ANATOMY, PHYSIOLOGY & PATHOLOGY NOTES OF THE

ENDOCRINE SYSTEM

PRE-SUMMARIZED
READY-TO-STUDY
HIGH-YIELD NOTES

FOR THE TIME-POOR
MEDICAL, PRE-MED,
USMLE OR PA STUDENT

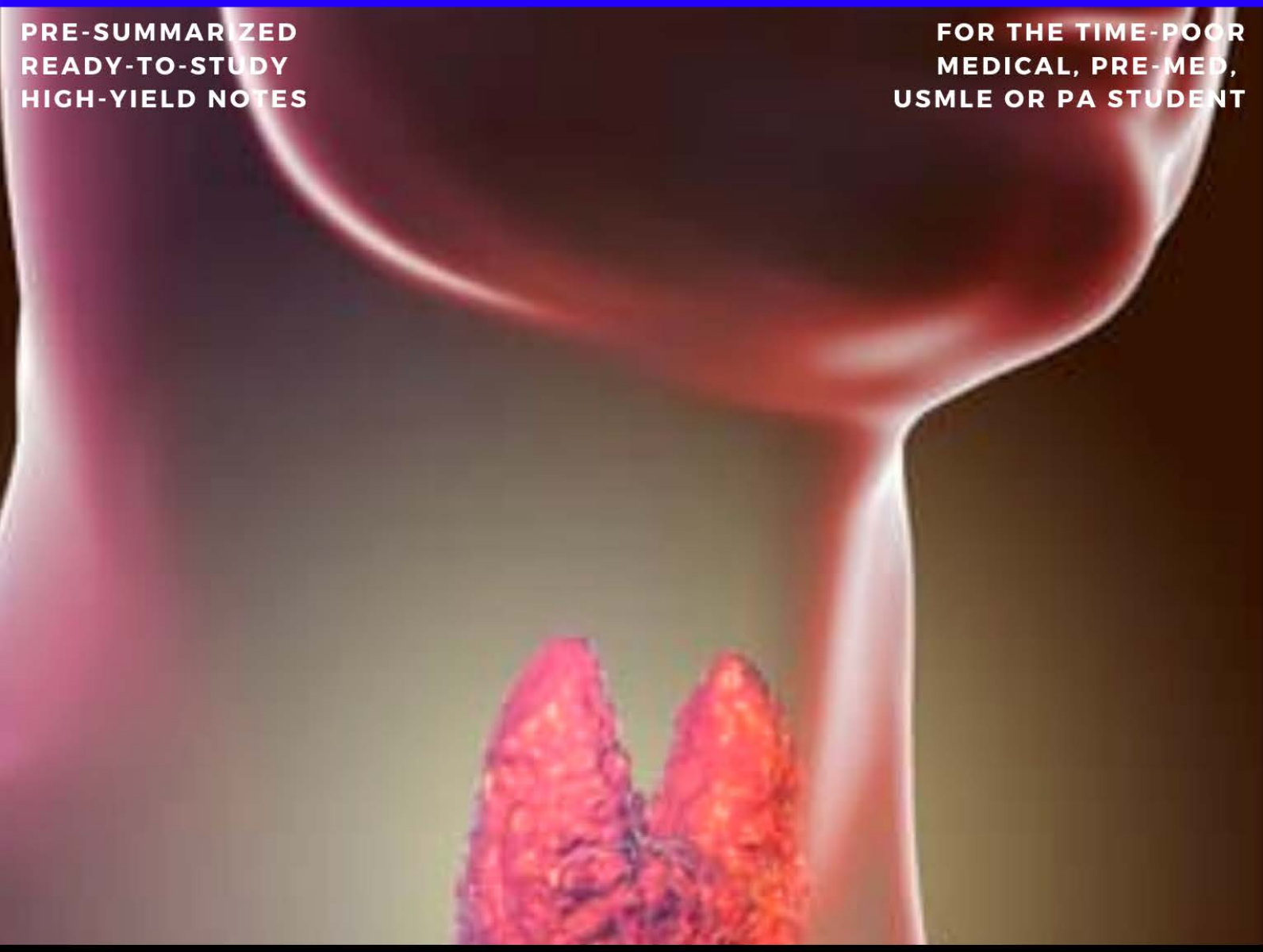

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Table Of Contents:

What's included: Ready-to-study anatomy, physiology and pathology notes of the endocrine system presented in succinct, intuitive and richly illustrated downloadable PDF documents. Once downloaded, you may choose to either print and bind them, or make annotations digitally on your iPad or tablet PC.

File List:

System: Endocrinology

Endocrinology:

- **Endocrinology:** The scientific study of **Hormones (Chemical Messengers)** and the endocrine organs.
- Endocrine system **maintains Homeostasis** in coordination with the nervous system.

Families of Chemical Messengers:

- **Amino Acid Derivatives:**
  - Catecholamines (Eg. Adrenaline, Nor-Adrenaline & Dopamine) (Derived from Tyrosine)
  - Histamine (Derived from Histidine)
  - All Thyroid Hormones (Derived from Tyrosine)
- **Proteins:**
  - All Pituitary Hormones
- **Steroids:**
  - Sex Hormones (Derived from Cholesterol)
- **Fatty-Acid Derivatives:**
  - Prostaglandins
  - Thromboxanes
  - etc.
- **Purines**
- **Gases:**
  - Eg. Nitric Oxide.
- **Acetylcholine**

What is a Hormone?

- Long distance chemical signals secreted by endocrine glands into the extracellular fluids
- Travel in blood or lymph throughout the body.
- **ARE BIOLOGICALLY SPECIFIC:** Interact with **specific receptors** of **specific cells** of **specific target organs.**
- **Either AMINO ACID BASED OR STEROIDS (cholesterol based) – Mostly amino acid based.**
  - Only **gonadal & adrenocortical** hormones **are steroids**
- Travel in blood or lymph throughout the body.

Synthesis of Chemical Messengers:

- **Steroidogenesis:**
  - All steroid hormones are derived from Cholesterol.
  - **There are 5 Families of Steroids, each with their main physiological member:**
    - Progestagens (Progesterone)
    - Androgens (Testosterone)
    - Mineralocorticoids (Aldosterone)
    - Glucocorticoids (Cortisol)
    - Oestrogens (Oestrogen)
- **Protein/Peptide Synthesis & Processing:**
  - Synthesis of polypeptide hormones can be more complex than Transcription & Translation.
  - Some Protein Hormones are initially synthesised as longer ***Pre-Prohormones***.
  - These ***Pre-Prohormones*** are then cleaved, leaving ***Prohormones***.
  - These ***Prohormones*** are then cleaved again, leaving active ***Hormones***.

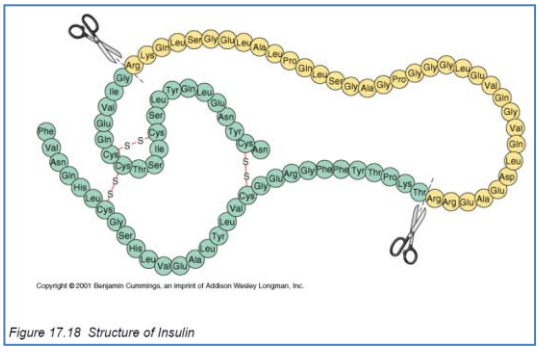


Figure 17.18 Structure of Insulin

'Reactive' Properties of Chemical Messengers:

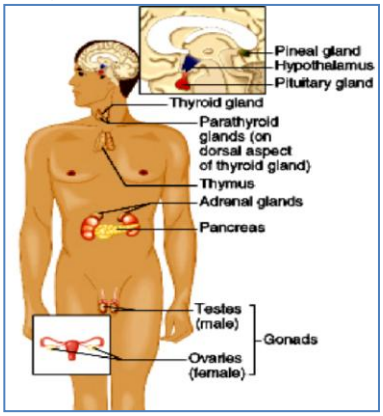
- **Biological Specificity:** Certain Chemical Messengers will only fit into certain receptors.
- **Affinity:** The degree to which a chemical is attracted towards a receptor.
- **Efficacy:** The degree of effectiveness of the binding of the messenger to the receptor.
- **'Agonists':** Chemical Messengers with **High Affinity** & **High Efficacy.**
- **'Antagonists':** Chemical Messengers with **High Affinity** but **Low Efficacy.**
  NB: There are no Endogenous *Receptor*-Antagonists, Only Exogenous (Drugs)
- **Hormone Binding Proteins:** Proteins that inactivate hormones by binding to them, limiting Bioactivity.
- **Epitope:** An Immunologically active binding site on a protein to which an antibody can attach.

Endocrine (diffuse) Glands:

- **Endocrine Glands** are **Ductless** and secrete by **Exocytosis** into the **Extracellular Fluid** → Diffuses into Blood.

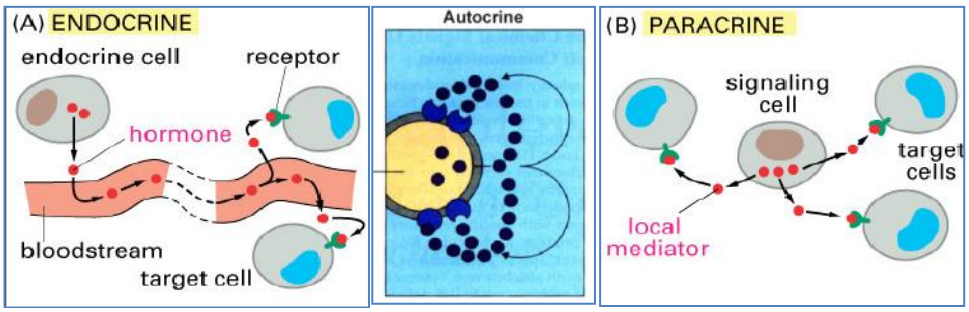
Classical Endocrine Glands:

- Pineal gland
- Hypothalamus
- Pituitary gland
- Thyroid gland
  - Parathyroid glands (dorsal aspect of thyroid gland)
- Thymus
- Adrenal glands
- Pancreas (has exocrine in parts)(endocrine part secretes insulin)
- Gonads: Testes/Ovaries (also exocrine)



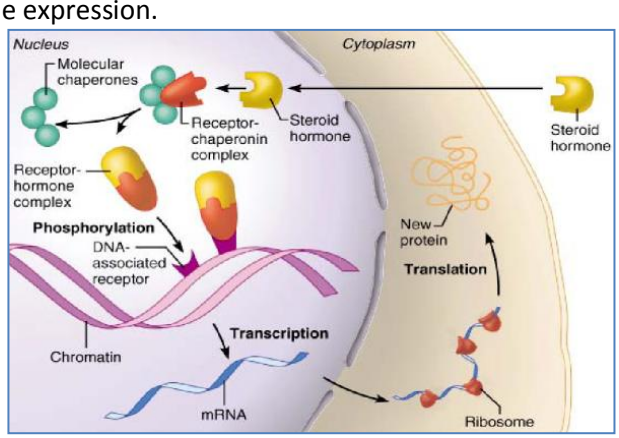
Long or Short Range?

- **Endocrine:** Some signals are "broadcasted" throughout the entire body via bloodstream. → **Hormones** (produced by endocrine cells) [TV]
- **Autocrine:** Signals that affect only cells of the same cell type as the emitting cell. [doctor conference]
- **Paracrine:** Signals (aka local mediators) that act on cells in the vicinity of the emitting cell but on different cell types than the emitting cell. [Lecture]



2 Main Receptor Types: (Intracellular & Membrane-bound Receptors)

- **Intracellular Receptors:**
  - Lipid-soluble hormones (steroid/thyroid hormones) & even gasses (nitric oxide-blood vessel dilation)
    - **Steroid hormones** bind to receptor proteins in the cytosol or the nucleus that regulate gene expression.



- **Plasma-Membrane-Bound-Receptors:**
  - Most signal molecules can't cross the plasma membrane of the target cell.
  - Most intracellular signalling proteins act as **molecular switches** activated by either **phosphorylation** OR **GTP-Binding** (swapping a GDP for a GTP)
  - **3 Types:**
    - **Ion-Channel-Linked Receptors**
      - Resulting signal is a flow of ions across the membrane – produces an electric current.
    - **Enzyme-Linked Receptors**
      - When activated – act as enzymes or are associated with enzymes inside the cell.
    - **G-Protein-Linked Receptors (more common)**
      - Binds to a class of membrane-bound **GTP-Binding-protein (G-Protein)**→ becomes activated and released to migrate across the membrane, initiating a cascade of other effects.
      - Some G-Proteins directly regulate ion channels in the plasma membrane.
      - Other G-Proteins activate membrane-bound enzymes. Eg. **adenylyl-cyclase** → increases the **[second messenger (cyclic-AMP)]** → activates an intracellular **signalling protein** (eg. A protein kinase) OR turns on **genes via activated Protein Kinase 'A' (PKA)**.

Tissue Responsiveness:

- **Receptor Downregulation:**
  - Where a ***decreased receptor density*** in the membrane decreases the responsiveness of that cell to that receptor's stimuli.
  - This is achieved **by *Internalising*** the **receptor-ligand complex**, dissociating the ligand, and recycling the receptor back to the surface.

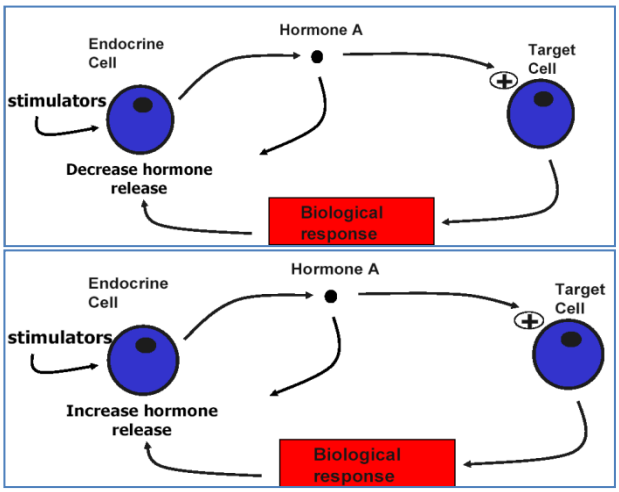
- **Receptor Desensitisation:**
  - Where a ***change in receptor structure*** decreases the responsiveness of that cell to that receptor's stimuli.
  - Why? To prevent multiple, rapid stimulations.

Regulation of Hormone Release:

- **3 Mechanisms:**
  - **1. Humoral:**
    - Where the concentration of a solute in the blood (Eg. High Glucose/Low Calcium) is detected by a specific gland, stimulating hormone release (Eg. Insulin/Parathyroid Hormone)
  - **2. Neural:**
    - Where the Nervous System Directly stimulates hormone release.
    - Eg. Sympathetic NS Activated → Stimulates Adrenal Medulla → Secretes Catecholamines.
  - **3. Hormonal:**
    - Where one hormone stimulates the release of another hormone from a different cell.
    - Eg. The Hypothalamus secretes hormones → Stimulate Ant. Pituitary → Secretes Hormones.
    - Eg. The Ant. Pituitary secretes Hormones → Stimulate other organs to secrete hormones.

FEEDBACK:

- **Negative:**
  - Most common
  - Maintains levels around a stable intrinsic/preset level.
  - Involved in homeostatic control.
- **Positive:**
  - Uncommon
  - Unstable mechanism
  - Stopped by removal of initial stimulus.



Levels of Feedback Loops:

- Feedback may occur at many different levels within a single 'Hypothalamo-Pituitary-Target' axis.
  - **Ultra-Short Loop:**
    - Autocrine Feedback - The secreted hormone feeds back to the same tissue that secreted it.
      - Eg. A Hypothalamic Hormone feeds back to the Hypothalamus.
  - **Short Loop:**
    - The secreted hormone feeds back to the tissue that stimulated its secretion.
      - Eg. The Hormone secreted by the Target Organ feeds back to the Pituitary.
      - Or. The Hormone secreted by the Pituitary feeds back to the Hypothalamus.
  - **Long Loop:**
    - The hormone secreted by the target organ feeds directly back to the Hypothalamus.

Endocrine Disorders:

- **Level-Of-Function Disorders:**
  - **Hypofunction Disorders:**
    - Where the gland produces less than it should.
    - **Common Causes:**
      - Loss of reserve
      - Hypo-secretion
      - 'Agenesis' – failure to develop embryonicaly
      - Atrophy – Wasting away due to injury/disease/lack of use.
      - Active Destruction
      - Tumour
  - **Hyperfunction Disorders:**
    - Where the gland produces more than it should.
    - **Common Causes:**
      - Hyper-secretion
      - Loss of suppression
      - Hyperplasia (↑Proliferation)
      - Neoplastic Change (Tumour)
      - Hyperstimulation
      - Ectopic Sites of Secretion (Some far-off tumours secreting hormone)

- **Hierarchical Classification of Hypothalamo-Pituitary Axis Disorders:**
  - **NB:** Endocrine disorders of the Hypothalamo-Pituitary Axis are often classified in a Hierarchical Fashion depending on the origin of the disorder:
  - **Primary:**
    - Disorder of the Target Gland
    - (eg. *Primary Hypothyroidism* – the Thyroid Gland *itself* is under-responsive to TSH stimulation)
  - **Secondary:**
    - Disorder of the Pituitary Gland
    - (eg. *Secondary Hypothyroidism* – the Pituitary Gland is under-producing TSH)
  - **Tertiary:**
    - Disorder of the Hypothalamus
    - (eg. *Tertiary Hypothyroidism* – the Hypothalamus is under-producing TRH)

Testing for an Endocrine Disorder:

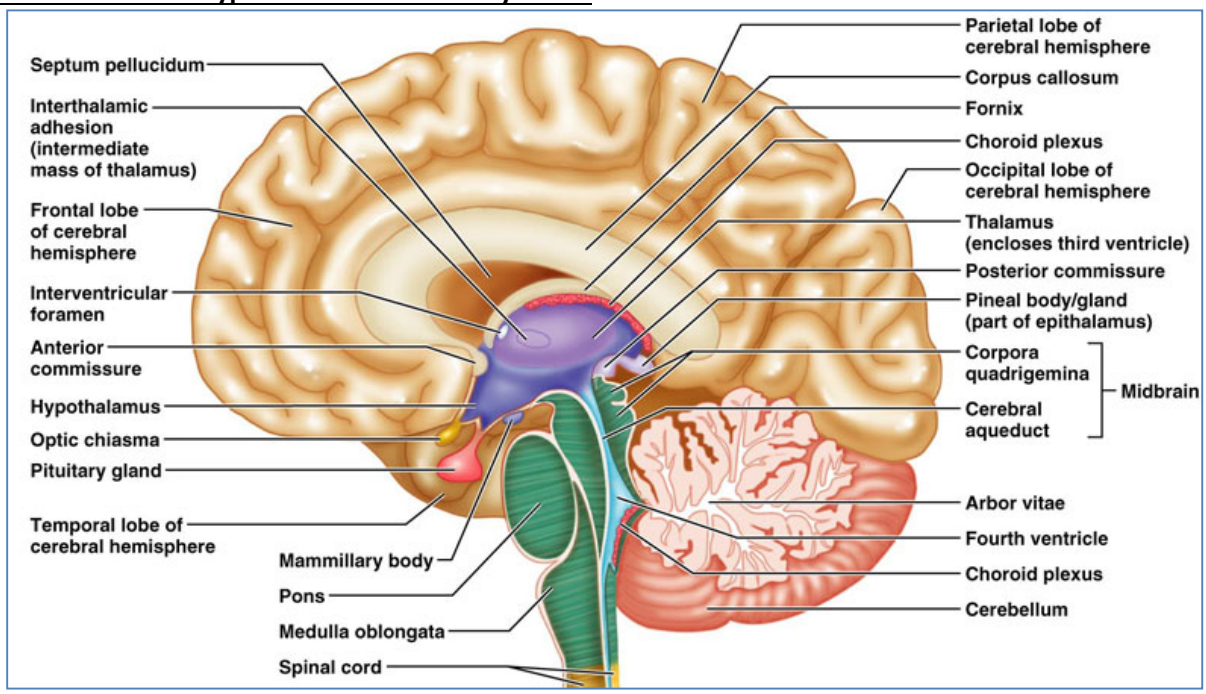
- **Basal Hormone Testing:**
  - A single 'snapshot' measurement of the concentrations of specific hormones.
    - Eg. High [Thyroid-Stimulating Hormone] → Therefore Primary Hypothyroidism.
  - Problem – Some secretions are ***Pulsatile***, meaning random measurements don't accurately diagnose a disorder of that gland. The Solution: Dynamic Hormone Testing.
- **Dynamic Hormone Testing:**
  - Using exogenous chemicals/hormones to Stimulate/Suppress activity of a target gland. This tests the responsiveness of a target gland to feedback stimuli.
    - **Suppression Tests:**
      - When Hyperfunction is suspected, an inhibitor is administered and then the hormone concentration is re-measured to see if it has decreased. If not, Hyperfunction is confirmed.
    - **Stimulation Tests:**
      - When Hypofunction is suspected, a stimulator is administered and then the hormone concentration is re-measured to see if it has increased. If not, Hypofunction is confirmed.

Typical *Endocrine* Symptoms:

- **Diabetes (1 & 2):**
  - Weight Change
  - Polyuria, Nocturia & Thirst
  - Visual Disturbances
  - Infections & Immunosuppression
  - Constant Hunger
  - Nausia + Vomiting
  - Fatigue
  - DKA (Diabetic Ketoacidosis) = Emergency Presentation
- **Hyperthyroidism:**
  - Weight Loss
  - Fatigue
  - Suppressed TSH
  - Elevated T4
- **Hypothyroidism:**
  - Weight gain
  - Pretibial Myxoedema
  - Periorbital Oedema
  - Bradycardia
  - Bradypnoea
- **PolyCystic Ovarian Syndrome:**
  - Weight Gain
  - Hirtism
  - Infertility
- **Cushings Syndrome:**
  - Caused by Excess Corticosteroids
  - Moon Facies (Fat, white, round faces)
  - Muscle Wasting + Weakness
  - Weight Gain (Truncal Obesity)
  - Stretch Marks due to Weight Gain
- **Pituitary Adenoma:**
  - Peripheral Vision Loss
  - Compression symptoms or Secretory Symptoms
  - Secretory → eg. Prolactin → Galactorhoea + Gynacomastia
    → eg. GH → Gigantism (Pre-Purbety) → Acromegaly (Post Puberty)
    → eg. ACTH: → Cushing's Syndrome
- **Acromegaly:**
  - Soft-Tissue Swelling
  - Arthritis
  - Hyperhydrosis
  - Headache + Visual Field Defect
- **Addisons:**
  - Autoimmune
  - Weight Loss
  - Fatigue
  - Hypotension
  - Hyponatraemia
  - Hyperkalaemia
  - Hyperpigmentation
- **Anorexia:**
  - Weight Loss
  - Fatigue
  - ↓BMI
  - ↑FSH + LH (Due to no ovulation)
  - ↑GH
  - Hypokalaemia (often due to vomiting) → Arrhythmias

Endocrinology Notes
The Hypothalamo-Pituitary Axis

General Location of the Hypothalamus & Pituitary Gland



Embryology of the Pituitary Gland:

- **Q: Why is the Ant. Pituitary Endocrine, & the Post. Pituitary Neuronal?**
- **A: Because they have different embryonic origins.**
  - **Anterior Pituitary:**
    - Arises from an upward out-pouching of the **Oral-Ectoderm** from the roof of the oral cavity called **Rathke's Pouch.** This pouch pinches off from the oral cavity and is later separated by the sphenoid bone.
    - Consists of **Epithelial/Glandular Tissue**, & therefore **Manufactures & Secretes Hormones**.
  - **Posterior Pituitary:**
    - Originates from a downward out-pouching of **Neuro-Ectoderm** from the brain in the floor of the 3rd ventricle.
    - Consists of **Neural Tissue**, & therefore **Secretes Neurohormones.**

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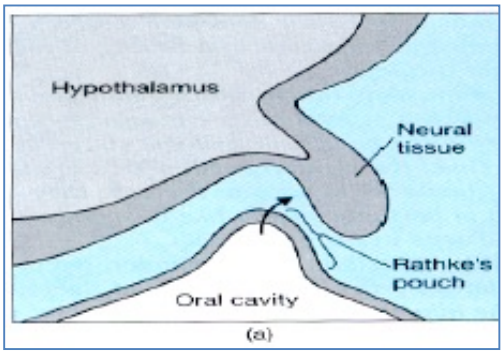

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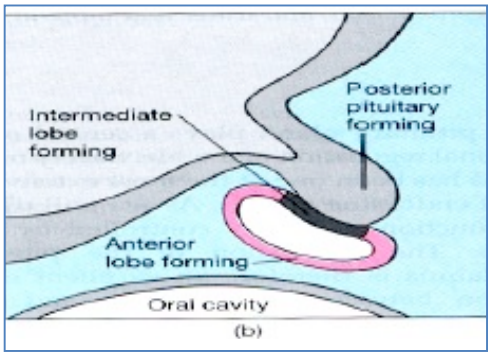

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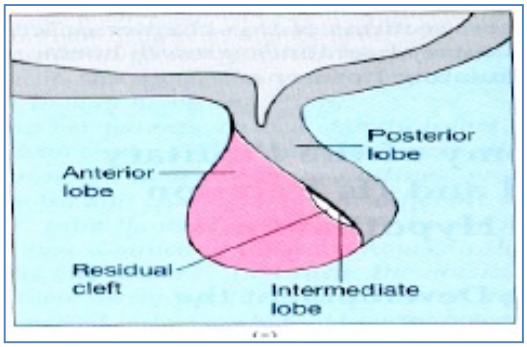
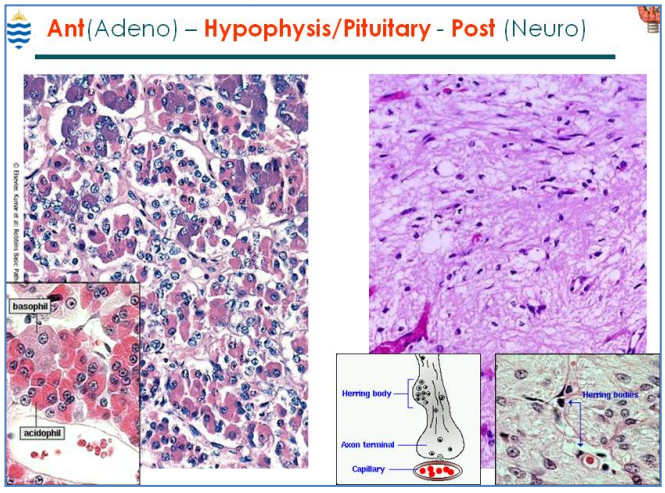


The Hypothalamus & Pituitary Glands:

- **Hypothalamus:**
  - Links the nervous system to the endocrine system via the pituitary gland.
  - Controls body temperature, hunger, thirst, fatigue, anger, and circadian cycles.
  - Secretes neurohormones (hypothalamic-releasing hormones) → Stimulate/Inhibit Pituitary Gland.

