Objectives

- Describe the major clinical features and pathology of common diseases of the adrenal gland and parathyroid gland

Outline

I. Adrenal Gland

a. **Basic histology:** *Adrenal cortex, Adrenal medulla*
b. **Adrenocortical hyperfunction:** *Hypercortisolism, Hyperaldosteronism, Adrenogenital / virilizing syndromes*
c. **Adrenocortical insufficiency:** *Primary (acute vs chronic), Secondary*
d. **Adrenocortical neoplasms:** *Adenoma, Carcinoma*
e. **Adrenal medulla neoplasms:** *Pheochromocytoma*

II. Parathyroid Gland

a. **Basic histology and function**
b. **Hyperparathyroidism:** *Primary, Secondary, Tertiary*
c. **Hypoparathyroidism**

References

Kumar V, Abbas A, Aster J. *Robbins & Cotran Pathologic Basis of Disease*. 10th ed.

***Note**: Pathweb Study Notes are based on the key topics covered in the lectures in the Yong Loo Lin School of Medicine, as well as additional topics covered in major texts. For more comprehensive discussion on specific pathology topics, readers are advised to refer to the recommended texts in your respective courses.*

I. ADRENAL GLAND

Basic histology

- Combined weight of both adrenal glands in the adult: approximately 10 g
- Adrenal cortex: 3 zones –
    - Zona glomerulosa: secretes mineralocorticoids (e.g. aldosterone)
    - Zona fasciculata (~75%): secretes glucocorticoids (e.g. cortisol)
    - Zona reticularis: secretes sex steroids (e.g. oestrogens and androgens)
- Adrenal medulla: chromaffin cells that secrete catecholamines (e.g. epinephrine)

Adrenocortical hyperfunction (hyperadrenalism)

Syndrome	Features
Hypercortisolism (Cushing syndrome)	Elevated glucocorticoid levels **Clinical features / consequences**: Central adipose deposition (truncal obesity, moon facies, buffalo hump), proximal muscle weakness and wasting, metabolic disturbances (hypertension, diabetes), catabolic effects (skin thinning, poor wound healing, osteoporosis), immunosuppression
	Causes: - **Exogenous** i.e. iatrogenic. Most common cause - **Endogenous**: o ACTH-dependent (70-80%): **ACTH-secreting pituitary adenoma (60-70%)**: Cushing disease **Ectopic ACTH**: e.g. from small cell lung carcinomas, carcinoids o ACTH-independent (20-30%): **Adenoma** (10-20%) **Carcinoma** (5-7%): produces greater hypercortisolism vs adenomas/hyperplasia **Hyperplasia**: macro or micronodular; rare
	Gross: - **Pituitary gland**: Cytoplasmic changes (Crooke hyaline change) due to high levels of glucocorticoids - **Adrenal gland**: Depending on cause – o Exogenous glucocorticoids: suppresses endogenous ACTH → bilateral cortical atrophy o Endogenous hypercortisolism: either diffuse hyperplasia, nodular cortical hyperplasia or adenoma / carcinoma
Hyperaldosteronism	Chronic excess aldosterone secretion **Clinical features / consequences**: Secondary hypertension (most common cause); hypokalemia from renal potassium wasting
	Causes: - **Primary**: Autonomous overproduction of aldosterone o **Bilateral idiopathic hyperaldosteronism** (60%), usually sporadic o **Adrenocortical neoplasm**: adenoma (Conn syndrome - 35%); rarely carcinoma o **Familial hyperaldosteronism** (5%) - **Secondary**: Aldosterone secretion in response to activation of the renin-angiotensin system (RAAS) due to extra-adrenal causes o **Decreased renal perfusion** (e.g. renal artery stenosis)

	○ **Arterial hypovolemia** (e.g. congestive heart failure)
Adrenogenital or virilizing syndromes	Excess secretion of dehydroepiandrosterone and androstenedione, that are converted to testosterone in peripheral tissues **Clinical features**: Depending on cause, can manifest in perinatal period, childhood or adulthood. Neonates with ambiguous genitalia, masculinisation in females and precocious puberty in prepubertal males. May also result in salt (sodium) wasting
	Causes: - **As part of Cushing disease** (ACTH-secreting pituitary adenoma): because ACTH regulates adrenal androgen formation unlike gonadal androgens - **Adrenocortical neoplasms**: more likely to be androgen-secreting adrenal carcinomas than adenomas - **Congenital adrenal hyperplasia (CAH)**: most common genetic cause is 21-hydroxylase deficiency (*CYP21A2* mutations)

