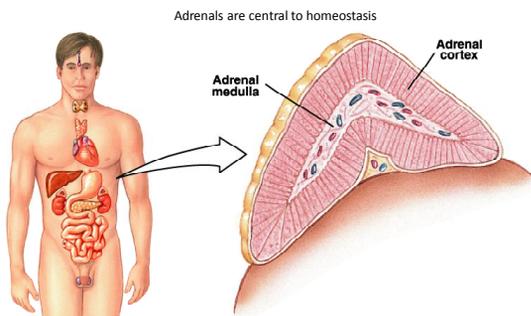


The Adrenals

anatomy and physiology

V. Interná klinika LF UK a UN, Bratislava



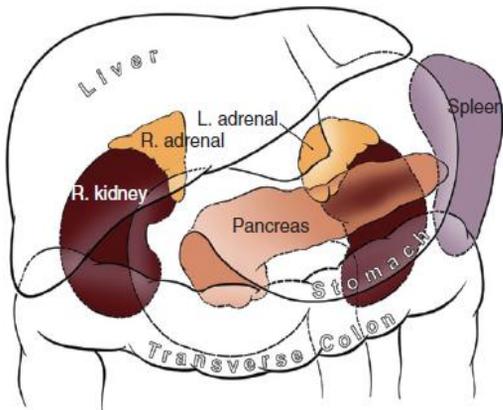
HISTORICAL BACKGROUND

- Distinguished anatomists such as Galen, da Vinci, and Vesalius omitted the adrenal glands in their descriptions of the retroperitoneum.
- Bartholomaeus Eustachius was the first to describe them in mid-16th century
- In mid-19th century Thomas Addison, an English physician, described a series of patients with the condition of adrenal insufficiency that now carries his name
- Charles Brown-Sequard, through a series of animal experiments demonstrated that bilateral adrenalectomy uniformly resulted in death, suggesting that the adrenals were indispensable to the survival of the host
- William Osler was the first to report treatment of Addison disease with hormonal replacement in 1896. He administered crude extract from adrenals of pigs to a patient with Addison disease and produced significant weight gain in this one individual
- In the ensuing half-century "adrenalin" was discovered, and its production was localized to the adrenal medulla (Oliver and Sharpey-Schafer, 1895).

HISTORICAL BACKGROUND

- The ability of adrenaline to produce a sustained rise in blood pressure was subsequently determined (Abell and Crawford, 1897). Moreover, the failure of this substance, later termed "epinephrine" to sustain life following bilateral adrenalectomy underscored the complexity and multifunctionality of the adrenal gland and established Addison disease as an ailment of the adrenal cortex (Scott, 1990; Porterfield et al, 2008).
- Discovery and isolation of cortisol from the adrenal gland in the 1930s and subsequent work on its use to treat rheumatoid arthritis produced a 1950 Nobel Prize in Physiology and Medicine for Edward Kendall, Philip Hench, and Tadeus Reichstein (Scott, 1990).
- Aldosterone was ultimately isolated from the bovine adrenal in 1952 (Grundy et al, 1952).
- The latter part of the 20th century witnessed a rapid transformation in our understanding and treatment of adrenal disorders lead by pioneers such as Jerome Conn, Lawson Wilkins, Grant Liddle, and Earl Sutherland

ANATOMY



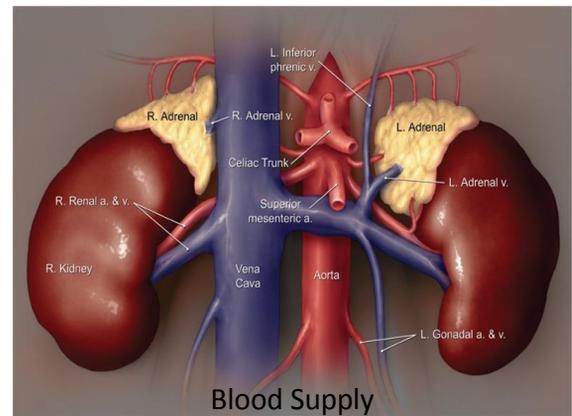
Blood supply

Arterial Supply

- 3 arterial sources of flow:
 - Branches from Inferior Phrenic Artery → Superior Adrenal A.
 - Direct visceral branches from Aorta → Middle Adrenal A.
 - Branches from Renal Artery → Inferior Adrenal A.
- The main adrenal arteries → branch to form a subcapsular plexus
- From subcapsular plexus
 - Some branches continue directly → to medulla
 - Others form sinusoids → to cortex

Venous Drainage:

- Medullary veins coalesce to form adrenal vein
- Adrenal vein is surrounded by medullary tissue within the gland.
- Single main vein on each side
- Most important surgical structure
- Right adrenal vein
 - Short
 - Drains directly into post IVC
- Left adrenal vein
 - Long as compared to right adrenal vein
 - Joined by Inferior Phrenic vein prior to draining into Left Renal Vein
- The overlapping of both arterial and venous anatomy makes partial adrenalectomy possible with little risk of subsequent adrenal infarction



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Nerve Supply

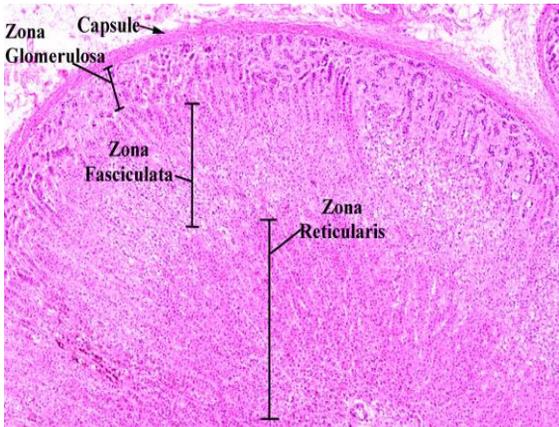
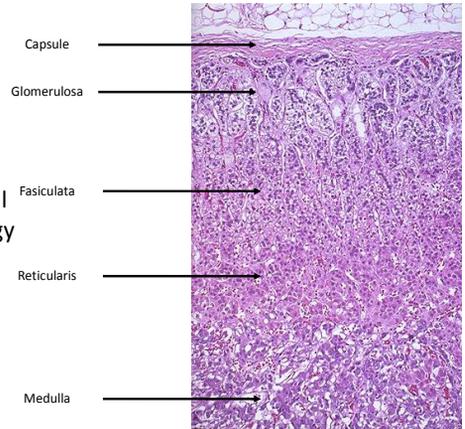
- Sympathetic
 - Medulla
 - Preganglionic sympathetic fibers from sympathetic trunk directly to chromaffin cells
 - Cortex
 - Postganglionic fibers from splanchnic ganglia
- Parasympathetic to adrenal cortex and medulla
 - Not well defined
 - Branches from Vagus nerve **may be** present

HISTOLOGY

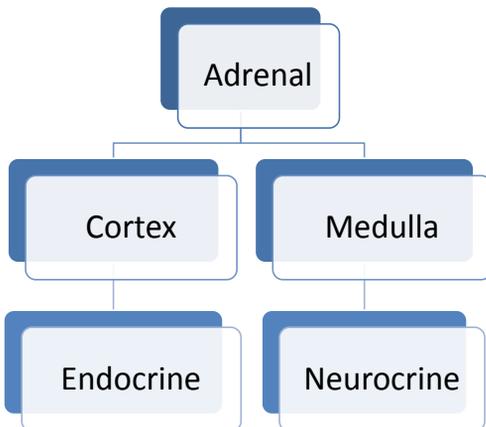
Histology

- Each adrenal gland is enclosed within a fibrous capsule
- Directly beneath the capsule is the **cortex**, which comprises three zones:
 - **Zona Glomerulosa** (Outermost Layer)
 - Small polyhedral cells with scant eosinophilic cytoplasm and dark round nuclei.
 - **Zona Fasciculata**
 - Broad layer of large pale cells arranged in vertical columns beneath glomerulosa
 - **Zona Reticularis** (Innermost layer)
 - Round dark staining cells

Adrenal Histology



ADRENAL PHYSIOLOGY



ADRENAL PHYSIOLOGY - CORTEX

Adrenal Cortex: Steroid Hormone Production

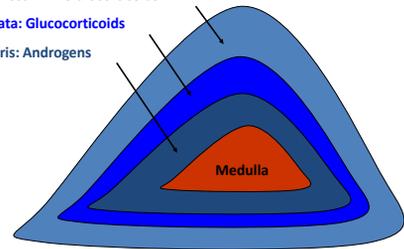
- Hormones produced by the adrenal cortex are referred to as corticosteroids
- These comprise
 - Mineralocorticoids (Aldosterone)
 - Glucocorticoids (Cortisol)
 - Sex hormones (Androgens)
- Synthesized from cholesterol–steroid ring

Adrenal Cortex

Zona Glomerulosa: Mineralocorticoids

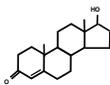
Zona Fasciculata: Glucocorticoids

Zona Reticularis: Androgens

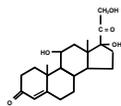


Hormones of the Adrenal Cortex

- All adrenal cortex hormones are steroid



testosterone



cortisol

- **Not stored** - synthesized as needed

Zona Glomerulosa (ZG)

- Outermost region of adrenal cortex - just below the adrenal capsule
- Secretes Mineralocorticoids. The naturally synthesized Mineralocorticoid of most importance is Aldosterone.
- Aldosterone = 1^o human Mineralocorticoid
- Only zone of adrenal gland that contains enzyme Aldosterone synthase (CYP11B2). As a result → sole source of Aldosterone
- Mineralocorticoids are aptly termed as they are involved in regulation of electrolytes in ECF.

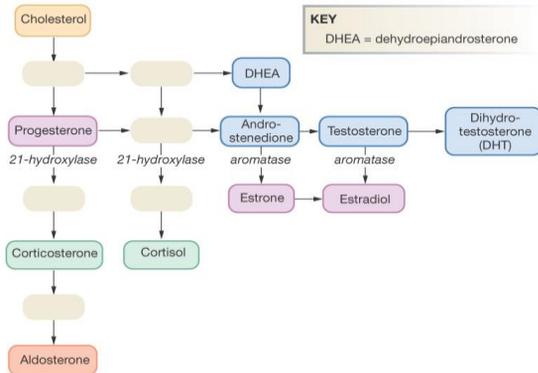
Zona Fasciculata (ZF)

- Middle zone – between the glomerulosa and reticularis
- Site of Glucocorticoid production due to expression of 17 α -hydroxylase, 21 hydroxylase, and 11 β -hydroxylase enzymes
- Primary secretion is Glucocorticoids. Glucocorticoids, as the term implies, are involved in the increasing of blood glucose levels. However they have additional effects in protein and fat metabolism.
- Cortisol = 1^o Glucocorticoid in humans
- Its secretion is under tight control of ACTH. Production of cortisol by adrenal follows a strict circadian schedule. Majority of cortisol is secreted in the early morning
- Glucocorticoids are essential to life and modulate complex physiologic pathways that include metabolism, immunity, maintenance of intravascular volume, regulation of blood pressure, and complex modulation of CNS with significant effects on mood, sleep, and potentially memory
- Cortisol and ACTH are a part of a classic hormonal negative feedback system that features hypothalamus, pituitary gland and adrenal.
- Some androgen synthesis also occurs in zona fasciculata

Zona Reticularis (ZR)

- Innermost zone of adrenal cortex – between fasciculata and medulla
- Primary secretion is androgens.
- Presence of 17 α -hydroxylase and 17,20-lyase → production of Dehydroepiandrosterone (DHEA), sulphated DHEA (DHEA-S) and Androstenedione
- Adrenal Androgens exhibit ~ same effects as male sex hormone (testosterone).
- Adrenal Androgen secretion appears to be under control of ACTH, and, like cortisol, exhibits circadian patterns
- DHEA, DHEA-S, and Androstenedione comprise the greatest portion of steroid hormone that is produced by the adrenals (>20 mg/day), but appear to be the least important for adult physiologic homeostasis
- However, pharmacologic manipulation of adrenal androgen production remains a viable and increasingly targeted strategy for advanced prostate cancer
- NB.: Overlap in secretions of Androgens and Glucocorticoids exist b/w ZF and ZR

Adrenal Cortex: Steroid Hormone Production



ADRENAL PHYSIOLOGY - MEDULLA

Adrenal Medulla

- Adrenal medulla comprises less than 10% of total adrenal mass.
- Embryologically derived from pheochromoblasts (Neuroectoderm)
- Differentiate into modified neuronal cells
 - More gland than nerve
 - Chromaffin cells

Functions of Adrenal Medulla

- It is an integral part of autonomic nervous system (extension of Sympathetic NS)
- Acts like sympathetic ganglion (**Acts as a peripheral amplifier**)
- Activated by same stimuli as the sympathetic nervous system (examples – exercise, cold, stress, hemorrhage, etc.)
- Chromaffin cells of medulla are innervated by preganglionic sympathetic fibers of T₁₁ to L₂, making them analogous to cells of the sympathetic ganglia.

