

Cushings Disease

History of Presenting Illness

- weight gain, → BUFFALO HUMP with supraclav fat pads, moon face, central obesity
- purple stretch marks,
- easy bruising,
- skin thinning.
- irregular menses hirsutism.
- difficulty climbing stairs, getting out of a low chair, and raising their arms.
- Depression
- cognitive dysfunction
- emotional lability
- bone disease (fractures)
- STOMACH ULCERS from corticosteroid excess
- Appetite Gain!
- Exacerbation of diabetes
- Hypokalemia (weakness)
- hypernatremia

HEADACHE, POLYURIA, NOCTURIA, GALACTORRHOEA?
Changes in pigmentation?? DARKER? *Acanthisis Nigricans?*
It can only be → **ACTH SECRETING ADENOMA!!**

CUSHINGOID FEATURES WITH HIRSUTISM AND VIRILISATION? → BUT NO PIGMENT CHANGES??
Think about an **ADRENAL CARCINOMA!!**

ACUTELY cortisol excess causes EUPHORIA
CHRONICALLY cortisol excess causes DEPRESSION

ELECTROLYTES ALL WRONG? MUCH ACNE, FLORID HYPERTENSION, OEDEMA, HIGH GLUCOSE,
...BUT: NO FAT REDISTRIBUTION? ACUTE ONSET?
Sounds like an **ECTOPIC NEOPLASTIC SOURCE**

Differential Diagnoses

- Hypothalamic disease (too much CRH)
- Primary Cushing Disease (ACTH-secreting pituitary adenoma)
- Adrenal cortisol-secreting adenoma
- Ectopic Neoplastic Source of cortisol eg. lung cancer (→ disease of decrepit old men)
- Use + Abuse of corticosteroid medication
- Hypercortisolism secondary to alcoholism
- Depression
- Hypothyroidism
- Hypoadrenalism

~ADRENAL CRISIS~

- hypotension
- Abdominal pain
- Vomiting
- Confusion
- Hypoglycaemia
- Hyponatremia (neuro symptoms)
- HYPERKALEMIA (!! → asystole)
- Metabolic acidosis

Findings on Examination

Hypertension

Proximal Muscle Weakness

MOUTH: candida infection?

SKIN :

Thinner, less subcutaneous tissue

(easily bruised and makes little wrinkly folds when pinched)

ECCHYMOSES

Acanthisis Nigricans → increased ACTH, therefore CANNOT be an adrenal carcinoma

→ A.N. points to pituitary or ectopic ACTHoma

Virilisation → adrenal carcinoma

Epidemiology

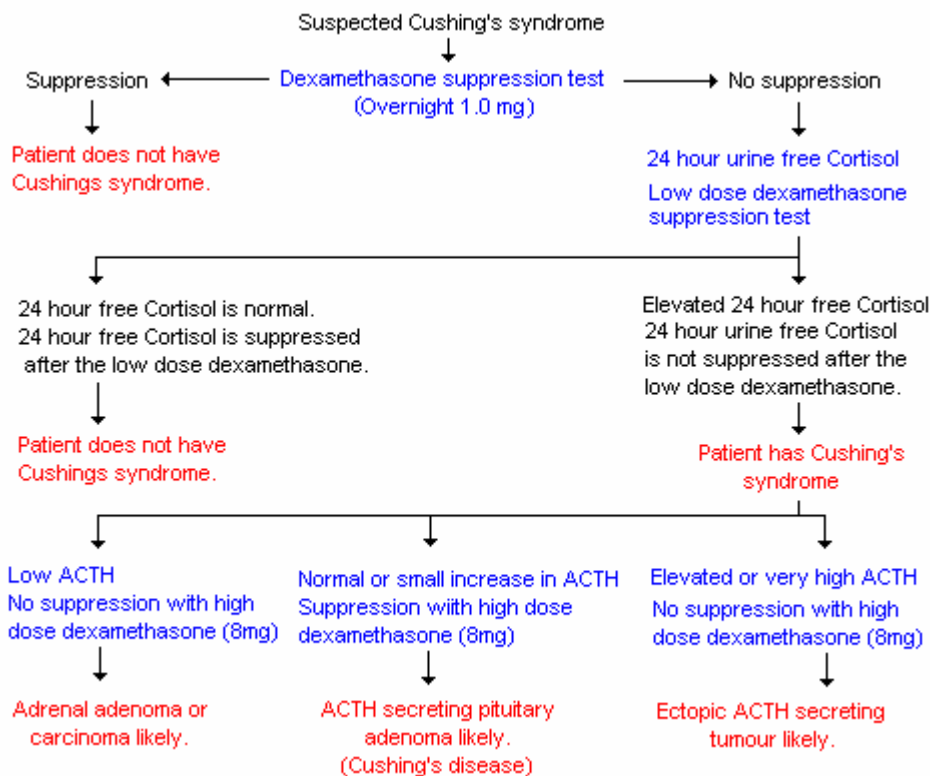
Sex:

- The female-to-male incidence ratio is approximately 5:1 for Cushing syndrome due to an adrenal or pituitary tumor.
- Ectopic ACTH production is more frequent in men than in women, due to the increased incidence of lung tumors in this population.

Age:

- The peak incidence of Cushing syndrome due to either an adrenal or pituitary adenoma occurs between ages 25 and 40 years. Ectopic ACTH production due to lung cancer occurs later in life.

Tests and Investigations: How is this diagnosis made?



Thus:

1. overnight dex test;
 2. low dose 48hr dex test
 3. 24hr free urine cortisol
 4. high dose dex test
 5. ACTH assay
- * ACTH assay will show whether the adrenal gland is responsible or not; obviously if the ACTH is high its not the adrenal's fault. The high dose dex test, therefore, will show if the extra ACTH is produced in the pituitary or in some other site (eg. lung cancer → because only the pituitary will be suppressed by the high dose dex; the cancer will not care about dex.

Firstly, you need to demonstrate an increased level of Cortisol.

Thus,

24 hour URINARY FREE CORTISOL:

measure the filtered cortisol in a 24 hour urine collection;

THIS WORKS because cortisol is filtered in the urine **IN PROPORTION** to its plasma concentration

SIMULTANEOUSLY measure the creatinine, so as to be sure it's a 24hr sample

NORMALLY: subject to diurnal variation

normal morning values (8-10am) in the range 200-650 nM

normal evening values approximately halved (120-390 nM).

Normal 24hr values: 200-800 nmol

MIDNIGHT PLASMA CORTISOL

Night-time dip in cortisol levels is only something that happens to normal people;

THUS: if the level is way high, its certainly Cushings;

If the level is normal, THIS TEST WILL RULE OUT CUSHINGS

DEX SUPPRESSION TEST: overnight or low-dose (48hr)

ingestion of 1 mg of dexamethasone at 11 PM, with measurement of an 8-AM serum cortisol the next morning. **Dex pretends to be cortisol; THUS cortisol levels should be low by morning (negative feedback @ pituitary)**

IF THEY ARE STILL HIGH, THERE IS AN ABNORMALITY (OVERSECRETION)

Patients with pituitary dependent Cushings usually suppress their cortisol levels on high doses but patients with adrenal adenoma or carcinoma or ectopic ACTH do not.

High-Dose DEX SUPPRESSION TEST: 2mg every 6 hrs for 8 doses, + UFC

A decrease in UFC of greater than 50% is suggestive of an anterior pituitary adenoma, rather than ectopic ACTH or a primary adrenal tumor.

