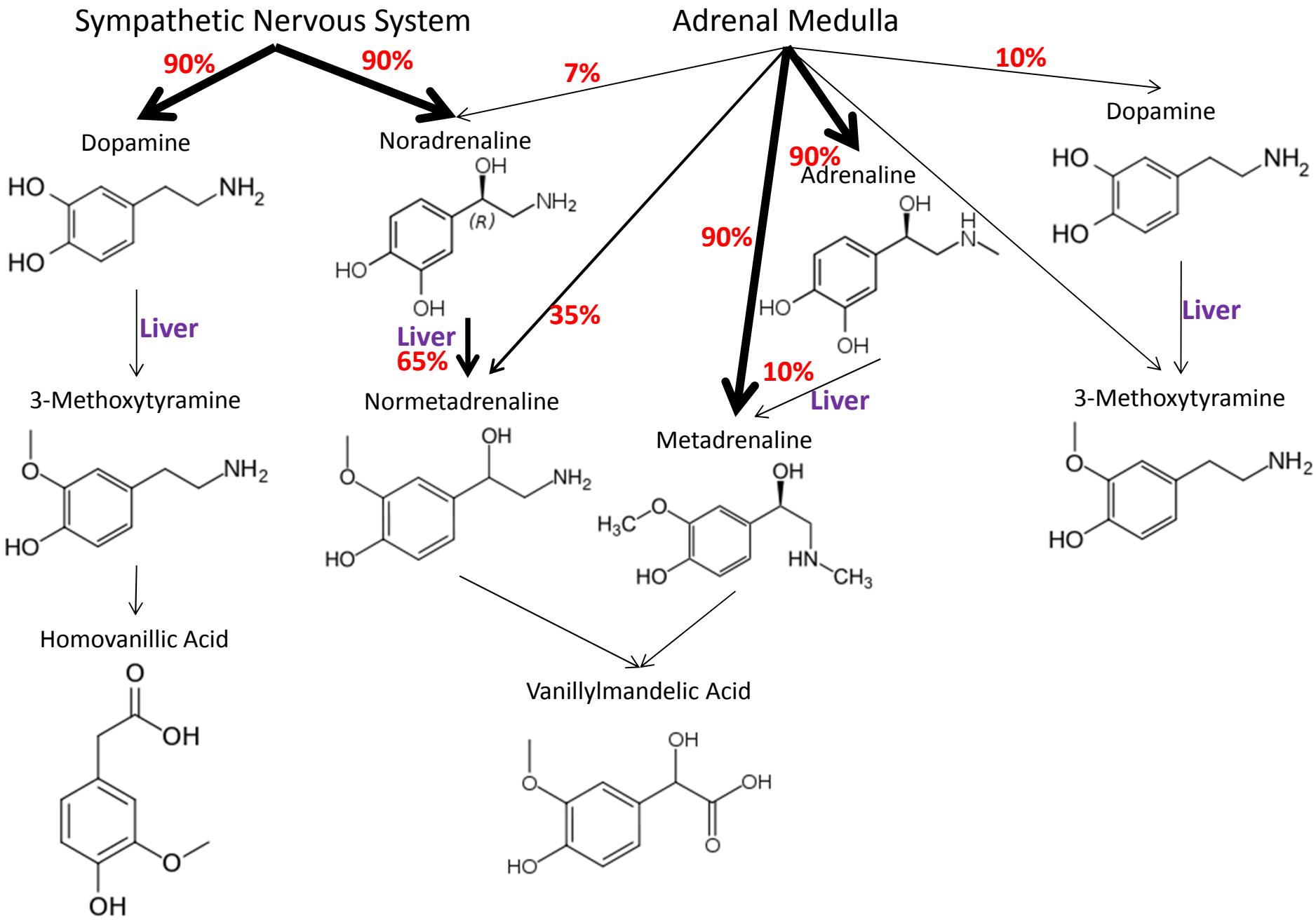
Understanding the biochemical rationale for investigation of phaeochromocytoma

Catecholamines (Ad/Nad/Dop) continuously leak from the chromaffin cells of the adrenal medulla and in a phaeochromocytoma into the cell cytoplasm. They are converted to metadrenalines (MetAd, NorMetad, and 3MT) resulting in a continuous release of metadrenalines, independent of catecholamine secretion. Catecholamines secreted by the adrenal medulla and a phaeochromocytoma are also metabolised to metadrenalines outside the adrenal medulla, and then further to vanillyl mandelic acid.