- Medulla secretes
 - Epinephrine (80%)
 - Norepinephrine (19%)
 - Dopamine (1%)
- These substances, collectively known as catecholamines, are produced from the amino acid tyrosine and modulate the systemic stress response. Hormones are secreted and stored in medulla and released in response to appropriate stimuli
- Effects of these catecholamines are mediated through their binding to Adrenoreceptors located on target organs. The nature of these effects depend on the adrenoreceptor subtypes located and stimulated on a particular end organ
- Enzyme phenylethanolamine-Nmethyl transferase (PNMT), which catalyzes the conversion of norepinephrine to epinephrine, is relatively unique to the adrenal medulla (the brain and organ of Zuckerkandl also express this enzyme).

- Important for clinical purposes :
 - 3 metabolites
 - Metanephrine
 - Normetanephrine
 - Vanillyl Mandelic Acid
 - 2 enzymes
 - Catechol-O-Methyl Transferase (COMT)
 - Mono Amine Oxidase (MAO)
- Methylation of Epinephrine by COMT = Metanephrine
- Methylation of Norepinephrine by COMT = Normetanephrine

COMT:

- Large amounts present in the liver and kidneys
- Majority of adrenal catecholamine metabolites are methylated by COMT within the cells of the adrenal medulla
- > 90% of Metanephrine and ~ 20% of normetanephrine in blood stream are derived from the adrenal medulla.
- Therefore a measurable rise in the level of these metabolites is very useful when diagnosing potential pheochromocytoma.
- In the urine, the majority of these metabolites are excreted in a sulfonated form.

MAO:

- MAO and other enzymes subsequently convert catecholamine metabolites to VMA
- VMA is the primary catecholamine metabolic end product, VMA is largely formed by liver
- Nonadrenal catecholamines from sympathetic nervous system are also similarly converted to VMA

Aldosterone

- Exclusively synthesized in ZG
- Essential for life

Functions of Aldosterone

- Regulates electrolyte metabolism by stimulating epithelial cells of distal nephron to reabsorb Na^+ and Cl^- , while secreting H^+ and K^+
- Promotes Sodium retention and Potassium elimination by kidney
- Expands ECF volume
- Aldosterone exerts the 90% of the Mineralocorticoid activity. Cortisol also have Mineralocorticoid activity, but only 1/400th that of Aldosterone
- Aldosterone increases renal tubular (principal cells) reabsorption of sodium & secretion of potassium
- Although Aldosterone levels have a profound effects on total body Na^+ , concentration of the ion does not change, whereas reabsorption of sodium is accompanied by reuptake of free water. Therefore Aldosterone primarily affects total body volume and not sodium concentration

Detailed Physiology

HORMONES OF CORTEX

Aldosterone

Functions contd..

- Excess Aldosterone \uparrow ECF volume & arterial pressure, but has only a small effect on plasma sodium concentration
 - Increased extracellular K^+
 - Decreased osmolarity
 - ACTH
- Excess Aldosterone causes hypokalemia & muscle weakness
- Excess Aldosterone increases tubular (intercalated cells) hydrogen ion secretion, with resultant mild alkalosis
- Aldosterone stimulates sodium & potassium transport in sweat glands, salivary glands, & intestinal epithelial cells

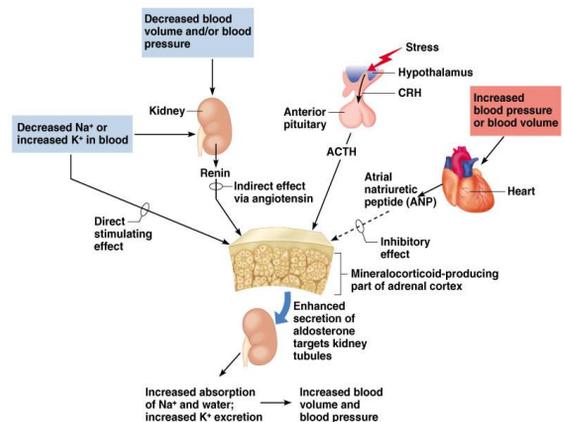
Aldosterone

Regulation of Aldosterone secretion:

- Primarily regulated by
 - Angiotensin II through Renin-angiotensin-aldosterone system (RAAS)
 - Directly by serum potassium levels
- Primary stimulus for release of Aldosterone is **Angiotensin II**
- Other: ACTH, low serum Na, elevated K, JGA via low kidney perfusion
- Rise in ACTH can also increase Aldosterone (much less potent stimulus).
- Inhibitory regulators:
 - ANP = main inhibitor, providing an imp link b/w cardiac, adrenal and renal function
 - Somatostatin, dopamine, and others may also play a role

Regulation of Aldosterone Release

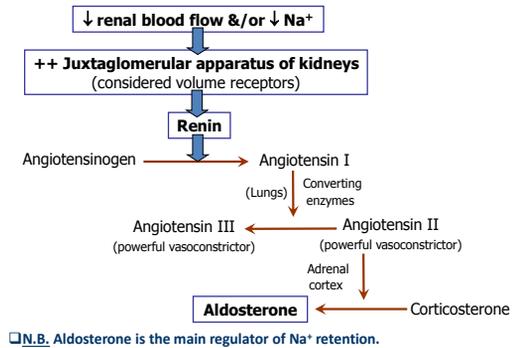
- Direct stimulators of release
 - Increased extracellular K^+
 - Decreased osmolarity
 - ACTH
- Indirect stimulators of release (RAAS)
 - Decreased blood pressure
 - Decreased macula densa blood flow



RAA Axis

- Principal factor controlling Angiotensin II levels = Renin
- Decreased circulating volume stimulates Renin release via:
 - Decreased BP (Symp effects on JGA).
 - Decreased [NaCl] at macula densa (“NaCl sensor”)
 - Decreased renal perfusion pressure (“renal” baroreceptor)

• Renin-Angiotensin System:



Aldosterone: Role in Diseases

- Complete failure to secrete Aldosterone leads to death (dehydration, low blood volume).
- Hyperaldosterone states: Contribute to hypertension associated with increased blood volume.

GLUCOCORTICOIDS - CORTISOL

Cortisol

- Glucocorticoids (including cortisone and cortisol)
- Steroid hormone
 - Plasma bound to corticosteroid binding globulin (CGB) or transcortin
 - Essential for life (long term)
 - The net effects of cortisol are catabolic
 - Prevents against hypoglycemia
 - Produced in the middle layer of the adrenal cortex - ZF
 - Promote normal cell metabolism
 - Help resist long-term stressors
 - Released in response to increased blood levels of ACTH

Physiological Actions of Cortisol

- Promotes Gluconeogenesis
- Promotes breakdown of skeletal muscle protein
- Enhances fat breakdown (Lipolysis)
- Breakdown of bone matrix (high doses)
- Suppresses immune system
- Anti-inflammatory Effects of Cortisol
 - Reduces phagocytic action of white blood cells
 - Reduces fever
 - Suppresses allergic reactions

Physiological Actions of Cortisol

Effect on Blood Cells and Immunity

- Decrease production of eosinophils and lymphocytes
- Suppresses lymphoid tissue systemically therefore decrease in T cell and antibody production thereby decreasing immunity

Effect of cortisol on protein metabolism

- Reduction of protein storage in all cells except those of liver – ↑ protein catabolism & ↓ protein synthesis
- Cortisol increases liver & plasma proteins
- Mobilizes amino acids from non hepatic cells, thus increase blood amino acid level.
- ↑ amino acid transport to liver cells & ↓ transport of amino acids into other cells

Physiological Actions of Cortisol

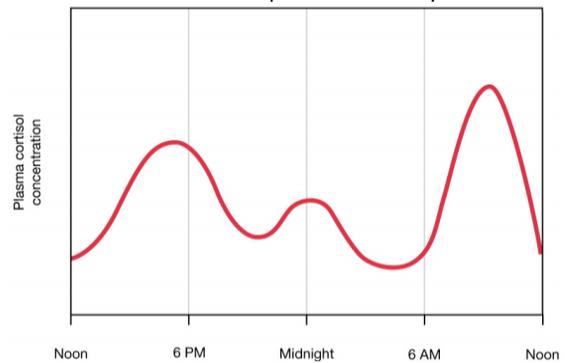
Permissive Effects of Cortisol on Development

- Cortisol is required for normal development
- Permissive role in final maturation of many organs
- Required for synthesis of digestive enzymes, surfactant
- Required for skeletal growth in children
- Circadian rhythms

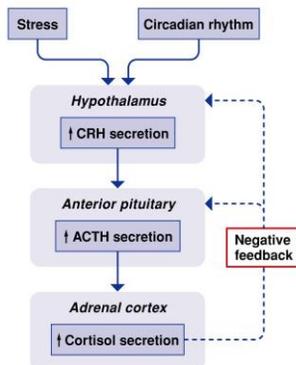
Regulation Of Cortisol Secretion

- Cortisol release is regulated by ACTH
- Release follows a daily pattern – circadian
- Negative feedback by cortisol inhibits the secretion of ACTH and CRH
- Enhanced release can be caused by:
 - Physical trauma
 - Infection
 - Extreme heat and cold
 - Exercise to the point of exhaustion
 - Extreme mental anxiety

Cortisol Levels as per Circadian rhythm



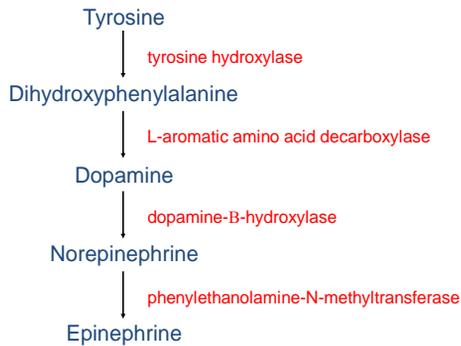
Regulation Of Cortisol Secretion



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DETAILED PHYSIOLOGY MEDULLA

Catecholamine Synthesis



Mechanism of Action

- receptor mediated – adrenergic receptors
- peripheral effects are dependent upon the type and ratio of receptors in target tissues

Receptor	α	β
Norepinephrine	+++++	++
Epinephrine	++++	++++

Relative effects of epinephrine and norepinephrine on α and β adrenergic receptors.
Guyton

Differences between Epinephrine and Norepinephrine

- Epinephrine >> norepinephrine – in terms of cardiac stimulation leading to greater cardiac output (β stimulation).
- Epinephrine < norepinephrine – in terms of constriction of blood vessels – leading to increased peripheral resistance – increased arterial pressure.

