Origin and anatomy of the adrenal medulla:

- The adrenal medulla consists of irregularly shaped cells called chromaffin cells grouped around blood vessels, ganglion cells & sustentacular cells.
- Medullary cells are derived from the embryonic neural crest (neuroectoderm) and, as such, are simply modified neurons.
- Differentiation of precursor cells is stimulated by Cortisol and nerve growth factor.
- Some cells migrate to form paraganglia.
- The largest paraganglion is called the organ of Zuckerkandl.
- These cells are part of the effector limb of the sympathetic N. S. innervated by thoracolumber axons.

Functions of the adrenal medulla:

- Together with the post – ganglionic sympathetic axons, they produce and store catecholamines (epinephrine and norepinephrine and dopamine)
- Catecholamines are stored in chromaffin vesicles.
- These catecholamines function as neurotransmitters and hormones.
- They are released into the blood stream through the adrenal vein.

Catecholamine Biosynthesis and metabolism:

- Tyrosine
- DOPA
- Dopamine
- Norepinephrine
- Epinephrine
- Metanephrine
- Vanillylmandelic acid
- Vanilmandelic acid
Location and Anatomy of the Adrenals

- Enzymes involved:
  - Synthesis: thyrosine hydroxylase (TH), DOPA decarboxylase, dopamine β-hydroxylase, phenylethanolamine-N-methyltransferase respectively.
  - Metabolism: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT).
  - Catecholamines in blood are also excreted by the kidney directly or by sulphoconjugation.

Cathecholamine action:
- The physiologic effects of epinephrine and norepinephrine are initiated by their binding to adrenergic receptors on the surface of target cells (α and β receptors).
- The main receptor subtypes affected are: α1 (vascular, vasoconstrictive), α2 (neuronal and vascular), β1 (cardiac, inotropic & chronotropic), β2 (vascular, vasodilatory).
- Common stimuli for secretion of adrenomedullary hormones include exercise, hypoglycemia, hemorrhage and emotional stress.

Physiologic Effects of Medullary Hormones
- Increased rate and force of contraction of the heart muscle.
- Constriction of blood vessels.
- Dilation of bronchioles.
- Stimulation of lipolysis in fat cells and glycogenolysis.
- Increased metabolic rate.

Pathophysiology
- Pathology within the adrenal medulla and the autonomic nervous system is primarily because of neoplasms.
- The most common is Pheochromocytoma occurring in the chromaffin cells.
- Neoplasms may also be of neuronal lineage, such as neuroblastomas and ganglioneuromas (Lau et al. 2006).

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<tr>
<th>Receptor</th>
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<tr>
<td>Alpha₁</td>
<td>Epinephrine, Norepinephrine</td>
<td>Increased free calcium</td>
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<tr>
<td>Alpha₂</td>
<td>Epinephrine, Norepinephrine</td>
<td>Decreased cyclic AMP</td>
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<tr>
<td>Beta₁</td>
<td>Epinephrine, Norepinephrine</td>
<td>Increased cyclic AMP</td>
</tr>
<tr>
<td>Beta₂</td>
<td>Epinephrine</td>
<td>Increased cyclic AMP</td>
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Dilation of the pupils: particularly important in situations where you are surrounded by velociraptors under conditions of low ambient light.

Inhibition of certain "non-essential" processes: an example is inhibition of gastrointestinal secretion and motor activity.
Location and Anatomy of the Adrenals

**Pheochromocytoma**

- Phaeochromocytoma is a chromaffin cell neoplasm that typically causes symptoms and signs from episodic catecholamine release, including paroxysmal hypertension.
- The diagnosis of phaeochromocytoma is typically made in the fourth or fifth decade of life without gender differences and incidence increase with age.

- About 90% of phaeochromocytomas exist as solitary, unilateral and encapsulated adrenal medullary tumours.
- The ‘rule of 10s’ is useful to recall approximate frequencies of pheochromocytoma that vary from the usual: 10% bilateral, 10% extra-adrenal, 10% malignant, 10% pediatric and 10% without blood pressure elevation (O’Connor, 2003).