Abbreviation	Full Name	Stimulated/Inhibited Hormone
GRH	Growth-Hormone Releasing Hormone	Stimulates Release of Growth Hormone
SS	Somatostatin	Inhibits Release of Growth Hormone & TSH
TRH	Thyrotropin Releasing Hormone	Stimulates Release of TSH & Prolactin
PRF	Prolactin Releasing Hormone	Stimulates Release of Prolactin
GnRH	Gonadotropin Releasing Hormone	Stimulates Release of Gonadotropins; FSH & LH
CRH	Corticotropin Releasing Hormone	Stimulates Release of ACTH

- **Pituitary Gland:**
  - **Has 2 Major Lobes:**
    - **Posterior Pituitary: (Neurohypophysis)**
      - Nervous Tissue
      - **Supraoptic & Paraventricular Nuclei** in the hypothalamus synthesize Oxytocin & ADH →Transport them to their axon terminals in the **Posterior Pituitary.**
        - Hormones released as needed via exocytosis in Post.Pituitary
          - ADH
          - Oxytocin
      - **Normal Histology – Just like normal brain tissue. (Neural Origin)**
        - NB: NO neurones, but plenty of axons.
        - Many supporting cells (Astrocytes, oligodendrocytes)
        - Plus Blood Vessels (neither arteries or veins; but 'Portal Vessels' – Ie. Blood comes *only* from the hypothalamus → carries the hypothalamic hormones.)
    - **Anterior Pituitary: (Adenohypophysis)**
      - Glandular Tissue (adeno = gland)
      - **Releasing-Hormones** from **Ventral Hypothalamus** that stimulate Ant. Pituitary:
        - CRF
        - TRF
        - GRH → FSH/LH
        - GHRH
        - Prolactin Releasing Factor (PRF)
      - **Normal Histology – Glandular structure:**
        - Clusters of acini surrounded by blood vessels
        - Acini - mosaics of different cells:
          - (acidophils –red, basophils – dark blue, chromophobes - colourless)
          - NB: Pituitary Tumours may be from any of the 3 cells
        - PLENTY of blood vessels (neither arteries or veins; but 'Portal Vessels' – Ie. Blood comes *only* from the hypothalamus → carries the hypothalamic hormones.)



- **Blood Supply:**
  - Arterial blood enters via **Hypophyseal Branches** of the **Internal Carotid Arteries.**
  - **(BUT SHASHI SAYS – *NO ARTERIES…PORTAL SYSTEM*)**
- **Venous Drainage:**
  - Venous blood leaves via **venules** which drain into the **Dural Sinuses**.

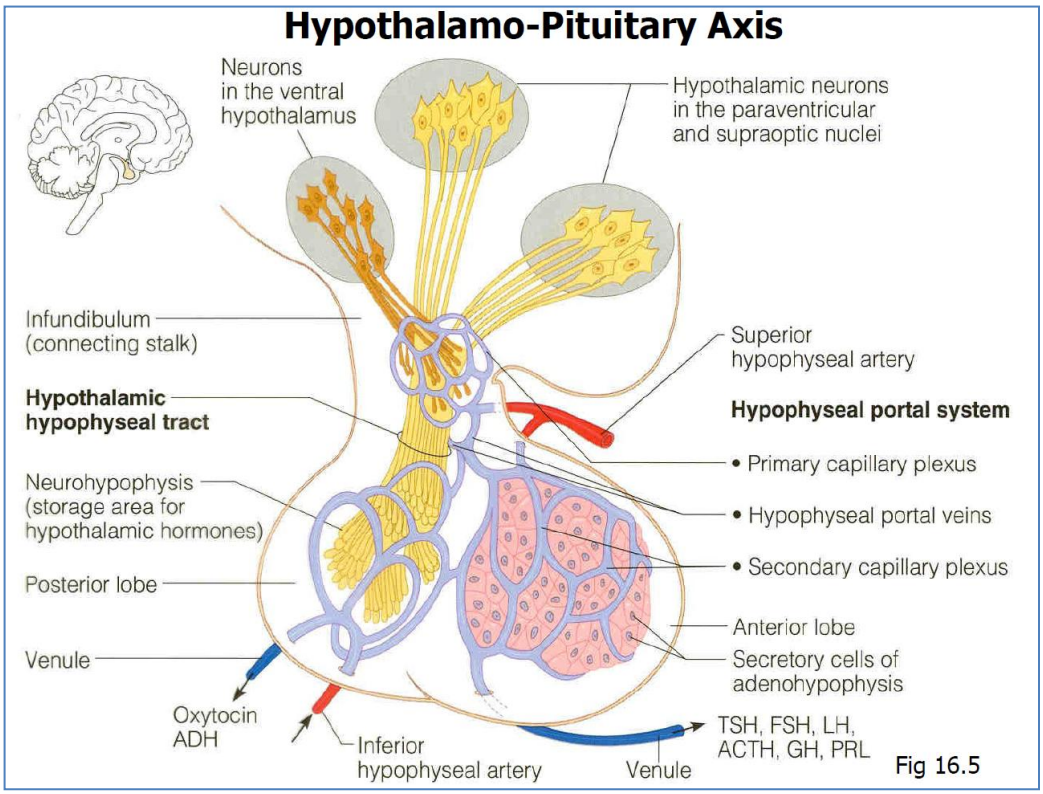
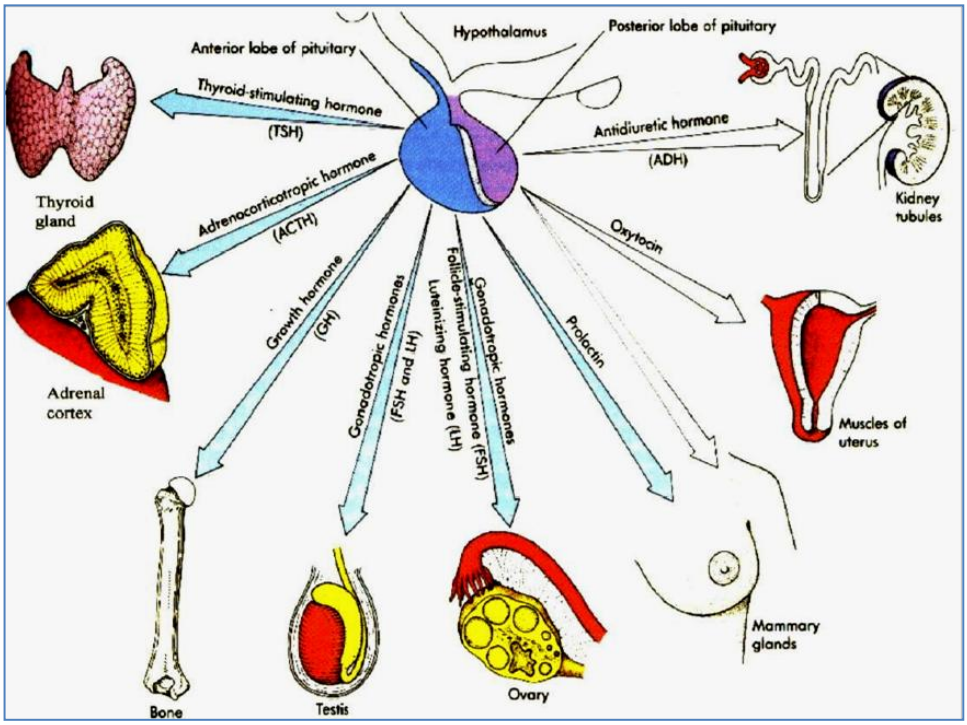


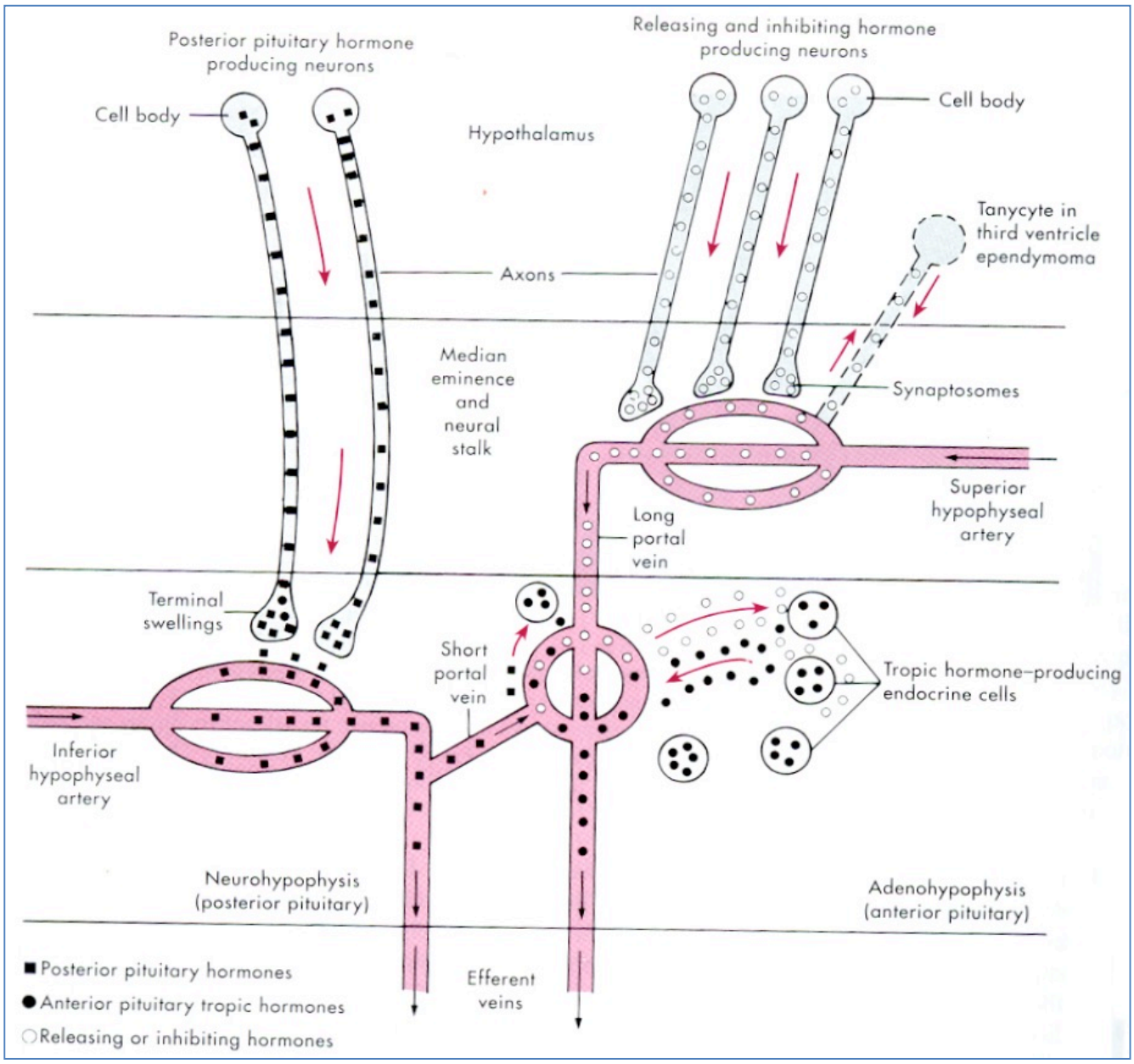
Fig 16.5

- **<u>Pituitary Hormones & their Target Tissues/Organs</u>**
  - NB: All these hormones are **PROTEIN**-based **hormones**.



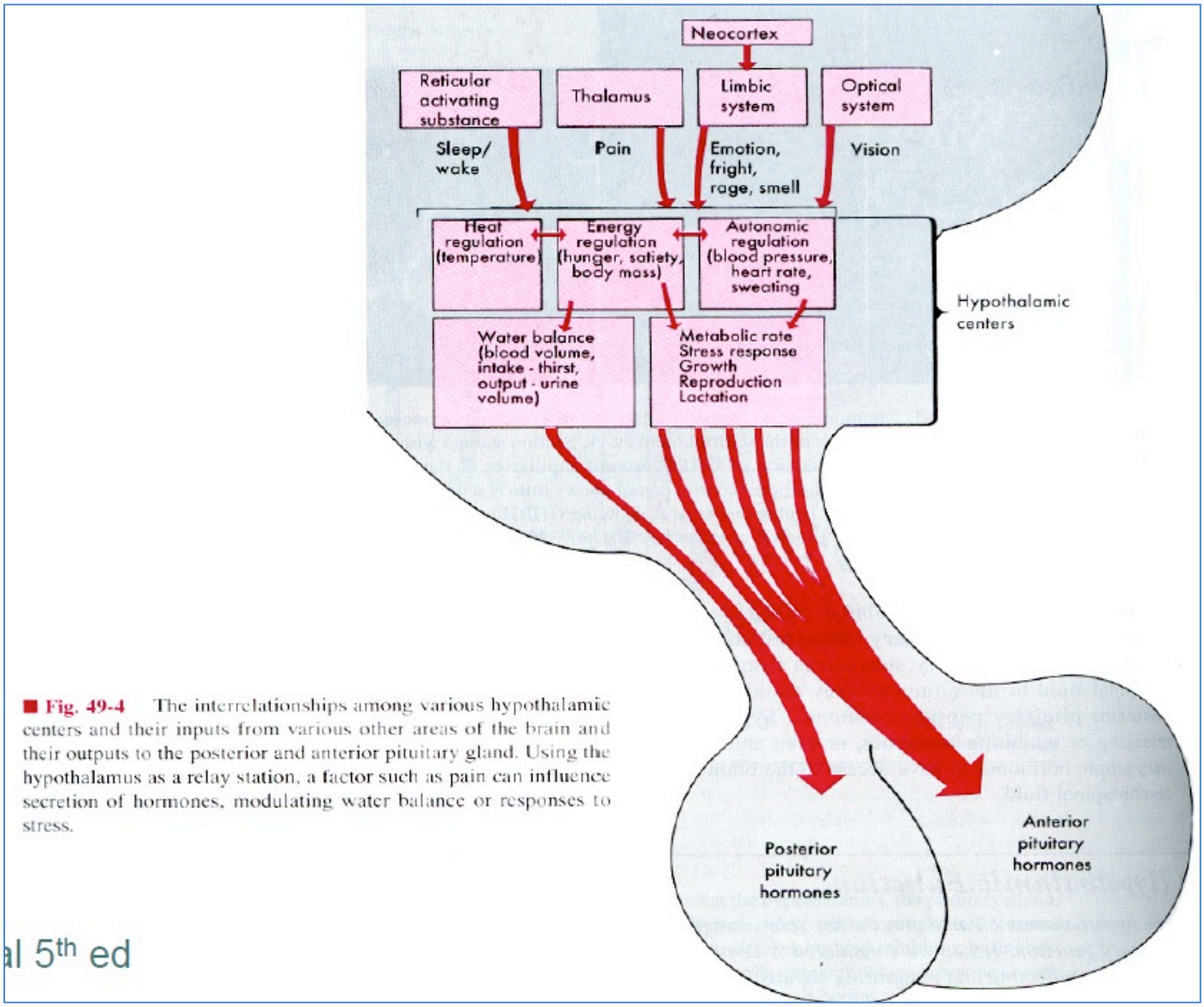
Secretory Setup of the Hypothalamus & Pituitary Gland:

- **Anterior Pituitary:**
  - Neurons of the **Ventral Hypothalamus** terminate in the **Primary Capillary Plexus** within the **Infundibulum (Stalk)**.
  - These Neurons secrete **Releasing-Hormones** into the **Primary Cap. Plexus,** which flow to the **Secondary Capillary Plexus,** stimulating *Endocrine* Cells of the Ant. Pituitary to synthesize/secrete hormones.
- **Posterior Pituitary:**
  - Neurons of the **Supraoptic & Paraventricular Nuclei** synthesize Oxytocin & ADH in the hypothalamus, then transport them as granules to their axon terminals which terminate in the **Posterior Pituitary.**
  - When one of the hormones is needed, it is released from the axon via **exocytosis** into the bloodstream via the **Inferior Hypophyseal Circulation.**
- **NB:** Remember that the Ant. & Post. Pituitary don't act entirely independently (there is some flow of hormones from the Post. Pituitary → Ant. Pituitary via the **'Short Portal Vein'**)



The Hypothalamus: A 'Relay-Station' for Higher Brain Centres:

- The Hypothalamus receives information from multiple higher brain centres, integrates it, decides on a response, and orders the pituitary to secrete specific hormones to elicit the response.
- **Inputs:**
  - RAS (Reticular Activating System/Substance) – Regulates drowsiness by releasing Serotonin.
  - Thalamus – Plays a role in Pain Perception
  - Neocortex & Limbic System – Emotional Centre
  - Optical System – Vision
- **Outputs:**
  - Anterior Pituitary
  - Posterior Pituitary
  - Brain-Stem (Autonomic NS)



■ Fig. 49-4 The interrelationships among various hypothalamic centers and their inputs from various other areas of the brain and their outputs to the posterior and anterior pituitary gland. Using the hypothalamus as a relay station, a factor such as pain can influence secretion of hormones, modulating water balance or responses to stress.

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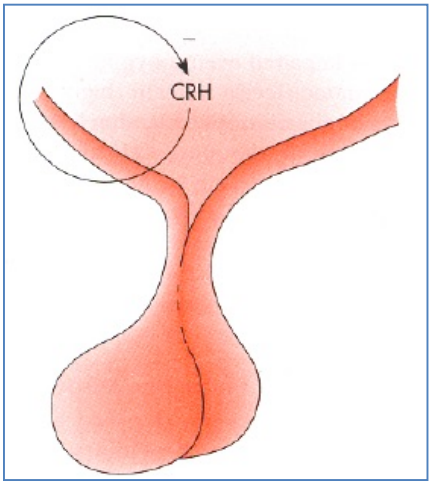
Feedback Control:

- **Negative:**
  - Where the **Biological Response** causes a **Decreased Hormone Release.**
  - Maintains levels around a stable intrinsic/preset level.
- **Positive:**
  - Uncommon (Lactation & Parturition)
  - Where the **Biological Response** causes an **Increased Hormone Release**
  - Are therefore Unstable mechanisms
  - Stopped by removal of initial stimulus.

Levels of Feedback Loops:

- Feedback may occur at many different levels within a single 'Hypothalamo-Pituitary-Target' axis.
    - **Ultra-Short Loop:**
        - The secreted hormone feeds back to the same tissue that secreted it.
            - Eg. A Hypothalamic Hormone feeds back to the Hypothalamus.



    - **Short Loop:**
        - The secreted hormone feeds back to the tissue that stimulated its secretion.
            - Eg. The Hormone secreted by the Target Organ feeds back to the Pituitary.
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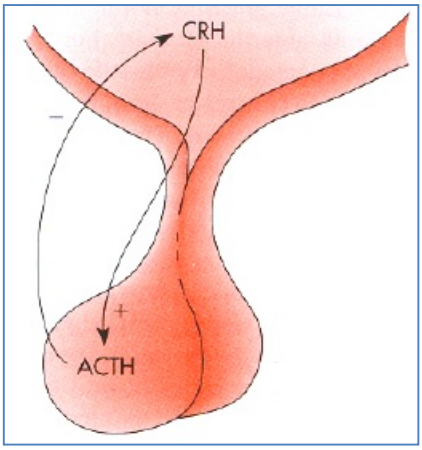
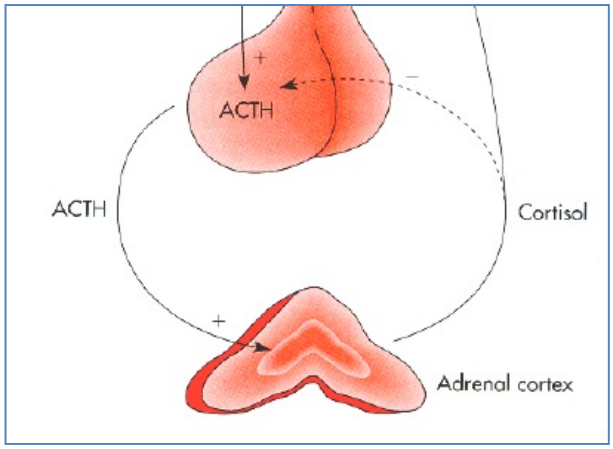
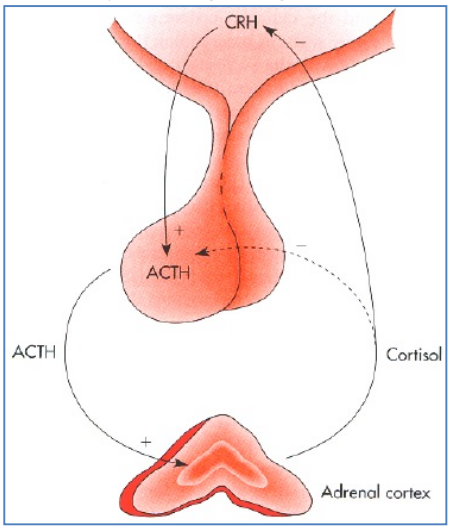




    - **Long Loop:**
        - The hormone secreted by the target organ feeds directly back to the Hypothalamus.



Endocrine Regulation of Growth

Phases of Growth:

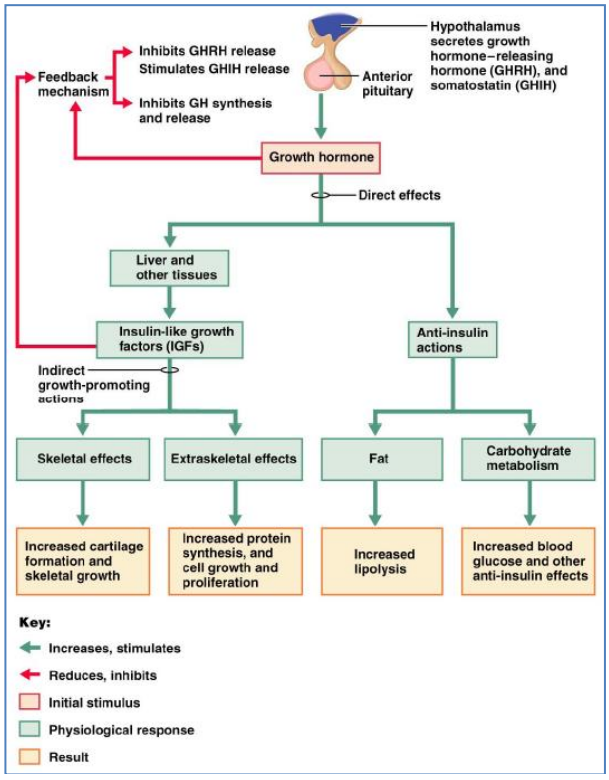
- **NB:** These Differ in their ***Rates of Growth*** and ***Regulators/Contributors***:

Phase of Growth	Major Regulators/Contributors		
	Nutrition	**Hormonal**	**Genetics**
Foetal (In Utero)	**Yes - #1**	**Insulin** (Acts as a growth factor in this phase) **IGF-I**	No
Infantile (Birth → 2yrs)	**Yes - #1**	GH & IGF is present, but in low amounts – NOT Imperative.	Yes – (Only after a few months *after birth*)
Pre-Pubertal (Childhood)	-Ve influence only if malnourished	- **IGF** Levels Increase - **GF** Receptors Increase	**Yes - #1**
	NB: Growth *Velocity* progressively declines during this phase (Transition from Infant → Child) **NB:** Body Proportions start to change.		
Pubertal (Early Teens)	-Ve influence only if malnourished	**Sex Hormones:** - →GH Release - →Epiphyseal Closure **GH** → Causes **IGF** Release **GH + IGF** → Bone Elongation	
Post-Pubertal (Late Teens)	**NB:** Growth *Velocity* peaks & then stays same for ≈6yrs. - (The last 3 years mainly concern the Trunk)		

Major Hormones involved with Growth:

- **Growth Hormone,** AKA: Somatotropin
- **Insulin-like Growth Factors (Somatomedins)** (IGF-I & IGF-II)
- **Somatostatin** (Inhibits secretion of GH from Ant. Pit.)
- **Thyroid Hormone**
- **Cortisol** – (Not Direct – has a 'permissive' role. Ie. Other growth hormones are more effective if it's present)
- **Sex Hormones (Oestrogen/Testosterone)**

The Growth Hormone Axis:



Hypothalamic Hormones of Growth:

- **(+) GRF (Growth-Hormone Releasing Factor)/GRH (Growth-Hormone Releasing Hormone):**
  - **Produced Mainly in:** Hypothalamus (But also in GIT, Pancreas & Placenta)
  - **Exerts Effects on:** Somatotropes (Anterior Pituitary) → ↑Growth Hormone Release.

- **(-) Somatostatin:**
  - **What is it?:**
    - Produced almost everywhere: (Hypothalamus, Gut, Pancreas, CNS)
      - → Inhibits Somatotropes → ↓Growth Hormone.
  - **Actions of Somatostatin:**
    - **Inhibits some Hypothalamic-Releasing Hormones:**
      - ***GH*** (Grow Hormone)
      - ***TSH*** (Thyroid Stimulating Hormone)
      - ***PRL*** (Prolactin)
      - ***ACTH*** (Adreno-Cortico Tropic Hormone)

Anterior Pituitary Hormone of Growth:

- **Growth Hormone:**
  - **Produced by:** Anterior Pituitary (After ≈2mths old)
  - **Regulation of Release:**

Stimulation	Inhibition
GRH - (Growth-Hormone Releasing Hormone)	Somatostatin

  - **Actions:**
    - ***Growth-Promoter*** from ***Early Childhood → Onwards***
      - Longitudinal Bone Growth & Remodelling
      - Skeletal Muscle Growth
      - Liver Growth
      - Stimulates IGF-Binding Protein Synthesis (Important carrier for IGF)
      - Stimulates IGF Synthesis
    - ***Metabolic Effects:***
      - Stimulates:
        - Lipolysis
        - Ketogenesis
        - Gluconeogenesis
        - Protein Synthesis
        - Lactation
      - Inhibits Insulin Action.
      - Boosts Immune Function.