Effects of Epinephrine

- metabolism
 - glycogenolysis in liver and skeletal muscle
 - lead to hyperglycemia
 - mobilization of free fatty acids
 - increased metabolic rate
 - O₂ consumption increases
 - decreased gastrointestinal and genitourinary function

ADRENAL DISORDERS

Increased Adrenal Function
Cushing's Syndrome
Primary Aldosteronism
Pheochromocytoma

Decreased Adrenal Function
Addison's

Abnormal Adrenal Function
CAH

Benign Lesions
Malignant Lesions

Adrenal Disorders

CUSHING'S SYNDROME

Cushing's Syndrome

CUSHING'S SYNDROME

Harvey Williams Cushing

(April 8, 1869 – October 7, 1939)

was an **American neurosurgeon**. A pioneer of brain surgery, he was the first person to describe Cushing's disease.

He is often called the "father of modern neurosurgery."

- Cushing's Syndrome is a relatively rare endocrine system disorder caused by the body's exposure to excessive amounts of the hormone cortisol.
- Incidence: 2 - 5 /million people/yr
- 1st reported by American neurosurgeon, Dr. Harvey Cushing in 1932.
- Recent studies show that 3-5% of poorly controlled diabetics may have Cushing's.

Pathophysiology

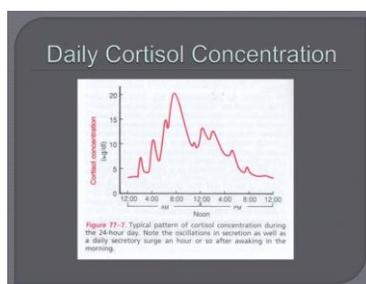
- Normal cortisol secretion → >20 mg/d
- Regulation is by **HPA axis**
 - Hypothalamus secretes a hormone called CRH that stimulates the pituitary to release ACTH. ACTH then stimulates adrenals to make more cortisol.
 - As cortisol levels rise, a "negative feedback" mechanism lets the hypothalamus and pituitary gland know that there is enough cortisol, thus decrease their production of CRH or ACTH. *This does not occur in a patient with Cushing's.*
- ACTH
 - Production of Glucocorticoids and Androgens by adrenal cortex
 - Also plays a critical role in maintaining adrenal cortical vitality. Without ACTH, all but ZG cells arrest hormone production and undergo apoptosis
- In addition to ACTH, splanchnic nerves that innervate the adrenals also appear to affect Glucocorticoid production

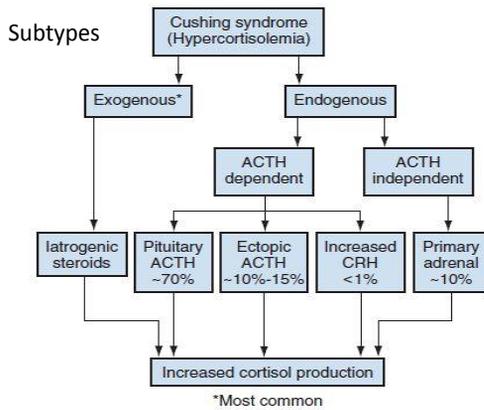
Pathophysiology

- CRH secretion is under tight control of the hypothalamic suprachiasmatic nucleus and follows circadian patterns
- Glucocorticoids bind receptors in the hypothalamus and the pituitary and complete the negative feedback loop
- Highest level of cortisol in healthy subjects is detected in the mornings, while the nadir is observed at approximately 11 PM.

Causes of Cushing syndrome

- Endogenous
 - *ACTH-dependent*
 - Upto 85% of cases of endogenous
 - Pathology extrinsic to adrenals
 - Pituitary tumor can secrete excess ACTH
 - A benign or malignant tumor on lung/other organ can also secrete excessive ACTH
 - *Cushing's due to a pituitary tumor is called Cushing's Disease*
 - All other causes are termed Cushing's Syndrome.
 - *ACTH-independent*
 - Tumors of adrenal can secrete too much cortisol by themselves.
 - Relatively rare
- Exogenous - Iatrogenic Glucocorticoid administration





Exogenous Cushing Syndrome

- Also called Iatrogenic Cushing's syndrome
- Most common cause of Hypercortisolism
- Can result even from the administration of even low doses of exogenous steroids administered orally, topically, or by inhaled preparations in the treatment of other diagnosed conditions like severe asthma, rheumatoid arthritis or serious skin conditions.
- Careful patient history is therefore essential
- Sometimes patient is either unaware of steroid use (e.g. use of herbal remedies, nasal sprays) or is surreptitiously self-administering Glucocorticoids (e.g., for performance enhancement)
- Relieved by dosage adjustments or a change to another type of medication.
- Patients must not stop medications without consulting a medical professional

ACTH-Dependent Cushing Syndrome

- 80% to 85% of endogenous Cushing's
- ~80% is due to pituitary pathology and is known as *Cushing disease*.
- Excessive secretion of ACTH by pituitary adenomas.
- Pituitary Adenomas are small, usually non-cancerous tumors which cause hormonal imbalances.
- MC cause = corticotropin-producing *microadenoma* (< 10 mm). Upto 2/3rd are female (5 times MC in women)
- Large *macroadenomas* of 1 cm or more = found in about 5% only
- *Non-secretory tumors*: problems due to large size, or prevent normal hormone production (headaches, affecting of optic nerve...)
- *Secretory tumors*: produce excess of a particular hormone. 15 % of functional adenomas secrete ACTH
- *Hyperplasia* of ACTH-producing cells and *pituitary carcinoma* can also oversecrete ACTH but are extremely rare

ACTH-Dependent Cushing Syndrome

ECTOPIC ACTH SYNDROME (Liddle and associates, early 1960s)

- Production of ACTH by **nonpituitary tumours**
- Approximately 10% of Cushing syndrome
- These corticotropin-producing tissues are **nearly always malignant**
- The timing and onset of Hypercortisolism varies and can precede the diagnosis of an extra-adrenal malignancy by many years, resulting in diagnostic difficulties and the clinical conundrum, whereby a subclinical pituitary adenoma is suspected but not radiographically identified
- Moreover, Hypercortisolism in end-stage debilitated cancer patients is almost certainly underdiagnosed
- As a result of higher ACTH levels, *adrenal glands of patients with ectopic ACTH syndrome are generally more markedly hyperplastic and larger than in patients with Cushing disease*

ACTH-Dependent Cushing Syndrome

- ECTOPIC CRH
 - Production of CRH by malignancies is extremely rare
 - < 1% of cases of Cushing syndrome
 - Bronchial carcinoma is the most common culprit, and concurrent ACTH secretion is usually seen

ACTH-Independent Cushing Syndrome

- Adrenal neoplasms and rare forms of bilateral adrenal disease
- ADRENAL TUMOURS
 - ~ 10% of Cushing syndrome
 - Release excessive cortisol independently of ACTH production by pituitary
 - MC = unilateral benign adenomas (Cortisol-secreting benign adenomas) (MC result from dominant unilat.hyperplastic nodule)
 - Multifocal bilateral functional adrenal hyperplasia may also occur (< 10%)
 - Adrenocortical carcinomas (~ 8%)
 - May cause high hormone levels and rapid development of Cushing's
 - Radiographically undetectable, benign adrenal cortisol producing lesions → may be responsible for subclinical Cushing's

ACTH-Independent Cushing Syndrome

- ACTH-Independent Macronodular Adrenal Hyperplasia (AIMAH)
 - < 1% of Cushing syndrome (very rare)
 - Weights > 200 g/gland have been reported
 - Glands are enlarged (each gland > 60 g) and have multiple large nodules (upto 4 cm), which may be pigmented or non-pigmented.
 - Usually affects both glands
 - Some respond to hormones such as gastric peptides, adrenalin, and vasopressin. Any increase in these hormones can cause a rise in cortisol.
- McCune-Albright syndrome:
 - B/I macronodular hyperplasia
 - Polyostotic fibrous dysplasia
 - Dermatologic manifestations
 - Other endocrine abnormalities

Mc Cune Albright



31y old pt with MCA in our care

Mc Cune-Albright



Signs

- Caffé au lait
- Precocious puberty
- Fibrous dysplasia
- Hyperthyroid
- Cushing
- osteomalcia

Any combination of two or more of these typical findings = McCune-Albright Syndrome

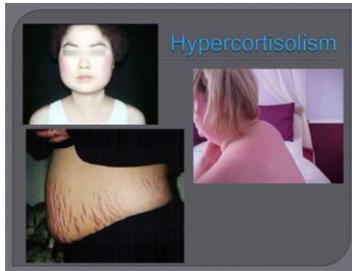


Clinical Features

- 90 – 100 %
 - Central obesity
 - Rounded face (“moon face”)
 - Facial plethora
 - Decreased libido
- 70 - 90 %
 - Purple striae
 - Menstrual disturbances
 - Hirsutism
 - **Erectile dysfunction**
 - Hypertension
- 50 - 70 %
 - Muscle weakness
 - Posterior neck fat deposit (“buffalo hump”)
- Body bruising
- **Glucose intolerance/diabetes**
- Osteopenia/osteoporosis
- Emotional lability/depression
- 20 - 50 %
 - Headache
 - Backache
 - Limb edema
 - Recurrent infections
 - Hypokalemic alkalosis
 - **Nephrolithiasis**
- 0 - 20 %
 - Acne
 - Alopecia

Classical Cushing Syndrome

- Many of the classic symptoms of hypercortisolism, such as central obesity, moon faces, buffalo hump, proximal muscle weakness, easy bruisability, and abdominal striae, are non-specific.
- Cushing syndrome also results in systemic symptomatology, such as central obesity, dyslipidemia, insulin resistance, and hypertension, that is identical to the highly-prevalent metabolic syndrome
- **Relatively common occurrence of hypogonadal hypogonadism in men with Cushing syndrome.** A low threshold for initiating a hypercortisolism workup should exist in these men with libido or erectile problems, low testosterone, and low gonadotropin levels.
- **Up to 50% of patients with Cushing syndrome exhibit urolithiasis;** therefore stone formers with cushinoid features also deserve a hypercortisolemia evaluation. Interestingly, definitive treatment of Cushing syndrome in these patients reduces the risk of stone formation, but does not bring the risk back to that of the general population



Hypercortisolism



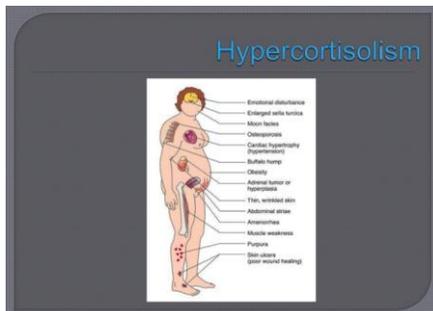
(d) Addison's disease is caused by hyposecretion of corticosteroids, especially glucocorticoids. Pigment changes result from stimulation of melanocytes by ACTH, which is structurally similar to MSH.



(e) Cushing's disease is caused by hypersecretion of glucocorticoids. Lipid reserves are mobilized, and adipose tissue accumulates in the cheeks and at the base of the neck.



Subclinical Cushing Syndrome



Hypercortisolism

- When patients with type II diabetes and poor glucose control are screened for hypercortisolism, some 2% have subclinical Cushing syndrome.
- Adrenalectomy in subclinical Cushing may improve glucose control, hypertension, and result in weight loss.
- *Surgical indications and benefits* (still a matter of debate)
 - Some authors argue that adrenalectomy should be performed only in patients who are potentially symptomatic and exhibit clinical signs, such as hypertension, obesity, glucose intolerance, or osteopenia.
 - Others propose that surgery must be offered to all patients in order to prevent the sequelae of hypercortisolism
 - Patients with subclinical Cushing syndrome may be at higher risk for postadrenalectomy adrenal insufficiency than those patients with non-cortisol-secreting adrenal pathologies, because functionality of the contralateral gland may be suppressed

Diagnosis

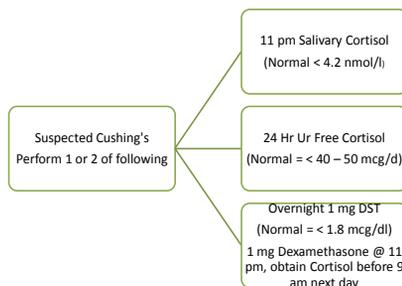
Who Should Be Screened for Cushing's Syndrome?