Unfortunately, the sensitivity of this test is only 80%, with a specificity of 70-80%.

The more stringent criterion of a 90% decrease in UFC levels excludes the diagnosis of ectopic ACTH and has 100% specificity for anterior pituitary disease.

Failure to suppress cortisol on 8 mg/day indicates adrenal neoplasm or ectopic ACTH syndrome. In Cushing's disease, ACTH is suppressed by high dose dexamethasone; in the ectopic ACTH syndrome, ACTH is not suppressed; in adrenal neoplasia, ACTH levels are low in the baseline specimen.

NEGATIVE IMAGING FINDINGS DO NOT RULE OUT ANY TUMOUR!!!

SYNACTHEN STIMULATION TEST

First : take blood, test for cortisol and ACTH

Then: give intramuscular Synacthen

Then: collect blood @ 30, then 60 minutes.

Application: Investigation of suspected primary or secondary [adrenocortical insufficiency](#).

Interpretation: Failure to respond indicates adrenal insufficiency.

If basal ACTH is elevated, this suggests primary adrenal failure. Rarely, the test may be done after 3 days of priming the adrenal cortex with 1 mg depot Synacthen daily. This allows differentiation between primary adrenocortical failure (no response) and secondary adrenocortical failure.

Management

Step 1: If you're sick from the steroids, STOP THE DAMN STEROIDS.

Otherwise, surgery is the treatment of choice.

IF ACTH-SECRETING ADENOMA:

- **Trans-sphenoidal surgery**
- **And/or IRRADIATION** (indicated if tumour histology suggests metastatic risk; also improves long-term prognosis)

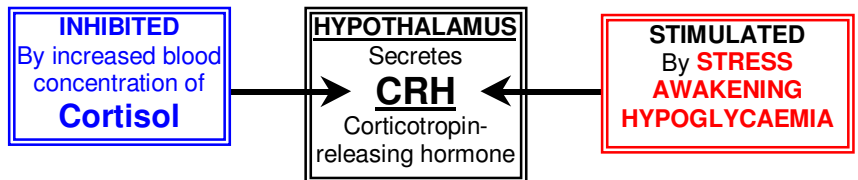
Psychosocial treatment may be necessary for sequelae of obesity

Then → you must replace the hormones of whatever gland you excised

Prognosis

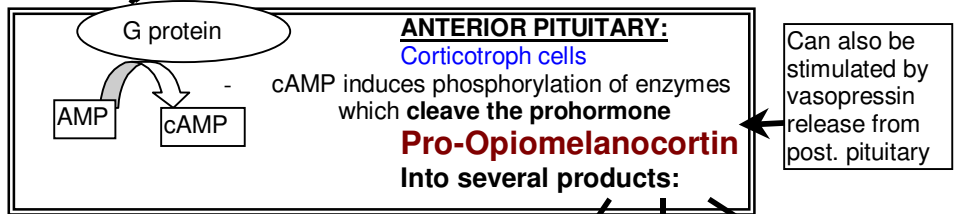
→ favourable if the surgery is curative, if the steroids are ceased without incident (i.e underlying disease controlled by some other means) and if the complications of cortisol excess are managed adequately

Cushings Disease from Exogenous Corticosteroid Excess 7.03



Cortisol Pharmacology:

- Circulates bound to **Cortisol Binding Globulin**
- Penetrates membranes easily, being a lipid-soluble steroid
- **Binds to cytoplasmic receptor**
- Receptor has to dimerise
- Dimer migrates to nucleus
- **Binds to relevant DNA portion**
- Activates mRNA transcription



KIDNEY: early effects, within hours
Cortisol binds equally well to gluco- and mineralo-corticoid receptors;
HOWEVER at MC receptors there is usually an enzyme (**11-beta- HSD**) which deactivates cortisol into cortisone. At high enough concentrations, it becomes oversaturated and cortisol acts on GC receptors.

THUS: cortisol causes aldosterone effects: Increased Na⁺, H₂O retention
Increased K⁺ excretion

THUS:

- **oedema**
- **hypertension**
- **hypokalemia**
- **hypernatremia**

THUS overproduction of ACTH will be accompanied by **HYPERPIGMENTATION** (*Acanthosis Nigricans*)

MSH
Melanocyte stimulating hormone

endorphins

ACTH
Adreno - Cortico - Tropic Hormone

Circulating ACTH will eventually reach the **ADRENAL CORTEX: ZONA FASCICULATA (middle ctx)**
Where it induces **CORTISOL** production via the G-protein cAMP cascade (phosphorylation of about ten enzymes necessary to turn **cholesterol** into **cortisol**)

Exogenous steroids

Cortisol cross-reacts with androgen receptors at high enough concentrations; thus → **HIRSUTISM**

PSYCHOLOGICAL CHANGES
Acutely: **Euphoria**
Chronically: **Depression**
Plus, **INCREASED APPETITE**

CORTICO-STEROID EXCESS

BLOOD VESSELS:
Increased sensitivity to Noradrenaline
THUS → **HYPERTENSION**

ANTERIOR PITUITARY
Sensitisation to vasopressin, resulting in more ACTH release (...?)

LIVER
Stimulation of **glyconeogenesis** and **glycogen storage**; glucose for this is made from amino acids in the bloodstream

PERIPHERAL ADIPOCYTES
Expression of **hormone-sensitive lipase** → thus, lipolysis and release of free fatty acids into the bloodstream

CENTRAL ADIPOCYTES
...don't seem to have H-SL and thus continue to accumulate lipids as per normal;
THUS fat is redistributed towards the centre;
→ **TRUNKAL OBESITY**

MUSCLES: insulin resistance @proximal type 2a glycolytic fibres → lower glucose uptake, thus switch to pyruvate metabolism, and production of lactate: → **MYALGIA acutely, then WASTING** in the long term as the muscle fibres starve

MOST TISSUES: upregulation of **UBIQUITIN**, thus proteolysis and release of amino acids for the liver

SKIN: Proteolysis of collagen and inhibition of its synthesis → **THINNING of SKIN, EASY BRUISING** due to loss of subcutaneous collagen padding

VASCULAR ENDOTHELIUM
Reduced expression of Tissue Plasminogen Activator, THUS → reduced clot lysis → **BRUISES PERSIST**