Sympathetic nerves secrete Nad and dopamine. Secretion of these is increased by stress and many drugs, leading to rapid fluctuations in plasma levels.

Production of catecholamines by a phaeochromocytoma shows considerable variation in levels released, depending on expression of adrenal enzymes. Most will predominantly produce Nad some will produce Nad and Ad, few produce predominantly Ad, and typically dopamine is a minor component (except in rare dopamine producing phaeochromocytomas and paragangliomas).

Origins of Catecholamines and Metadrenalines



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Understanding the biochemical rationale for investigation of phaeochromocytoma (2)

The adrenal medulla contributes about 90% of metadrenaline and 35% of normetadrenaline in plasma. For a phaeochromocytoma to become biochemically detectable, normetadrenaline would need to increase four-fold, whereas noradrenaline would need to increase 15 fold.

In a phaeochromocytoma, there is increased metabolism of catecholamines to metadrenalines, causing a large increment above basal in plasma free metadrenalines than plasma free catecholamines. Plasma metadrenalines may also be less prone to rapid fluctuations than plasma catecholamines. This contributes to the higher sensitivity and specificity of metadrenalines over catecholamines. Measurement of plasma free metadrenalines may be useful for differential diagnosis of phaechromocytoma in patients with renal failure, as the clearance is independent of renal function.

Phaeochromocytomas typically secrete catecholamines, but they continuously metabolise catecholamines to metadrenalines results in a continuous independent release of metadrenalines. Non-functioning, or silent tumours do not secrete sufficient amounts of catecholamines to become biochemically detectable, but they do synthesise and convert catecholamines to metadrenalines and this requires a smaller increase to become biochemically detectable. Therefore, some patients with phaeochromocytoma have elevated metadrenalines with normal catecholamines, or only show elevations in catecholamines during acute attacks.

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Understanding the biochemical rationale for investigation of phaeochromocytoma (3)

Metabolism of catecholamines to metadrenalines within a phaeochromocytoma shows a positive correlation with tumour size as measured by urinary total fractionated, or plasma free fractionated metadrenalines.

Total metadrenalines refers to the measurement of NorMet, MetAd and 3MT after a hydrolysis step that converts high concentrations of the conjugated metabolites into free metadrenalines. Fractionated metadrenalines refers to the chromatographic separation of metadrenalines to NorMet, MetAd and 3MT. Free catecholamine release from a phaeochromocytoma as measured by plasma or urinary catecholamines shows poor correlation with tumour size.

Plasma free dopamine is derived substantially from sympathetic nerves. Urine dopamine is excreted in amounts greater than can be accounted for my glomerular filtration, and is therefore produced renally. The source of dopamine sulphate is predominatly from the GI tract and may act as a physiological reservoir to provide active free dopamine to the kidney. Dopamine is a naturietic and may play a role in sodium homeostasis. A phaeochromocytoma, especially when located at an extra-adrenal site, may secrete dopamine only. It is therefore important that a screening test includes dopamine or its metabolite 3MT.

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Biochemical Diagnosis of a Phaeochromocytoma

An algorithm for sequential biochemical investigations for a phaeochromocytoma should be developed by each institution. Generally, the first line test recommended is 24 hour urine metadrenalines and this has been recommended at three international meetings on phaeochromocytoma due to high sensitivity. The higher the levels, the higher the probability of a phaeochromocytoma.