- **Signs and Symptoms**
- **Central obesity with Facial rounding with plethora Increased supraclavicular and dorsocervical fat Cutaneous wasting with ecchymoses Wide violaceous striae (>1 cm) Proximal myopathy Increased lanugo hair Superficial fungal infections Growth retardation (in children)**
- **Clinical Diagnosis**
- **Metabolic syndrome X**
 - Diabetes mellitus (Hgb A_{1c} > 8%)
 - Hypertension
 - Hyperlipidemia
 - Polycystic ovary syndrome
- **Hypogonadotropic hypogonadism**
 - Oligomenorrhea
 - amenorrhea,
 - Infertility
 - Decreased libido and impotence
 - Osteoporosis (especially rib fracture) Patients aged < 65yr Incidental adrenal mass

Diagnosis

- **The first step** in diagnosing Cushing's is to determine whether the patient has high levels of cortisol.
- Cortisol levels vary throughout the day, making testing more difficult. The normal "diurnal rhythm" for cortisol secretion is that cortisol and ACTH levels are the highest in the morning and the lowest at 11PM to midnight.
- Mild or cyclical cases of Cushing's can be very difficult to diagnose and repeated testing is very often required.
- Cyclic Cushing's will only show abnormal test results when the tumor is active.
- **The second step** in the diagnosis of Cushing's is to determine whether the cortisol production is **dependent on ACTH** (pituitary or ectopic sources) or **ACTH independent** (adrenal tumors). This is termed the "differential diagnosis".

Suspected Cushing's



Diagnosis

- **MC tests performed**
 - 24-hour urinary free cortisol evaluation (UFC)
 - Overnight low-dose dexamethasone suppression test (LD-DST)
 - Late-night salivary cortisol
- **Second-line tests**
 - 2-day LD-DST
 - Midnight plasma cortisol testing
 - Plasma ACTH level

Diagnosis

LD-DST

- This test has been used for 40 years. It is still widely used and useful when combined with other tests.
- Patients take 1 mg of dexamethasone, a synthetic steroid, at 11 pm and cortisol and ACTH are measured at 8 the next day.
- It checks the patient's *Glucocorticoid negative feedback system*
- Normally, dexamethasone acts on corticotrophic cells of anterior pituitary → suppresses ACTH production → reduction of cortisol
- Cushing's patients "do not suppress" thus the cortisol levels remain elevated.
- Does not delineate the etiology of hypercortisolism, but simply suggests its presence.
- Despite the "low-dose" designation, the dosage of dexamethasone administered = 3-4 times levels of physiologic Glucocorticoid.
- Exogenous dexamethasone is not detected by serum cortisol assay.

Diagnosis

- During testing
 - Normal persons will show low ACTH and low cortisol due to proper functioning of feedback system.
 - A patient's failure to suppress cortisol levels is indicative of Cushing syndrome.
 - ACTH-independent Cushing syndrome and ectopic ACTH secretion fail to suppress
 - However, the reason for failure of patients with Cushing disease to suppress cortisol secretion is less obvious.
- **95-97% efficiency** in diagnosis of Cushing's.
- **2 Day LD DST** is less practical and is reserved for second-line testing.

Diagnosis

Late-night salivary cortisol and midnight plasma cortisol measurements

- Common feature of all causes of Cushing syndrome = loss of diurnal variation of cortisol levels.
- The abnormality is the inability to suppress cortisol levels at night.
- Peak morning cortisol levels are often within normal range
- Midnight plasma cortisol measurement is clinically impractical in an outpatient setting
- Late-night salivary cortisol:
 - This is the latest diagnostic test for Cushing's.
 - Elevated cortisol levels b/w 11 PM & midnight = earliest indications of disease.
 - Easy test for patients to perform
 - **93-100% accuracy**
 - Normal levels of cortisol at this time of day virtually eliminates a diagnosis of Cushing's

Diagnosis

Dex-CRH Stimulation

- In patients with equivocal results, combination of dexamethasone suppression with a stimulation test using the hypothalamic hormone CRH can be useful in making the diagnosis of Cushing's syndrome. This study should only be performed in a setting by endocrinologists who have had experience with the test to ensure it is performed properly.

Hypercortisolism

Laboratory Tests

- Glucose tolerance impaired - hyperglycemia
- CBC - leukocytosis
- Hypokalemia particularly with ectopic ACTH secretion
- Dexamethasone suppression test
 - Initial screening test
 - Administer 1 mg of dexamethasone orally at 11PM
 - Obtain serum cortisol level at 8 AM next morning
 - Cortisol level < 2 mcg/dL excludes Cushing's syndrome with 98% certainty

Hypercortisolism

Laboratory Tests

- 24 Hour urine for free cortisol
 - Order if dexamethasone suppression test shows cortisol level >2 mcg/dL
 - >50µg/d helps confirm hypercortisolism
 - Increased: Pregnancy, Carbamazepine, Fenofibrate
- If Cushing's syndrome is confirmed
 - Obtain plasma ACTH
 - <20 pg/ml indicates probable adrenal tumor
 - >60 pg/ml ACTH indicates pituitary or ectopic ACTH-secreting tumors

Identifying the Cause – dif.dg.

- Once it is established that cortisol levels are elevated, several tests are used to determine the cause of Cushing's:
 - Measurement of serum ACTH – ACTH will be elevated in patients with pituitary tumors and ectopic tumors. ACTH will be low or not detectable in patients with adrenal tumors.
 - High Dose Dexamethasone Suppression Test: Endocrinologists may perform high-dose dexamethasone suppression testing to help distinguish a pituitary from a non-pituitary ACTH-secreting tumor.
- First, ACTH-dependent disease must be distinguished from the ACTH-independent causes.
- This is done by measurement of serum ACTH.
- Low serum ACTH points to ACTH-independent pathology, and abdominal imaging is indicated to identify the adrenal source.
- If the adrenals are unremarkable on cross-sectional imaging, exogenous steroids as a cause of Cushing syndrome, or much less commonly PPNAD, must be suspected. Interestingly, the presence of PPNAD often can be confirmed by a delayed "paradoxical rise" in the 24-hour urinary cortisol sampling following dexamethasone administration.
- Upto 10% of patients with adrenal Cushing syndrome have bilateral adrenal lesions. Adrenal venous sampling may be helpful in this setting

Identifying the Cause

- True diagnostic difficulty lies in distinguishing Cushing disease from ectopic ACTH syndrome for patients who have high serum ACTH levels. This problem stems from the fact:
 - Both pituitary microadenomas and ACTH producing tumours can be very difficult to localize with modern imaging.
 - Meanwhile, incidental imaging findings in the lungs, pancreas, and pituitary are relatively common
 - For instance, 10% of the general population exhibit an abnormality upon imaging of the pituitary gland, while some 50% of patients with Cushing disease have no abnormality on pituitary MRI

Identifying the Cause

Petrosal Sinus Sampling - PSS

- Direct measurements of ACTH in inferior petrosal sinus (a downstream venous plexus that drains the pituitary) following CRH stimulation has become the gold standard approach for distinguishing ectopic ACTH production from Cushing disease.
- High levels of ACTH in the inferior petrosal sinus, when compared to those in peripheral blood, indicate Cushing disease, while levels similar to peripheral plasma suggest an ectopic ACTH source
- This test is useful in differentiating pituitary and ectopic sources of ACTH. PSS uses catheters inserted through the large veins in the groin to sample ACTH levels as they drain from the pituitary veins. This test is most useful when combined with CRH stimulation and can in some cases localize the pituitary tumor to one side of the pituitary gland.
- This particular study needs to be performed by a skilled interventional radiologist with extensive experience. It has a diagnostic accuracy rate is between 95-98%.

MRI & CT Scan

- If ACTH levels are increased, the next step in the diagnosis is to determine the location of the ACTH producing tumor. Hopefully direct visual imaging associated with MRI of the pituitary gland will show the tumor. If a tumor greater than 5mm is clearly identified, further testing may not be needed, however care needs to be exercised as approximately 10% of the population have small non-functioning pituitary tumors. In about 50% of cases, the pituitary tumor is so small that it can not be seen with conventional imaging techniques.
- If ACTH is elevated, and the pituitary MRI is "normal", further testing is required to differentiate between unseen pituitary sources and an ectopic tumor located elsewhere in the body.
- If ACTH levels are low or not detectable, a CT or MRI of the adrenal glands almost always identifies the tumor or tumors.

High-dexamethasone suppression test

- Was used in the past to differentiate pituitary and ectopic ACTH sources
- Value of the test is limited
- Principle:
 - High doses of dexamethasone suppresses ACTH production by pituitary adenomas
 - Ectopic ACTH production is not suppressed
- Unfortunately some nonpituitary ACTH-producing tumours also possess Glucocorticoid receptor and also reduce ACTH production upon high-dose dexamethasone administration
- Currently, high-dexamethasone suppression testing is not routinely employed

Causes of Hypercortisolism in the Absence of Cushing Syndrome

Some clinical features of Cushing syndrome may be present

1. Pregnancy
2. Depression
3. Alcohol dependence
4. Glucocorticoid resistance
5. Morbid obesity
6. Poorly controlled diabetes mellitus

Unlikely to have any clinical features of Cushing syndrome

1. Physical stress (hospitalization, surgery, pain)
2. Malnutrition, anorexia nervosa
3. Intense chronic exercise
4. Hypothalamic amenorrhoea
5. CBG excess (increased serum but not in urine cortisol)

Pseudo Cushings

- patients with nonendocrine disorders that mimic the clinical and sometimes biochemical manifestations of Cushing's syndrome must be separated from those patients with true Cushing's syndrome; these patients have been said to have pseudo-Cushing's syndrome. Abnormally regulated cortisol secretion, albeit mild, may exist in as many as 80% of patients with major depression and can occur commonly in patients with chronic alcoholism

Treatment

- Approach = multidisciplinary
- Treatment goals:
 - Correction of hypercortisolemia
 - Restoration of HPA axis
 - Management of Cushing syndrome sequelae

Treatment

Exogenous Cushing Syndrome

- Cessation of Glucocorticoids must be gradual, so that hypothalamic-pituitary-adrenal axis has ample time to recover
- Can take weeks to months
- "Steroid withdrawal syndrome" where the patient cannot tolerate steroid dose reduction despite apparent normalization in hypothalamic-pituitary-adrenal axis testing

Treatment

Cushing Disease (Pituitary)

1. The first choice in treating pituitary tumors is surgical removal. The current standard of care = transsphenoidal surgical resection of pituitary adenoma
 - Cure = only 60 - 80%
 - Upto 25% of individuals relapse → Long-term follow-up is necessary
 - Macroadenomas (> 1 cm) are resistant to neurosurgical treatment → <15% cure
 - Provided that normal pituitary tissue remains, normal pituitary function returns gradually.
 - Complications:
 - Severe addisonian state: Glucocorticoid replacement → necessary in the year following surgery
 - Hypopituitarism (< 5 - 50% for various pituitary metabolic products). Careful patient monitoring by expert endocrinologists is essential