Adrenocortical insufficiency

Type	
Primary acute adrenocortical insufficiency (adrenal crisis)	**Causes**: - Acute stress requiring an immediate increase in steroid output in patients with chronic adrenocortical insufficiency (see below) - Rapid withdrawal of steroids in patients taking exogenous corticosteroids (adrenal glands have become atrophic due to negative feedback) - Massive adrenal haemorrhage that damages the adrenal cortex sufficiently (e.g. in Waterhouse-Friderichsen syndrome in disseminated bacterial infection)
Primary chronic adrenocortical insufficiency (Addison disease)	**Clinical features**: Insidious onset with initial non-specific manifestations e.g. fatigue and weakness. Decreased glucocorticoid and mineralocorticoids also result in hypoglycemia, hyperkalemia, hyponatremia etc. Can have hyperpigmentation of sun-exposed skin and pressure areas e.g. neck, elbows, knees, due to raised pro-opiomelanocortin (POMC – precursor of ACTH and melanocyte-stimulating hormone) secreted from the anterior pituitary in response to primary adrenal insufficiency
	Causes: Progressive destruction of the adrenal cortex by causes including – - **Autoimmune adrenalitis**: e.g. as part of an autoimmune polyendocrinopathy like APS-1 - **Infections**: e.g. tuberculosis, fungal - **Metastatic neoplasms**: e.g. lung or breast carcinomas, if they destroy enough adrenal cortex to produce insufficiency - **Genetic causes**: e.g. congenital adrenal hypoplasia, adrenoleukodystrophy
Secondary adrenocortical insufficiency	Hypoadrenalism resulting from disorders of the hypothalamus and pituitary that cause decreased ACTH secretion **Clinical features**: Unlike Addison disease, no hyperpigmentation or manifestations from decreased aldosterone synthesis are seen
	Causes: - Metastatic cancer, infection, infarction or irradiation damage of the hypothalamus / pituitary - As part of panhypopituitarism

Adrenocortical neoplasms

- Tumour arising from the adrenal cortex; less common than metastases to the adrenal cortex
- **Clinical features**: Adenomas and carcinomas are equally frequent in adults; carcinomas predominate in children. Not all adrenocortical neoplasms are functioning (carcinomas are more likely to be functional than adenomas; adenomas are more often incidental imaging or autopsy findings); functioning adenomas are more likely to be associated with hyperaldosteronism and Cushing syndrome, while a virilizing neoplasm is more likely to be a carcinoma
- **Pathogenesis**:
    - **Sporadic**: Majority
    - **Familial cancer syndromes**: Li-Fraumeni syndrome (*TP53* mutations), Beckwith-Wiedemann syndrome

	Gross	Micro
Adrenocortical adenoma	Well-circumscribed solitary nodule with yellow-brown cut surface (due to lipid). Adjacent cortex may be atrophic if the nodule is functional	Cells resemble those in the normal adrenal cortex; low proliferative index
Adrenocortical carcinoma	Usually large invasive poorly demarcated lesions with variegated cut surface	Cells can resemble those in normal adrenal gland or can be markedly pleomorphic; high proliferative index

Adrenal medulla neoplasms – Pheochromocytoma

- Tumour of chromaffin (neuroendocrine) cells that synthesize and secrete catecholamines; those that arise outside the adrenal are called paragangliomas
- **Clinical features**: 'Rule of 10s' - 10% of sporadic tumours are bilateral, 10% are malignant, 10% are not associated with hypertension. Of the 90% of patients presenting with hypertension, majority have paroxysmal episodes (i.e. abruptly elevated blood pressure associated with tachycardia, palpitations etc., induced by a sudden release of catecholamines). Up to 25% are associated with familial syndromes (e.g. MEN2, NF1, VHL) – in these cases, tumours are more often bilateral and occur at a younger age. **Complications**: Catecholamine cardiomyopathy (myocardial infarction, congestive heart failure and ventricular arrhythmias). **Clinical course**: Isolated benign tumours can be surgically excised after medication with adrenergic-blocking agents to prevent a hypertensive crisis. Definitive malignancy is only diagnosed in the presence of metastases rather than any single histologic feature
- **Gross**: Can be small circumscribed and yellow-tan, or large and haemorrhagic with necrosis and cystic change. Remnant adrenal gland is often attached at one edge or stretched over the tumour
- **Micro**: Classically, the chromaffin cells are arranged in nests and surrounded by sustentacular cells and a richly vascularised thin stroma

II. PARATHYROID GLAND

Endocrine organ that secretes parathyroid hormone (PTH) and is important in the regulation of calcium. Tumours usually result in functional abnormalities (hyperparathyroidism) – e.g. parathyroid adenoma is the commonest cause of primary hyperparathyroidism.