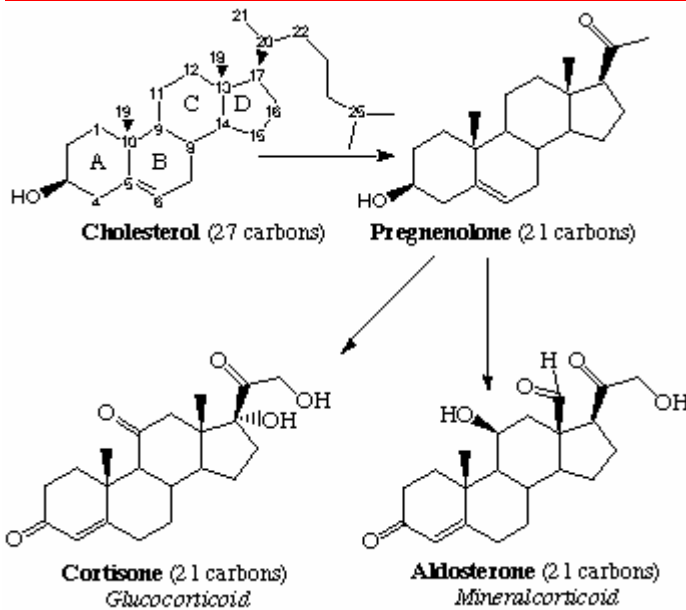
IMMUNE SYSTEM

1. Inhibition of COX2 enzyme expression
2. Expression of lipocortin; thus → inhibition of phospholipase A2
3. Macrophages apoptose.
4. Inhibition of protease, elastase, collagenase, etc. THUS → decreased migration of granulocytes
5. Inhibition of IL-12
thus shift from Th1 to Th2 cells (less cellular, more humoral immunity)
6. Inhibition of T-cell maturation
7. sequestration of eosinophils in secondary lymphoid organs;

so, overall,
IMMUNE SUPPRESSION

PHARMACOLOGY OF GLUCOCORTICOIDS

Cholesterol, and each of the steroid hormones, have four rings designated A, B, C, and D



formation is stimulated by the anterior pituitary hormone ACTH

THERE ARE five major classes of steroid hormones.

- **progestagens** (progestational hormones),
- **glucocorticoids** (stressing hormones),
- **mineralcorticoids** (Na⁺ uptake regulators),
- **androgens** (male sex hormones),
- **estrogens** (female sex hormones).

Pregnenolone is an intermediate in the synthesis of all steroid hormones. It is derived from cholesterol by two hydroxylations (two steps), at C20 and C22, followed by cleavage between C20 and C22 as catalyzed by the mitochondrial enzyme desmolase (below). The net result is that six (6) carbons are removed from the C17 sidechain. All three steps require molecular oxygen (O₂) and NADPH. Pregnenolone

GLUCOCORTICOIDS:

- synthesised in the adrenal cortex from cholesterol.
- The major hormone is hydrocortisone (cortisol).

Important synthetic steroids

- prednisolone,
 - dexamethasone,
 - beclomethasone,
 - betamethasone,
 - budesonide
 - fluticasone.
- **act on intracellular steroid receptors in the cytoplasm.**
- On binding the receptor **translocates to the nucleus**
- There it **binds to special nucleotide sequences** on target genes known as **glucocorticoid response elements** (GRE)
- The bound receptor **initiates, or represses, the transcription of mRNA encoding particular proteins.**

Important therapeutic actions are anti-inflammatory and immunosuppressant.

Thus: physiological actions on carbohydrate, protein and fat metabolism are generally unwanted, *except when hydrocortisone is used for hormone replacement in Addison's disease.*

GLUCOCORTICOIDS HAVE SOME MINERALOCORTICOID ACTIVITY!

- causing Na⁺ retention, K⁺ and Ca⁺⁺ loss.

The therapeutic implications of the cellular actions of GCs are:

- effects depend on changing protein transcription, do not occur for several hours
- regular use of GCs is important for maximum benefit
- non-selectivity of GCs results in many unwanted side-effects

Only about 10% of circulating cortisol is free. The remaining majority circulates bound to plasma proteins, particularly corticosteroid-binding globulin (transcortin). This protein binding likely decreases the metabolic clearance rate of glucocorticoids and, because the bound steroid is not biologically active, tends to act as a buffer and blunt wild fluctuations in cortisol concentration.

Nearly all cells express GC receptors; within each are 10-100 GREs.

mechanism of the anti-inflammatory action is not fully understood.

- GCs inhibit the expression of the enzyme cyclooxygenase-2 (COX-2).
- Whereas COX-1 is constitutive (ie is always present), COX-2 is inducible (ie is present only under certain circumstances such as inflammation).
- COX activity stimulates the formation of inflammatory prostanoids (eg PGE2 and PGD2).
- GCs also induce the formation of lipocortin 1 which inhibits phospholipase A2 (PLA2).
- **Inhibition of PLA2 inhibits**
- the synthesis of the inflammatory mediators leukotrienes (eg LTB4 and LTD4),
- platelet activating factor (PAF)
- prostanoids.

Hence, the net result of stimulation of GC receptors is reduced synthesis of all the inflammatory mediators derived from phospholipids.

Eicosanoids are involved in early inflammatory reactions eg as oedema, vasodilatation and migration of leucocytes. **Therefore, inhibition of the arachidonic acid cascade** accounts partly for the **early antiinflammatory** activity of glucocorticoids.

GCs also inhibit the late manifestation of inflammation

(proliferation of capillaries and fibroblast, deposition of collagen)

, in part, by inhibiting the production and/or function of lymphokines such as IL1, IL2 and TNF.

Inhibition of lymphokine activity also suppresses the immune system.

The name *glucocorticoid* derives from early observations that these hormones were involved in glucose metabolism.

In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood.

These effects include:

- **Stimulation of gluconeogenesis, particularly in the liver:** This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.
- **Mobilization of amino acids from extrahepatic tissues:** These serve as substrates for gluconeogenesis.
- **Inhibition of glucose uptake in muscle and adipose tissue:** A mechanism to conserve glucose.
- **Stimulation of fat breakdown in adipose tissue:** The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

- Inhaled (topical) GCs, beclomethasone, budesonide and fluticasone, are used in asthma for treatment and prophylaxis, (most potent), usually 2-4 times daily.
- Orally active GCs include, dexamethasone, betamethasone and prednisolone (least potent) and often the drug of choice in acute deteriorations of asthma.
- Oral GCs are also used for rheumatoid arthritis, inflammatory bowel disease and as an immunosuppressant after organ or bone marrow transplantation.
- Dexamethasone and betamethasone have little mineralocorticoid activity, appropriate when suppression of ACTH secretion is required (eg adrenal hyperplasia).
- They are also used to reduce cerebral oedema in patients with brain tumours.
- **Dexamethasone is used to test for Cushing's disease.**
- The endogenous hormone hydrocortisone is given iv for emergency treatment of anaphylaxis and severe asthma, and for the treatment of Addison's disease along with fludrocortisone (mineralocorticoid).
- Hydrocortisone is also used topically for the management of inflammatory skin conditions.

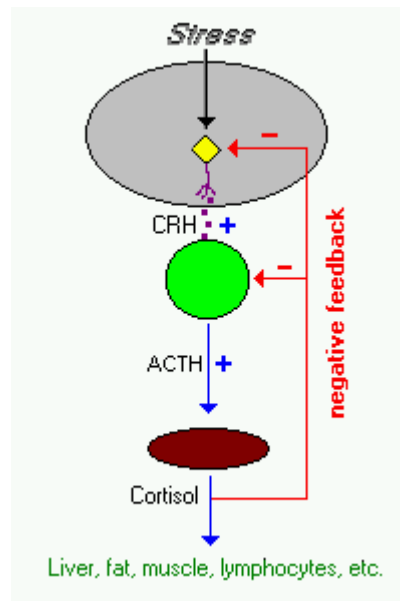
Pharmacokinetic properties of GCs vary;

- $t_{1/2}$ being for hydrocortisone short of 8-12 hours;
- prednisolone intermediate 12-36 hours; dexamethasone and betamethasone long, 36-72 hours.

GCs are metabolised in the liver and excreted in urine.

Unwanted effects are numerous, usually dose related:

- diabetes,
- muscle wasting (**proximal myopathy**),
- hypertension,
- adrenal suppression,
- bruising,
- thinning of skin,
- psychiatric disturbances,
- osteopaenia
- Cushings syndrome (including moon face, striae and acne).