Traditionally 3 separate urine collections are made to allow for intermittent secretion of catecholamines and the inherent unreliability of 24 hour urine collections. Catecholamine secretion is lower during recumbency and sleep and is increased by physical activity and stress, so an overnight collection has been shown to have good sensitivity and specificity in screening for a phaeochromocytoma.

There is no gold-standard test available, which is why there are institutional differences in the approach to biochemical screening.

The prevalence of a phaeochromocytoma is low, therefore false-positive results exceed true-positive results. Assay sensitivity is high because it is an important diagnosis not to miss. Only after a possible sporadic phaeochromocytoma has been diagnosed biochemically is it cost effective to request imaging to identify the tumour site. The sensitivity of imaging is less than biochemical screening so cannot be used to rule out a phaeochromocytoma.

Assay Interference

	Urine						Plasma					
Physiological Interference	NA	A	D	NMA	MA	3MT	NA	A	NMA	MA	**Examples**	**Mechanism of Action**
Alpha Blocker (Selective)	■										Doxazosin, Tetrazosin, Prazosin	Block pre-synaptic α2-adrenoceptors, attenuates α receptor feedback inhibition
Alpha Blocker (Non-specific)	■			■			■		■		Phenoxybenzamine	
Beta Blocker	■	■		■	■					■	Atenolol, Propanolol, Oxprenolol	
Calcium Channel Blocker	■	■					■				Amlodipine, Diltiazem	Activate sympathetic nervous system
Tricyclic Antidepressant	■			■			■		■		Amitriptyline, Clomipramine, Dosulepin	Block NA re-uptake. In acute administration – suppress release of NA from sympathetic nerves (↓NA)
MAOI, Phenothiazines				■	■				■	■	Phenelzine, Isocarboazid	Block conversion of NA and A to DHPG
Sympathomimetic Factors	■	■		■	■		■	■	■	■	Methyphenidate, amphetamines, ephedrine	Activation of adrenergic receptors
Dopamine Agonists			■			■					L-DOPA	Metabolised by enzymes that also convert catecholamines
Stimulants	■	■					■	■			Caffeine, Nicotine	Activation of adrenergic receptors
Selective Serotonin Reuptake Inhibitors (SSRI)				■					■		Citalopram, Fluoxetine, Sertraline	Block NA re-uptake
Selective Noradrenaline Reuptake Inhibitors				■					■		Venlafaxine	Inhibit NA and A re-uptake
Centrally Acting anti-Hypertensive Drugs	■	■					■	■			A-Methyldopa	Metabolised by enzymes that also convert catecholamines
Analytical Interference												
Buspirone					■							
Paracetamol	■	■		■	■				■	■		

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Other causes of a raised Noradrenaline

Via stimulation of the sympathetic nervous system, the following factors can result in an increase in noradrenaline and dopamine:

- Physiological stress
- Illness
- Sleep apnoea
- Heart failure
- Surgery
- Cold exposure
- Exercise
- Myocardial infarction
- Insulin-induced hypoglycaemia
- Severe injury
- High protein meals
- Excessive Vitamin C intake
- Pregnancy
- Subarachnoid Haemorrhage

Phaechromocytoma: Diagnostic challenges for biochemical screening and diagnosis. Barron J Clin Pathol 2010;63:669-674

Pattern of Elevation of Urine Catecholamines in Intracerebral Haemorrhage. Hamann G et al. Acta Neurochir (Wien) 1995;132: 42-47

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Back to the case…

- 45 year old man
- Two slightly elevated urine noradrenaline
- One slightly elevated urine normetadrenaline
- One borderline elevated plasma normetadrenaline
- Clinically – Diabetic, hypogonadal, non-functioning pituitary adenoma

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On discussion at Endocrine MDT obtained further clinical history

- Mixed obstructive and central sleep apnoea
- Raised BP
- Overweight
- Anxious
- Medications
    - Gabapentin
    - Zopliclone
    - Etoricoxib
    - Lisinopril
    - Sustanon

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MIGB Scan – Normal

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Likely pseudopheo secondary to sleep apnoea.