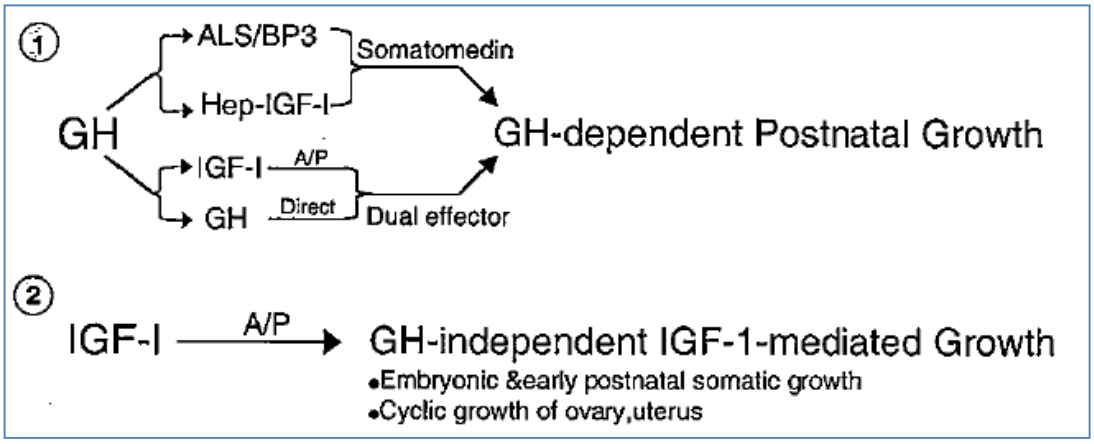
Defects in Endocrine Control of Growth:

- **Hyper:**
  - **Too Much Growth Hormone &/or Growth Factors (Rare):**
    - Eg. Childhood Gigantism
    - Eg. Adults - Acromegaly
  - **Non-GH Causes:**
    - Eg. Precocious Puberty
- **Hypo:**
  - **Defective Growth Hormone Axis:**
    - **GH-Deficiency:**
      - **Primary GH Deficiency:**
        - Hypothalamic Defect
        - And/Or Pituitary Defect
      - **Secondary Pituitary Deficiency:**
        - Eg. Tumour & other Destructive Diseases.
        - Eg. Psychosocial Deprivation (Ie. Kids in abusive/non-supportive environments → GH-Deficiency → exhibit slowed growth)

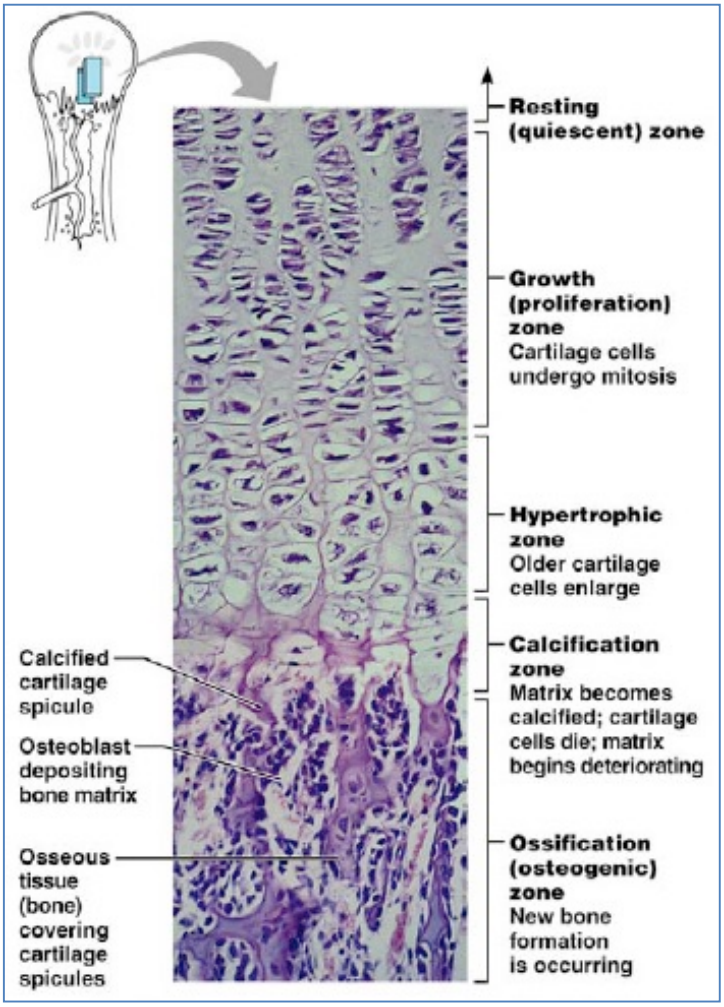
Liver

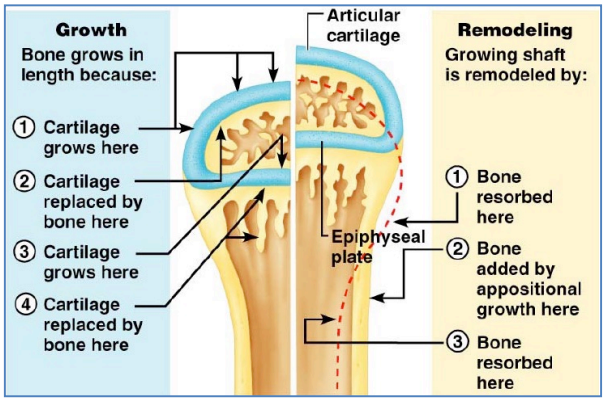
Insulin-Like Growth Factors (IGF's):

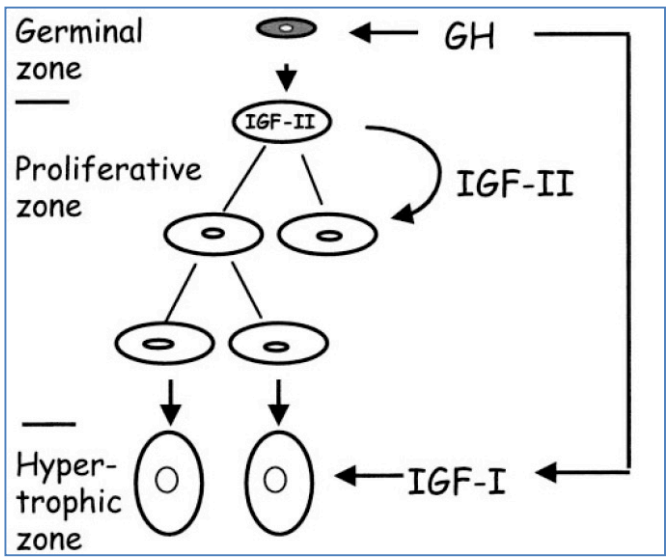
- Both IGF-I & IGF-II are **Structurally Similar to Proinsulin** (The Insulin Precursor)
- IGF-I - Chromosome 12
- IGF-II - Chromosome 11
- Circulates bound to **IGFBP (Insulin-like Growth Factor Binding Protein)**
- Bind to **Specific Receptors**
- **Stimulate Cell Division** together with other Growth Factors.
- **Foetal Life:**
  - Act in **Paracrine** Fashion
  - IGF made by all foetal tissues (However, mainly by liver after birth)
  - **Absence** of **IGF-I** in Foetal Life → **Intra Uterine Growth Retardation**



Long Bone Growth



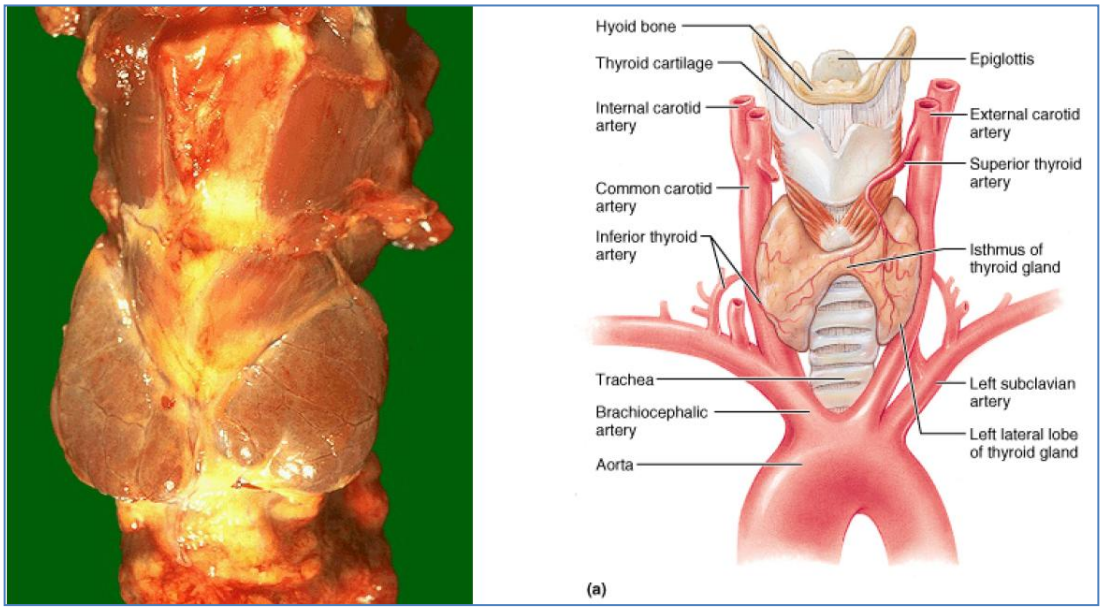




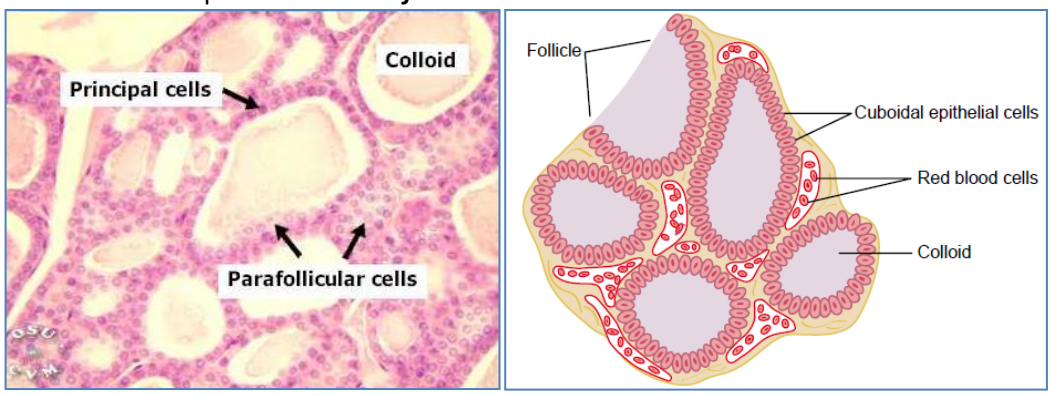
Thyroid Function

Anatomy of Thyroid Gland:

- A ***Bilobar*** Gland (2 Lobes – L&R) connected in the middle by the ***"Isthmus"*** of the Thyroid.
- **Location:**
  - Immediately below the Larynx on each side of, and anterior to, the Trachea.
- **Rich Blood Supply:**
  - Required for Building Blocks of Hormones.
  - Required for Quick Release of Hormones.
  - Flow - Regulated by the Sympathetic NS.



- **Composed of Millions of "*Follicles*":**
  - Each contains a pool of Thyroid *"**Colloid**"* of stored Thyroid Hormones bound to ***Thyroglobulin***.
    - Allows for a 2-3mth reserve of thyroid hormones.
  - Each pool is lined by a layer of ***"Principal/Follicle Cells"*** that secrete **Thyroid Hormones** (T_3 & T_4).
  - There are also patches of ***"Parafollicular Cells"*** that secrete **Calcitonin**.

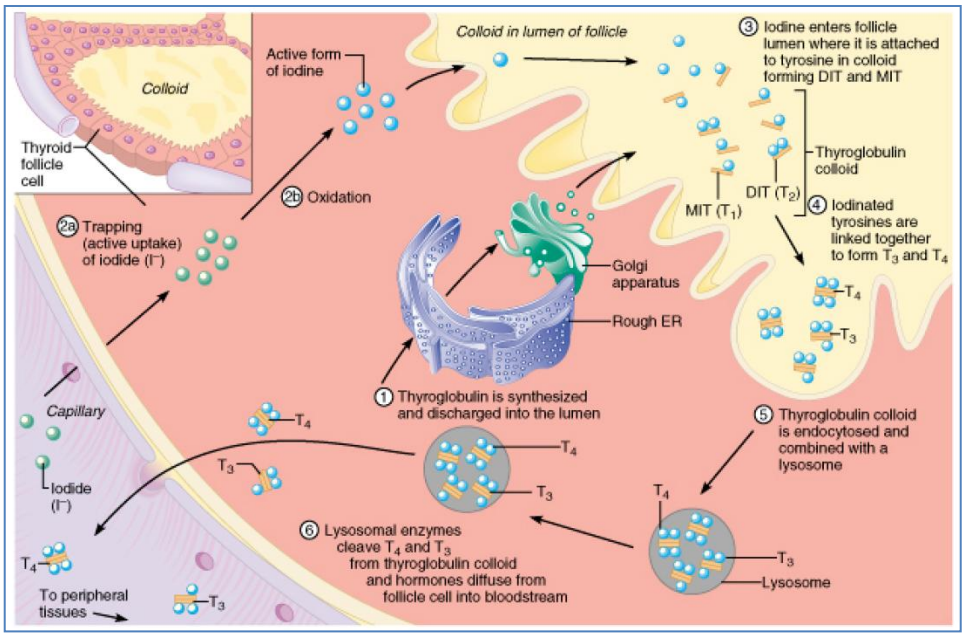


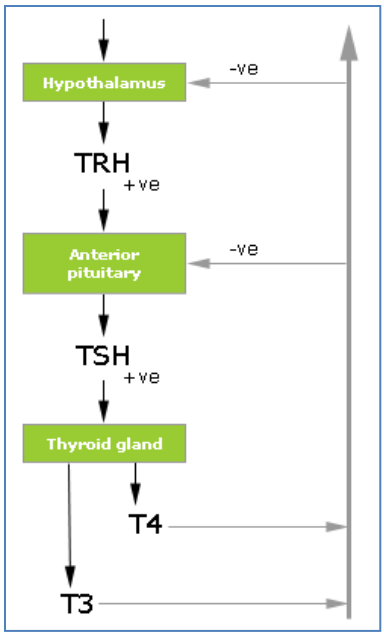
Physiology of the Thyroid Gland:

- **Iodine Balance:**
  - NB: Iodine is essential for Thyroid Hormone Production.
  - Iodine is *Actively* taken up by Thyroid Gland via ***"Iodine Trapping"***.
  - ↑TSH → ↑Thyroid Iodine Uptake
- **Main Hormones:**
  - **T_4 – Thyroxine (93%)** (*Iodinated Tyrosine – 4x Iodines*) (Less Biologically Active)
  - **T_3 – Triiodothyronine (7%)** (*Iodinated Tyrosine – 3x Iodines*) (**Most Biologically Active**)
  - **Calcitonin** (Polypeptide)
    - **Secreted By –** The Parafollicular Cells of the Thyroid Gland
    - **Function: ↓*Plasma-Ca^+ levels*** (By ↓Osteoclast Activity & ↑Osteoblast Activity)
    - **Stimulated By:** ↑Extracellular [Ca^+] (NB: Opposite of PTH)
- **Effects of TSH on the Thyroid:**

- Thyroid Follicle Hyperplasia
- ↑Iodine Uptake from the Blood. (*Iodine Trapping*)
- ↑Thyroid Hormone Synthesis
- ↑Release of T_3 & T_4

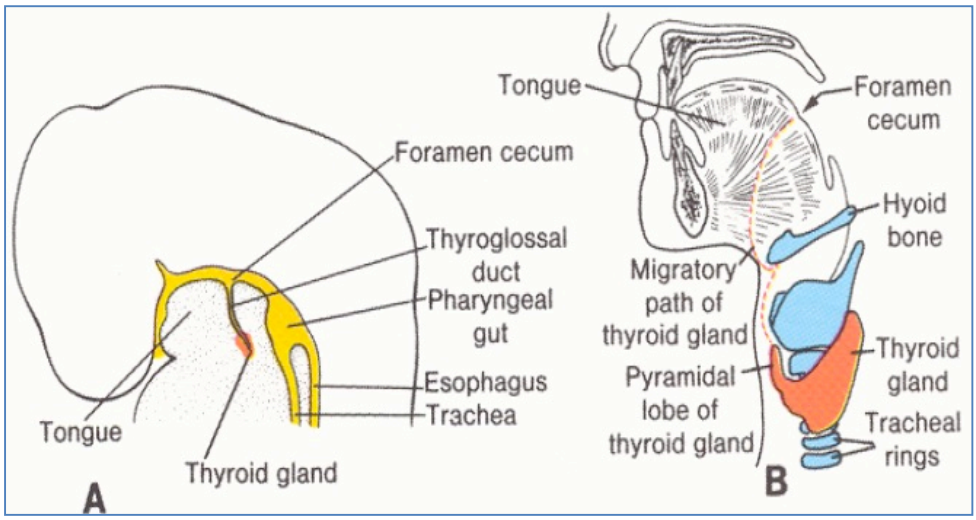
- **Synthesis of Thyroid Hormone:**
  - 1. Iodide Uptake ("Iodine Trapping")
  - 2. Iodide Activation via Oxidation
  - 3. Secretion of Active/Oxidised Iodine into Colloid
  - 4. Synthesis of Thyroglobulin from Tyrosines & Secretion into Colloid
  - 5. Iodines stick to Thyroglobulin in Colloid → DIT or MIT (Di/Mono-Iodo Tyrosine)
- **Release of Thyroid Hormone:**
  - Colloid is Endocytosed and Enzymatically Cleaved into T_3 & T_4.
  - Vesicles of T_3 & T_4 release contents into Cytosol
  - T_3 & T_4 Diffuse out of Follicle Cell & Into Bloodstream
  - Thyroxine-Binding Proteins (incl. Albumin)in Blood transport T_3 & T_4 to the rest of the body.
- **Metabolic Effects of Thyroid Hormone:**
  - **NB:** Because Thyroid Hormones act by Gene Activation, they are said to have a ***Long 'Latent Period'***, during which they seem to have no discernible effect.
  - **Skeletal -** ↑Bone Turnover & ↑Resorption
  - **Muscular -** ↑Speed of Contraction & ↑Speed of Relaxation.
  - **Sympathetic NS -** ↑Catecholamine Sensitivity of Heart, Muscle, Fat & Lymphocytes.
  - **CVS -** ↑HR & ↑CO
  - **GI -** ↑Gut Motility, ↑Secretion, ↑Appetite
  - **Carbohydrate Metabolism -** ↑Hepatic Gluconeogenesis, ↑Hepatic Glycolysis.
  - **Lipid Metabolism -** ↑Lipolysis (↑FFA in Plasma)
  - **Metabolic Changes:**
    - ↑Carbohydrate/Fat/Protein Metabolism
    - ↑Mitochondrial Activity & Number
    - ↑Na/K-ATPase Activity
    - ↑O_2 Consumption
    - ↑[FFA] in Plasma
  - **Bodily Changes:**
    - ↑Body Temp → Sweating
    - ↑Metabolism (Basal Metabolic Rate)





Thyroid Embryology:

- Forms from ***Pharyngeal Pouches*** (@4-5wks)
- Forms from the ***Endoderm*** germ layer.
- Once formed, it migrates downwards & becomes Bi-lobed.
    - NB: Sometimes things go wrong during this migration, leaving a person's thyroid gland between the back of the tongue & where it normally sits. (See dotted red line on pic below)



Major Thyroid Hormones Produced (And Proportions):

- **T_3 – Triiodothyronine (7%)** (*Iodinated Derivative of Tyrosine – 3x Iodines*) (Most Biologically Active)
- **T_4 – Thyroxine (93%)** (*Iodinated Derivative of Tyrosine – 4x Iodines*) (Less Biologically Active)
  NB: Because these hormones are stored in the 'Colloid', there is ≈2-3mths of 'backup' *Reserve.*
- **Calcitonin** (Polypeptide)

Iodine Balance:

- **NB: Iodine is an essential component of the 2 major Thyroid Hormones & Is a Dietary Requirement.**
- **Of the Iodine ingested;**
    - 20% is Selectively Removed from blood by Thyroid Gland & used in Thyroid Hormone Synthesis.
    - 80% is Excreted by the Kidneys
- **NB:** This process of Active Iodine Uptake by the Thyroid Gland is called ***"Iodine Trapping"***.
- **NB:** The ***Rate*** of Iodine Uptake (Trapping) depends on ***TSH Concentration.***

How TSH Stimulates Thyroid Hormone Synthesis/Secretion:

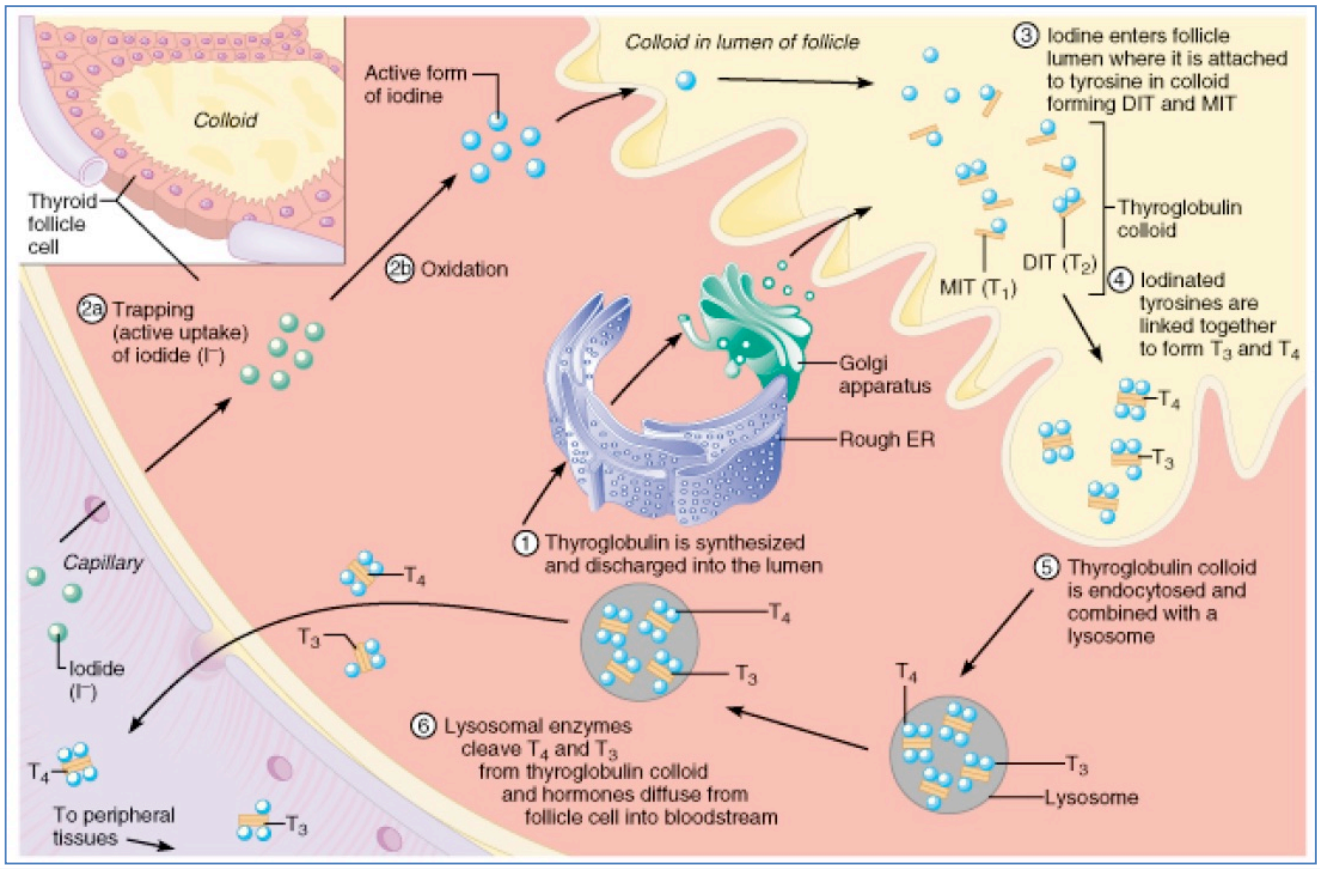
- **Binding of TSH to Follicle Cell → Activates AdenylylCyclase → ↑cAMP → Activates pKa (Protein Kinase A) → Phosphorylates Various Enzymes in Follicle Cell → Changes Activity of:**
    1. ↑Cleavage of Thyroglobulin in Lysosomes (Ie. ↑Release of T_3 & T_4)
    2. ↑Activity of Iodine Pump (The Rate Limiting Step) → ↑Iodine Available for Synthesis
    3. ↑Iodination of Tyrosine → ↑Synthesis of DIT's & MIT's → ↑Thyroid Hormone Synthesis
    4. ↑Size & Secretory Activity of Follicle Cells
    5. ↑# of Follicle Cells

Synthesis of Thyroid Hormone: (Stimulated by TSH)

1. **Active Uptake of Iodide by the Principal/Follicle Cells (Iodide "Trapping"):**
   a. Active Iodide uptake against massive Electrochemical Gradient.
   b. NB: This is the Rate-Limiting Step of TH Synthesis.
2. **Iodide Oxidation (by Peroxidase):**
   a. Oxidation of Iodide Ions (I^-) → Iodine Molecules (I_2).
3. **Secretion of Active Iod*ine* into Lumen of Colloid:**
4. **Synthesis of Thyroglobulin by Rough-ER+Golgi & Secretion into Lumen of Colloid:**
   a. Tyrosines – the basis of Thyroglobulin (A large poly-peptide of ≈70 Tyrosines)
5. **Iodines stick to the Tyrosines on the Thyroglobulin in Colloid → DIT or MIT** (Di/Mono-Iodo Tyrosine)

Hormone Release Mechanism:

6. **Some of the Thyroglobulin Colloid is Endocytosed + Combined with Lysosome:**
   a. Lysosomal Enzymes cleave the T_3 & T_4 from the Thyroglobulin.
   b. NB: In the process, many of the unpaired DIT's/MIT's are also released. These are De-Iodinised by ***Deiodinase.*** Both the freed Iodines & Tyrosines are recycled.
7. **Vesicle of Cleaved T_3 & T_4 Breaks Down, Releasing Hormones into Cytosol**
8. **Hormones in Cytosol Diffuse through Basement Membrane → Combine with Binding Proteins in the Blood Stream (Thyroxine-Binding Protein/Albumin)**



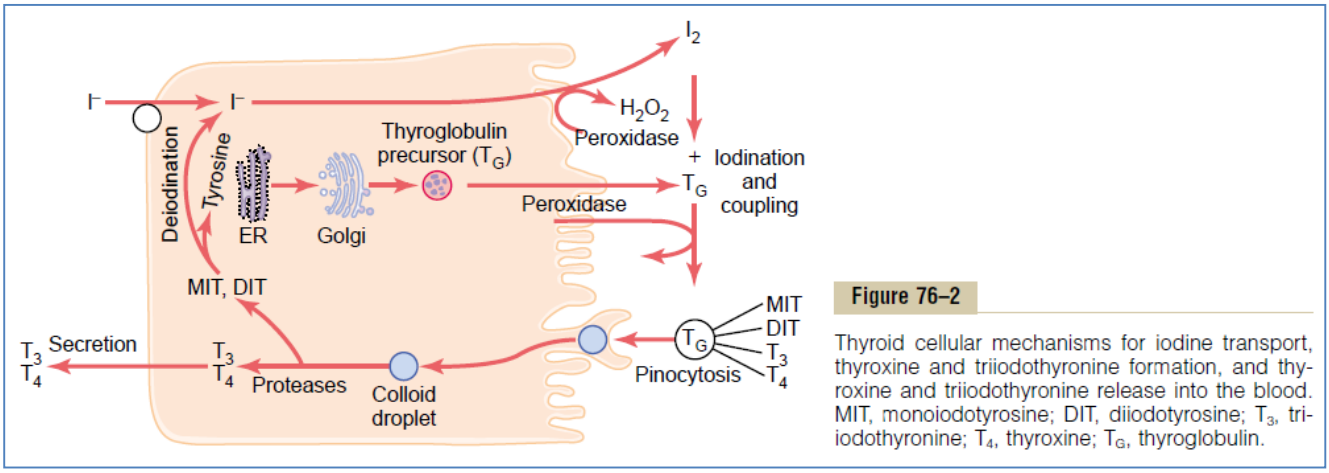
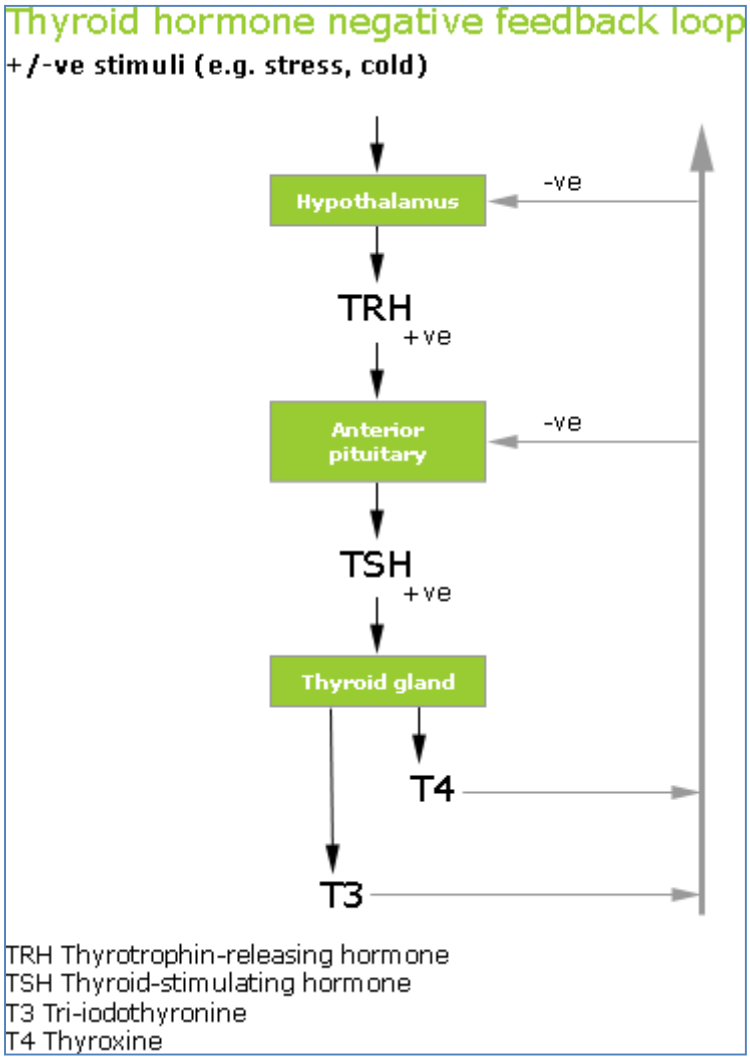


Figure 76–2

Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. MIT, monoiodotyrosine; DIT, diiodotyrosine; T_3, triiodothyronine; T_4, thyroxine; T_G, thyroglobulin.