Topical application reduces, but does not completely eliminate, the unwanted systemic actions of GCs.

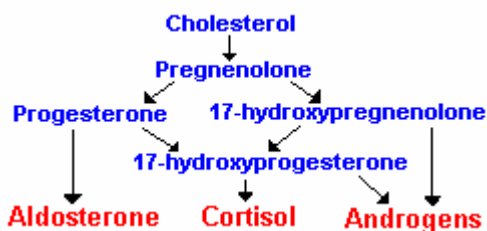
Systemic effects may occur with a daily dose above 1200 µ g, especially if other risk factors are present. Topical GCs have additional, site specific, side effects. Inhaled, they commonly cause oral candidiasis, dysphonia and sore throat, effects minimised by using a spacer device. On the face, GCs may cause acne rosacea and perioral dermatitis.

In children, growth suppression can occur with oral GCs

With inhaled GCs, monitoring of linear growth is recommended, although not usually a problem.

During pregnancy, adrenal development in the foetus may be affected

- . Infections, eg. tuberculosis, fungal diseases or cellulitis, may be exacerbated or reactivated.
- Long-term use of oral GCs is associated with adrenal atrophy up to 36 months after stopping therapy.
- Such patients may require treatment with GCs (usually hydrocortisone), in the event of an illness or surgical emergency, to prevent acute adrenal insufficiency.



Like all steroid hormones, cortisol and aldosterone bind to their respective receptors, and the resulting hormone-receptor complexes bind to a hormone response element to modulate transcription of responsive genes. **Although the physiologic effects of these two steroid hormones are distinctly different, their receptors are quite**

STEROID BIOSYNTHESIS

Steroids are bioactive agents that are synthesised from cholesterol. They have a common carbon-based nucleus composed of three six membered rings (rings A to C) fused to a single five membered ring (D)

Steroids (excluding vitamin D which is a related chemical species) fall into five main groups:

- Glucocorticoids (especially Cortisol ie., hydrocortisone)
- Mineralocorticoids (especially Aldosterone)
- Androgens (especially Testosterone and Dihydrotestosterone but also adrenal androgens)
- Estrogens (especially Estradiol)
- Progestogens (especially Progesterone).

They are synthesised at the following sites:

- **The adrenal cortex:** aldosterone, cortisol and adrenal androgens (androstenedione and DHEA)
- **The gonads (testis or ovary):** testosterone, estradiol, progesterone
- **The placenta:** estradiol and progesterone
- **Fat:** peripheral conversion of testosterone to estradiol

The Adrenal Cortex

The adrenal cortex is organised into **three circumferential zones:**

- **zona Glomerulosa**, aldosterone, controlled by renin-angiotensin system
- **zona Fasciculata**, of cortisol, controlled by pituitary ACTH
- **zona Reticulatum**, androgens, (androstenedione and dehydroepiandrosterone) controlled by pituitary ACTH

The nature of the major steroids synthesized in the adrenal cortex depends upon the level of key enzymes expressed there.

The Testis

Leydig cells synthesize testosterone. Following bilateral orchidectomy, men become, impotent and infertile.

Testosterone production is normally stimulated by luteinising hormone (LH) secreted by the anterior pituitary under the influence of hypothalamic gonadotrophin releasing hormone (GNRH).

Some estradiol is produced in men by aromatase present in fat cells, but not in testis.

The Ovary

Estradiol is produced principally in ovarian follicular cells are the major sites of estradiol production in non-pregnant, pre-menopausal women, promoted by follicle stimulating hormone (FSH) from the anterior pituitary gland under the influence of hypothalamic GNRH. After ovulation, the corpus luteum synthesizes and releases progesterone under stimulation by LH.

The Placenta

During pregnancy, the cytotrophoblasts and syncytiotrophoblasts of the placenta secrete estradiol and progesterone under the control of placental (human) chorionic gonadotrophin (HCG).

A common plan of steroid synthesis

Basic steroid synthesis is similar at each production site, different products depend on upon whether or not key enzymes are expressed. Steroid synthesis proceeds from cholesterol to *pregnenolone* and *progesterone* key intermediates. Progesterone is then converted to cortisol, aldosterone or one of the sex steroids

Control of adrenal steroid synthesis

Aldosterone synthesis depends on release of the protease renin from the renal juxtaglomerular apparatus when salt is depleted. Renin converts circulating angiotensinogen to angiotensin-I (A-I). A-I is converted to A-II by angiotensin converting enzyme (ACE). A-II activates aldosterone synthesis and release.

Cortisol and adrenal androgen is synthesised when ACTH activates a surface receptor coupled to cyclic AMP generation. ACTH is released by hypothalamic corticotrophic releasing hormone (CRH) The hypothalamus-pituitary-adrenal cortex axis is under negative feedback control by cortisol.

Cushing's Disease

Cushing's Disease, one cause of Cushing's syndrome (elevated levels of circulating glucocorticoids), is due to an ACTH - secreting pituitary tumour. Increased circulating ACTH accelerates cortisol synthesis and release as well as adrenal hyperplasia. Elevated cortisol is responsible for most clinical features, although ACTH induces skin hyperpigmentation.

Addison's Disease

Autoimmune-mediated atrophy of the adrenal cortex results in reduced cortisol, aldosterone and adrenal androgen. The disease can be life-threatening particularly at times of stress. Low cortisol results in hypersecretion of ACTH and hyperpigmentation.

Congenital Adrenal Hyperplasia

A deficiency of an enzyme (e.g., 21-hydroxylase) reduces circulating cortisol levels. Aldosterone synthesis may also be impaired, with salt wasting and life-threatening hypotension. Low cortisol reduces normal feedback, leading to uncontrolled ACTH secretion, stimulating adrenal hyperplasia the synthesis of adrenal androgens. Thus, masculinization is a feature of the disorder in female infants.

Glucocorticoid effects on intermediary metabolism

Glucocorticoids (e.g., cortisol) have important tissue-specific effects on carbohydrate, protein and fat metabolism **that persist for hours**. In general, **cortisol acts to redistribute fuel reserves from peripheral sites**, especially from muscle and peripheral fat stores, **to the liver and central fat stores**. Physiologically, cortisol levels **are highest in the early morning and lowest at night** but its effects on bodily metabolism persist for hours after its peak levels are attained because of its effects on the size and distribution of energy stores.

Muscle

Cortisol has a number of effects on muscle including:

- suppressed glucose oxidation resulting in the production and release of lactate (by anaerobic glycolysis)
- decreased glucose uptake (it reduces the sensitivity of muscle to insulin)
- elevated proteolysis leading to the release of amino acids (chiefly glutamine and alanine)

Protein breakdown in muscle is normally offset by continued protein synthesis but may be excessive under conditions of continuing elevated serum cortisol levels (Cushings syndrome) leading to muscle wasting (myopathy).

Liver

Lactate and amino acids released from muscle under the influence of cortisol are taken up by the liver and converted to glucose by the enzymes that constitute the biochemical pathway known as gluconeogenesis. The redistribution of glucose from muscle to the liver via lactate and gluconeogenesis is known as the *Cori cycle*. In the presence of cortisol, glucose produced from gluconeogenesis is not released by the liver but is stored as glycogen. Hepatic glycogen is an important source of glucose during short-term fasting e.g., during sleep. Amino groups, which are released in hepatocytes from amino acids as toxic ammonium ions, are eliminated by the hepatic synthesis of urea followed by renal excretion.