Treatment

2. Adrenalectomy:

- Indications:
 - Currently bilateral adrenalectomy is most often recommended when at least one attempt to treat the primary tumour has failed.
 - It is also necessary in rare instances when hypercortisolism is life-threatening and swift definitive treatment is mandatory
- Advantages:
 - Lack of postoperative hypopituitarism
 - Extremely high success rate with rapid resolution of hypercortisolism

Treatment

- Complications:
 - Lifelong Mineralocorticoid and Glucocorticoid replacement required in all
 - Risk for progressive growth of their pituitary adenoma resulting in:
 - Ocular chiasm compression
 - Oculomotor deficiencies
 - Nelson-Salassa/ Nelson syndrome
 - » Rise in intracranial pressure
 - » 8 - 29% of patients following bilateral adrenalectomy
 - » Prophylactic radiation therapy has been shown to prevent the phenomenon in some but not all. Currently, routine use of prophylactic radiotherapy is controversial
 - Rare possibility of residual, functioning adrenal tissue after surgery

Treatment

ECTOPIC ACTH SYNDROME (Non-pituitary, extra adrenal)

- Resection of the primary ACTH producing tumour is the single best therapeutic approach
- Primary tumour resection is possible in approximately 10% of patients
- B/l adrenalectomy with lifelong replacement therapy in case of
 - Unresectable primary tumours
 - Primary ACTH-producing tissue cannot be identified (up to 35% of cases)

Treatment

ACTH-Independent (Adrenal Cause)

- U/l adrenal mass → ipsilateral adrenalectomy
- Partial adrenalectomy when preserving adrenals is essential
- AIMAH and PPNAD
 - B/l adrenalectomy with lifelong replacement.
 - Success with U/l resection of largest gland in AIMAH patients also reported
- Small adenomas can be removed with laparoscopic surgery techniques.
- Larger tumors are removed using open surgical techniques.
- If a rare tumor is found, surgery may be followed by radiation or chemotherapy.
- In cases of bilateral adrenal hyperplasia, both glands may need to be removed. In this case, the patient will need hormone replacement for the rest of their life.

Treatment

Medical Treatment of Hypercortisolism

- Employed for bridging a patient to surgery
- When surgical intervention is not possible
- Medications that block enzymes of steroid synthesis, such as metyrapone, aminoglutethimide, trilostan, ketoconazole, and etomidate
- Mitotane, can also be used
- Inhibitors of 17 α -hydroxylase (cyp17), such as abiraterone, may also be useful

Post operative recovery

- should not expect immediate recovery following surgery.
- The length of time the patient's body was exposed to the excessive cortisol is an indication for the length of the recovery period.
- Patients who have had pituitary surgery or radiation should be periodically evaluated for deficiencies of other hormones such as thyroid and Growth Hormone.
- During the recovery process, it is usual to experience fatigue, muscle aches and pains, a lack of appetite and mild nausea.
- Following curative surgery, cortisol levels drop to virtually zero. Cortisol is needed by the body, thus replacement medication is needed.
- Patients must be informed about adrenal insufficiency "**sick day rules**". Patients who are prescribed physiological replacement need to know that additional doses are required during acute illnesses/stress to prevent serious problems such as low blood sugar level or a drop in blood pressure.

Adrenal disorders

Primary hyperaldosteronism (PH)

Primary hyperaldosteronism

- **Dr. Jerome Conn** first described primary aldosteronism in 1955 in a 34-year-old female presenting with hypertension and hypokalemia. Urine assays demonstrated a markedly elevated level of Mineralocorticoid activity. The patient's condition greatly improved following the removal of a 4cm unilateral adrenal tumour.

Primary Aldosteronism

- Prevalence: 5 - 13% of hypertensive patients

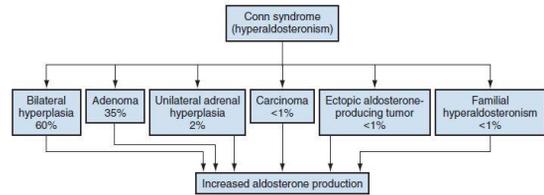
Pathophysiology

- RAAS is a key regulator of BP and ECF Volume
- **Release of renin** from JG cells is the **rate-limiting step**
- Under normal physiologic conditions, renin release is stimulated by several conditions including low renal perfusion pressure, increased renal sympathetic nervous activity, and low sodium concentration sensed by the macula densa
- Renin then cleaves angiotensinogen to angiotensin I, which in turn is cleaved by angiotensin-converting enzyme to angiotensin II.

- Angiotensin II functions as both a potent vasoconstrictor and triggers the release of aldosterone from the zona glomerulosa. Additional regulators of aldosterone release include potassium and ACTH.
- **Primary aldosteronism**
 - Aldosterone secretion is independent of RAAS
 - Plasma **renin levels** \rightarrow **suppressed**
- **Secondary hyperaldosteronism**
 - **Elevated renin** \rightarrow elevation of aldosterone
- Following release from the adrenal cortex, aldosterone increases sodium reabsorption and potassium secretion in the distal nephron
- Hyponatremia does not occur as sodium reabsorption is accompanied by water uptake, thereby maintaining isotonicity.
- The resultant volume expansion is limited by **Mineralocorticoid escape**.

Subtypes

- Mineralocorticoid escape is mediated by pressure-natriuresis, atrial natriuretic peptide secretion, and changes in electrolyte transporters in the distal nephron, which result in limiting volume expansion to approximately 1.5 kg or less
- Increased plasma aldosterone and decreased plasma renin activity is common to all subtypes with primary aldosteronism



Subtypes

- Aldosterone-producing adenomas:**
 - more profound hypertension and hypokalemia in comparison with idiopathic hyperplasia,
 - Unilateral adrenal hyperplasia**
 - Uncommon
 - Potentially curable with adrenalectomy following confirmation of lateralizing aldosterone secretion
- Less common causes of PAL:**
- Adrenal cortical carcinomas**
 - Rare
 - <1% of cases of primary aldosteronism
 - 2.5% to 5% of adrenal cortical carcinomas

Subtypes

- Ectopic aldosterone-producing tumours**
 - Extremely rare
 - Should raise suspicion for the presence of
 - Accessory adrenal tissue
 - Adrenal heterotopia
- Familial hyperaldosteronism (FH)**
 - Two types: type I and type II
 - FH type I (Glucocorticoid-remediable aldosteronism)**
 - Autosomal-dominant
 - Chimeric fusion of the promoter region of the 11β-hydroxylase gene (CYP11B1) and the coding region of the aldosterone synthase gene (CYP11B2)
 - Results in aldosterone synthase activity being **controlled by ACTH**. Thus aldosterone is secreted acc. to circadian rhythm of ACTH (**not by RAAS**)
 - Patients often have early-onset refractory hypertension and early onset hypertension or cerebral vascular accidents

Subtypes

Subtypes of Primary Aldosteronism	
SURGICALLY CORRECTABLE	NOT CORRECTABLE BY SURGERY
Aldosterone-producing adenoma	B/l adrenal hyperplasia
Primary u/l adrenal hyperplasia	Familial hyperaldosteronism type I
Ovarian aldosterone-secreting tumour	Familial hyperaldosteronism type II
Aldosterone-producing carcinoma	

Clinical Characteristics

- Third to sixth decades of life
- No specific symptoms in most patients when evaluated for HTN
- The degree of hypertension is typically graded as moderate to severe with the mean blood pressure of 184/112 with primary aldosteronism
- Mean B.P. = significantly higher in HTN with PAL than in patients without PAL
- The association between primary aldosteronism and the severity of hypertension
 - Demonstrated by Mosso and colleagues (2003)
 - Prevalence of primary aldosteronism in hypertensives
 - Stage 1 (140 to 159/90 to 99) = 2 %
 - Stage 2 (160 to 179/100 to 109) = 8 %
 - Stage 3 (>180/>110) = 13 %

Clinical Characteristics

- 63% and 91% of newly diagnosed patients are normokalemic
- In minority of patients, hypokalemia is accompanied by headache, polydipsia, palpitations, polyuria, nocturia, and muscle weakness.
- Due to Mineralocorticoid escape, Hyponatremia is uncommon
- Sodium levels are similar to other forms of Hypertension
- Cardiovascular and renal damage is a concern
- The incidence and severity of target organ damage → > in PAL as compared to other forms of HTN
- Cardiac abnormalities
 - Left ventricular filling and diastolic dysfunction
 - Increased left ventricular mass measurement

Diagnosis

- Involves screening, confirmatory testing, and subtype differentiation.

Indications for Primary Aldosterone Screening (SHARE-USE)

- Severe hypertension ($\geq 160/\geq 110$)
- Hypertension with hypokalemia
- Adrenal Incidentaloma with hypertension
- Resistant hypertension (three or more oral agents with poor control)
- Early-onset hypertension (<20) or stroke (<50 years)
- Unexplained hypokalemia
- Whenever considering Secondary causes of hypertension (i.e., pheochromocytoma or renovascular disease)
- Evidence of target organ damage disproportionate to degree of hypertension
 - > 30 for ARR
 - > 20 ng/dL for PAC

Diagnosis

- Screening for primary aldosteronism begins by obtaining a morning (between 8 and 10 AM) plasma aldosterone concentration (PAC) and plasma renin activity (PRA)
- PAC and ARR are used to screen for autonomous aldosterone secretion
- ARR is dependent on PRA
- It is recommended that the lowest PRA value be set at 0.2 ng/mL/hr to avoid falsely elevated ratios
- PAC and ARR that define a positive screen and suggest the diagnosis of PAL are not standardised.
- The National Institutes of Health (NIH) Consensus Statement (2002) on the management of the clinically inapparent adrenal mass suggests cut-offs of
 - > 30 for ARR
 - > 20 ng/dL for PAC

Clinical Characteristics

- As compared to patients with essential hypertension:
 - 4 times more likely to be diagnosed with a stroke
 - 6.5 times more likely to be diagnosed with a myocardial infarction
 - 12 times more likely to be diagnosed with atrial fibrillation
 - Increased proteinuria
- The increased risk of CVS disease may be associated with the increased prevalence of metabolic syndrome in these patients

Diagnosis

Screening

- Prior to screening
 - Hypokalemia should be corrected
 - All contraindicated medications to be discontinued
- Can continue majority of antihypertensive agents
- **Potassium-sparing diuretics and Mineralocorticoid receptor blockers** greatly alter the RAA axis and should be **stopped at least 6 weeks prior** to aldosterone renin ratio (ARR) testing.
- Patients requiring Mineralocorticoid Receptor blockers for control of severe hypertension should be transitioned to agents such as α 1-receptor blockers or long-acting CCBs
- Other antihypertensive agents can alter screening values, but not to the extent that mandates their discontinuation

Diagnosis

CONFIRMATORY TESTING

- Of the patients with positive screening tests, only 50% to 70% will be diagnosed with PAL on confirmatory testing
- Patient preparation is required
 - Correction of hypokalemia
 - Discontinuation of Mineralocorticoid receptor antagonists
- Of the confirmatory tests available
 - 3 evaluate suppression of aldosterone following sodium loading
 - 1 evaluates suppression of ARR following administration of an ACE inhibitor (not in use in our conditions)
- The selection of the confirmatory test used depends on individual patient characteristics and physician preferences. Blood pressure should be monitored closely in all patients during confirmatory testing.