Regulation of Thyroid Hormone Production/Release:

1. **Hypothalamus Secretes *"Thyrotropin-Releasing Hormone" (TRH)*** into portal circulation of Pituitary.
2. **TRH Stimulates Anterior Pituitary to Secrete *"Thyroid Stimulating Hormone" (TSH)***.
3. **TSH Stimulates Thyroid Gland to Secrete:**
   a. *Primarily Thyroxine (T_4) (The relatively inactive Thyroid Hormone → converted to T_3)
   b. And Some Triiodothyronine (T_3) (The most active Thyroid Hormone)
4. **T_3 & T_4 Circulate in the Bloodstream Eliciting their effects + Provide Neg.Feedback to Ant. Pituitary**



Transport of Thyroid Hormones (Binding Proteins):

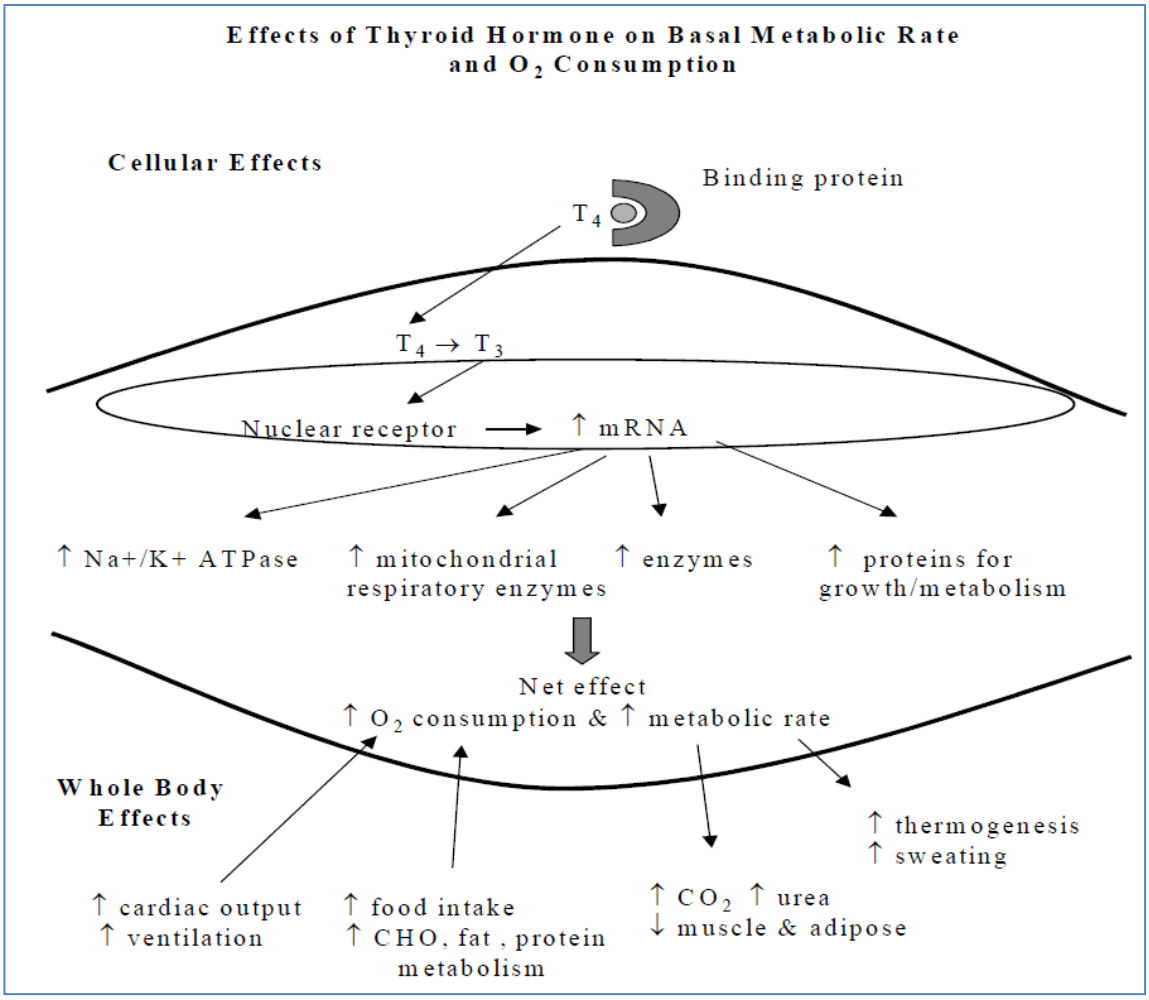
- NB: 75-100µg of Thyroid Hormone is secreted per day
- Thyroid hormone must be bound to carrier proteins when in bloodstream to avoid filtration by kidneys.
- **Common Thyroid-Hormone Carrier Proteins:**
  - 70% - *"Thyroxine-Binding Globulin" (TBG)*
  - 30% - Albumin
  - NB: The minute %age of unbound Thyroid Hormones are those eliciting their effects.
    - Ie. TH must be unbound to be able to enter cells & bind to Intracellular Receptors.

Mechanism of Action of Thyroid Hormone:

1. Thyroxine (T_4) reaches target cell
2. Binding Protein releases Thyroxine (T_4)
3. Thyroxine (T_4) diffuses into cytosol → Converts to T_3
4. T_3 (The most active form) enters Nucleus → Binds to Nuclear Receptor on DNA → Alters Gene Transcription.
5. Activating Different Genes → leads to Change in Cell's Protein/Enzyme profile → Change in Activity.

- **Cellular Changes:**
  - ↑Carbohydrate/Fat Metabolism
  - ↑Glucose Uptake
  - ↑Protein Synthesis + Catabolism
  - ↑Mitochondrial Activity & Number
  - ↑Na/K-ATPase Activity
- **Bodily Changes:**
  - ↑O_2 Consumption → ↑Cardiac Output, HR & Respiration
  - ↑Food Intake (↑Glucose Absorption from GIT)
  - ↑Secretion of Digestive Juices
  - ↑GIT Motility
  - ↑Insulin Secretion
  - ↑[FFA] in Plasma
  - ↑Body Temp → Sweating
  - ↑Metabolism (Basal Metabolic Rate)
  - ↑Vitamin Requirements due to ↑Quantities of Enzymes (Of which vitamins are a vital component)

- **NB:** Because Thyroid Hormones act by Gene Activation, they are said to have a ***Long 'Latent Period'***, during which they seem to have no discernible effect.
  - **Thyroxine:** 2-3 Days
  - **Triiodothyronine:** 6-12 Hours



Regulation of Metabolism – Insulin, the Counter-Regulatory Hormones & Diabetes

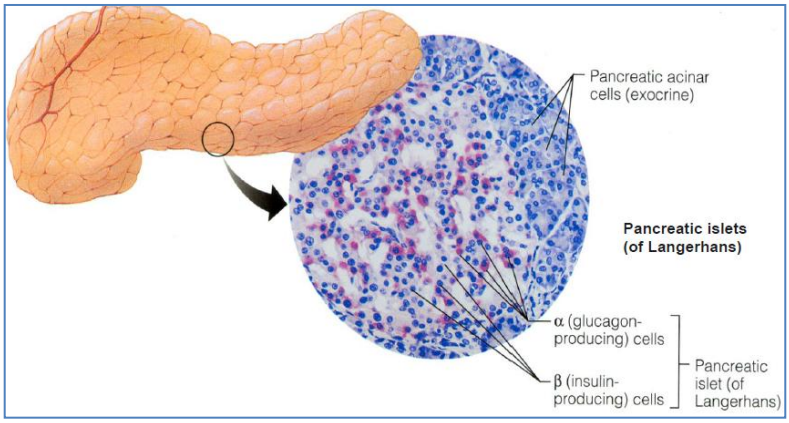
NB: Insulin = the only Hypoglycaemic Hormone. (NB: Incretins – Intestinal Hormones which ↑Insulin Secretion)
NB: The Counter Regulatory Hormones counter this → ↑Glucose Levels (Hyperglycaemic Function)

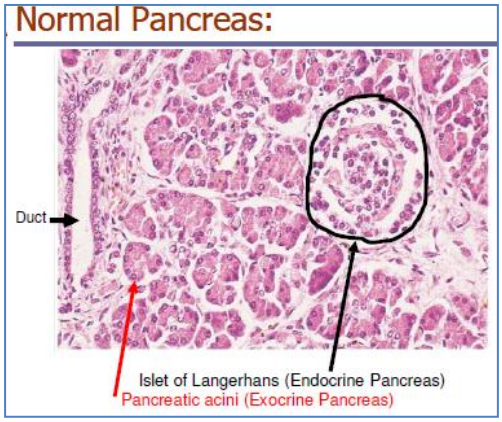
Blood [Glucose] Range:

- **Basal:** 4mMols/L
- **Peak:** 7-8mMols/L

Major Endocrine Organs that Regulate Metabolism:

- **#1. Pancreas:**
  - 99% of Cells are **'Acinar' *Exocrine* Cells** - (Secrete digestive enzymes into GIT via Pancreatic Duct)
  - Therefore, **only 1% are *Endocrine* 'Islet' Cells -** (Diffuse, Hormone-secreting). ***Of these*:**
    - 25% are Alpha Cells – Secrete **Glucagon**
    - 60% are Beta Cells – Secrete **Insulin**
    - 10% are Delta Cells – Secrete **Somatostatin**
    - (5% are PP Cells – Secrete **Pancreatic Polypeptide** (Autoregulation of Pancreas))





- **Anterior Pituitary:**
  - Responsible for Growth Hormone Secretion.
- **Adrenal Gland:**
  - Responsible for Cortisol Secretion.

3 Insulin *Dependent* Tissues – (Involved in Nutrient Processing/Storage):

- **Liver**
- **Muscle**
- **Adipose Tissue**

Insulin *Independent* Tissues:

- **Blood Vessels (Endothelium)**
- **Myocardium of Heart**
- **Nervous System**
- **Red Blood Cells**
- **Kidneys**
- **Eyes**

Hormones of Glycaemia:

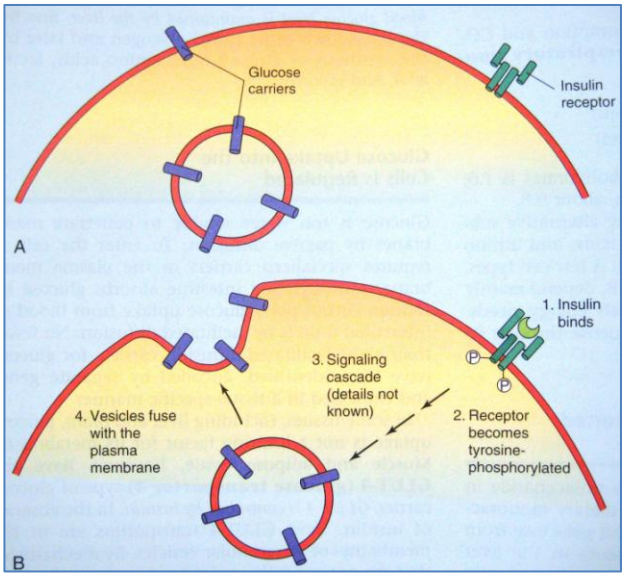
- **Hypoglycaemic Hormones:**
  - **Insulin** (By b-Cells of Pancreas) = the only Hypoglycaemic Hormone.
  - **NB: Also *Incretins*** = Secreted by the Intestines → Act to increase action of Insulin
- **Hyperglycaemic Hormones (Counter-Regulatory Hormones):**
  - **Glucagon** (By a-Cells of Pancreas)
  - **Growth Hormone** (By Ant.Pituitary)
  - **Cortisol** (By Adrenal Cortex)
  - **Catecholamines** (By Adrenal Medulla)

Mechanism of Insulin Release from β-Cells of Pancreas:

1. ↑Blood Glucose → ↑ *Insulin-Independent* Uptake of Glucose into Pancreas (Via GLUT-2)
2. → ↑ATP Production in β-Cell.
3. ↑ATP Closes the ATP-Gated-K^+ Channels in β-Cell Membrane → Depolarises the β-Cell
4. Depolarisation → opens Voltage-Gated Ca^+ Channels → Influx of Ca^+
5. Influx of Ca^+ → Ca^+ Mediated Exocytosis of Insulin Vesicles (Similar to ACh Release in Muscles)

Mechanism of Insulin Action (Glucose Uptake):

- **Insulin only affects *Insulin Sensitive* Tissues (Ie. Those that expresses GLUT-4 Transporters):**
  - Liver
  - Muscle
  - Adipose Tissue
- **Insulin →↑Glucose Uptake in tissues by ↑ Expression of GLUT-4 Transporters in the PM.**
  - **Fasted State:**
    - Some GLUT-4 Expression; But most will be imbedded in Cytoplasmic Vesicles within the cell.
  - **Fed State:**
    - Insulin → Insulin Receptors → Upregulation of GLUT-4 in PM → ↑Glucose Uptake



The "Fed State" – Directly After a Meal:

- **↑INSULIN:**
  - **Stimulates:**
    - **Nutrient Uptake from the Blood:**
      - **Glucose** (Liver, Muscle & Adipose)
        - Via ↑GLUT-4 Receptors (***Muscle & Adipose***)
      - **Amino Acids** (Liver, Muscle & Adipose)
      - **Fatty Acids** (Liver & Adipose)
    - **Macromolecular Synthesis (& Storage):**
      - **Glycogenesis** (Liver & Muscle) – (NB: Glucose → Triglycerides in Adipose)
      - **Proteingenesis** (Liver, Muscle & Adipose)
      - **Lipogenesis** (Liver & Adipose)
    - **Glycolysis – In all body cells**
  - **Inhibits:**
    - **Gluconeogenesis** (Liver)
    - ****Ketogenesis** (Liver) – (Therefore *even Low* Insulin (DM2) Prevents Ketoacidosis)
      - A problem for D1M due to *NO* insulin → Diabetic Ketoacidosis
    - **Macromolecular Breakdown:**

- **NB: "Incretin Effect":**
  - **Incretins (Released by GIT after a meal) Further Stimulates Insulin Release from Pancreas.**
  - Hence → The Insulin Response to Oral Glucose is much Greater & Quicker than IV Glucose.
  - **:. New Avenue for Diabetes Management:**

- **Incretins:**
  - *Intestinal* glucose intake → Intestines release **Incretins (glucagon-like peptide-1 [GLP-1] and Glucose-dependent Insulinotropic Polypeptide [GIP])** → Stimulate β Cells to ↑Insulin Release and Suppress α-Cells and ↓Glucagon.
- **NB: Incretins are Destroyed by Dipeptidyl Peptidase-4 (DPP-4)**
  - :. By Inhibiting DPP, you can Prolong the Action of Incretins.

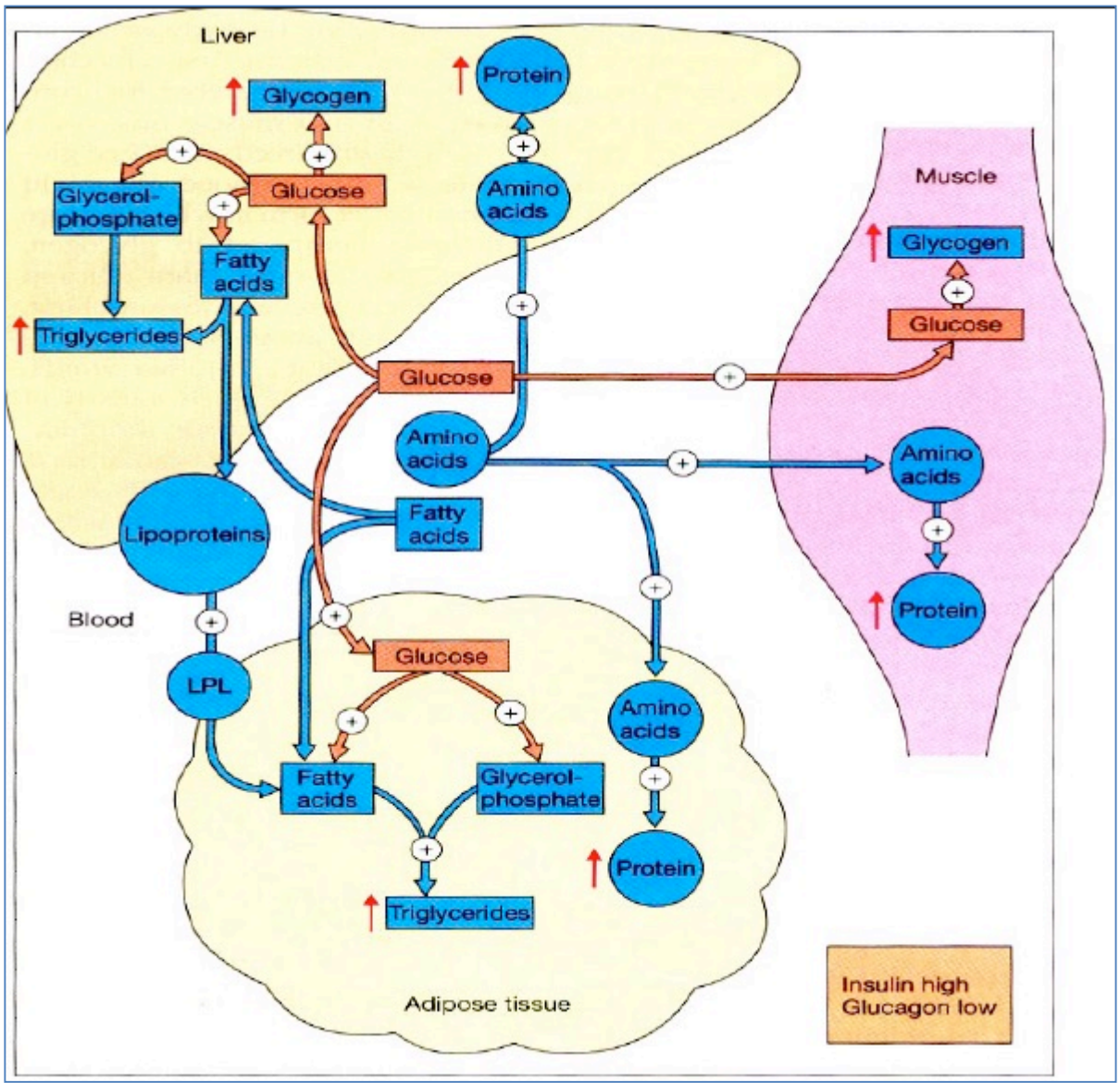
The "Fasted State" - ≈3hrs After a Meal:

- **↑GLUCAGON**
  - ***Activates Glycogenolysis (Liver)** → ↑Blood [Glucose]
  - **Activates Gluconeogenesis (Liver)** → ↑Blood [Glucose]
  - **Activates Lipolysis (Adipose)** → ↑Blood [FA's] (NB: Glucagon = Powerful Lipolytic)
  - **Stimulates Ketogenesis (Liver)**
- **NB: Even in the "Fasted State", There is still enough *INSULIN* to Prevent:**
  - *Massive* Lipolysis (As Glucagon is a powerful lipolytic)
  - *Massive* Ketogenesis (Normally, ↑Insulin Inhibits Ketogenesis) – Therefore *Low* Insulin allows some Ketogenesis but Prevents Ketoacidosis.)
  - *Massive* Proteolysis
  - **(This is why people with Type II Diabetes typically DON'T present with Diabetic Ketoacidosis DKA)**

INSULIN & GLUCAGON

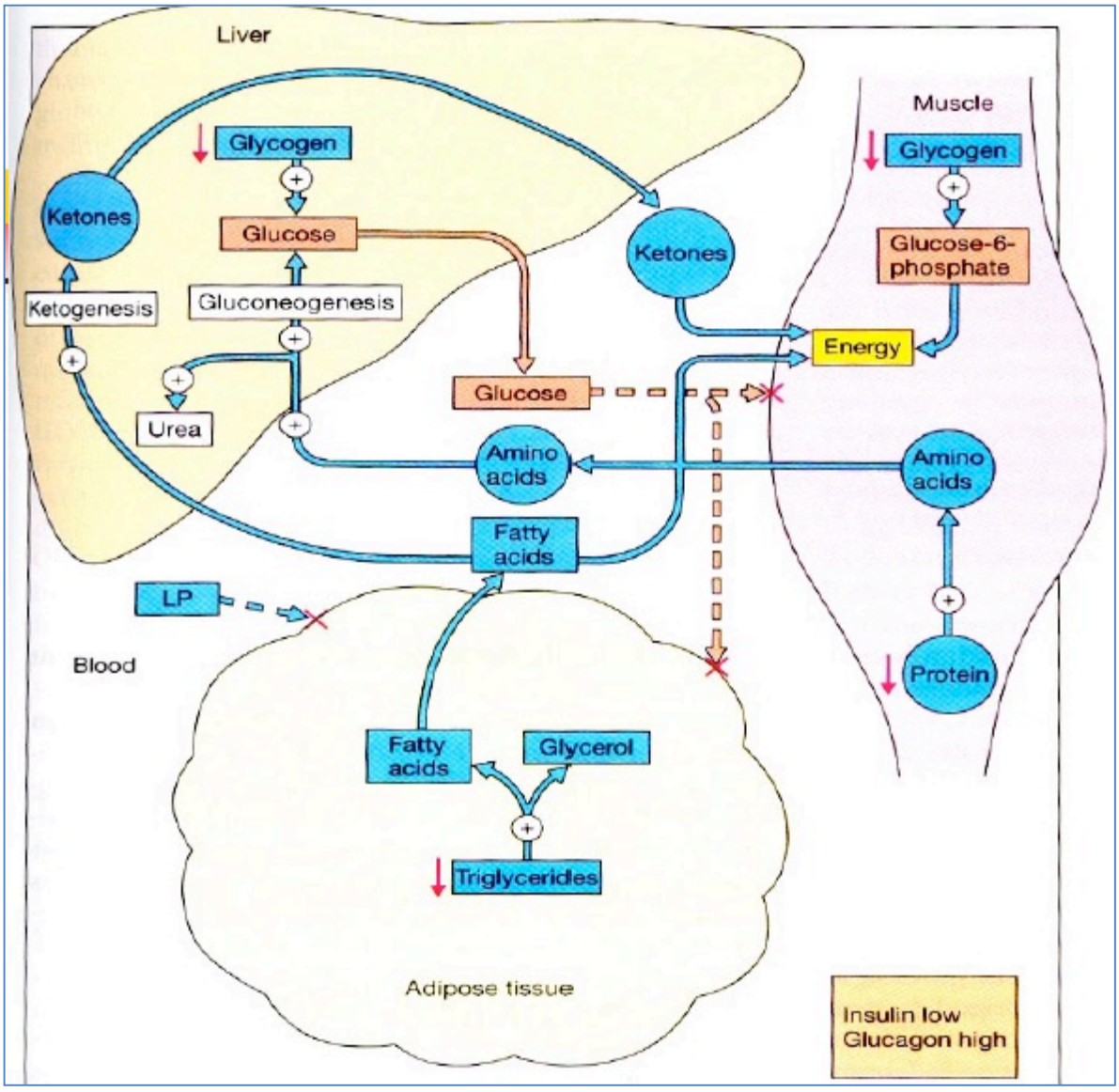
The "Fed State" – Directly After a Meal:

- **↑INSULIN:**
  - **Stimulates:**
    - **Nutrient Uptake from the Blood:**
      - **Glucose** (Liver, Muscle & Adipose)
        - Via ↑GLUT-4 Receptors (***Muscle & Adipose***)
        - Via ↑Glucose Utilisation (Liver)
      - **Amino Acids** (Liver, Muscle & Adipose)
      - **Fatty Acids** (Liver & Adipose)
        - Via ↑*Lipoprotein Lipase (LPL)* Activity in Adipose Tissue.
    - **Macromolecular Synthesis (& Storage):**
      - **Glycogenesis** (Liver & Muscle) – (NB: Glucose → Triglycerides in Adipose)
      - **Proteingenesis** (Liver, Muscle & Adipose)
      - **Lipogenesis** (Liver & Adipose)
    - **Glycolysis – In all body cells**
  - **Inhibits:**
    - **Gluconeogenesis** (Liver)
    - **Ketogenesis** (Liver)
    - **Macromolecular Breakdown:**
      - **Lipolysis** (Liver & Adipose)
      - **Glycogenolysis** (Liver & Muscle)
      - **Proteolysis** (Liver, Muscle & Adipose)



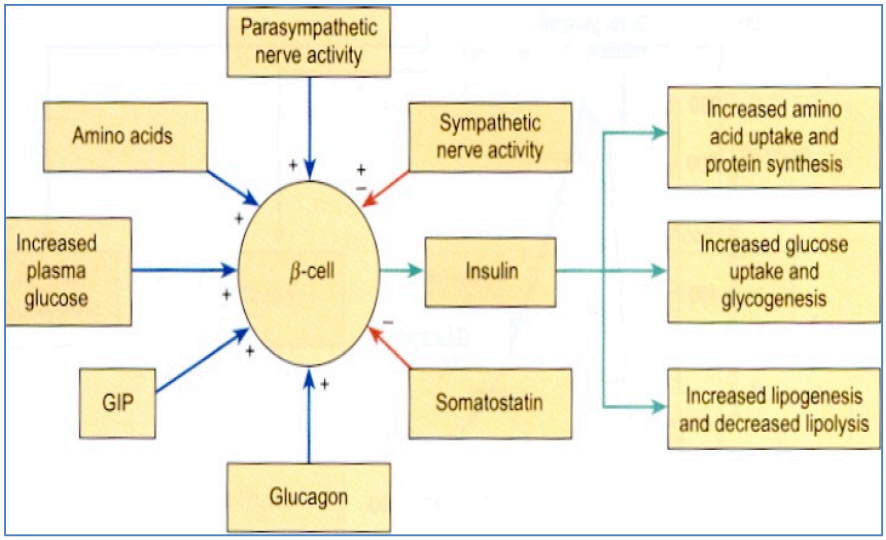
The "Fasted State" - ≈3hrs After a Meal:

- **↑GLUCAGON**
  - *Activates Glycogenolysis (Liver) → ↑Blood [Glucose] (NB: Glucagon = Powerful Glycogenolytic)
  - Activates Gluconeogenesis (Liver) → ↑Blood [Glucose]
  - Stimulates Amino Acid Uptake (Liver) → ↑Gluconeogenesis → ↑Blood Glucose
  - Activates Lipolysis (Adipose) → ↑Blood [FA's] (NB: Glucagon = Powerful Lipolytic)
  - Stimulates Ketogenesis (Liver)
- **↓INSULIN→ "Glucose-Sparing" Effect:**
  - **Increased Availability of Gluconeogenic Substrates:**...due to:
    - ↓Inhibition of Gluconeogenesis – (↑Level of Gluconeogenesis)
    - ↓Inhibition of Lipolysis – (↑ Level of Lipolysis)
    - ↓Inhibition of Proteolysis – (↑ Level of Proteolysis)
  - **↓Glucose Uptake by:**
    - Muscle
    - Liver
    - Adipose.
  - **Glucose-Sparing →** More Glucose for Brain & Nerves (Glucose = 1° Fuel)
- **NB: Insulin is Low, but is still high enough to prevent:**
  - *Massive* Lipolysis (As Glucagon is a powerful lipolytic)
  - *Massive* Ketogenesis (Normally, ↑Insulin Inhibits Ketogenesis) – Therefore *Low* Insulin allows some Ketogenesis but Prevents Ketoacidosis.)
  - *Massive* Proteolysis



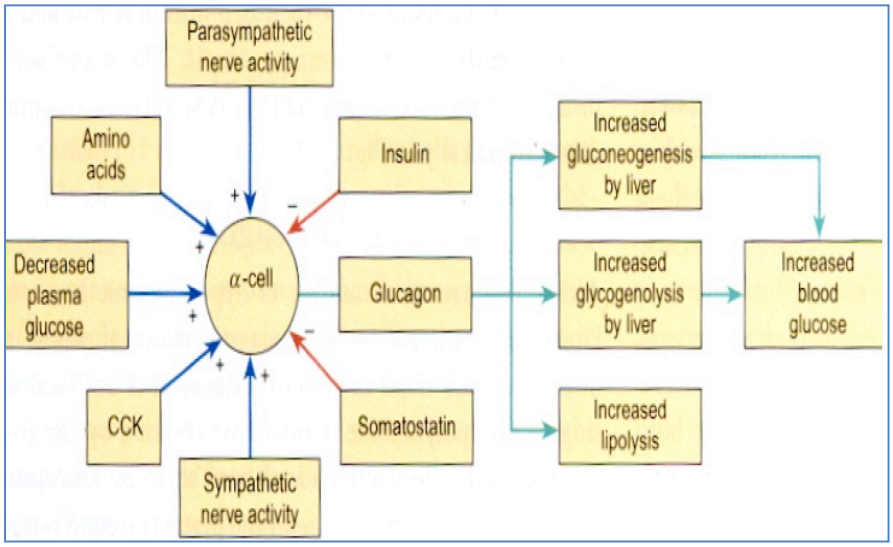
Regulation of INSULIN Secretion:

- **Stimulators:**
  - Parasympathetic NS (Rest & Digest)
  - ↑Blood [Amino Acids]
  - ↑Blood [Glucose]
  - Gastrointestinal Peptide (GIP)
  - Glucagon – (Weak Stimulator)
- **Inhibitors:**
  - Sympathetic NS (Acts to ↑Blood [Glucose] for Fight/Flight Response)
  - Somatostatin



Regulation of GLUCAGON Secretion:

- **Stimulators:**
  - ? Parasympathetic NS
  - ? Amino Acids
  - ↓Blood [Glucose]
  - Cholecystokinin (CCK)
  - Sympathetic NS (Acts to ↑Blood [Glucose] for Fight/Flight Response)
- **Inhibitors:**
  - Insulin (NB: Inhibition of Glucagon Secretion in Hyperglycaemia requires a small amount of Insulin)
    - Hence this can be a problem for Type 1 Diabetics (Insulin Deficiency)
  - Somatostatin



Fluid & Electrolyte Balance

Why Maintain Fluid & Electrolyte Balance?:

- Critical for Normal Cell Function
- Critical for Chemical Stability (Homeostasis) of Surrounding Fluids
- *Electrolyte Balance (Particularly **Na^+** & **K^+**) – Critical for function of Excitable Tissues
- Critical for Blood Pressure Homeostasis

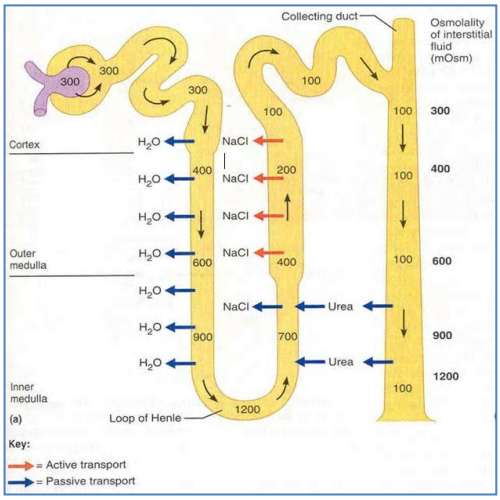
FLUID BALANCE:

Regulation of Water Intake (Thirst) – Hypothalamic Triggers:

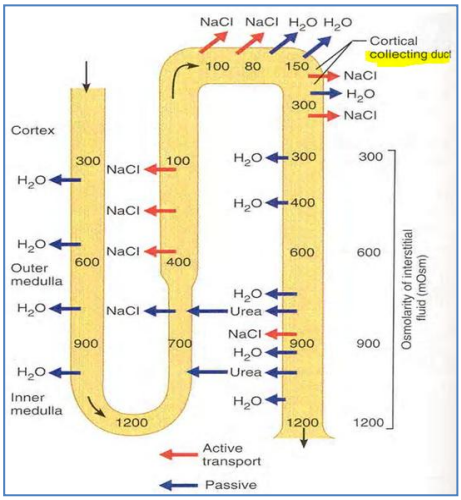
- **1. Decreased Plasma Volume → Reduced Blood Flow to Salivary Glands → Cellular Dehydration of Salivary Gland Cells → *"Dry Mouth"* → Triggers Thirst Centre in Hypothalamus.**
- **2. Increased Plasma Osmolarity → Directly Causes Cellular Dehydration of Osmoreceptors in the Hypothalamus → Stimulates the Thirst Centre.**

Regulation of Water Output:

- **Anti-Diuretic Hormone (ADH) → ↓Water Output:**
  - Acts to increase Blood Volume.
  - Released from the Posterior Pituitary Gland
  - **Released in response to:**
    - ↑Plasma Osmolarity (↑[Na^+]) → Stimulation of Osmoreceptors in Hypothalamus
    - ↓Plasma Volume.
  - **Works by INCREASING H_2O Permeability of Distal & Collecting Ducts:**
    - Distal Tubules & Collecting Ducts are Normally *Impermeable to H_2O.*
    - However, the Presence of ADH → ↑# of Aquaporins In Membrane →↑Permeability to H_2O.
    - This ↑Permeability to H_2O + High [Solute] in Medulla →H_2O Reabsorption (From Collecting Duct→ Interstitium →Blood)



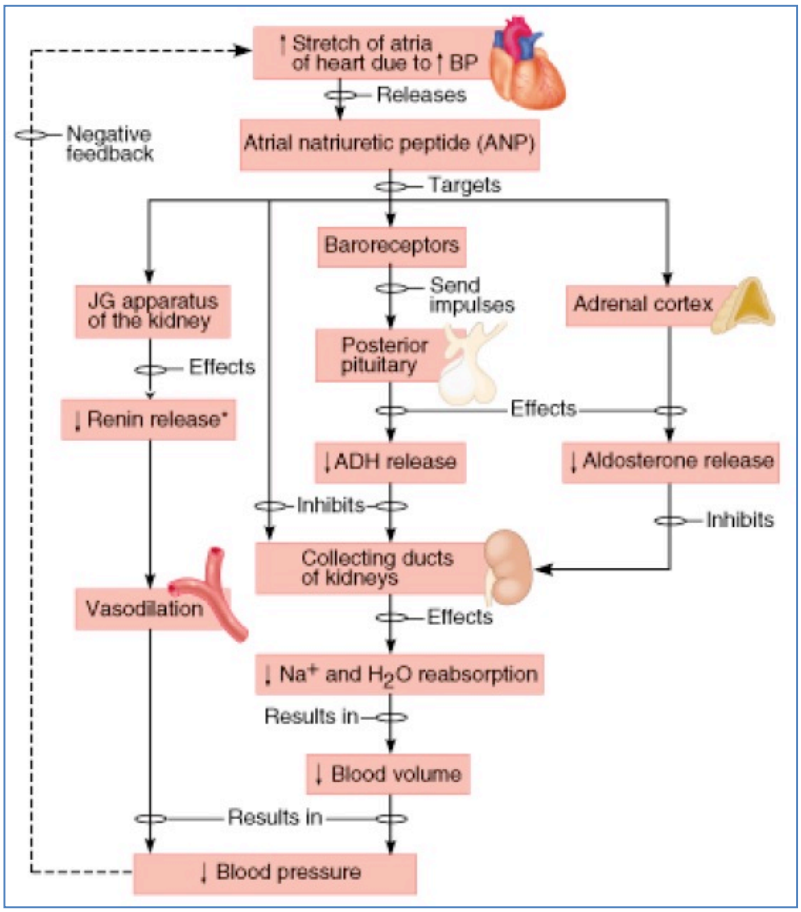
Absence of ADH



Presence of ADH (+Aldosterone)

- **Atrial Natriuretic Peptide (ANP) → ↑ Water Output:**
  - **Acts to:**
    - ↓blood volume
    - ↓Blood [Na]
  - **Secreted by** Atrial Myocytes of the Heart
  - **Released in response to:**
    - High Blood Pressure (Atrial Stretch)
  - **Works by:**
    - Dilating Afferent Glomerular Arteriole
    - Constricting Efferent Glomerular Arteriole
      - ↑Filtration Pressure → ↑ Filtration → ↑H_2O & Na Excretion.

- **Atrial Natriuretic Peptide (ANP):**
  - **Acts to:**
    - ↓blood volume
    - ↓Blood [Na]
    -
  - **Secreted by** Atrial Myocytes of the Heart
  - **Released in response to:**
    - High Blood Pressure (Atrial Stretch)
  - **Works by:**
    - Dilating Afferent Glomerular Arteriole
    - Constricting Efferent Glomerular Arteriole
      - ↑Filtration Pressure → ↑ Filtration → ↑H_2O & Na Excretion.
    - Inhibits Renin Secretion → Inhibits Renin-Angiotensin System
    - Inhibits Aldosterone Secretion from Adrenal Cortex.
    - Inhibits ADH Release from Post. Pituitary



ELECTROLYTE BALANCE:

Significant Electrolytes:

- **Na^+** = Major Extracellular Cation
- **Cl^-** = Major Extracellular Anion

} Account for 80% of Osmolarity of Interstitial Fluid & Plasma.

- **K^+** = Major Intracellular Cation - Accounts for 50% of Osmolarity of Intracellular Fluid

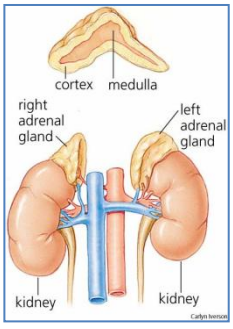
Why Maintain Electrolytes

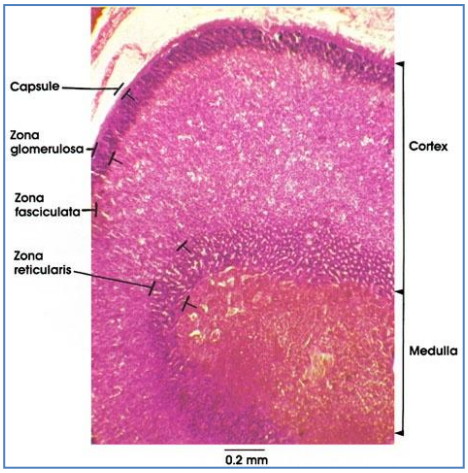
- **Na^+** = Important for Heart & Nerve Function/Cellular Transport
- **K^+** = Important for Heart Function/Cellular Transport
  - (**NB:** too high *Extracellular* K^+ interferes with Cardiac Function = Fatal)
- **Ca^+** = Important for Muscle, Heart & Nerve Function/Bone Formation
- **Mg^+** = Important for AcetylCholine Release → Important for Neural & Cardiac Function
- **HPO_4^{2-}** = Important for Bone Formation (Bone salts – primarily calcium & phosphates)

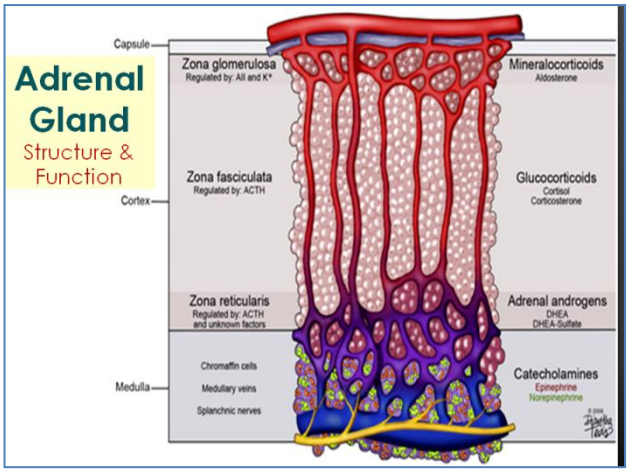
ELECTROLYTE BALANCE:

Adrenal (AKA: Suprarenal) Anatomy & Physiology:

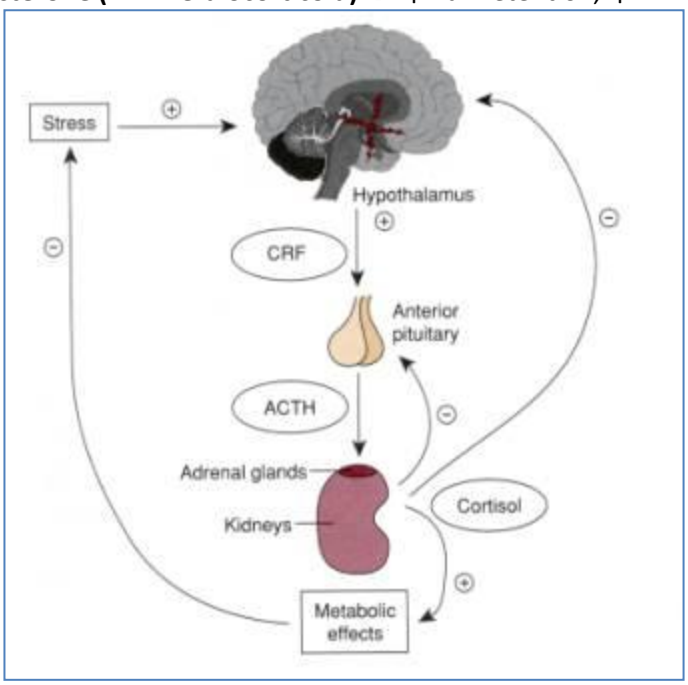
- **Anatomy:**
  - **Endocrine Glands that sit on top of the Kidneys**
  - **Retroperitoneal**
  - **Two Layers:**
    - **1. Cortex (3 Zones)** *(Remember GFR)*
      - **1. Zona Glomerulosa (Outer)** → Mineralocorticoids (**Aldosterone**)
      - **2. Zona Fasciculata** → Glucocorticoids (**Cortisol**)
      - **3. Zona Reticularis (Inner)** → Adrenal **Androgens** (DHEA)
    - **2. Medulla (Middle)**
      - Chromaffin Cells → Catecholamines (**Adrenaline**, **Noradrenaline**)







- **Physiology:**
  - **Stress Hormones:**
    - **Corticosteroids (Cortisol)** → ↑Blood Glucose, Immunosuppression, ↓Bone Formation.
    - **Catecholamines (Adrenaline)** → ↑Blood Glucose, ↑HR & BP, ↓Parasympathetics.
  - **Electrolyte Balance:**
    - **Aldosterone (A Mineralocorticoid)** → ↑Na^+ Retention, ↑K^+ Excretion, ↑BP



Significant Electrolytes:

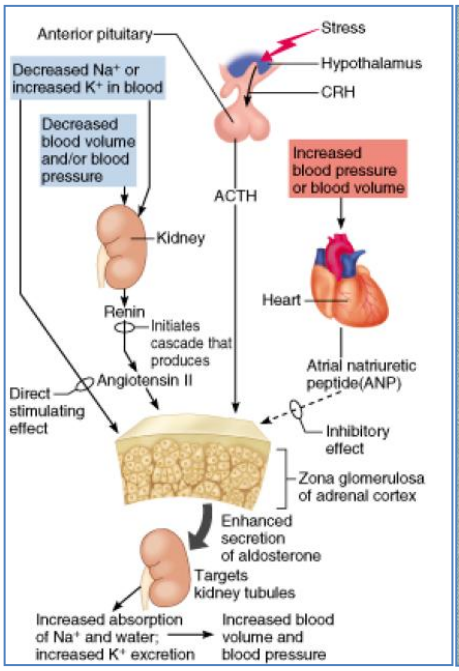
- **Na^+** = Major Extracellular Cation } Account for 80% of Osmolarity of Interstitial Fluid & Plasma.
- **Cl^-** = Major Extracellular Anion }
- **K^+** = Major Intracellular Cation - Accounts for 50% of Osmolarity of Intracellular Fluid

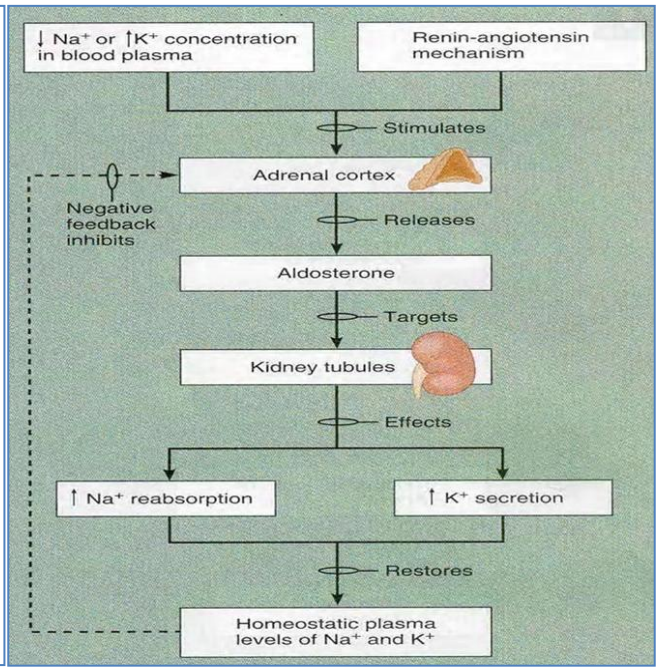
Why Maintain Electrolytes

- **Na^+** = Important for Heart & Nerve Function/Cellular Transport
- **K^+** = Important for Heart Function/Cellular Transport
  - (**NB:** too high *Extracellular* K^+ interferes with Cardiac Function = Fatal)
- **Ca^+** = Important for Muscle, Heart & Nerve Function/Bone Formation
- **Mg^+** = Important for AcetylCholine Release → Important for Neural & Cardiac Function
- **HPO_4^{2-}** = Important for Bone Formation (Bone salts – primarily calcium & phosphates)

Regulation of Na^+ - (The Main *Extracellular* Electrolyte):

- Extracellular [Na^+] is normally stable & is **Regulated by levels of Aldosterone:**
- **Aldosterone → ↑Na Resorption:**
  - Aldosterone = Steroid Hormone Released from The Adrenal Cortex.
  - **Released in response to:**
    - *Angiotensin-II, Part of the Renin-Angiotensin System (Due to Renin Release by Kidneys)
    - *Hyponatraemia (Low Na^+ in Blood)
    - *Hyperkalaemia (High K^+ in Blood)
    - Stress





  - **Works by:**
    - **ACTIVATING the Na/K-ATPases in the Principal Cells of Distal & Collecting Ducts:**
      - Increases Na^+ & Cl^- Reabsorption
      - Increases K^+ Secretion
  - **Effects:**
    - Increases Na^+ Reabsorption of the Principal Cells of the Distal & Collecting Ducts of the Nephron.
    - **If Aldosterone is High –** *All* Na in Filtrate is reabsorbed
    - **If Aldosterone is Low** – *No* Na in Filtrate is reabsorbed

K^+: The Primary Intracellular Electrolyte:

- Primary Roles in Normal Neuromuscular Function, Membrane Potentials & Membrane Transport.
- **Deficient Intracellular K^+:**
  - Cell membrane will be more Negative than normal (Ie. *Hyperpolarised*)
  - Therefore it'll be harder to initialize an action potential as it takes more to reach threshold.
- **Excess Intracellular K^+:**
  - Cell membrane will be more Positive than normal (Ie. *Depolarised*)
  - Therefore it'll be easier to initialize an action potential as it takes less to reach threshold.
- **Affect on the Heart:**
  - The heart is particularly sensitive to K^+ Levels.
  - Both Too High & Too Low K^+ Levels will Disrupt Electrical Conduction of the Heart → Can be Fatal.
- **Regulating K^+ Levels:**
  - Relies solely on K^+ Secretion by the ***"Principal Cells"*** in the Collecting Ducts of the Kidneys.
  - **Principal Cells Detect [K^+] in the Blood:**
    - High Blood [K^+] → K^+ Secretion is Increased
    - High Blood [K^+] → K^+ Secretion is Decreased
  - **Adrenal Glands Detect [K^+] in the Blood:**
    - High Blood [K^+] DIRECTLY Stimulates **Aldosterone** Release from Adrenal Cortex.
  - **Aldosterone** → Activates Na^+/K^+-ATPase's in the Distal Tubules & Collecting Ducts:
    - This Increases Reabsorption of Na^+, Cl^- & H_2O from Distal Tubule→Interstitium
    - But ALSO causes Secretion of K^+ into the Filtrate.

Disorders of Fluid/Electrolyte-Regulating Hormones:

- **Disorders of ADH:**
  - **Diabetes Insipidus:**
    - Condition characterised by Excessive Thirst & the inability to Concentrate Urine.
    - **2 Types:**
      - Neurogenic - ADH Insufficiency
      - Nephrogenic – Insensitivity of the kidneys to ADH
    - **Signs/Symptoms:**
      - Extreme Thirst
      - Excessive Urination
      - Risk of Hypokalaemia
    - **Diagnosis Criteria:**
      - Normal Blood Glucose
      - Normal Blood Bicarb
      - Normal Blood Calcium

      } To Rule out other causes of Excess Urination.
      - Urinalysis – Low Osmolarity, Electrolytes & Specific Gravity
      - Fluid Deprivation Test - No change in urine osmolarity
      - Desmopressin Stimulation – Distinguishes between Neurogenic & Nephrogenic.
    - **Treatment:**
      - Patients compensate by ↑H_2O Intake.
      - If Neurogenic – Desmopressin (Synthetic ADH) → ↓Urine Production.
      - If Nephrogenic – Hydrochlorothiazide Diuretic → ↓Urine Output in patients with DI.

  - **SIADH (Syndrome of Inappropriate ADH secretion):**
    - Condition characterised by Excessive ADH Release from Post. Pituitary Or Ectopic Source.
    - **5 Cardinal Signs/Symptoms:**
      - Fluid Overload (*Without* oedema or hypertension)
      - Hyponatraemia (Dilutional) →
        - Headache
        - Nausea
        - Vomiting
        - Confusion
        - Convulsions (If Severe)
        - Coma (If Severe)
      - Natriuresis (Excretion of Sodium in Urine – usually excessive)
      - High Urine Osmolarity relative to Plasma Osmolarity.
      - Normal Renal & Adrenal Function
    - **Caused by:**
      - Insensitivity of Hypothalamic Osmoreceptors to ↓Plasma Osmolarity
      - Therefore, ADH release isn't inhibited by ↓Plasma Osmolarity
    - **Treatment:**
      - Fluid Intake Restriction
      - Drugs:
        - Demeclocycline – Induces Nephrogenic Diabetes Insipidus as a Side Effect.
          - Hence desensitises ADH receptors in the Nephron.
        - Conivaptan – Inhibits 2 of the 3 ADH Receptors.
        - Tolvaptan – Competitive inhibition of ADH Receptors.