Basic histology

- Normal parathyroid glands usually measure between 3-5 mm in size and weigh between 30 – 60 mg each
- Two cell types:
    - **Chief cells**: Majority cell; have secretory granules containing PTH
    - **Oxyphil cells**: Scattered singly or in small clusters; contain abundant mitochondria and glycogen
- Amount of intraglandular stromal fat increases to approximately 30% of the gland from childhood to ~25 years of age, then plateaus

Function

- Regulates calcium homeostasis through the activity of PTH
    - Increased renal tubular reabsorption of calcium
    - Increased conversion of vitamin D to its active dihydroxy form in the kidney → increase GI calcium absorption
    - Increased urinary phosphate excretion → decreases serum phosphate and increases calcium (since phosphate binds to ionized calcium)
    - Enhanced osteoclastic activity → increase bone resorption thereby releasing ionized calcium
- The net increase in calcium inhibits further PTH secretion (negative feedback loop)

Hyperparathyroidism (elevated PTH)

Type	Features
Primary hyperparathyroidism	*Autonomous overproduction of PTH. Most common cause of asymptomatic hypercalcemia* **Clinical features**: F:M = 4:1; usually middle-aged or older adults. Asymptomatic (incidental finding) or symptomatic ("painful bones, renal stones, abdominal groans and psychic moans")

	Causes:
	- **Adenoma** (85-95%): sporadic or familial (e.g. MEN1, MEN2, MEN 4 syndrome)
	  ○ **Gross**: Usually solitary, circumscribed, soft, tan-reddish-brown nodule with thin capsule; the other 3 parathyroid glands appear normal or atrophic due to negative feedback
	  ○ **Micro**: Mainly chief cells, fewer oxyphil cells, no stromal fat unlike normal parathyroid gland
	- **Primary hyperplasia** (5-10%): sporadic or familial (e.g. MEN syndrome)
	  ○ **Gross**: Usually all 4 glands enlarged but may be asymmetric
	  ○ **Micro**: Usually diffuse or nodular chief cell hyperplasia, no stromal fat unlike normal parathyroid gland

	- **Parathyroid carcinoma** (1%)
	  ○ **Gross**: Solitary, can be circumscribed or have irregular borders
	  ○ **Micro**: Can be indistinguishable from adenoma, requires invasion of surrounding tissues and/or metastasis to diagnose malignancy

	Consequences: - **Skeletal abnormalities**: Osteoporosis (due to increased osteoclast activity), brown tumour (mass of reactive tissue due to microfractures and haemorrhage resulting in reparative fibrous tissue), osteitis fibrosa cystica (hallmark of severe parathyroidism, resulting from a combination of increased osteoclast activity, peritrabecular fibrosis and cystic brown tumours) - **Urinary tract stones** (nephrolithiasis) and **renal calcification** (nephrocalcinosis) - **Effects of hypercalcemia** e.g. Metastatic calcifications in the stomach, heart and blood vessels; GI abnormalities including pancreatitis; CNS disturbances including depression, lethargy; Neuromuscular abnormalities e.g. weakness and fatigue
Secondary hyperparathyroidism	*Increased compensatory production of PTH secondary to conditions that cause chronic hypocalcemia* **Clinical features**: Usually dominated by the cause (e.g. renal failure); skeletal abnormalities tend to be milder vs primary hyperparathyroidism
	Causes: Renal failure (most common – may be related to hyperphosphatemia from decreased phosphate excretion thereby lowering serum calcium levels, or decreased renal synthesis of active vit D. Phosphate binders and/or dietary vit D supplementation may help); vit D deficiency etc.
	Gross: Parathyroid gland hyperplasia
Tertiary hyperparathyroidism	*Excessive (quasi-autonomous) secretion of PTH after longstanding secondary hyperparathyroidism* Results in hypercalcemia and often requires surgery to remove one or more parathyroid glands

Hypoparathyroidism (decreased PTH)

- Much less common compared to hyperparathyroidism
- **Causes**: Acquired (post-surgical removal, intentionally or otherwise) or genetic (e.g. in autoimmune hypoparathyroidism – APS-1; congenital absence as part of DiGeorge syndrome)
- **Consequences**: Depends on the severity and duration of the resultant hypocalcemia e.g. tetany (neuromuscular irritability), alterations in mental status, paradoxical calcification in the brain and lens (may be related to increased phosphate levels), dental abnormalities
- **Pseudo-hypoparathyroidism**: due to end-organ resistance to PTH effects (PTH levels are actually normal or elevated), usually from genetic defects affecting the G-protein-coupled receptors