Diagnosis

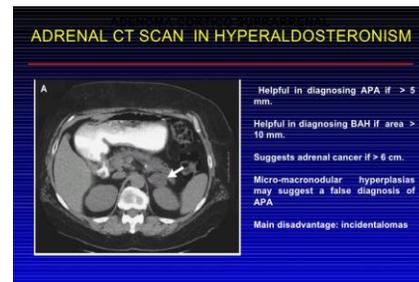
- Sodium loading tests: **loading will decrease plasma renin and aldosterone production in patients without autonomous aldosterone secretion**
- **Fludrocortisone suppression test**
 - Administration of Fludrocortisone (0.1 mg every 6 hours) and NaCl (2 g every 8 hours) for 4 days.
 - Following 4 days loading, PAC measured in upright position.
 - Failure to suppress PAC to <6 ng/dL is diagnostic
 - Once considered the gold standard
 - Supplanted by oral sodium loading test and intravenous infusion test due to **risks of severe hypertension and hypokalemia**

Diagnosis

- **Intravenous saline infusion test**
 - Spares the patient from several days of sodium loading
 - Administration of 2 L of 0.9% NaCl intravenously over 4 hours.
 - Infusion is performed in the morning after an overnight fast, while the patient is in a recumbent position.
 - Following infusion, PAC are measured
 - Level > 5 ng/dl = diagnostic of PAL
 - Levels > 10 ng/dl = suggestive of aldosterone-producing adenomas

Diagnosis

- **Captopril suppression test**
 - Administer 25 to 50 mg of Captopril
 - Followed by the measurement of PAC while the patient remains recumbent
 - Suppression of the RAAS should be noted in patients without PAL
 - Those with autonomous aldosterone secretion will have persistently elevated PAC > 15 ng/dL
 - Further standardization and validation is needed
 - **At this time, captopril suppression is recommended for patients with cardiac and renal disease, which prohibits sodium loading**



Diagnosis

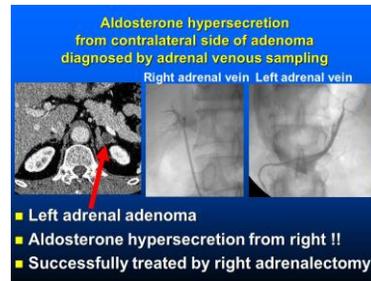
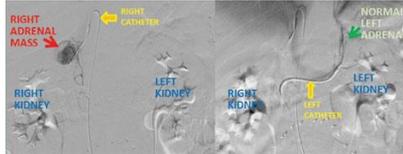
Lateralisation Studies

- To establish lateralization of aldosterone secretion in surgical candidates, **adrenal vein sampling** should be performed.
- By establishing lateralization, one can differentiate between subtypes of primary aldosteronism and identify patients in which adrenalectomy is potentially beneficial.
- The value of adrenal vein sampling was illustrated by Young and colleagues (2004), who noted that 22% of patients would have been incorrectly excluded from adrenalectomy, and 25% would have been inappropriately recommended to undergo adrenalectomy based on CT findings instead of adrenal vein sampling studies.

Diagnosis

- Adrenal vein to IVC ratios below the cut-off, on either side, should be considered "nonselective" and discarded.
- **Adrenal vein to IVC ratio above cut-off, bilaterally = "selective,"** and comparisons between aldosterone concentrations can be made to determine the presence of lateralization.
- Lateralization of aldosterone secretion is determined by comparing the aldosterone to cortisol ratios of the dominant to nondominant sides using the formula (Adominant/Cdominant)/(Anondominant/Cnondominant).
- Aldosterone is considered to be lateralized if ratio is greater than 2-4 : 1, depending on the use of ACTH stimulation
- **Sensitivity of 95% and specificity of 100%** in detecting lateralized autonomous aldosterone secretion

Adrenal vein sampling



Diagnosis

- Alternative studies when AVS is inconclusive due to sampling error
 - Nuclear Scintigraphy
 - Postural stimulation testing and
 - Measurement of cortisol metabolites
- **Nuclear Scintigraphy**
 - Provides both functional and anatomic data (necessary when considering surgical intervention)
 - ^{131}I -6 β -iodomethyl-norcholesterol (NP59) is a cortisol analog that can label adrenal cortical cells in order to evaluate for areas of hypersecretion
 - Prior to injection of the radiotracer, saturated potassium iodine (Lugol solution) is administered to protect the thyroid from uptake of free ^{131}I .
 - Additionally suppression of ACTH with dexamethasone (1 mg every 6 hours for 7 days) is necessary.

Treatment

- Goal of treatment in primary aldosteronism is to control and prevent the morbidity associated with Mineralocorticoid excess.
- Treatment strategies aim to
 - Remove the source of Mineralocorticoid excess or
 - Block the effect of aldosterone on target organs
- Treatment strategies are primarily dependent on subtype classification and surgical candidacy
 - U/I adrenalectomy
 - Medical therapy

Diagnosis

- **Posture stimulation test**
 - To distinguish between aldosterone-producing adenomas and idiopathic hyperplasia based on changes in PAC levels in response to changes in posture.
 - By comparing PAC levels after patient has been recumbent overnight, and again after 4 hours of being upright.
 - In theory, increase of angiotensin induced when upright leads to an increase of plasma aldosterone concentration in normal patients that is two- to fourfold greater when compared with recumbent levels.
 - In comparison, patients with idiopathic hyperplasia will demonstrate an increase of at least 33% over baseline
 - Patients with aldosterone-producing adenomas or FH type I will not demonstrate an increase
 - Although the test can be helpful in distinguishing between aldosterone-producing adenomas and idiopathic hyperplasia, it does not provide information regarding the location

Treatment

- **Surgery**
 - Aldosterone-producing adenomas:
 - Usually small sized
 - Offer laparoscopic adrenalectomy
 - Adrenal cortical carcinoma
 - Open procedure recommended
 - Improvement in blood pressure
 - 33 - 73% of patients do not require antihypertensives postoperatively
 - **Predictors of persistent hypertension following adrenalectomy for PAL**
 - Age > 50
 - Use of two or more antihypertensive agents preoperatively
 - Having a 1st degree relative with hypertension
 - Prolonged duration of hypertension prior to adrenalectomy
 - Renal insufficiency

Treatment

Medical treatment

- in patients with nonsurgically correctable subtypes and those who are not surgical candidates
- **Aldosterone receptor antagonists** (Spironolactone and Eplerenone) are successful in lowering BP and are the antihypertensive agents of choice
- **Spironolactone**
 - Initiated at doses of 25 to 50 mg/day
 - Can be titrated up to 400 mg/day, depending on blood pressure, serum potassium levels, and side effects.
 - Side effects:
 - Gynecomastia, impotence, and menstrual disturbances.

Treatment

- **Eplerenone**
 - More favorable side-effect profile
 - Increased selectivity for aldosterone receptor
 - Initiated with 25 mg twice per day
 - Titrated up to 100 mg per day
 - Other antihypertensive agents will often be needed.
 - Lifestyle modifications: weight loss, low-sodium diet, and regular exercise
 - **FH type I** can be treated with oral Glucocorticoids.
 - Glucocorticoid → reduce ACTH release → decreased aldosterone production
 - When BP is not controlled with Glucocorticoids alone
 - Development of Iatrogenic Cushing's
- } Add aldosterone receptor antagonist

Adrenal Disorders

Pheochromocytoma (PCC)



Pheochromocytoma

- **DEFINITION:** catecholamine-producing tumor derived from the sympathetic and parasympathetic nervous system, usually located in the adrenal gland

Pheo = Pusky Chromo = Color Cytoma = Cell Tumor

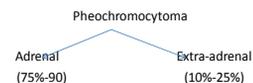
The name refers to the color the tumor cells acquire when stained with chromium salts

Introduction

- Tumour of catecholamine-producing cells of adrenal medulla
- Incidence: ~ 1 – 2/1,00,000
- Responsible for approximately 0.5% of cases of hypertension
- Amongst adrenal incidentalomas → ~5% = pheochromocytoma
- Incidentally discovered lesions = 10% to 25% of all PCC
- Extra adrenal PCC (Paraganglioma)
 - Upto 25%
 - Arise from paraganglia, a network of chromaffin-producing neural crest tissue that anatomically parallels sympathetic and parasympathetic ganglia
 - Can arise in head, neck, thorax, abdomen, and pelvis (including bladder).
 - The chromaffin bodies that lie between the aortic bifurcation and the root of the inferior mesenteric artery are known as the organ of Zuckerkandl, and are a common site for Paraganglioma

Introduction

- Some authors reserve term Paraganglioma for tumours only in head and neck, where they tend to be non-functional



Pathophysiology

Hereditary PCC

- Familial cases ~ 1/3rd of PCCs
- Many cases initially appear sporadic, are later found to be hereditary on genetic testing
- 24% of patients who present with isolated PCC and lack any significant F/H exhibit a germ-line mutation that predisposes them to PCC
- At least five genes - familial PCC
 - Rearranged Transfection proto-oncogene (**RET**)
 - Von Hippel-Lindau (**VHL**)
 - Neurofibromatosis type 1 (**NF1**)
 - Mitochondrial Succinate Dehydrogenase subunits D and B genes (**SDHD**, **SDHB**)
- Probably, these abnormalities **modulate neuronal apoptosis** and are related through signal transduction pathways downstream from nerve growth factor (NGF)

Clinical Features

- Classically, pheochromocytoma has been called the "10% tumour": 10% extra-adrenal, 10% familial, 10% bilateral, 10% paediatric, and 10% malignant
- Extra-adrenal → Upto 25%
- Familial → Upto 30%
- Malignancy
 - Is rare in sporadic (upto 5%) and hereditary cases
 - It occurs in > 1/3rd of extra-adrenal PCC
- Nonhereditary cases are most often diagnosed in 4th & 5th decades
- Familial tumours tend to occur at a younger age
- Paediatric PCC
 - Despite being uncommon, paediatric PCC = MC endocrine neoplasm in children.
 - Upto 40% = familial
 - > 20% = bilateral

Clinical Features

- For reasons that are unclear, tumours arising from right adrenal are more common, tend to be larger, and recur more frequently than those that arise in the left gland
- Classic hallmark of PCC = triad of headache, episodic sudden perspiration, and tachycardia
- Paroxysmal hypertension
 - "Episodic spikes in blood pressure"
 - Classic presenting symptom
 - Seen in only 30 to 50%
 - Can occur in the backdrop of baseline essential hypertension.
- The remainder of patients demonstrate persistently elevated blood pressure
- Minority = entirely normotensive
- More than 20% of patients can be asymptomatic

Clinical Features

Clinical Manifestations

Clinical Manifestations	FREQUENCY
• Headache	60%-90%
• Palpitations	50%-70%
• Sweating	55%-75%
• Pallor	40%-45%
• Nausea	20%-40%
• Flushing	10%-20%
• Weight loss	20%-40%
• Tiredness	25%-40%
• Psychologic symptoms (anxiety, panic)	20%-40%
• Sustained hypertension	50%-60%
• Paroxysmal hypertension	30%
• Orthostatic hypotension	10%-50%
• Hyperglycemia	40%

Clinical Features (Hereditary PCC)

- Occur at a younger age
- Tend to be multifocal and/or bilateral at presentation
- Pheochromocytomas in patients with
 - MEN-2 → nearly always arise from adrenal
 - VHL → extra-adrenal ~ 12%
 - Neurofibromatosis-1 (NF1) → extra-adrenal ~ 6%
- **SDHB and SDHD mutations**
 - Mostly extra-adrenal and multifocal
 - Solitary adrenal masses may also arise
 - Mutations in the *SDHB* gene → a/w very high risk of malignancy

Clinical Features (Malignant PCC)

- Mets → more common in **extra-adrenal lesions**
- **SDHB mutation** is strongly associated with metastatic disease
 - Classically majority of patients exhibit extra-adrenal disease
 - However, a significant proportion have adrenal lesions at presentation
- More likely to exhibit **elevated dopamine** levels
- Tend to be larger (>5 cm)
- However, a preclinical diagnosis of malignant potential is not possible
- MC sites of Mets: Bone, lungs, liver, and lymph nodes
- Metastatic pheochromocytoma can be present at diagnosis or be detected during surveillance after excision of the primary tumour.
- Most metastases are discovered within 5 years of the original diagnosis, but metastatic spread more than 15 years following initial excision has been reported