- **Disorders of Aldosterone:**
  - **Aldosteronism:**
    - Hypersecretion of Aldosterone
    - **Signs/Symptoms:**
      - Hypertension
      - Hypernatraemia
      - Hypokalaemia
      - Metabolic Alkalosis (Due to ↑H^+ secretion by the kidney)
    - **Aldosterone 'Escape':**
      - 1. Escape from sodium-retaining effects of ↑↑Aldosterone.
      - 2. Inability of ACE-Inhibitor Therapy to suppress Aldosterone release.
    - **Diagnosis:**
      - Very Low Renin-Aldosterone Ratio (Ie. ↓Renin & ↑Aldosterone)

  - **Addison's Disease:**
    - Hyposecretion of Aldosterone (Amongst other Glucocorticoids produced by the Adrenals)
    - **Signs/Symptoms:**
      - Hyponatraemia
      - Hyperkalaemia
      - Metabolic Acidosis – due to Na^+ Reabsorption being linked to H^+ Secretion.
    - **Addisonian Crisis:**
      - A crisis of multiple symptoms indicating severe adrenal insufficiency.
      - Result of – Previously undiagnosed Addison's Disease
        - Acute disease affecting adrenal function

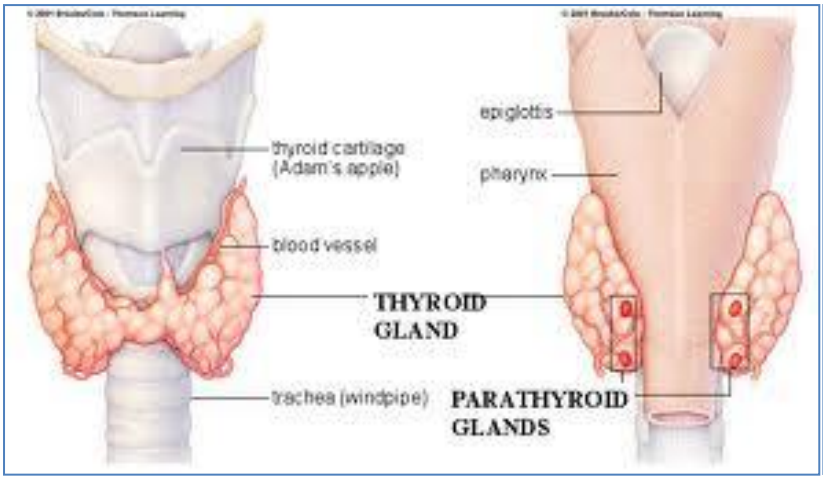
GLS Questions:

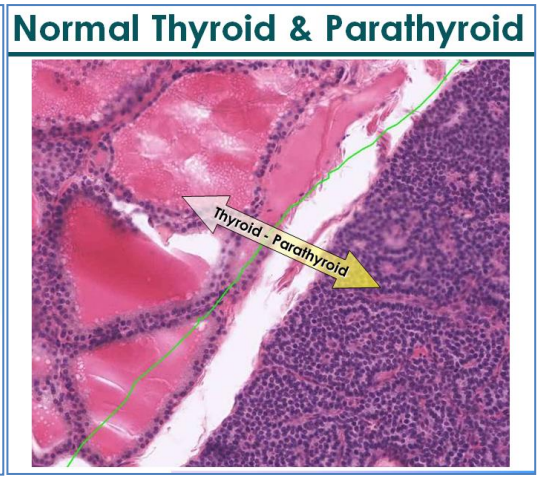
- **Define the Term '*Third Space*' in relation to body fluid & briefly describe how it can arise:**
  - When body fluids collect in a 'third' body compartment that isn't normally perfused with fluids, causing depletion of the fluids in the first & second compartments.
    - Eg. Ascites
    - Eg. Haemorrhage
    - Eg. Pleural Effusion
    - Eg. Joint Swelling
- **What is Renin?**
  - A Protein Enzyme that converts Angiotensinogen to Angiotensin I
- **Where is Renin Released:**
  - From the Juxtaglomerular Cells of the Kidneys
- **What stimulates renin release:**
  - Decrease in renal perfusion
  - Sympathetic Stimulation
- **What are the major effects of Angiotensin II:**
  - Peripheral Vasoconstriction
  - ↑BP
  - ↑Sympathetic Stimulation
  - ↑Aldosterone Release → ↑Na reabsorption & ↑K Secretion in Kidneys.

Calcium & Phosphate Metabolism

Parathyroid Anatomy & Physiology

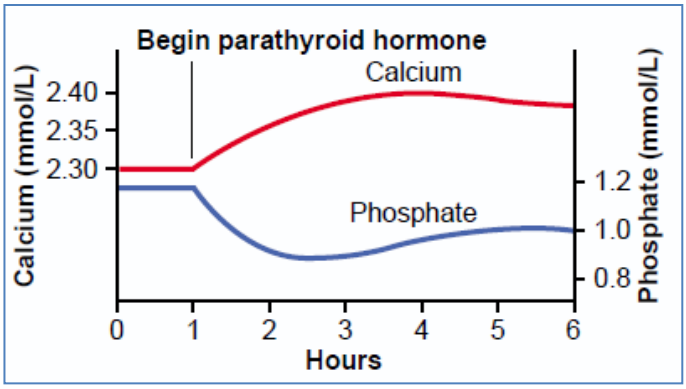
- **Anatomy:**
  - **Macro:**
    - 4x small Endocrine Glands on the Posterior Surface of the Thyroid Gland.
      - 2x on Left; 2x on Right
    - Size of a grain of rice.
  - **Micro:**
    - Densely packed cells (As opposed to follicle structure of Thyroid Gland)
    - **2 Cell Types:**
      - **Parathyroid Chief Cells:**
        - Secrete Parathyroid Hormone (PTH)
      - **Oxyphil Cells:**
        - Unknown function.



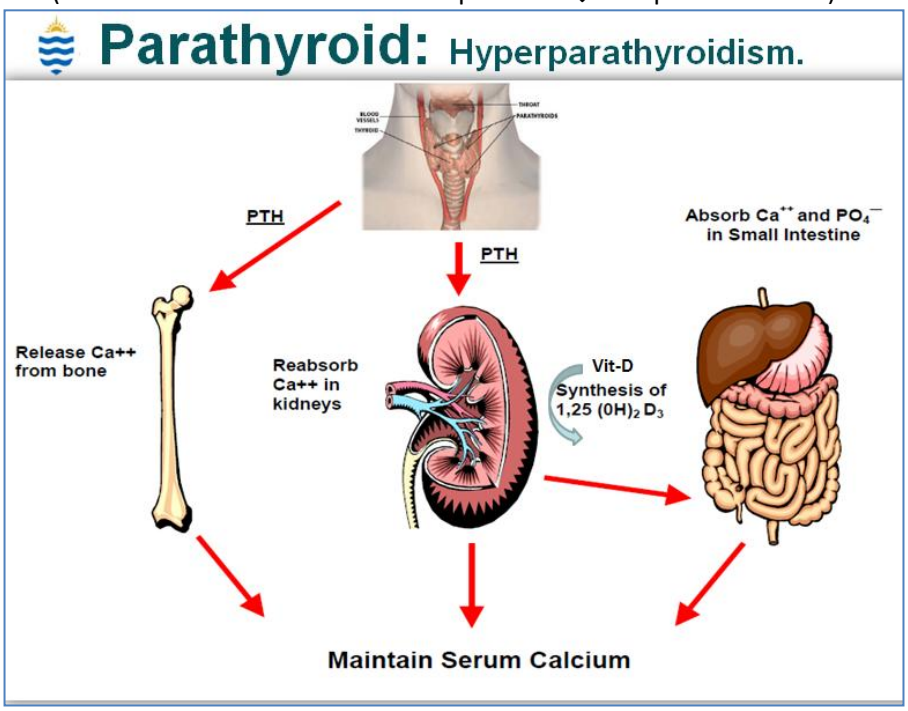


- **Physiology:**
  - **Function (Via PTH):**
    - **Calcium Homeostasis in Blood & Bones**
      - (Important for Excitable Tissues)
      - (Important for Bone Integrity)
    - **(Also has effects on Phosphate)**
  - **NB: Parathyroid Gland is NOT under Hypothalamic Control!!! – Functions Autonomously.**

- **Parathyroid Hormone (PTH):**
  - **Secreted by –** The Chief Cells of the Parathyroid Glands
  - **Release Stimulated By:**
    - ↓Extracellular [Ca^+] – Very Sensitive
  - **Release Inhibited By:**
    - ↑Extracellular [Ca^+] – Very Sensitive
  - **Aims to:**
    - ***↑Plasma-Ca^+ levels*** (By Increasing Bone Ca^+/P^- Resorption & ↓ Renal Ca^+ Excretion)
    - ***↓Plasma-P^- levels*** (By ↑Renal P^- Excretion so that it exceeds Bone P^- Resorption)



- **Primary Effects:**
  - Stimulates Osteoclasts → Mobilises Ca from Bone Matrix → ↑Calcium in Blood
  - Activates Vit.D in Kidneys → ↑GI Absorption of Ca^{+} → ↑Calcium in Blood
  - ↑Renal Calcium Reabsorption → ↓Renal Excretion →↑Calcium in Blood
  - (Increases Renal Excretion of Phosphate → ↓Phosphate in Blood)



Functions of Calcium & Phosphate:

- **Calcium:**
  - **Structural Purposes**:
    - Development & Maintenance of Skeleton
  - **Biochemical Purposes:**
    - Mediates exchange between Intracellular & Extracellular Compartements (eg. ACh Release)
    - Role in Muscle Contraction & Nerve Impulses
    - Role in Blood Clotting
- **Phosphate:**
  - **Structural Purposes:**
    - Development & Maintenance of Skeleton
    - Phospholipids are a major structural component of Plasma Membrane
  - **Biochemical Purposes:**
    - Phosphate Release from Nucleotides (eg. ATP → ADP) is the Major Source of Cellular Energy.
    - The Phosphodiester-Bond Provides the backbone for RNA & DNA.
    - Phosphorylation provides a basis for Receptor Activation & Signal Transduction.

Bone Chemistry:

- **Bone Consists of 2 Things:**
  - **30% (By Weight) = Organic Bone Matrix:**
  - **70% (By Weight) = Bone Salts:**
    - The major salt = *Hydroxyapatite* ($Ca_{10}(PO_4)_6(OH)_2$) (Mainly Calcium & Phosphate)

Serum Concentrations:

- **Calcium:**
  - **Intestinal Absorption/Renal Excretion/Bone Deposition - are Regulated by 3 Hormones:**
    - PTH - Parathyroid Hormone

Serum Concentrations:

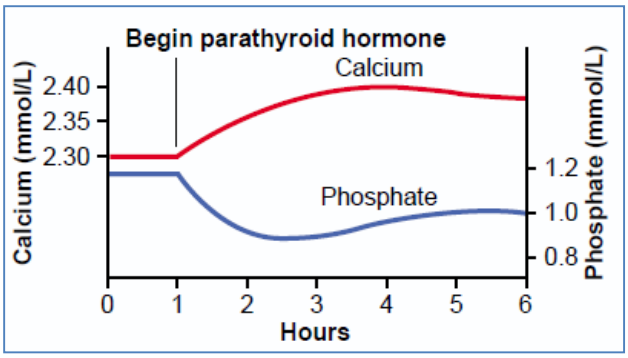
- **Calcium:**
  - **Levels depend on 3 Processes:**
    - Intestinal Absorption (Ie. To ↑ Serum Ca+)
    - Renal Excretion (Ie. To ↓ Serum Ca+)
    - Resorption/Deposition of Bone (Ie. To ↑ Serum Ca+)
  - **The Above Processes are Regulated by 3 Hormones:**
    - PTH - Parathyroid Hormone
    - Calcitonin
    - Vitamin D (The Active Form)
  - **Calcium levels are tightly regulated - @ ≈ 9.4mg/dl OR 2.4mmol/L.**
  - **NB: Only ≈1% of the Body's Ca^+ is Extracellular. The Rest is Stored in Bones.**
    - Hence, the Bones = Ca^+ Reservoir.
  - **Extracellular Ca^+ exists in 3 Forms:**
    - 50% Ionized = Ca^+ NOT Bound to Anything (Diffusable)
      - (NB: This is the functionally important form.)
    - 10% In Covalent Compounds (Diffusable)
    - 40% Bound to Plasma Proteins (Eg. Albumin) (Non-Diffusable)
- **Phosphorus:**
  - **Levels depend on:**
    - Age
    - Gender
    - Dietary Intake.
    - Calcium-Controlling Hormones.
  - **NB: Only ≈1% of the Body's Phosphate is Extracellular. The Rest is Stored in Bones.**
  - **Phosphorus levels are loosely regulated - @ ≈ 2.4 - 4.1 mg/dl.**

Regulation of Plasma Ca^+ & Phos. Levels:

- **Intestinal Absorption:**
  - **Calcium:**
    - Normally, Ca^+ is poorly absorbed by the Intestines.
    - **NB: *Vitamin D* Increases Ca^+ Absorption by the Intestines (POTENT)**
    - **NB: *PTH* indirectly promotes Intestinal Ca^+ Absorption by ↑Vit.D Activation by the Kidneys.**
  - **Phosphate:**
    - Absorption occurs very easily
    - (Ie. Almost all dietary Phosphate is absorbed into the blood, and later excreted in urine)
- **Renal Excretion:**
  - **Calcium:**
    - Normally, 99% of Filtered Ca^+ is Reabsorbed...
      - 90% happens in PCT, Loop of Henle & early DCT.
      - 10% happens in the late DCT – ***and is Very Selective (****Depending on Blood-Ca^+****)***
    - **If Blood-Ca^+ is Above Normal –** All remaining Ca^+ is expelled in urine.
      - **NB: *Calcitonin* weakly ↑ Calcium Excretion.**
    - **If Blood-Ca^+ is Below Normal –** All remaining Ca^+ is reabsorbed
      - **NB: *PTH* Greatly ↓ Calcium Excretion in the Kidneys. (Ie. ↑Reabsorption)**
  - **Phosphate:**
    - Renal Phosphate excretion is via an '*Overflow Mechanism*':
    - **If Blood-Phosphate is Below 1mmol/L –** All filtered Phosphate is Reabsorbed
    - **If Blood-Phosphate is Above 1mmol/L –** Phosphate is excreted @ a rate relative to its conc.
      - **NB: *PTH* Greatly ↑ Phosphate Excretion in the Kidneys.**
- **Resorption/Deposition of Mineralized Bone:**
  - ***PTH* promotes Osteoclast Activity (Bone Resorption)**
  - ***Vitamin D* promotes Bone Calcification (Deposition) (Mechanism Unknown)**
  - ***Calcitonin* promotes Bone Calcification (Deposition) (By *Inhibiting Osteoclast Activity*)**

The 3 Major Hormones:

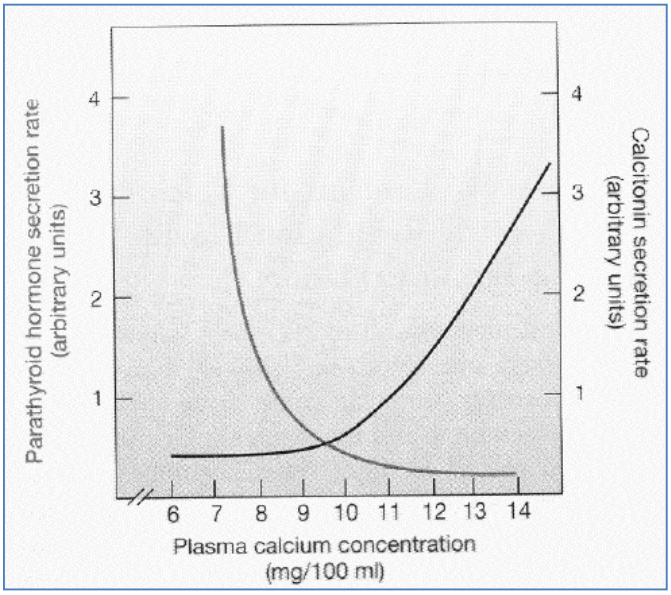
- **1. Parathyroid Hormone (PTH):**
  - **Secreted by –** The Chief Cells of the Parathyroid Glands
  - **Aims to:**
    - ↑***Plasma-Ca^+ levels*** (By Increasing Bone Ca^+/P^- Resorption & ↓ Renal Ca^+ Excretion)
    - ↓***Plasma-P^- levels*** (By ↑Renal P^- Excretion so that it exceeds Bone P^- Resorption)

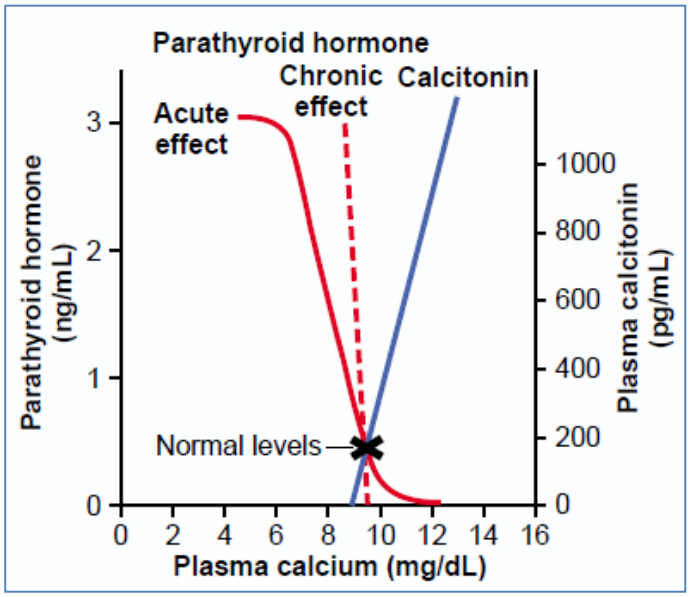


  - **Primary Effects:**
    - Mobilises Ca & Phos from bone Matrix (Bone Resorption) (By Stimulating Osteoclast Activity)
    - Stimulates Osteoblast & Osteoclast Proliferation → Promotes bone turnover.
    - Decreases Renal Excretion of Calcium (By Increasing Calcium Reabsorption in DCT)
      - NB: ***PTH*** is essential here to prevent excess loss of Calcium & therefore prevent calcium depletion in ECF & Bone.
    - Increases Renal Excretion of Phosphate (By Preventing Phosphate Reabsorption in PCT)
    - Increases Activation of Vit.D in Kidneys→ Indirectly increases intestinal absorption of Ca^+/P^-.
  - **Stimulated By:**
    - ↓Extracellular $[Ca^+]$ – Very Sensitive
  - **Inhibited By:**
    - ↑Extracellular $[Ca^+]$ – Very Sensitive

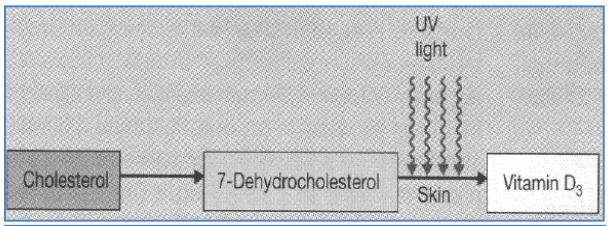
  - **Regulators (According to Dr. Seive)**

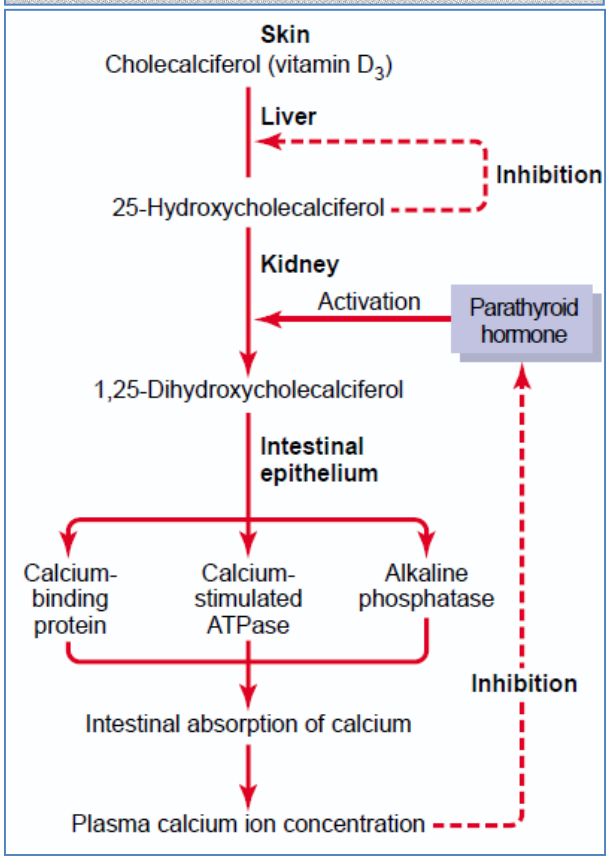
Stimulated By:	**Inhibited By:**
↓ Calcium	↑ Calcium
↑Phosphate (Indirect)	Vit D_3
↓Magnesium	
Cortisol	

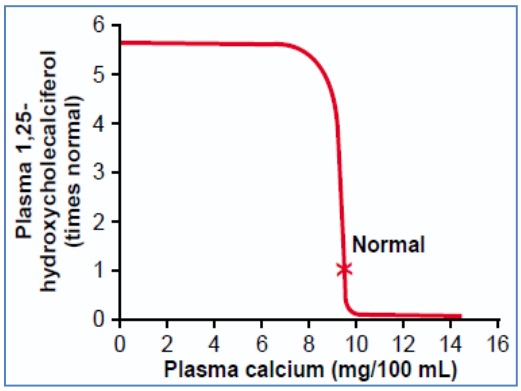


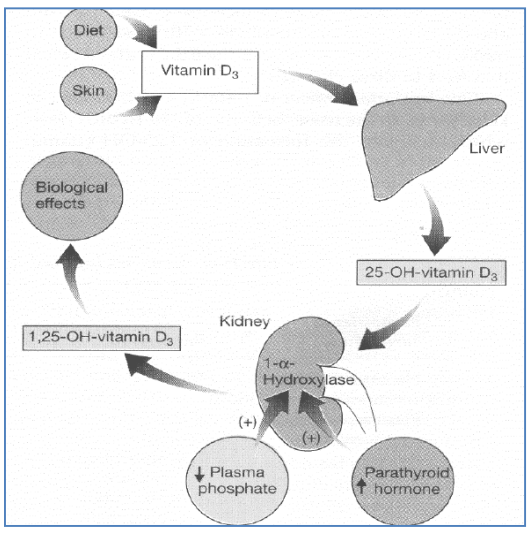


- **2. Vitamin D:**
  - **Aims to:**
    - **↑*Plasma-Ca^+/P^- levels*** (by Increasing intestinal Ca^+/P^- absorption)
  - **Primary Effects:**
    - ↑ Intestinal Calcium Absorption
    - ↑ Intestinal Phosphate Absorption (Even better than usual)
    - Aids ***PTH*** in mobilizing Ca & Phos from bone Matrix.
    - (In Small Quantities, it can ↑ Bone Mineralization (Mechanism Unknown))
  - **Vit.D Activation:**
    - Vit.D *itself* is not the active form that causes the above effects. It must first be ***Activated***.
    - Vit.D is converted through a series of reactions in the ***Skin, Liver*** & the ***Kidneys*** to produce the final active product = ***1,25-dihydroxycholecalciferol*** aka. ***1,25(OH)$_2$D$_3$***.
    - See Below for Steps:
      - **NB**: The conversion in the Liver has Neg.Feedback for 2 Important Reasons:
        - 1. Prevents excessive 25-Hydroxycholecalciferol in the plasma, which in turn prevents excessive activation by kidneys → maintains Ca^+ ion concentration.
        - 2. Conserves the Vit.D_3 stored in the Liver for future use. (Because the converted forms only last a few weeks, whereas Vit.D_3 lasts for months)
      - **NB**: The conversion in the Kidneys is controlled by ***PTH***:
        - Without PTH, none of the 1,25(OH)2D3 is formed.
        - Therefore, PTH has a huge influence on the levels of body's functional Vit.D.
          - **Furthermore**, since Plasma-Ca^+ levels determine PTH levels, Plasma-Ca^+ has an Indirect, but STRONG Negative Feedback Effect as well. **(Even a slight increase in [Ca^+] above 10mg/dL, sharply suppresses PTH secretion → ↓25-Hydroxycholecalciferol – See Diagram)**