Carbohydrate metabolism

Cortisol, along with glucagon from pancreatic islet α -cells, and circulating adrenalin from the adrenal medulla acts as a key counter-regulatory hormone to the glucose-lowering action of insulin i.e., cortisol elevates and maintains plasma glucose levels. This is particularly important for the brain which is absolutely dependent on glucose as a metabolic substrate. However, cortisol also promotes the production of hepatic glycogen (an important bodily glucose store), whereas glucagon and adrenalin promote its breakdown.

Protein metabolism

Cortisol effects are most pronounced on protein metabolism in muscle in which it acts to enhance protein breakdown. This effect is antagonised by several key hormones including insulin, insulin-like growth factor-1 (IGF-1) and testosterone. Cortisol appears to activate protein breakdown by first upregulating the

synthesis of a small protein called ubiquitin. Ubiquitin is covalently attached to proteins thereby marking them for degradation (Mitch and Goldberg, 1996).

Fat metabolism

Cortisol also results in a redistribution of body fat from the periphery to central sites. It does this by selectively promoting the activity of the enzyme hormone-sensitive lipase in fat cells in peripheral sites leading to the release of free fatty acids into the circulation. These fatty acids are processed by the liver to very low density lipoproteins (VLDLs). VLDLs act as a source of fatty acids for incorporation into triacylglycerols in fat cells at central sites (having high lipoprotein lipase activity and low hormone-sensitive lipase activity). Alternatively, under fasting conditions, fatty acids are used by some tissues (especially the heart) as a source of metabolic substrate. As a result of the redistribution of fat stores from the periphery to central sites, hypercortisolemia (Cushings syndrome) results in central (abdominal) obesity and characteristic accumulations of lipid in the face (moon face) and at the back of the neck (buffalo hump).

Cortisol effects are commonly delayed

Unlike many hormones, e.g., glucagon and adrenalin, whose effects occur immediately, cortisol has delayed effects that are most pronounced after several hours. The delay arises as a result of the time taken for activated glucocorticoid receptors (which are cytoplasmic) to transfer to the nucleus, dimerise and bind to key DNA sequences (cortisol response elements), then activate (or, in some cases, repress) the transcription of key cellular enzymes followed by the translation of these mRNA transcripts into proteins and their targeting to the appropriate cell compartment/s.

Enzymes that are up-regulated by glucocorticoids

A large number of enzymes are upregulated by glucocorticoids such as cortisol. Control of enzyme levels is critical to its influence on bodily metabolism. Enzymes that are up-regulated include enzymes of:

- the gluconeogenic pathway (e.g., pyruvate carboxylase, phosphoenolpyruvate carboxykinase and fructose 1,6-bisphosphatase)
- the glycogen synthesis pathway (glycogen synthase)
- fat breakdown (hormone-sensitive lipase)

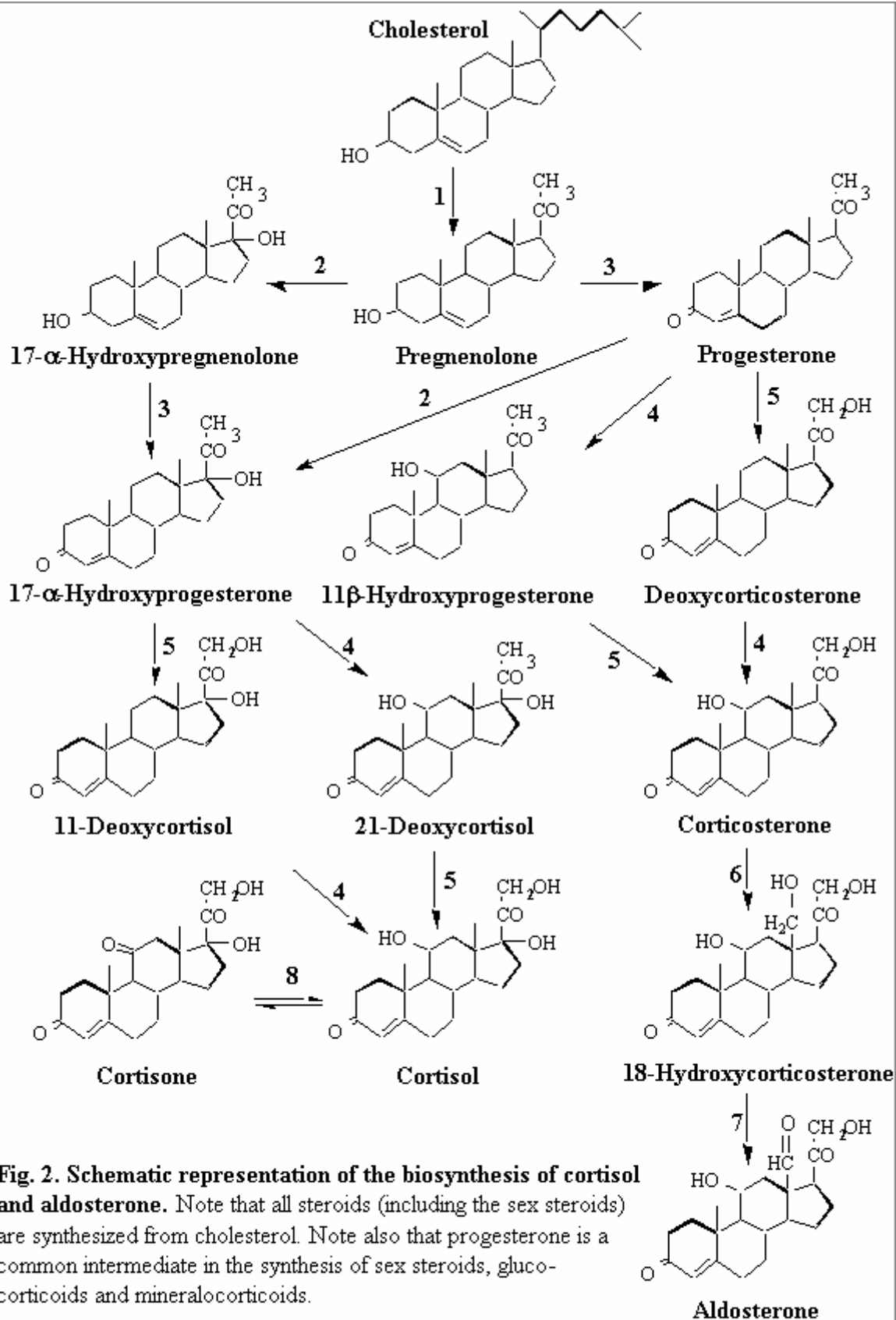
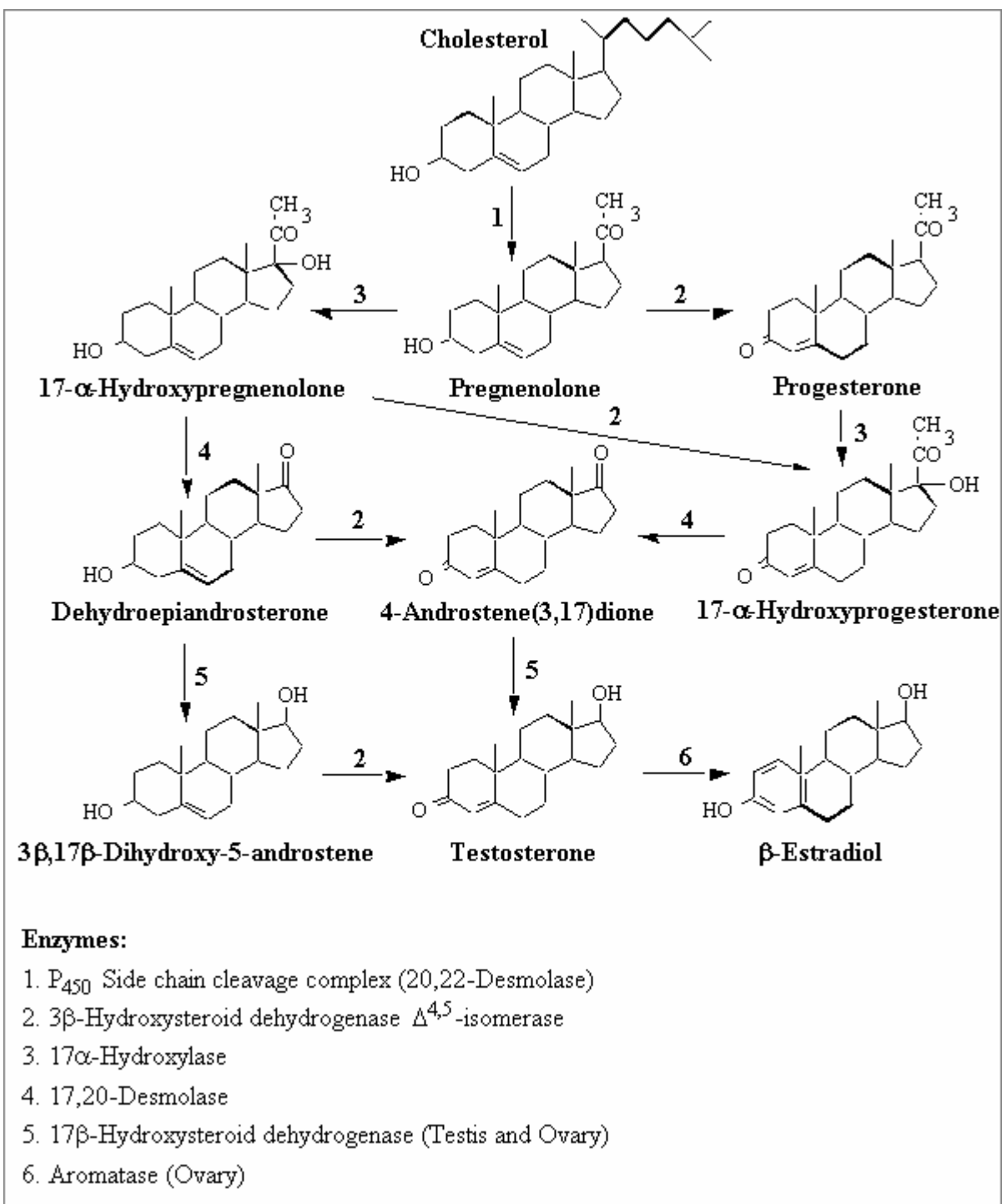