Biochemical Evaluation

- Catecholamines and their metabolites, including Metanephrines, are conjugated with a sulfate moiety in the bloodstream.
- "Free" → not conjugated and lack sulfate group.
- "Total" amounts of catecholamine metabolites
 - Used in the past
 - Not able to discriminate between "free" and "sulfonated" compounds
- "Fractionated" is used when laboratory reports
 - Amount of each compound type (e.g., Metanephrines) and also
 - Relative concentrations of each compound (e.g., Normetanephrine and Metanephrine)

Biochemical Evaluation

CATECHOLAMINE TESTING

- Catecholamines: Dopamine, Norepinephrine and Epinephrine
- Release of these compounds into the bloodstream is often paroxysmal
- Measurement of urinary and serum catecholamine levels
 - In the past → mainstay for evaluation
 - Sensitivity ≈85%
 - Specificity ≈85%
 - Largely replaced by measurement of Metanephrine levels (Methylated metabolites of catecholamines)
- Measurement of urinary catecholamines is still recommended in conjunction with urinary– fractionated Metanephrine testing

Biochemical Evaluation

CLONIDINE SUPPRESSION TESTING

- Clonidine, an α_2 agonist, suppresses catecholamine (specifically norepinephrine) production by the sympathetic nervous system but not by pheochromocytoma
- Comparison of normetanephrine levels before and after Clonidine administration has been shown to yield results with favorable test characteristics
- This evaluation is suggested for secondary testing in patients with pheochromocytoma who exhibit mild or borderline elevations in Metanephrine levels.
- When embarking on Clonidine suppression testing, one must be cognizant that Clonidine administration can result in significant hypotension in certain patients

Biochemical Evaluation

CHROMOGRANIN A TESTING

- Chromogranin A belongs to a group of compounds known as gransins, which exist in the secretory vesicles of the neuroendocrine and the nervous systems.
- Elevation of serum Chromogranin A levels has been documented in patients with pheochromocytoma
- Although the sensitivity of the test for detecting pheochromocytoma is suboptimal (≈85%)
- has a role for confirmatory testing in patients who have mild or moderate (less than a fourfold) elevation in free-plasma Metanephrine levels
- Chromogranin A is renally cleared, and the specificity of the test decreases significantly in patients with glomerular filtration rates less than 80 mL/min

Imaging

CROSS-SECTIONAL IMAGING (CT Scan)

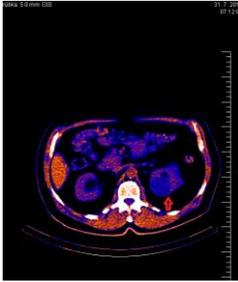
- Pheochromocytomas appear as well-circumscribed lesions
- Given their rich vascularity and low lipid content, Pheochromocytomas typically measure an attenuation > 10 HU on NCCT (mean ≈35 HU)
- This property affords ability to differentiate them from lipid-rich adenomas
- Can be distinguished from lipid-poor adenomas using CT contrast washout strategies
- Although nonspecific, Pheochromocytomas, unlike adenomas, do not exhibit rapid contrast washout on delayed imaging
- *Rare examples of low-density Pheochromocytomas that exhibit an unenhanced attenuation of less than 10 HU and demonstrate brisk contrast washout have been reported*
- In the past, iodinated IV contrast was believed to be a possible trigger for a hypertensive crisis. No evidence exists to support this misconception

Functional Imaging

METAIODOBENZYLGUANIDINE (MIBG) SCINTIGRAPHY

- MIBG is a small-molecule analogue of norepinephrine
- When tagged with ^{131}I or ^{123}I , MIBG Scintigraphy has been used to evaluate PCC
- Selective uptake of MIBG by pheochromocytoma cells occurs
- ^{123}I -MIBG for identification of pheochromocytoma
 - Sensitivity = 83% to 100%
 - Specificity = 95% to 100%
- Uses:
 - Extra-adrenal, metastatic, or recurrent PCC
 - To localize diseases in patients with biochemical evidence but negative imaging
 - for large (>5 cm) tumours is important to assess for presence of metastatic disease prior to surgery

MIBG



Genetic Testing

Screening for Hereditary Pheochromocytoma

- More than one third of Pheochromocytomas
- Furthermore, nearly one quarter of patients who appear to have sporadic nonfamilial disease at diagnosis demonstrate germline mutations upon genetic testing
- Despite this, the consensus of The First International Symposium on Pheochromocytoma in 2005 did not endorse universal genetic testing in all patients diagnosed with pheochromocytoma
- Figure 57–19 summarizes how clinical history and disease characteristics at presentation should guide genetic testing
- All patients under age 50 deserve genetic testing for the *RET*, *VHL*, *SDHB*, and *SDHD* gene mutations
- Routine testing for the *NF1* gene is not recommended in patients who do not meet clinical criteria for neurofibromatosis

Treatment

- Pheochromocytoma is a surgical disease
- Complete resection of tumour is advised whenever possible
- Laparoscopic adrenalectomy = standard of care for most tumours
- Open approach = for large and/or surgically difficult tumours



Pheochromocytoma

Differential Diagnosis

- Essential hypertension
- Panic attacks
- Use of cocaine or amphetamines
- Intracranial lesions
- Thyrotoxicosis
- Paroxysmal tachycardia

Preoperative Management

ALPHA BLOCKADE

- **Irreversible α (Catecholamine) Blockade:**
 - MC used = Phenoxybenzamine
 - Intraoperative catecholamine surges generally do not override its actions, because reversal of is only possible through synthesis of new receptor molecules
 - Started 7 to 14 days prior to surgery
 - Start: 10 mg BD, PO
 - Titrated by increases of 10 to 20 mg to BP = 120-130/80 mm Hg in a seated position
 - Mild postural hypotension with SBP > 80 mm Hg is acceptable
 - Final dosing of 1 mg/kg is usually sufficient to achieve adequate blockade

Preoperative Management

BETA BLOCKADE

- Should be used with caution in patients with PCC
- Use may be necessary due to reflex tachycardia and arrhythmias that can result upon initiation of α blockade
- **β # should never be started prior to appropriate α #**
- In absence of α #, β #s cause a potentiation of action of epinephrine on α 1 receptors (due to # of arteriolar dilation at β 2 receptor)
- For this reason, selective β 1 #s, such as atenolol and metoprolol, are generally preferred
- Dosing for these agents is summarized in Figure 57–20

Preoperative Management

CATECHOLAMINE SYNTHESIS BLOCKADE.

- Alpha-methyltyrosine (Metyrosine)
- Blocks the rate-limiting step in biosynthesis of catecholamines
- Inhibits tyrosine hydroxylase enzyme
- #s the conversion of tyrosine to L- dihydroxyphenylalanine (L-DOPA)
- Approximately 3 days treatment → to achieve full clinical effect
- Because blockade of catecholamine synthesis is incomplete → generally coupled with Phenoxybenzamine
- Central nervous system side effects
 - Sedation, Depression, and Galactorrhoea
 - Extra-pyramidal symptoms resembling parkinsonism can result and require cessation of Phenoxybenzamine
- Not routinely used. Reserved for refractory or metastatic patients

Preoperative Management

INTRAVASCULAR VOLUME MANAGEMENT

- Restoration of intravascular volume is the most important component of preoperative management
- Intake of salt and fluid is encouraged once catecholamine blockade has been initiated
- Admit patients the day before surgery and initiate aggressive IV fluid resuscitation
- The last dose of Phenoxybenzamine and/or Metyrosine is usually given on the night prior to surgery, and the next morning's dose is held. (minimizes potentially prolonged hypotension following resection)

Peroperative management

- Minimal handling
- Difficult phases are – induction, positioning, manipulation, removal.
- Adrenal vein ligated as a first step
- Sodium nitroprusside used intra operatively for lowering BP.

Postoperative Management

- Immediate postoperative period
 - Must be actively monitored
 - If Phenoxybenzamine was employed for preop α # → hypotension is common
 - Moreover, in a high catecholamine state, α_2 -adrenoreceptor stimulation inhibits insulin release. The withdrawal of this adrenergic stimulus following tumour resection, may result in rebound hyperinsulinemia and subsequent hypoglycaemia
- Follow-up
 - Repeat metabolic testing ~ 2 weeks after adrenalectomy
 - In patients in whom Metanephrine levels remain elevated → MIBG imaging
 - MIBG uptake by previously unseen mets may become evident following resection of primary tumour

Treatment of Malignant PCC

- Largely palliative
- Surgical metastatectomy of resectable disease is the standard of care
 - Little evidence exists to demonstrate that it prolongs patient survival or is more effective for symptomatic relief than medical treatment
- Medical treatment: with α/β blockade and α -methyl-Paratyrosine
- Local palliative tumour control → using ablation techniques and Embolisation
- Radiotherapy:
 - Systemic treatment of mets with radioactive ^{131}I -MIBG may be instituted.
 - Before initiation of therapy, MIBG uptake by tumour targets should be demonstrated with traditional MIBG imaging
 - Symptomatic response is seen in up to 2/3rd patients.
 - > 40% of patients → reduction in catecholamine levels
 - Tumour volume reduction ~ 30%
 - But, complete responses → < 5%

Treatment of Malignant PCC

- High-dose radiotherapy (Rose and colleagues (2003))
 - ^{131}I -MIBG at 2 to 3.5 times its usual dose
 - Although toxicity was not trivial, 25% of patients exhibited a lasting complete response
 - Two of these patients had both bony and soft tissue metastatic lesions.
 - Given significant toxicity, routine use continues to be controversial
- Chemotherapy

Treatment of Malignant PCC

- Combination of Cyclophosphamide, Vincristine, and Dacarbazine (CVD)
- Response rates can be significant
 - > 50% radiographic tumour response
 - ~ 75% biochemical response
 - Generally short-lived (2 years)
- Primarily used in patients who have
 - Failed MIBG therapy
 - Tumours which do not demonstrate MIBG uptake on initial MIBG imaging
- Combination therapy with CVD and MIBG has been explored but its risks and benefits are poorly defined

Prognosis

- Some patients with metastatic disease progress rapidly, while others exhibit nonaggressive disease and can live > 20 years
- Bone metastases appear to carry the most benign prognosis
- 5-year survival ~ 50%

Adrenal Insufficiency – addison's disease

- Addison's disease is named after Thomas Addison, Thomas Addison was born in April 1793, but his exact birthdate is not known.
- was a renowned 19th-century English physician and scientist. He is traditionally regarded as one of the "great men" of Guy's Hospital in London.
- Thanks to his teachers, Addison became fascinated by diseases of the skin. This fascination, which lasted the rest of his life, led him to be the first to describe the changes in skin pigmentation typical of what is now called Addison's disease, in 1849.
- The adjective "Addisonian" is used to describe features of the condition, as well as people with Addison's disease.
- Thomas Addison suffered from many episodes of marked depression. On 29 June 1860, he committed suicide.

Adrenal insufficiency

- Adrenal insufficiency may be due to
 - Primary adrenal failure or
 - Secondary to extra-adrenal mechanisms.
- Estimated prevalence = 39-60/million
- **If not anticipated and appropriate proactive therapies instituted, addisonian crises following simultaneous or staged bilateral adrenalectomy can result in death**

Pathophysiology: Primary Addison's

- In Western world, MC cause of primary adrenal insufficiency = autoimmune adrenalitis.
 - This condition can occur in isolation or as a constellation of pathologies known as autoimmune polyendocrine syndrome
- In developing countries = Tuberculosis is MC etiology of adrenal failure
- Other infectious causes:
 - CMV in setting of HIV infection
 - Rare fungal adrenalitis (destroys cortex)
- Bilateral adrenal haemorrhage
- Infiltrative diseases: such as amyloidosis, sarcoidosis, hemochromatosis

Pathophysiology: Primary Addison's

- Bilateral metastatic disease involving the adrenals, while classically described as a potential cause of adrenal insufficiency, is a very rare cause
- Simultaneous or staged surgical loss of bilateral adrenal tissue following treatment of adrenal or renal disease
- Pharmacologic adrenalectomy with inhibitors of steroid hormone synthesis (ketoconazole) or new 17 α -hydroxylase (CYP-17) inhibitors (Aberaterone)

APS 1

- also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), Whitaker syndrome
- or candidiasis-hypoparathyroidism-Addison's disease-syndrome
- It is a genetic disorder inherited in autosomal recessive fashion due to a defect in the AIRE (Auto immune regulator) gene which is located on chromosome 21 and normally confers immune tolerance.