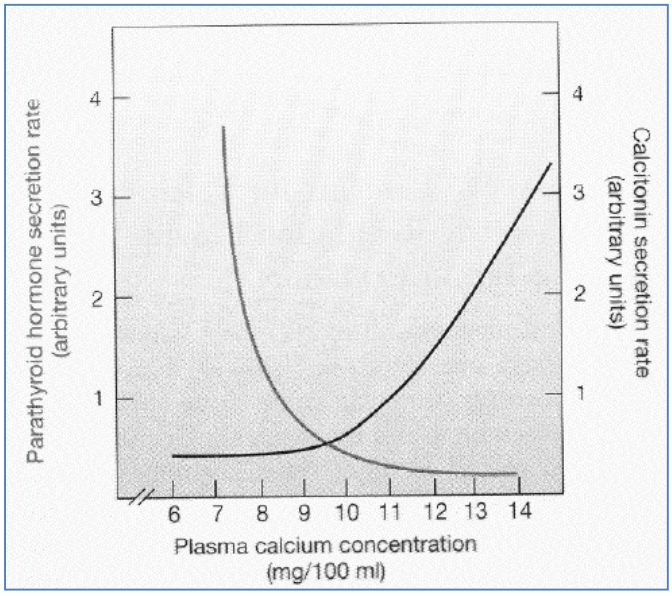


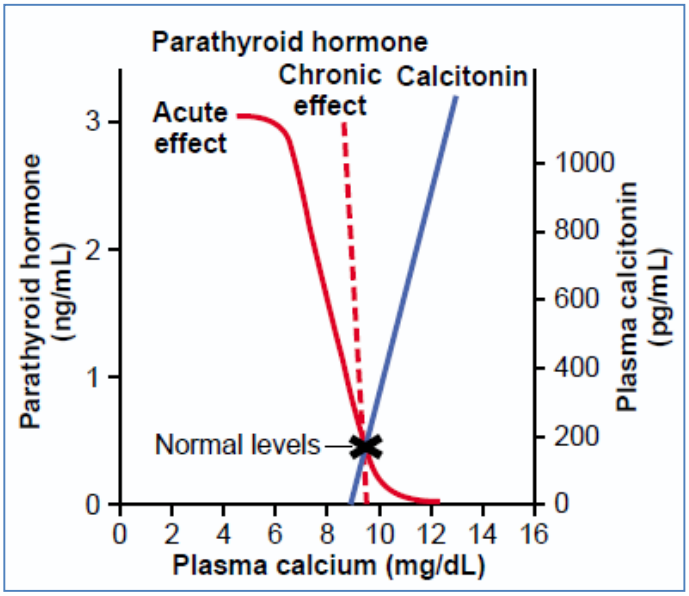




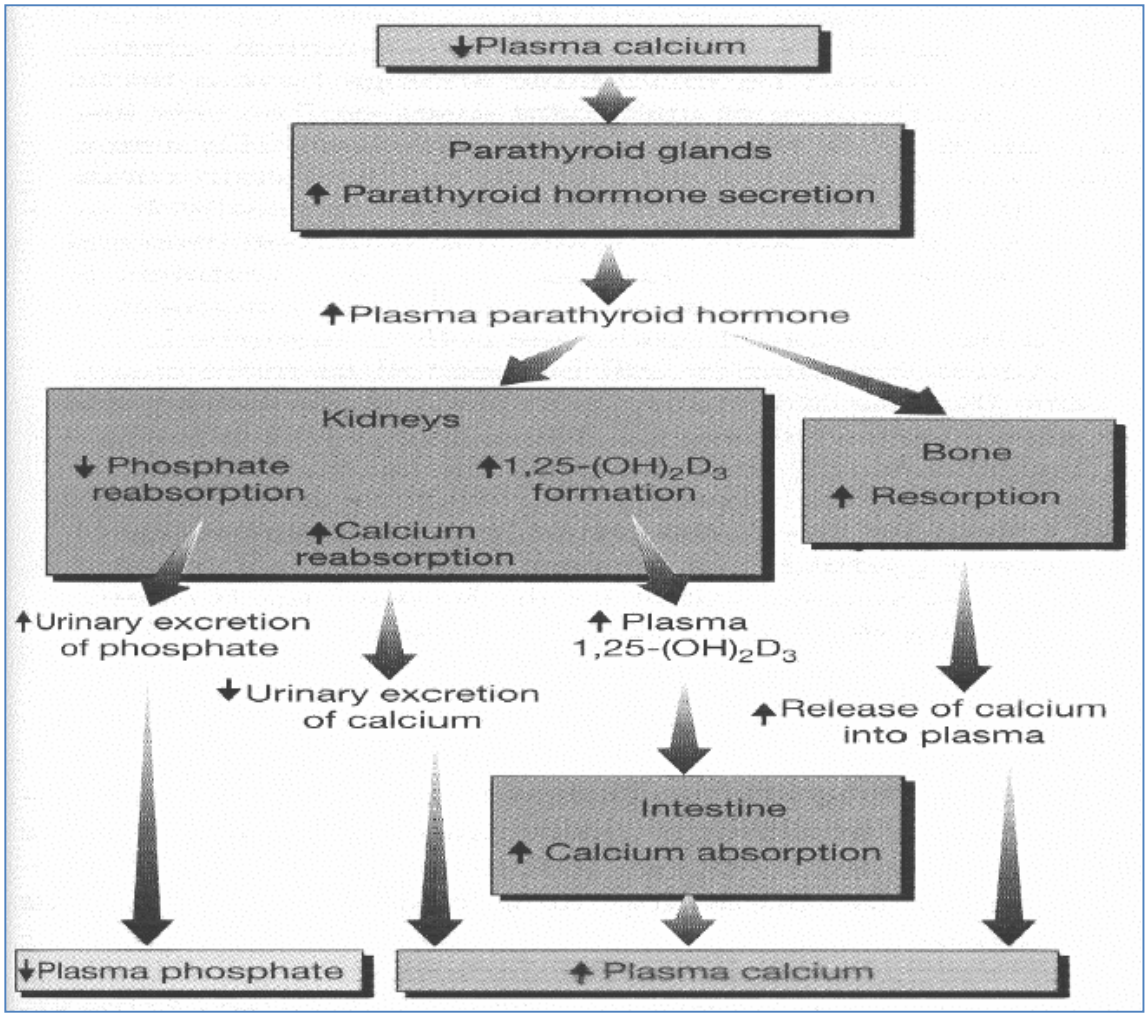


- **3. Calcitonin:**
  - **Secreted By –** The Parafollicular Cells of the Thyroid Gland
  - **Aims to:**
    - ***↓Plasma-Ca^+ levels*** (By ↓Osteoclast Activity so that Bone Deposition is Favoured)
      - This effect is much greater in children due to rapid remodelling.
  - **Primary Effects:**
    - Decreases the Activity & Proliferation of Osteoclasts → Favours Bone-Salt Deposition.
  - **Stimulated By:**
    - ↑Extracellular [Ca^+] (NB: Opposite of PTH) (See Below Diagrams)





Summary:

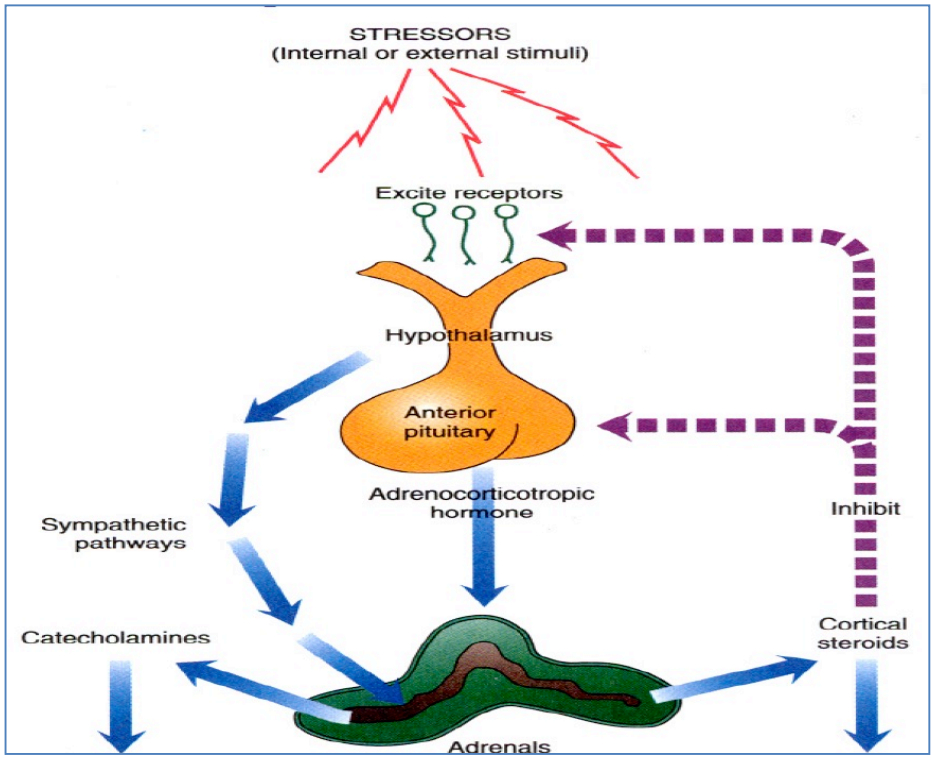


Endocrinology Notes

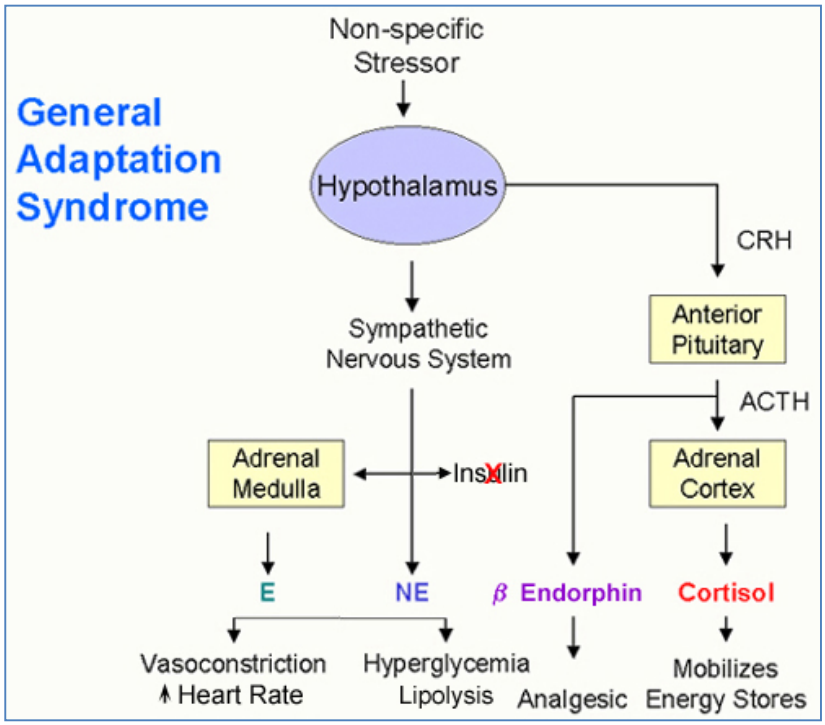
Physiological Response to Stress (Nervous & Endocrine)

Stress & The Hypothalamo-Pituitary Axis:

- 1. Stressors (Internal or External) trigger Receptors.
- 2. Receptors inform the Hypothalamus
- 3. Hypothalamus - Activates Sympathetic Pathways
  - Secretes Corticotropin-Releasing Hormone → Ant. Pituitary releases ACTH.
- 4. Both Sympathetic Activation & ACTH Release → Stimulate the Adrenal Glands.
- 5. Adrenal Glands - Secrete Catecholamines (Incl. Adrenaline)
  - Secrete Cortical Steroids (Incl. Cortisol)

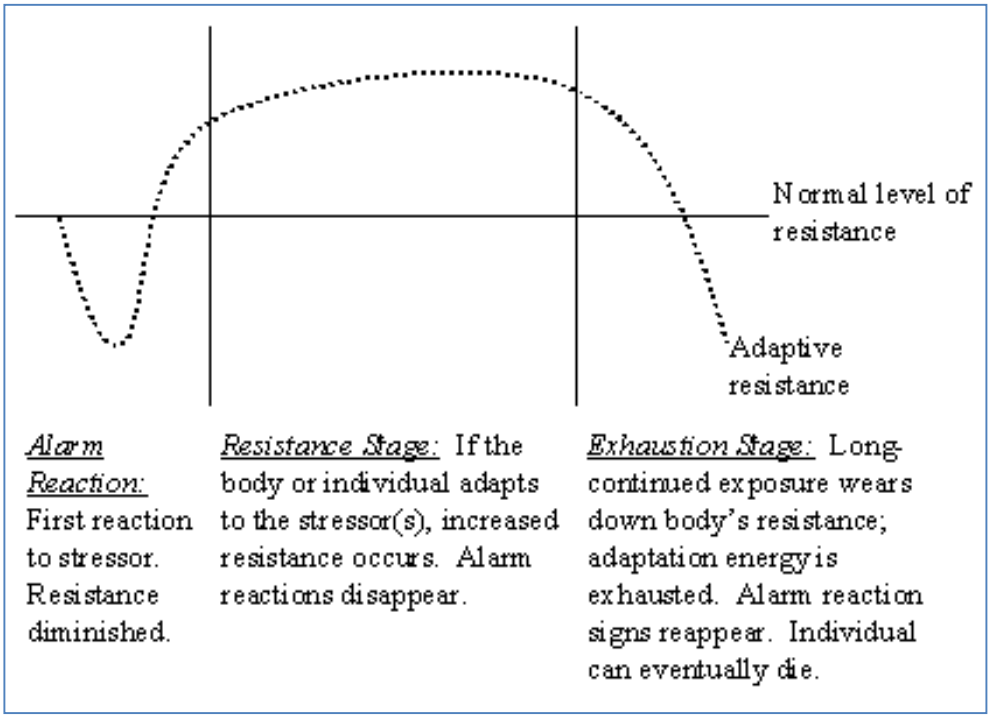


Adrenaline **Cortisol**



The Body's Responses to Stress:

- **Dr. Hans Selye proposed the "*General Adaptation Syndrome*" as the Body's Responses to Stress**
- **He also noticed 3 Universal Symptoms of Chronic Stress:**
  - Adrenal Cortex Enlargement
  - Atrophy of Lymphoid Tissues
  - Bleeding Ulcers in Stomach & GI Tract.
- ***General Adaptation Syndrome:***
  - **Overview:**
    - Stress → Causes Physiological Changes → Causes Symptoms
    - There are 3 stages. NB: If the stress is overcome during one of the stages, the 'GAS' will terminate in that stage.
  - **3 Stages of the General Adaptation Syndrome:**
    - **Stage 1: ALARM *REACTION*:**
      - When we are surprised or threatened → Immediate Physical Reaction.
      - Fight or Flight Response
      - Prepares the body for life-threatening situations, channelling resources away from things like the Digestive & Immune Systems, to more immediate muscular needs.
      - ***↑Sympathetic Nervous System***
      - ***↑Catecholamines from Adrenal Medulla***
    - **Stage 2: STAGE OF *RESISTANCE*:**
      - If stressors continue, the body enters the *Resistance Phase*, where we *feel* like we've adapted to the stressors, but the body is working at abnormally high levels to keep up with the ↑ demands.
      - ***↑ Cortisol Secretion***
      - ***Sustained Catecholamine Actions***
    - **Stage 3: STAGE OF *EXHAUSTION*:**
      - Eventually, the body gives up on maintaining a high level of stress. Parts of the body literally start to break down → Sickness → Possible Death.
      - ***↓ Adaptive Endocrine & Neuroendocrine Functions***



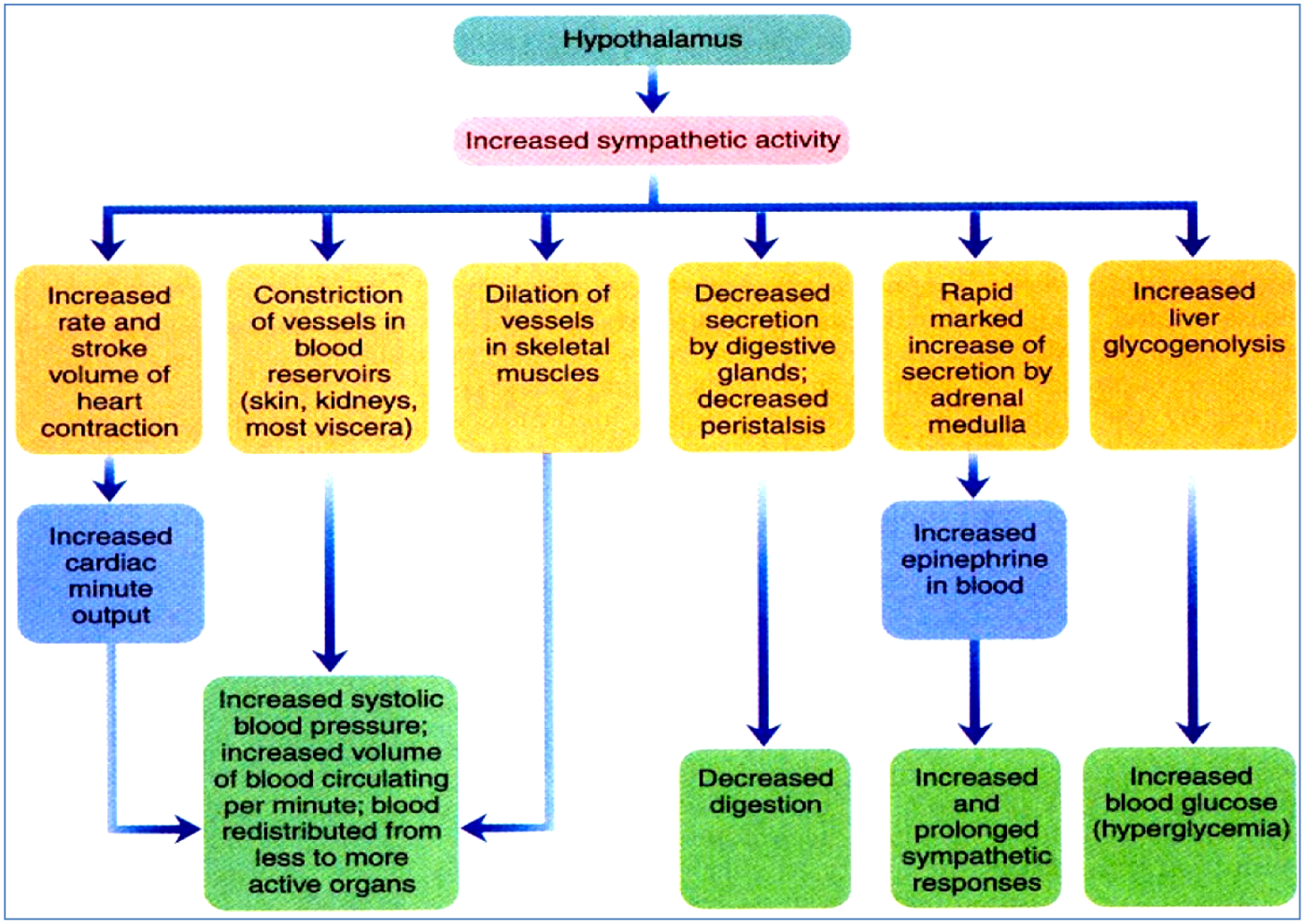
More About Stage 1 of The 'GAS': ALARM REACTION:

- **Physical/Visual Responses to Stress: (Fight/Flight Response)**
  - ↑Pupil Diameter
  - ↑Sweat Glands
  - ↓Other Glands (Nasal, Salivary, Gastric, Pancreatic)
  - ↑Bronchial Dilation
  - ↑Blood Flow to Heart & Skeletal Muscle
  - ↓Blood Flow to Kidneys & Skin (Cold & Clammy skin)
- **'Lay' Descriptions of the Above:**
  - Bug Eyed
  - Dry Mouth
  - Pounding Heart
  - Cold/Clammy Skin
  - Sweaty skin
  - Rapid Respiration
- **Physiological Responses Caused by ↑Sympathetic Activity:**
  - ↑HR & SV → ↑CO
  - Vasoconstriction (Skin, Kidneys, Most Viscera) } ↑BP, ↑Perfusion Rate, Redistribution of Blood.
  - Vasodilation in Skeletal Muscles

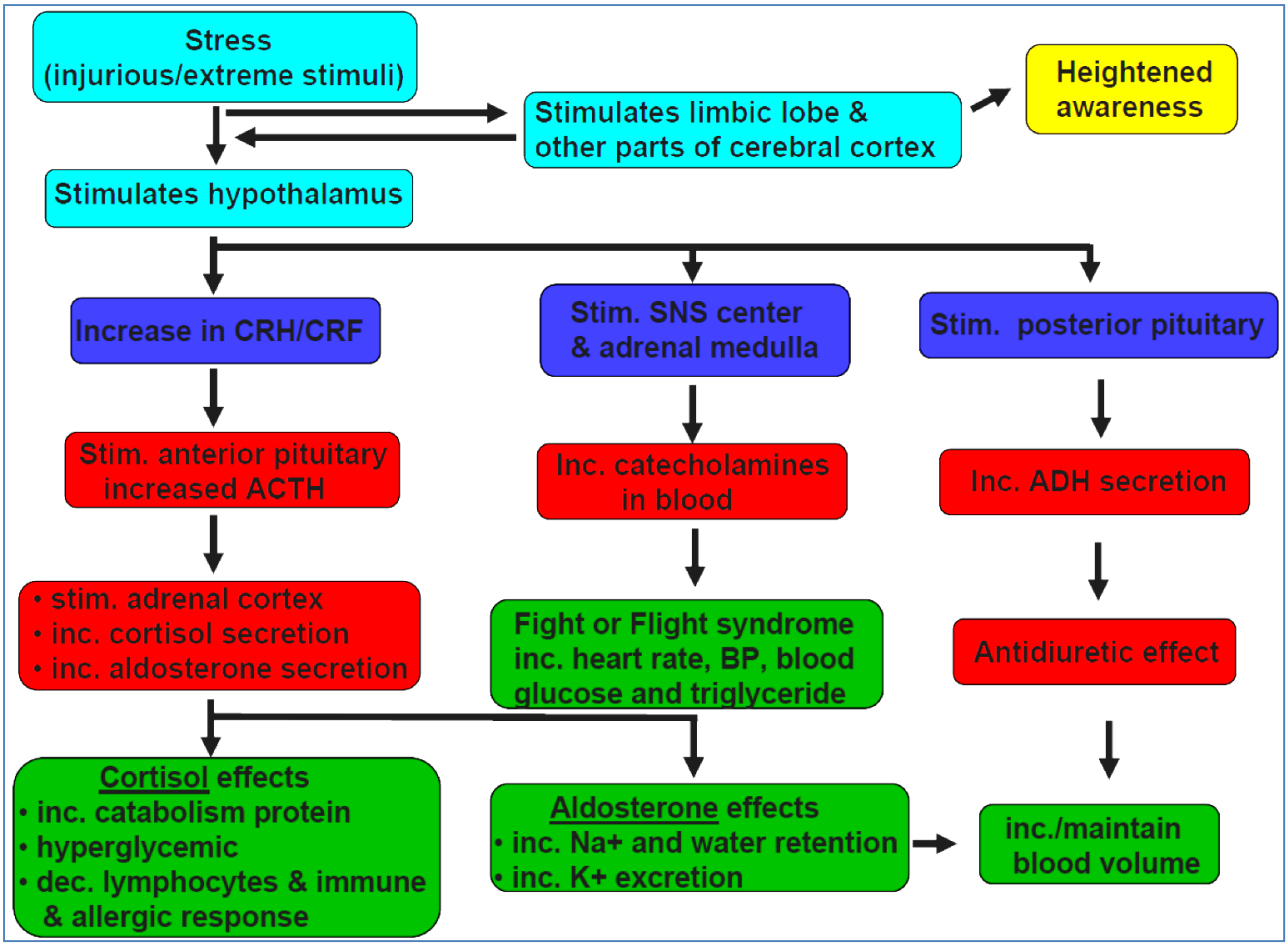
  - ↓Digestive Gland Secretion } ↓Digestion
  - ↓Peristalsis

  - ↑Adrenal Secretion → ↑Epinephrine Levels → Increased & Prolonged Sympathetic Activity.

  - ↑Glycogenolysis (Liver) → ↑Blood-Glucose. } ↑Energy Precursor Levels in Blood
  - ↑Lipolysis (Adipose) → ↑Free Fatty-Acids.

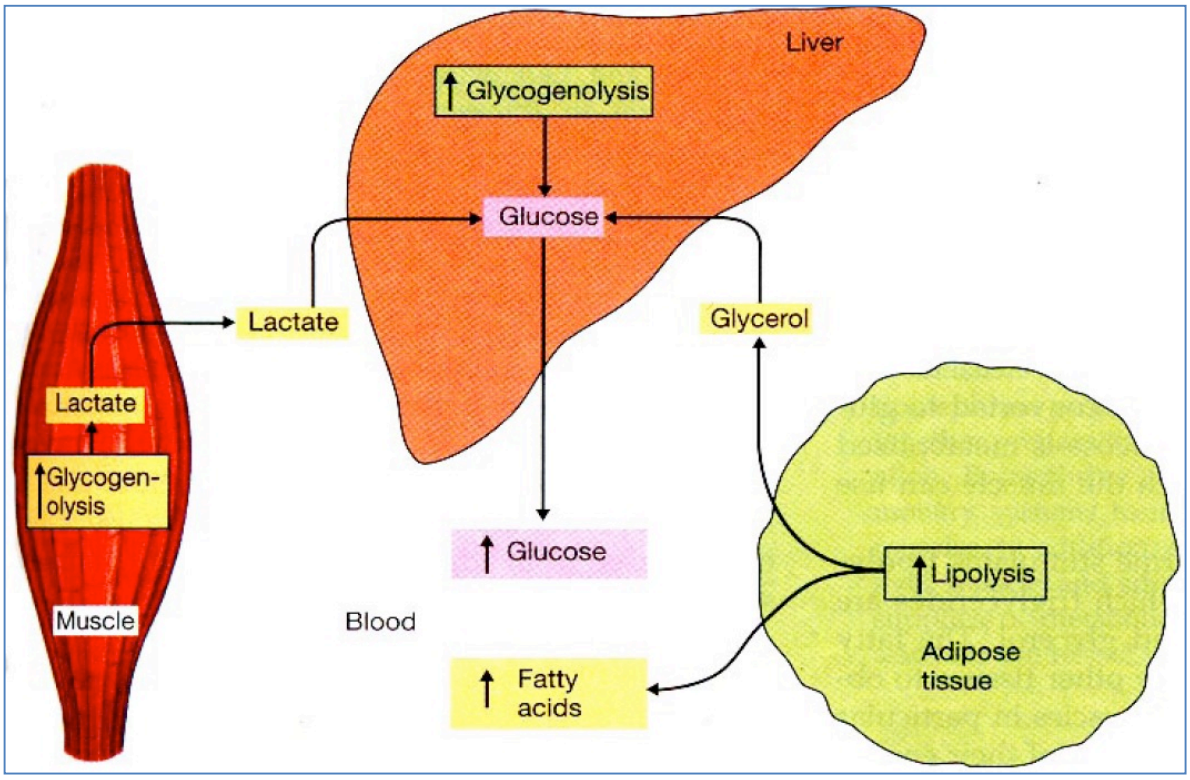


Overview of the Body's Response to Stress:



Metabolic Actions of Adrenaline/Epinephrine (Fight/Flight Response Hormone):

- ↑Glycogenolysis (Liver) → ↑Blood-Glucose. } ↑Energy Precursor Levels in Blood
- ↑Lipolysis (Adipose) → ↑Free Fatty-Acids. }
- ↑Glycogenolysis (Muscle)
  - → Fuels Muscle Cells
  - → Provides Lactate → Liver converts back to Glucose (Gluconeogenesis) → ↑Blood-Glucose



Stress & The Immune System:

- Studies have shown that ***Acute Stress ENHANCES*** the Immune System, but ***Chronic Stress SUPPRESSES*** the Immune System.
- **The Affect of Stress on the Immune System is *'BIPHASIC'*:**
    - 1. During Acute Stress – There is a shift towards ↑Innate Immune Responses.
        - (↑Granulocyte/Macrophage/NK-Cell Activity + ↑Complement & Acute-Phase Proteins)
    - 2. If Stress Continues – There is a shift from *Cellular* Immunity to *Humoral* Immunity.
        - ↓Type-1 Helper T-Cell Activity (→ Become Macrophages)
        - ↑Type-2 Helper T-Cell Activity (→ Become Plasma Cells → Secrete Antibodies)
    - 3. If Chronic Stress – There is a Decrease in almost all functional Immune Responses

  Hence: Increase in Stressor Duration → Shifts from Adaptive to Detrimental.

Questions:

- **Q. Given that Cortisol is released in response to stress & has a potent Hyperglycaemic action, Why is Adrenaline Release Needed to Increase Blood-Glucose in Acute Stress?**
    - **A.** Cortisol is a steroid hormone, meaning it takes a long time to synthesize, can't be stored (because it diffuses through membranes) and takes a while to elicit its effects. Hence, Adrenaline, which can be easily stored in vesicles and is more rapidly acting, is useful in Acute Stress where a more immediate response is required.