Fig. 2. Schematic representation of the biosynthesis of cortisol and aldosterone. Note that all steroids (including the sex steroids) are synthesized from cholesterol. Note also that progesterone is a common intermediate in the synthesis of sex steroids, glucocorticoids and mineralocorticoids.

Enzymes: 1. P₄₅₀ side chain cleavage (Desmolase) 2. 17- α -Hydroxylase
 3. 3 β -Hydroxysteroid dehydrogenase- $\Delta^{4,5}$ -isomerase 4. 11 β -Hydroxylase
 5. 21-Hydroxylase 6. 18-Hydroxylase 7. 18-Hydroxysteroid dehydrogenase
 8. 11 β -Hydroxysteroid dehydrogenase



Structure of the Adrenal gland

- The two adrenal glands are **embedded in the fat associated with the anterior poles of the kidneys**
- They lie beneath the peritoneum; they have a **flattened triangular shape**

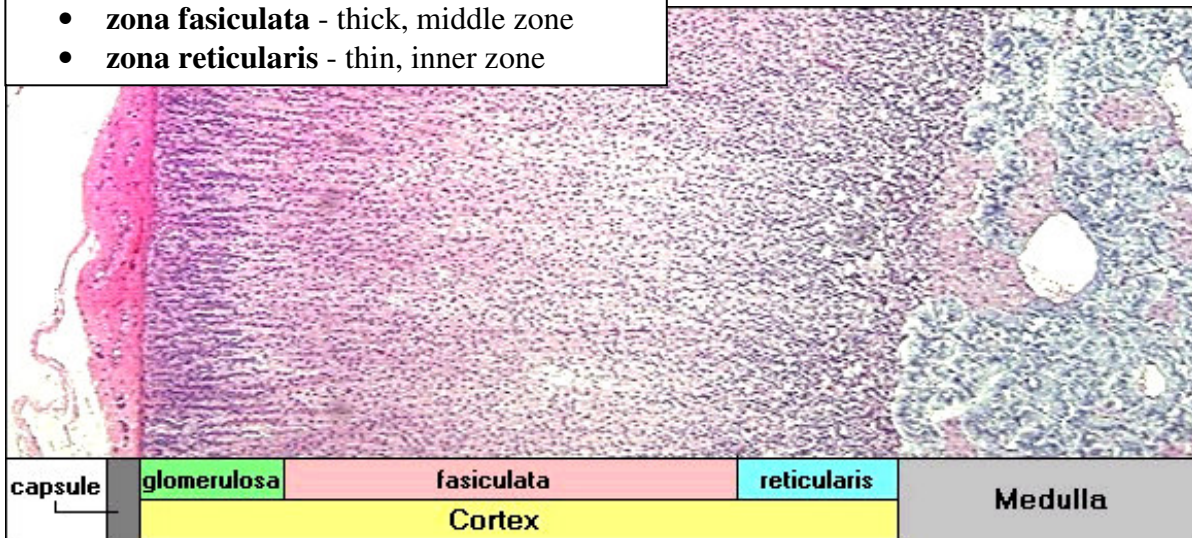
The glands are covered with a **thick connective tissue capsule**

finger-like processes (trabeculae) extend into the secretory parenchyma, carrying blood vessels and nerves,

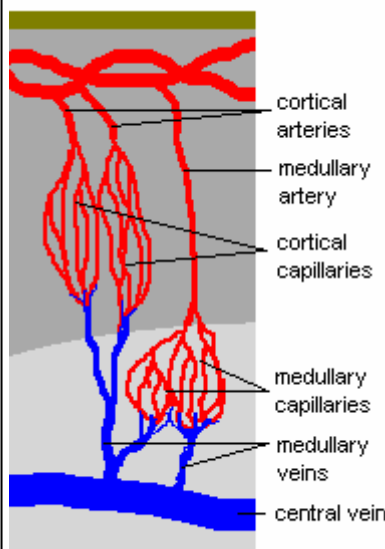
The most distinctive feature of the adrenal is its partitioning into cortex and medulla. The medulla is fairly homogeneous, but even when viewed a low power, **three concentric zones can be distinguished in the cortex:**

- **zona glomerulosa** - thin, outermost zone
- **zona fasciculata** - thick, middle zone
- **zona reticularis** - thin, inner zone

- An inner **medulla**, which is a source of the **catecholamines epinephrine and norepinephrine**. The **chromaffin cell** is the principle cell type. **The medulla is richly innervated by preganglionic sympathetic fibers and is, in essence, an extension of the sympathetic nervous system.**
An outer **cortex, which secretes several classes of steroid hormones**



Histologic examination of the adrenal reveals a rich vasculature. Numerous small arteries from several sources ramify over the surface of the gland and penetrate into the gland into two ways:
Cortical arteries and arterioles branch into capillary beds within the cortex to supply that area, then coalesce into veins at the corticomedullary junction.
Medullary arteries and arterioles penetrate the cortex without branching, then form capillary beds in the medulla. Blood from both cortical and medullary veins empties through a single large central vein, which leaves the adrenal and anastomoses with either the vena cava or renal vein.