**Etiology of pheochromocytomas**

- Familial phaeochromocytoma
- Multiple endocrine neoplasia (MEN) types 2A&B
- Hereditary neurofibromatosis, also known as von Recklinghausen’s disease,

**Clinical symptoms and signs of pheochromocytoma**

- The classical sign of phaeochromocytoma is hypertension, often labile or refractory to treatment.
- The classical triad of symptoms includes headache, diaphoresis and palpitations or tachycardia.
- Less common symptoms include anxiety, tremulousness, pain in the chest or abdomen, weakness or weight loss, Orthostatic hypotension, cholesterol gallstones

**Laboratory diagnosis of phaeochromocytoma**

- Typically, phaeochromocytoma is diagnosed by biochemical evidence of overproduction of catecholamines or their metabolites in plasma or urine samples.
- Urine tests measure free catecholamines and their metabolites (metanephrines and vanillylmandelic acid) in 24 hour urine samples and are usually highly specific.
- Blood test usually measure catecholamine concentrations but are less reliable since they are easily affected by stress.
- Normal resting plasma norepinephrine = 200 – 400 pg/ml and epinephrine = 20 – 60 pg/ml
- Plasma catecholamine ≥ 2000 pg/ml is diagnostic of pheochromocytoma
Location and Anatomy of the Adrenals

- Clonidine suppression test is usually done in cases where catecholamine measurements are equivocal (1000 – 2000 pg/ml).
- Catecholamine provocative tests such as the glucagon test are also used sometimes but they are quite dangerous.
- The location of the tumour(s) is crucial to plan the proper surgical route after catecholamine increase has been confirmed.

- The majority of these tumours can be visualized by one of three modalities:
  - computed tomography (CT),
  - magnetic resonance imaging (MRI) or
  - $^{[123]}I$-meta-iodobenzylguanidine (MIBG) scintigraphy.
- Ultrasound may also be utilized in cases where radiation must be minimized.

- Positron emission tomography (PET) using $^{[18]}F$-fluorodopamine,
- $^{[18]}F$-fluorodeoxyglucose,
- $^{[18]}F$-dihydroxyphenylalanine,
- $^{[1]}C$-hydroxyephedrine or
- $^{[1]}C$-adrenaline have been evaluated as improved localization techniques for undetectable phaeochromocytoma or metastases, but are not yet widely available (Ilias et al. 2003).

Pathophysiology and complications of phaeochromocytoma

- In addition to catecholamines, phaeochromocytomas also release a number of potentially vasoactive substances that may modify blood pressure or metabolism, such as calcitonin (O’Connor et al. 1983), serotonin, vasoactive intestinal polypeptide (Gozes et al. 1983), enkephalins (Parmer & O’Connor 1988), atrial natriuretic factor and somatostatin.

- Severe hyper- or hypotension, encephalopathy and lactic acidosis are also common.
- Congestive heart failure also occurs in some cases.
- These complications are usually reversed after surgical intervention.

Treatment of phaeochromocytoma

- After the diagnosis of phaeochromocytoma has been made, sufficient adrenergic alpha-blockade should be implemented for 1–4 weeks prior to surgical intervention to control blood pressure.
- Alpha-blockade is usually accomplished with oral phenoxybenzamine,
- doxazosin (at 2–8 mg once daily) or prazosin (at 0.5–16 mg per day), may be used (O’Connor, 2003).
Location and Anatomy of the Adrenals

• The beta-1-selective antagonists atenolol (50–100 mg daily) or metoprolol (50–200 mg daily) or the combined alpha/beta-antagonist labetalol (100–400 mg daily) may be effective. In subjects with contraindications to beta-blockade, lidocaine or amiodarone can be used for tachyarrhythmias.
• the tyrosine hydroxylase inhibitor alpha-methylparatyrosine can be added at an oral dose of 0.25–1.0 g four times daily.

• For intra-operative blood pressure surges, intravenous nitroprusside is often used. Alternatively, acute alpha-blockade can be accomplished with intravenous phentolamine. The calcium channel antagonist nicardipine has also been used.

• Malignant phaeochromocytoma
• Although most phaeochromocytomas are typically well-encapsulated, localized benign growths, approx. 5–10% are malignant, which is more common among extra-adrenal tumours. Because histopathology is not reliable, malignancy is diagnosed by distant metastatic spread of the tumour, commonly to the bone, lung, lymph nodes or liver.
• Increased plasma DOPA is usually an indication of malignancy.

• Catecholamine deficiency disease states
• Congenital absence of the adrenal cortex may cause a developmental absence of the adrenal medulla.
• Loss of both adrenal glands seldom produces a catecholamine deficiency state.
• Deficiency states are rare and also common in diabetics receiving insulin
• Congenital deficiency of dopamine beta hydroxylase has also been observed

• Incidentalomas also occur in some individuals but are hardly life threatening and disappear without treatment.

Conclusion
• Diseases of the adrenal medulla and chromaffin cells are fortunately rare and few in number, but they are potentially life threatening.
• Diagnosis requires a high index of suspicion and careful workup to rule out other sources of elevated catecholamines prior to diagnosis.
References