APS 2

- Polyglandular autoimmune syndrome type II (PGA-II) is the most common of the immunoendocrinopathy syndromes. It is characterized by the obligatory occurrence of autoimmune Addison disease in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus. Primary hypogonadism, myasthenia gravis, and celiac disease also are commonly observed in this syndrome.
- The definition of the syndrome depends on the fact that if one of the component disorders is present, an associated disorder occurs more commonly than in the general population. The most frequent clinical combination association is Addison disease and Hashimoto thyroiditis, while the least frequent clinical **combination is Addison disease, Graves disease, and type 1 diabetes mellitus**. The complete triglandular syndrome is sometimes referred to as **Carpenter syndrome**.
- PGA-II occurs primarily in adulthood, usually around the third and fourth decades of life. It is associated with HLA-DR3 and/or HLA-DR4 haplotypes, and the pattern of inheritance is autosomal dominant with variable expressivity.

Pathophysiology: Secondary Addison's

- Secondary = abnormalities in pituitary gland (MC) & hypothalamus (LC).
- Less Common
- Tumours
 - Radiation
 - autoimmune conditions
 - pituitary apoplexy (also known as Sheehan syndrome, when it occurs peripartally)
 - trauma are less common causes of the condition
- Rare
- Congenital conditions: Metabolic error in production of pituitary hormones, including ACTH

Pathophysiology: Secondary Addison's

- Exogenous chronic administration of Glucocorticoids → suppression of HPA axis → secondary adrenal insufficiency
- *Importantly, given that aldosterone secretion by the adrenals does not depend on ACTH, the zona glomerulosa continues to function appropriately in patients with secondary adrenal insufficiency. **Mineralocorticoid deficiency is therefore only present in patients with primary Addison disease***

Clinical Features

SYMPTOMS	PATHOPHYSIOLOGY
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency Adrenal androgen deficiency
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting (more frequent in primary adrenal insufficiency)	Glucocorticoid deficiency Mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency Glucocorticoid deficiency
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Dry and itchy skin (in women)	Adrenal androgen deficiency
Loss or impairment of libido (in women)	Adrenal androgen deficiency

Clinical Features

SIGNS	PATHOPHYSIOLOGY
Skin Hyperpigmentation (primary adrenal insufficiency only)	Excess of POMC-derived peptides
Alabaster-coloured pale skin (secondary adrenal insufficiency only)	Deficiency of POMC-derived peptides
Fever	Glucocorticoid deficiency
Low blood pressure (systolic RR < 100 mm Hg), postural hypotension (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency Glucocorticoid deficiency
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Hyponatremia	Mineralocorticoid deficiency Glucocorticoid deficiency (leading to SIADH)

Clinical Features

SIGNS	PATHOPHYSIOLOGY
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Anemia, lymphocytosis, eosinophilia	Glucocorticoid deficiency
Increased thyroid stimulating hormone (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)
Hypercalcemia (primary adrenal insufficiency only)	Glucocorticoid deficiency
Hypoglycaemia	Glucocorticoid deficiency
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency



President JFK and his family. Notice his noticeably darker skin, presumably due to the hyperpigmentation of Addison's Disease.
Photo courtesy: <http://www.americanpresidents.com/john-f-kennedy/>



Addison's Disease

Diagnosis

- Low plasma cortisol at 8am
- Cosyntropin stimulation test
 - Synthetic ACTH (cosyntropin), 250 µg, given parenterally (IM or IV)
 - Serum cortisol obtained 30 - 60 min later
 - Normally, cortisol rises to >20 µg/dL
- For patients taking steroids, hydrocortisone must not be given for at least 8 h before the test
- Other corticosteroids do not interfere with specific assays for cortisol (prednisone, dexamethasone)

Addison's Disease

• **Diagnosis**

- DHEA > 1000 ng/ml **RULES OUT** diagnosis
- Serum DHEA (Dihydroepiandrosterone) levels are <1000 ng/ml in 100% of patients with Addison's disease (not much help 15% normal patients also)

Addison's Disease

• **Imaging studies (if diagnosis not clear)**

- Chest x-ray for TB, fungal infection, or cancer
- Abdominal CT
 - Small noncalcified adrenals in autoimmune Addison's disease
 - Adrenals enlarged in about 85% of cases of metastatic or granulomatous disease
 - Calcification noted in cases of tuberculosis (~50%), hemorrhage, fungal infection, and melanoma

Treatment

- Perioperative stress-dose steroid administration = controversial
- *Although continuing the patient's usual steroid dose is usually sufficient, given the negligible downside of perioperative steroid coverage and the potential catastrophic consequences of failure to prevent an adrenal crisis, surgeons continue to administer stress-dose steroids perioperatively.*
- Again, because aldosterone physiology is not altered in these patients, **Mineralocorticoid replacement is unnecessary**

PERIOPERATIVE GLUCOCORTICOID DOSING IN PATIENTS ON CHRONIC STEROID THERAPY		
DEGREE OF SURGICAL STRESS	DEFINITION	GLUCOCORTICOID DOSE
Minor	Procedure under local anesthesia and less than 1 hour in duration (e.g., inguinal hernia repair)	Hydrocortisone 25 mg or equivalent
Moderate	Procedure such as vascular surgery of a lower extremity or a total joint replacement	Hydrocortisone 50 to 75 mg or equivalent This could be continuation of usual daily steroid dose (e.g., prednisone 10 mg per day) and hydrocortisone 50 mg intravenously during surgery
Major	Procedure such as esophagogastrectomy or operation on cardiopulmonary bypass	Usual glucocorticoid (e.g., prednisone 40 mg or the parenteral equivalent within 2 hours before surgery) and hydrocortisone 50 mg intravenously every 8 hours after the initial dose for first 48 to 72 hours of the postoperative period

Relative Potency Of Common Glucocorticoid Preparations

Name	T ½ (Hrs)	Relative Anti-inflammatory Potency	~ Adult Physiologic Replacement Dose mg/d
Hydrocortisone (cortisol)	8-12	1	20
Cortisone acetate		0.8	25
Prednisone	18-36	4	5
Prednisolone		4	5
Methylprednisolone		5	4
Triamcinolone		5	4
Dexamethasone	36-54	25-50	0.5

Prognosis

- Impact on life expectancy in 1^o adrenal insufficiency = not established
- Significant impact on patient's QoL
 - Decreased energy
 - Loss of libido
 - Psychologic maleffects
- Secondary adrenal insufficiency due to hypopituitary disease = established cause of premature death

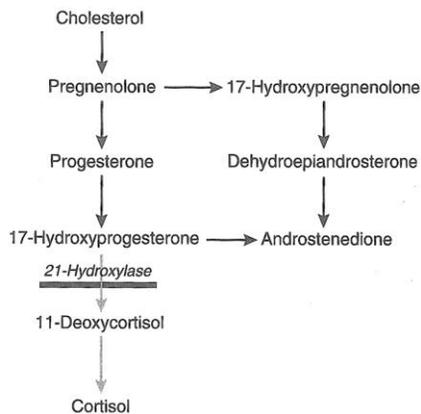
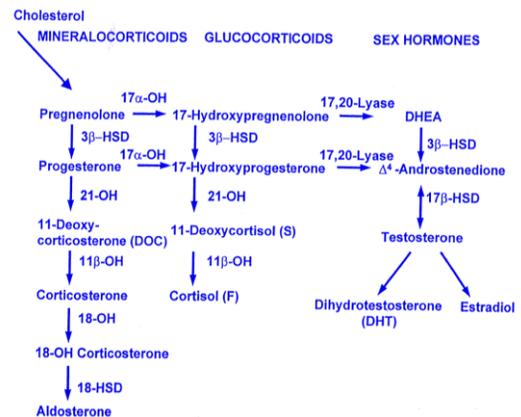
Congenital Adrenal Hyperplasia

Steroid biosynthetic enzymes

- 1) Cholesterol side chain cleavage=ccc (20,22 desmolase)
- 2) 3 β -Hyoxysteroid dehydrogenase
- 3) 17 α hydroxylase and 17,20 -lyase
- 4) **21 β -Hydroxylase**
- 5) 11 β -Hydroxylase
- 6) Aldosterone synthetase (11 β ,18 hydroxylase & 18 oxidase)

Congenital Adrenal Hyperplasia

- The first case was described in 1865
- Family of inherited disorders of adrenal steroidogenesis
- Each disorder results from a deficiency of one of several enzymes necessary for steroid synthesis
- Autosomal Recessive (M=F)
- 21-hydroxylase \downarrow is the common form



CAH due to 21-Hydroxylase Deficiency

- 90–95% of CAH cases are caused by 21- OHD
- Females affected with severe, classic 21- OHD are exposed to excess androgens prenatally and are born with virilized external genitalia

Presentations of 21 HCAH

- Ambiguous genitalia in girls
- Dehydration
- Shock
- Salt-loss presentations with electrolytes imbalance
 - Hyponatremia
 - Hyperkalaemia
- Hypoglycemia
- Hyperpigmentations

21-Hydroxylase Deficiency: 21-OHD-CAH

Classic: No or very little enzyme activity (1/15,000 births)

Nonclassic: Low enzyme activity (1/100 births)

Feature:	Classical:	Non-classical:
Prenatal virilization:	Present in Females	Absent
Postnatal virilization:	Males & Females	Variable
Salt-wasting:	> 75% of cases	Absent
Cortisol Deficiency:	100%	Rare

Virilized Females:



Adult Virilized female:



Congenital Adrenal Hyperplasia.

- An genetic disorder producing deficiency of the adrenal enzyme 21-hydroxylase.
- Not enough cortisol is produced, to inhibit adrenocorticotrophic hormone.
- Steroid synthesis increases.
- Affected females display masculinised genitals, and show masculinised behaviours ('tomboyian').
- Males may show precocious puberty.

<http://psych.umn.ac.uk/users/nick/hormonespp03/sld023.htm>



BOYS WITH CAH

Are unrecognized at birth because their genitalia are normal.

- Present early with salt wasting crisis resulting in dehydration, hypotension, hyponatremia and hyperkalemia

Or present later in childhood with early pubic hair, precocious puberty and accelerated growth



Increased androgen production results in ambiguous genitalia in newborn girls.

Nonclassical CAH

- ❑ **Residual enzyme activity.**
- ❑ **Non salt losing CAH**
- ❑ **present late in childhood with precocious pubic hair and/or clitoromegaly and accelerated growth.**
- ❑ **Present in adolescence or adulthood with varying virilizing symptoms ranging from oligomenorrhea to hirsutism and infertility.**

Diagnosis

- Serum electrolytes & glucose
 - Low Na & high K
 - Fasting hypoglycemia
 - Elevated serum urea due to associated dehydration
- Elevated plasma Renin & ACTH levels
- Low Cortisol
- High 17 – OHP
- High androgens especially testosterone level
- Low Aldosterone
- Urinary steroid profile
- Chromosomes
- Pelvic US

Management

- Hydrocortisone
- Fludrocortisone 0.05 - 0.2 mg/day
- Triple hydrocortisone during stress.
- During adrenal crisis intravenous hydrocortisone and IV fluid
- Surgery for female external genitalia