(glucocorticoids and mineralocorticoids, plus a few others).

Histologic examination of the cortex reveals **three concentric zones of cells** that differ in the major steroid hormones they secrete.

Despite their organization into a single gland, the medulla and cortex are functionally different endocrine organs, and have different embryological origins. The medulla derives from ectoderm (neural crest), while the cortex develops from mesoderm. The utility, if any, of having them together in one discrete organ is not obvious. In some species, amphibians and certain fish, for example, two separate organs are found.

The vessels give rise to three principal patterns of blood distribution.

Capsular capillaries that supply the capsule.
Fenestrated cortical sinusoidal capillaries that supply the cortex and drain into the fenestrated medullary capillary sinusoids.
Sinusoidal (spaces between endothelial cells) and fenestrated (holes in the cytoplasm of endothelial cells) capillaries are important in these regions because they **allow efficient passage of secreted hormones into the vessel lumen**. The medulla is also supplied by medullary arterioles that travel within the trabeculae and bring arterial blood to the medullary capillary sinusoids. The venules that arise from the cortical and medullary sinusoids drain to the small medullary veins that **join to form the large medullary vein (adrenal vein)** that drains into the inferior vena cava.

Cortex	zona glomerulosa	mineralocorticoids (aldosterone)
	zona fasciculata	glucocorticoids (cortisol)
	zona reticularis	sex steroids (androgens)
		catecholamines

HISTOLOGY OF THE ADRENOCORTICAL ZONES

The adrenal cortex is divided into three distinct zones on the basis of the arrangement of its parenchymal cells.

The outer zona glomerulosa cells

- are arranged in ovoid clusters
- constitute about 15% of the cortical volume.
- They are continuous with the zona fasciculata cells
- The zona glomerulosa cells produce mineralocorticoid hormones which have an important function in the regulation of sodium and potassium homeostasis and water balance.

The zona fasciculata cells

- are arranged in long straight cords and make up the bulk (about 80%) of cortical volume
- produce glucocorticoids
- are polyhedral and usually have a foamy appearance due to abundant lipid droplets.
- have the most pronounced features of steroid secreting cells; **abundant lipid droplets**, which contain the precursors of the steroid hormones, and **smooth endoplasmic reticulum**, where the hormones are synthesised.
- **The zona fasciculata is the middle and largest of the three zones in the cortex.**
- They also are arranged in distinctively straight cords that radiate toward the medulla.
- They secrete some glucocorticoids but their **principal secretion is weak androgens.**

The innermost zone of the cortex is the zona reticularis. the parenchymal cells assume a **net-like arrangement**

Cells within this zone are arranged in cords that **project in many different directions and anastomose with one another.**

zona reticularis makes up about 5-7% of cortical volume.

Cells of the fasciculata and reticularis atrophy after hypophysectomy (removal of the pituitary gland). Adrenocorticotrophic hormone (ACTH) from the pituitary is necessary for cell growth and maintenance and also stimulates steroid synthesis and blood flow through the adrenal gland. Circulating glucocorticoids largely exert their feedback control on neurons in the pituitary and inhibit the release of ACTH.

The parenchymal cells of the adrenal medulla are modified neurons. They are organised in ovoid clusters.

The distinguishing feature of these cells are the **numerous cytoplasmic granules that contain the catecholamines**, epinephrine and norepinephrine. **The production of these hormones involves amine precursor uptake and decarboxylation, hence they belong to the APUD class of endocrine cells.**

Glucocorticoids that reach the medulla through the cortical sinusoidal capillaries induce the enzyme that catalyses the methylation of norepinephrine to produce epinephrine. Both these hormones stimulate glycogenolysis and other aspects of the "fight or flight" response

HISTOLOGY OF THE MEDULLA:

The most abundant cell in the adrenal medulla is the chromaffin cell. That name derives from the phenomenon, observed long ago, that if adrenal gland is fixed in a solution containing chromium salts, it takes on a brownish appearance due to oxidation of catecholamines to melanin. Chromaffin cells are also referred to by some as pheochromocytes.

Chromaffin cells are columnar in shape and rather basophilic. At higher magnification, they are seen to have a granular cytoplasm due to hormone-containing granules. They are arranged in **clusters, usually around medullary veins**, as seen below in an image of rabbit adrenal (H&E stain).

The adrenal medulla is richly innervated by preganglionic sympathetic fibers. Additionally, **small numbers of sympathetic ganglion cells are commonly observed in the medulla.** Ganglion cells are round or polygonal with prominent nuclei.

CAUSES OF ADRENAL OVER AND UNDER ACTIVITY

GLAND PATHOLOGY OR ABNORMAL REGULATION?

SELECTIVE HORMONE DYSFUNCTION OR COMPLETE SET OF ALL HORMONAL GROUPS?

Unbalanced hormone production may also occur (eg. decreased glucocorticoids and mineralocorticoids with increased androgens) in the 21-hydroxylase deficiency form of congenital adrenal hyperplasia.

Adrenal hypofunction

Primary (pathology at the level of the adrenal glands)

Abnormalities are mainly

- destruction or infiltration,
- congenital abnormalities of enzyme function,
- or iatrogenic.

The major causes are congenital adrenal hypoplasia or aplasia, autoimmune (Addison's disease), adrenal haemorrhage or necrosis, infiltration (malignancy, amyloidosis, sarcoidosis others), infection (TB, fungal, others), congenital deficiency of one specific enzyme (most commonly is 21-hydroxylase deficiency with glucocorticoid and mineralocorticoid deficiency and androgen excess) and iatrogenic - suppression by glucocorticoid therapy, synthetic inhibitors of cortisol synthesis (eg. Ketoconazole, metyrapone), bilateral adrenalectomy.

Destruction of the adrenal gland results in loss of both mineralocorticoid and glucocorticoid function.

Pigmentation due to the increased ACTH drive and sodium deficiency with postural hypotension are common signs. Addison's disease is often insidious in onset. Isolated glucocorticoid deficiency or hypoaldosteronism are very rare conditions.

Secondary/tertiary (pathology at the hypothalamic-pituitary level)

Abnormalities are mainly related to congenital structural or functional defects, damage or destruction, or are iatrogenic (glucocorticoid therapy). Causes include anencephaly, pituitary hypoplasia, hypothalamic-pituitary tumours, destruction, surgery, infiltration, autoimmunity (hypophysitis). Glucocorticoid deficiency predominates and may be difficult to diagnose.

Suppression by pharmacological doses of glucocorticoids (oral, inhaled, topical) is the commonest cause of adrenal hypofunction (iatrogenic). Suppression occurs at both the adrenal and hypothalamic-pituitary levels.

Adrenal hyperfunction

Primary (pathology at the level of the adrenal glands)

Abnormalities relate to tumours or hyperplasia, adrenal tumours (adenoma, carcinoma), bilateral nodular adrenocortical hyperplasia, congenital adrenal hyperplasia (various forms; androgen and/or mineralocorticoid excess), primary hyperaldosteronism.

Secondary

Abnormal adrenal hormone secretion induced by pathology at the hypothalamic-pituitary level, ectopic trophic hormone secretion, or renal-electrolyte disorders. **Common causes include Cushing's disease (ACTH-dependent hypercortisolism), secondary hyperaldosteronism - salt wasting nephropathy, renal artery stenosis, Bartter syndrome and the ectopic ACTH or CRH syndrome.**

ADRENAL INSUFFICIENCY

There are **three adrenal hormones to consider which may be insufficient**

- cortisol (glucocorticoid),
- aldosterone (mineralocorticoid)
- adrenal androgens (of which DHEAS is the main form). **Loss of androgens is not life threatening.**

!! MAJOR ADVERSE EFFECTS !!

Adrenal insufficiency may be

- **primary** where the two adrenal glands are damaged, destroyed or absent;
- **secondary** when pituitary ACTH is deficient or absent;
- **tertiary** when hypothalamic CRH is deficient or absent.

mineralocorticoid lack is **only partial** because the major control of adrenal mineralocorticoid production is via the renin-angiotensin system

Adrenal insufficiency can further be defined by whether it is

- **permanent** (a destructive lesion)
- or **temporary** (exogenous steroid suppression)
- and by whether it is **complete or partial**.

if partial progresses to complete, replacement therapy may require adjustment.

Congenital adrenal hyperplasia is a complex clinical example of adrenal insufficiency where glucocorticoid is permanently deficient, mineralocorticoid is variably deficient and may lessen with age (and where there is also an excess of adrenal androgen).

The most common cause of adrenal insufficiency is suppression by exogenous steroid.

Clinically the patient may appear normal to Cushingoid, but if exogenous steroid is abruptly ceased they will develop symptoms of hypoadrenalism. Their own **hypothalamic - pituitary adrenal may take more than 12 months to recover.**

Primary adrenal insufficiency occurs when the adrenal glands are damaged.

Auto-immune disease and granulomatosis disease are common causes.

The onset may be slow and insidious (**whereas bilateral haemorrhage or removal will result in abrupt onset of symptoms.**)

The diagnosis should be considered, especially if there is evidence of other auto-immune disease. The first presentation may be life threatening, precipitated by intercurrent infection.

Treat with saline and intravenous glucocorticoid. Intravenous high dose glucocorticoid has adequate mineralocorticoid activity. Confirm the diagnosis later when the patient is stable with a **Synacthen stimulation test.**

Patients are hyperpigmented secondary to excess ACTH produced by the pituitary under lack of negative

cortisol feedback. Lifelong glucocorticoid and mineralocorticoid therapy is required, at a minimum of twice per day dose and the glucocorticoid needs to be adjusted with physical and/or psychological stress. Adults require approximately 37.5 mg of cortisone acetate (30 mg of hydrocortisone acetate daily) and 100 to 200 ug of fludrocortisone.

Secondary (tertiary) adrenal insufficiency can occur as a result of tumour, other destructive lesions and radiotherapy to the hypothalamic-pituitary area. **These patients are pale, because they have lost ACTH.** Mineralocorticoid secretion is partly maintained by the renin-angiotensin system. Symptoms of electrolyte disturbance - hypotension, nausea etc are less prominent. The diagnosis of secondary adrenal insufficiency requires stimulation of the hypothalamic - pituitary-adrenal axis by insulin induced hypoglycaemia to determine whether the cortisol response is absent. (This test can also be used to test whether the adrenals are suppressed by exogenous steroid). Generally only glucocorticoid replacement is required, at full replacement dose.

Diagnosis of adrenal insufficiency requires a high degree of suspicion. Once diagnosed, patients need a bracelet or neck tag identifying diagnosis and treatment. Patients need written instructions and education on managing glucocorticoid dosage in times of stress. They should also have one dose of parenteral glucocorticoid for self administration if persistent vomiting occurs and medical help is not immediately available.

STEROID MYOPATHY

Steroid myopathy is associated with high dose corticosteroids.

It affects proximal muscles and resolves once the corticosteroid is reduced or stopped.

- usually associated with high dose oral corticosteroids
- It affects both children and adults and is slightly more common in women, the female to male ratio being 10:7.
- The onset is insidious the first symptom being a **diffuse myalgia**.
- **Weakness develops in proximal muscles, initially in the legs.**
- The patient first complains of difficulty in getting out of a chair or walking up hills or stairs.
- **Finally, there is muscle wasting.**
- **It is unusual to have distal muscle involvement.**
- **The cranial nerves, sphincters and smooth muscle are not affected.**
- **Tendon reflexes and sensation are also normal.**

The **corticosteroid dosage required to produce myopathy is usually more than about 30 mg of Prednisone.**

Steroid myopathy is more commonly associated with the 9 alpha-fluorinated corticosteroids, Triamcinolone and Dexamethasone.

The diagnosis of steroid myopathy is difficult because **there are no specific diagnostic tests.** It is important to exclude other causes of proximal muscle weakness.

In asthma where the primary disease does not affect muscle, then this is usually not difficult.

However, in inflammatory disorders of the muscle, eg polymyositis, it can be difficult in determining whether the weakness is due to the polymyositis or the corticosteroids.

The muscle enzymes creatinine kinase and aldolase remain normal. If they are elevated another cause for the elevated levels needs to be found. Numerous abnormalities have been described on electromyography, but none of these are of any diagnostic value and there are no specific changes for steroid myopathy.

The main finding on muscle histology is **atrophy of the type IIB fibres.** These are the fast twitch fibres that use predominantly glycolytic metabolism and have a low resistance to fatigue.

There may be atrophy of the other fibre types, I and IIA, but this is less marked.

Electron microscopy has shown large mitochondria, an increase in subsarcolemmal nuclei and excessive glycogen accumulation.

The vessels and nerves are normal. **The mechanism by which corticosteroids affect muscles is not known although it is thought that it may affect some of the enzymes essential for muscle metabolism.**

Atrophy of type IIB fibres can also occur with disuse or be associated non-specifically with other systemic illnesses. Therefore, type IIB fibre atrophy is not diagnostic, but it is useful in excluding other causes for proximal muscle weakness.

Corticosteroids can also affect respiratory muscles. Steroid dependent asthmatics have reduced inspiratory muscle endurance and reduced inspiratory muscle strength.

The reduced inspiratory muscle strength has been shown to correlate with a reduction in strength of the hip flexor muscles. Studies in animals have shown that there is **loss of the type IIB muscle fibres in the diaphragm.**

The length of time from commencing corticosteroids to the onset of the myopathy is variable **but with high doses it can occur in two weeks.**

Once the corticosteroids are reduced or discontinued then **normal muscle power returns in about 1-4 months**

. Changing from a 9 alpha-fluorinated corticosteroid to Prednisone also produces an improvement in the myopathy.