- **Q. Adrenalin has an Endocrine Action in the Pancreas. What is its affect on Insulin & Glucagon Release & Why might this be important?**
    - **A.** Adrenaline → ↓Insulin & ↑Glucagon Release → ↑Blood-Glucose (Desired)

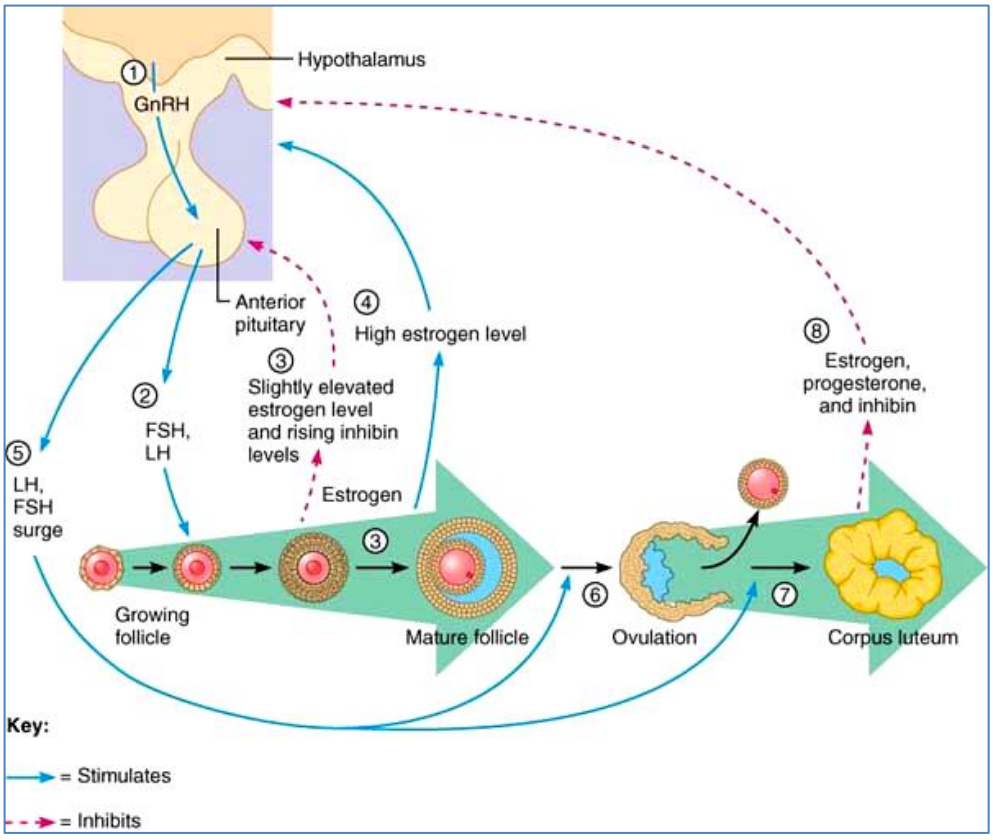
- **Q. What are the Causes of the 3 Universal Symptoms of Chronic Stress Discovered by Hans Selye:**
    - **Adrenal Cortex Enlargement:**
        - Hypertrophy & Hyperplasia of the Gland due to the Prolonged Tropic Hormone Stimulation (ACTH).
    - **Atrophy of Lymphoid Tissues:**
        - Due to the Immunosuppressive Actions of ↑Cortisol (Caused by Chronic Stress)
    - **Bleeding Ulcers in Stomach & GI Tract.**
        - Most ulcers have a microbial origin. Therefore some may be due to the ↓Immune System.
        - However, not all ulcers have a microbial origin. Ie. Some are purely due to stress.
            - How? – Due to ↓Secretion of Gastric Mucous Glands → Imbalance between Mucous & Acid in Stomach → Stomach Ulcers.
            - And/Or – Due to ↓Secretion of Pancreatic Neutralisers → ↑Acid load in GIT + ↓Peristalsis → Intestinal Ulcers.

Reproductive Endocrinology:

Hormonal Regulation of the Ovarian Cycle:

1) **Day 1** – Hypothalamus increases levels of GnRH (Gonadotropin-Releasing Hormone) and stimulates the Anterior Pituitary to produce FSH (Follicle-Stimulating Hormone)& LH (Luteinising Hormone).
2) FSH & LH stimulate follicle growth, maturation & oestrogen secretion.
- FSH targets follicle cells
- LH targets the thecal cells – makes thecal cells produce androgen.
    - Androgen diffuses through basement membrane, where the granulosa cells convert it to oestrogens.
3) Medium oestrogen levels exert **negative feedback** to the Ant. Pituitary, inhibiting FSH & LH release.
- Inhibin released by granulosa cells also exerts **negative feedback** on FSH release.
4) At a critically high oestrogen level, **positive feedback** is exerted on the brain & Ant. Pituitary.
5) **Midcycle –** This positive feedback causes the Ant. Pituitary to release a sudden burst of LH (and also some FSH – role midcycle is currently unknown).
6) **LH surge** stimulates the primary oocyte of the dominant follicle to complete MEIOSIS I, forming a secondary oocyte + first polar body.
- **LH surge** also triggers ovulation.
- After ovulation, oestrogen levels decline due to the damaged dominant oestrogen secretor.
7) **LH Surge** also transforms ruptured follicle into corpus luteum – stimulates it to produce progesterone & oestrogen.
8) Corpus luteum secretes inhibin along with progesterone & oestrogen, exerting a strong negative feedback signal to the Ant. Pituitary – Stops the release of LH & FSH.

- **End of cycle – LH levels fall → corpus luteum degenerates → no oestrogen or progesterone production by Corpus Luteum → no negative feedback to the hypothalamus → hypothalamus increases FSH & LH levels → Back to square #1.**

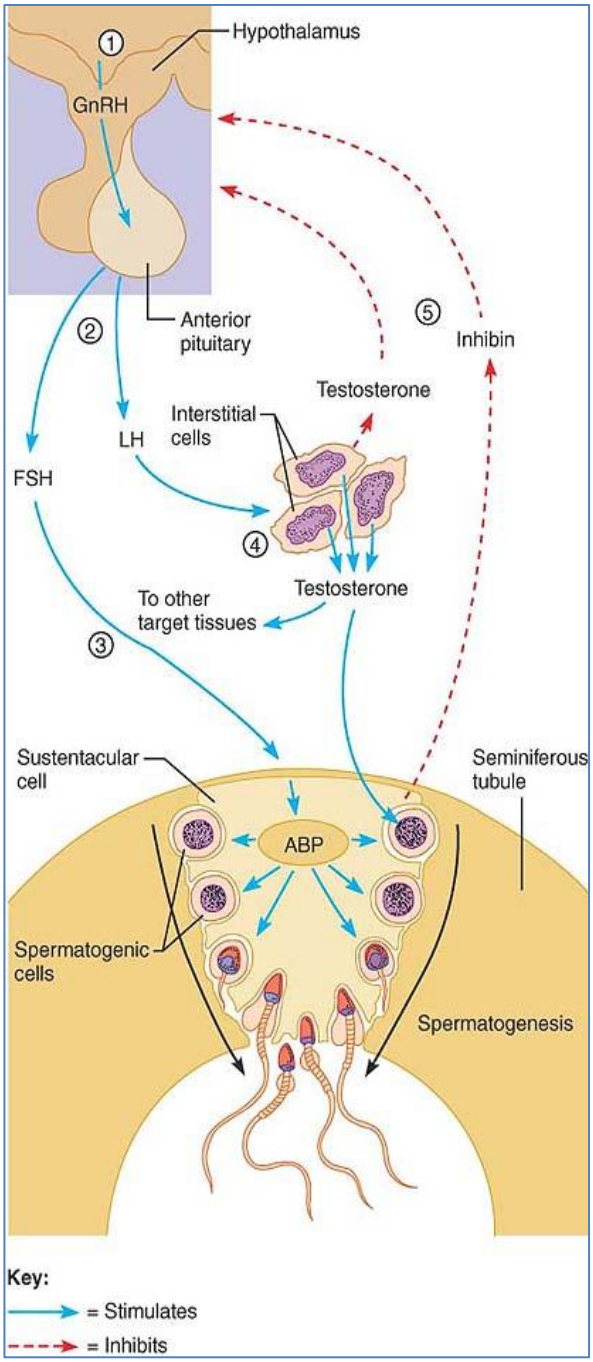


Neuroendocrine Control: Hormonal Regulation of Spermatogenesis:

1) **Hypothalamus** releases **GnRH (gonadotropin-releasing hormone)** which-
2) stimulates the release of gonadotropins: **FSH** (Follicle stimulating hormone) **& LH** (Luteinizing hormone).
3) **FSH:** stimulates sustentacular cells to release **Androgen-binding protein (ABP)** → Makes spermatagonium, spermatocytes, and spermatozoa **receptive to** the androgen: **Testosterone.**
4) **LH:** stimulates the **interstitial (Leydig) cells** [Basally external to Seminiferous tubules] to **produce testosterone** which **triggers & maintains spermatogenesis.**
5) **Testosterone** produced by Leydig (interstitial) cells **inhibits GnRH** production; as does **Inhibin**, produced by the sustentacular (sertoli) cells.

- When testosterone is at its peak → **sperm count is high (20Mil^{+})** → inhibin levels rise →GnRH decreases →FSH & LH levels decrease → Testosterone & ABP levels decrease → **spermatogenesis slows.**

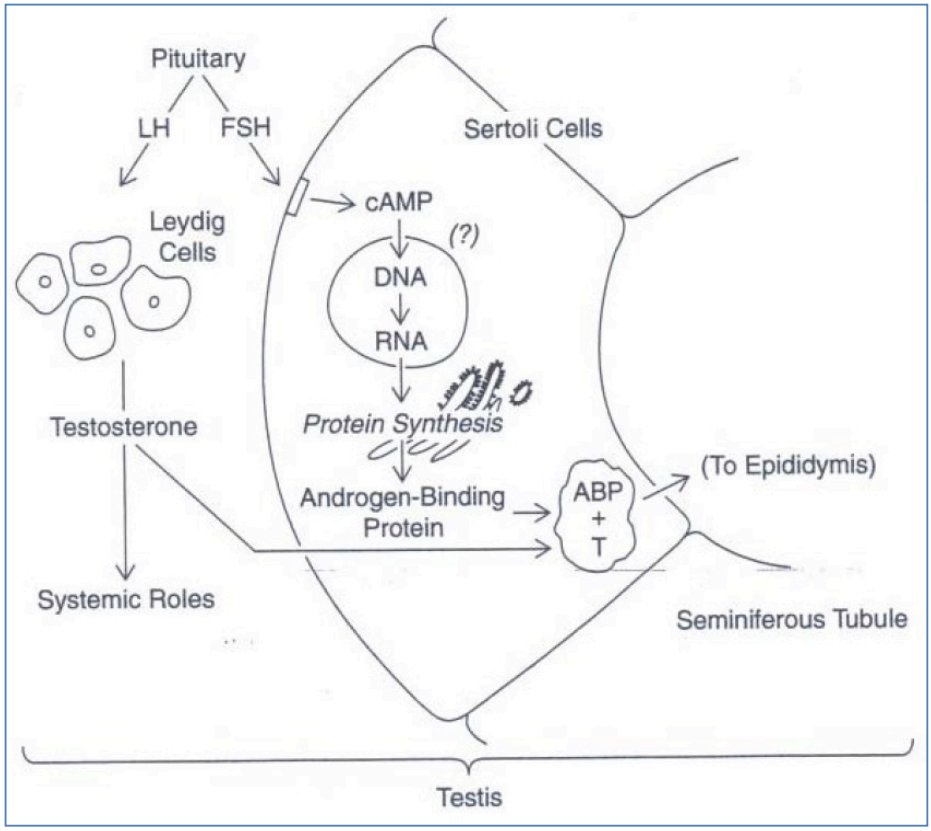
-When **sperm count is low (20Mil $^{-}$) →** inhibin & testosterone levels are low → no negative feedback to hypothalamus → hyp. Releases GnRH → Ant. Pituitary releases LH & FSH → FSH stimulates sustentacular (sertoli) cells to produce ABP; LH stimulates the interstitial (Leydig) cells to produce testosterone →Testosterone + ABP stimulates spermatogenic cells → **Spermatogenesis increases.**



Male Reproductive Endocrinology

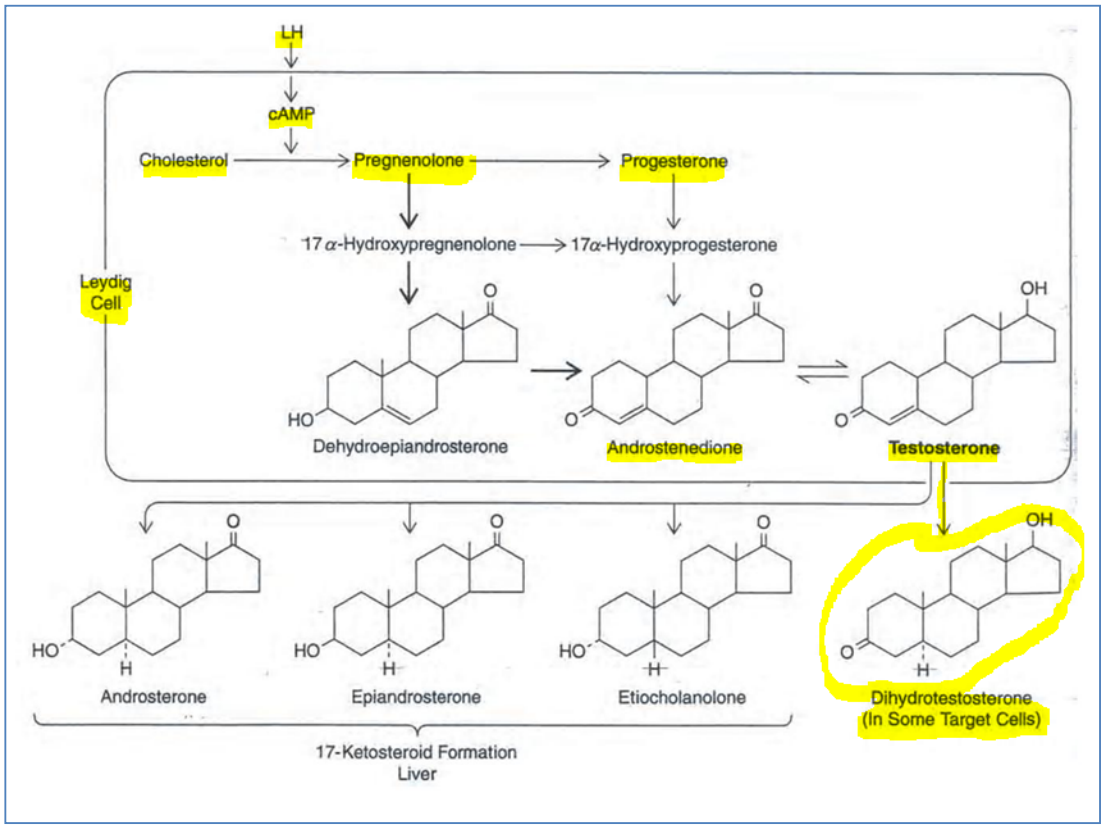
Functional Micro-Anatomy of the Testes:

- **Leydig Cells (In Interstitium of the Testes):**
  - #1 Function = Produce Testosterone (Stimulates Spermatogonia to enter Spermatogenesis)
  - Stimulated by **LH** (Luteinising Hormone)
- **Seminiferous Tubules (In Lobules of Testes):**
  - **Spermatogonia (Germ/Stem-Cells):**
    - In Basal Lamina of Seminiferous Tubules
    - #1 Function = Are the precursors for Spermatogenesis
    - Stimulated by **Testosterone**.
  - **Sertoli/Sustentacular Cells:**
    - Make up the Walls of the Seminiferous Tubules
    - Main Functions =
      - Endocrine – Production of ***Androgen Binding Protein*** (ABP)
        - – (Makes Spermatogenic Cells *receptive to Testosterone*)
      - Endocrine – Production of ***Inhibin***
        - – (Provides negative feedback to the *Hypothalamus*)
      - Blood-Testes Barrier (because spermatids are genetically unique & require protection from autoimmunity)
      - Nourish Sperm
      - Phagocytosis – (mop up any dead/underdeveloped spermatids)
      - Produce Tubular Fluid – (Help transport the sperm)
      - Produce Plasminogen Activating Factor – (Help free the sperm from tubule wall)



The Important Androgens:

- **#1 – Testosterone** - Affects Mainly the Testes
  - 40% - Bound to SHBG (Sex-Hormone Binding Globulin)
  - 60% - Bound to Albumin
  - 2% - Free (Active) – (Receptors are intracellular :. Must be able to enter the cell)
- Dehydroepiandrosterone (Sulphate) – DHEA(S) - Affects Mainly the Periphery
- Androstenedione - Affects Mainly the Periphery



- **NB: Sex Hormone Binding Globulin is an Important Transporter:**
  - Secreted by the Liver
  - Increased by ↑Oestrogen
  - Decreased by ↑Androgen
  - Constant in Males
  - Cyclical in Females – (but During Pregnancy, ↑↑Oestrogen → ↑SHBG)

- **Measuring Androgen Levels – "The Free Androgen Index":**
  - Gives a measure of the "free" active fraction of Androgens.

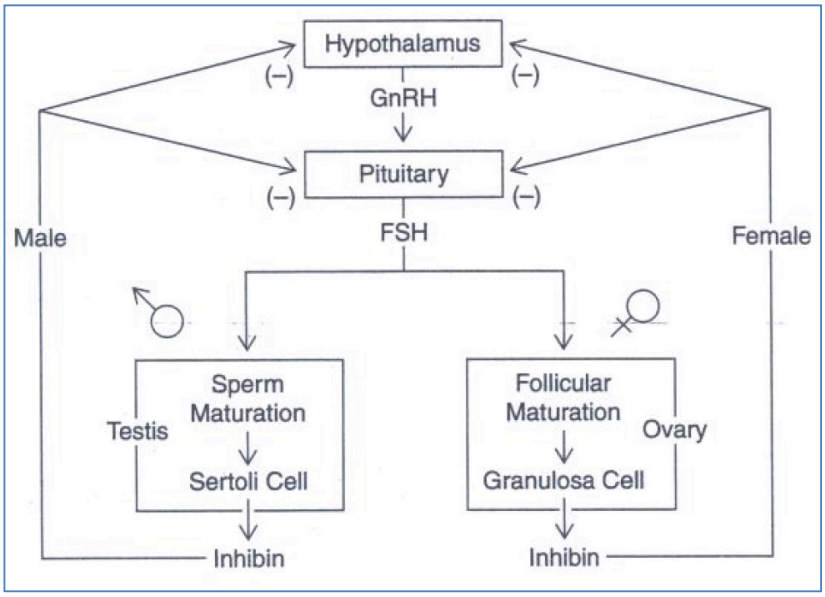
$$\frac{\text{Testosterone (nmol/l)}}{\text{SHBG (nmol/l)}} \times 100$$

Female	0 – 11
Male	25 – 190

SHBG = sex hormone binding globulin

The Other Hormones:

- **Gonadotropin-Releasing Hormone (GnRH):**
  - Peptide Hormone
  - Pulsatile Release (≈90mins)
- **Gonadotropins - FSH & LH:**
  - Are *Glycoproteins*
  - Released by the Anterior Pituitary in response to Pulsatile release (90mins) of **GnRH**.
  - Share a common α-Subunit
  - Differ by unique β-Subunits
  - Act on G-Protein-Linked Receptors.
- **Inhibin:**
  - Produced by the Sustentacular/Sertoli Cells (Male) & Granulosa Cells (Female).
  - Released in response to high FSH.
  - Inhibits FSH release via Hypothalamic Inhibition.



Actions of Androgens:

- **Primary Sex Characteristics:**
  - Growth & Maturation of Reproductive Tract @ Puberty
  - Maintenance of Reproductive Tract in Adulthood
  - Libido
  - Enhance Spermatogenesis
- **Secondary Sex Characteristics:**
  - Body Hair
  - Deep Voice
  - Thick, rough skin
  - Bone Growth
  - Androgen Binding Protein Synthesis (in Sertoli/Sustentacular Cells)
  - ↑Musculature

Male Hypogonadism:

- **What is it?**
  - A deficiency in Testosterone due to problems with either:
    - 1) Testes, or - Primary
    - 2) Hypothalamus/Pituitary - Secondary

- **Hypergonadotropic:**
  - ***Primary Hypogonadism***
  - Ie. Problem with the Leydig Cells in the Testes → ↓↓Testosterone Production → ↑↑Hypothalamo-Pituitary release of Gonadotropins (FSH/LH).
  - **Causes:**
    - Trauma/Irradiation of Testes.
    - Mumps
    - Klinefelter's Syndrome (Extra X-Chromosome)
    - Androgen Resistance
    - Autoimmune
    - Congenital

- **Hypogonadoptropic:**
  - ***Secondary Hypogonadism***
  - Ie. Problem with the Hypothalamo-Pituitary Axis → ↓↓Gonadotropin Release (FSH/LH) → ↓↓Testosterone Production
  - **Causes:**
    - Developmental
    - Pituitary Tumour/Trauma/Autoimmune
    - Genetic Syndromes

- **Effects of ↓↓Testosterone:**
  - Infertility (Low Sperm Count)
  - ↓Libido
  - ↓Muscle Mass
  - ↓Beard/Body Hair
  - Erectile Dysfunction
  - ↑Breast Tissue
  - ↓Bone Mass
  - ↑Body Fat
- **Range of Treatments – Testosterone Replacement Therapy:**
  - Buccal
  - Oral
  - Trans-Cutaneous (patch/gel)
  - IM Injection
  - Implant

Male Infertility:

- **Normal Semen:**
  - 2-5mLs
  - Sperm Concentration – At least 20 Million/mL
  - Total sperm count – At least 40 Million (To be “fertile”)
  - >75% should be Alive
  - >30% should be of normal Shape/Form.
  - >25% should be rapidly Swimming Forward
  - >50% should be Motile
- **Causes of Infertility:**
  - Problem with Sperm Production:
    - Chromosomal/genetic causes
    - Undescended Testes (Heat)
    - Infections
    - Torsion
    - Radiation
  - Blockage of Sperm Transport (Basis of Vasectomy)
  - Sperm Antibodies (Autoimmune reaction due to poor blood-testes barrier.)
  - Sexual Problems
  - Hormonal Imbalances (Hypogonadism – Primary/Secondary)

ENDOCRINOLOGY Pathology:
ADH DISORDERS

Disorders of Fluid/Electrolyte-Regulating Hormones:

- **Disorders of ADH:**
  - **Diabetes Insipidus (↓ADH):**
    - Condition characterised by Excessive Thirst & the inability to Concentrate Urine.
    - **2 Types:**
      - **Neurogenic (Neuro)** - ADH Insufficiency
      - **Nephrogenic (Renal)** – Insensitivity of the kidneys to ADH
    - **Signs/Symptoms:**
      - Extreme Thirst
      - Excessive Urination
      - Risk of Hypokalaemia
    - **Diagnosis Criteria:**
      - Normal Blood Glucose
      - Normal Blood Bicarb
      - Normal Blood Calcium

      } To Rule out other causes of Excess Urination.
      - Urinalysis – Low Osmolarity, Electrolytes & Specific Gravity
      - Fluid Deprivation Test - No change in urine osmolarity
      - Desmopressin Stimulation – Distinguishes between Neurogenic & Nephrogenic.
    - **Treatment:**
      - Patients compensate by ↑H_2O Intake.
      - If Neurogenic – ***Desmopressin*** (Synthetic ADH) → ↓Urine Production.
      - If Nephrogenic – ***Hydrochlorothiazide*** Diuretic → ↓Urine Output in patients with DI.

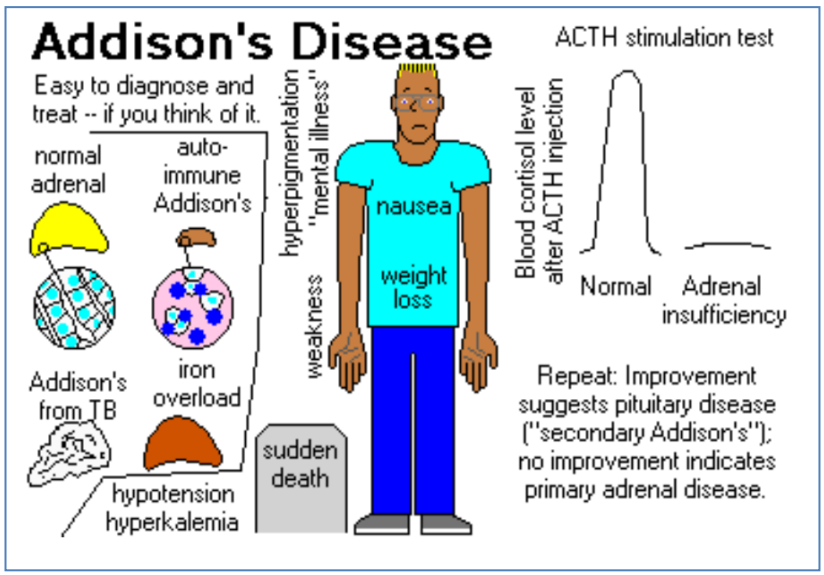
  - **SIADH (Syndrome of Inappropriate ADH secretion) (↑ADH):**
    - **Caused by:**
      - Insensitivity of Hypothalamic Osmoreceptors to ↓Plasma Osmolarity
      - Therefore, ADH release isn't inhibited by ↓Plasma Osmolarity
    - **Condition characterised by Excessive ADH Release from Post. Pituitary Or Ectopic Source.**
    - **5 Cardinal Signs/Symptoms:**
      - 1. Fluid Overload (*Without* oedema or hypertension)
      - 2. Hyponatraemia (Dilutional) →
        - Headache
        - Nausea
        - Vomiting
        - Confusion
        - Convulsions (If Severe)
        - Coma (If Severe)
      - 3. Natriuresis (Excretion of Sodium in Urine – usually excessive)
      - 4. High Urine Osmolarity relative to Plasma Osmolarity.
      - 5. Normal Renal & Adrenal Function
    - **Treatment:**
      - **Fluid Intake Restriction**
      - **Drugs – (*ADH Inhibitors*):**

ENDOCRINOLOGY Pathology:
ADRENAL CORTEX DYSFUNCTION

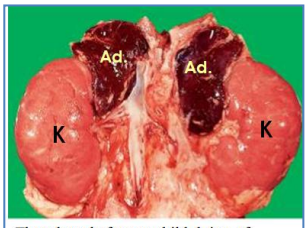
Adrenal Disorders:

Adrenocortical Insufficiency (Hyporadrenal) Syndromes:

- **ADDISON'S DISEASE (Primary Chronic Adrenocortical Insufficiency):**
  - **Aetiologies (Multiple Possible):**
    - **Most Common = Autoimmune Adrenalitis (70%)**
  - **Pathogenesis (Autoimmune Adrenalitis):**
    - **↓↓Aldosterone**
    - **↓↓Cortisol**
  - **Clinical Features:**
    - **Initially:** Progressive Weakness, Fatigue, Lethargy, Depression
    - **Later:**
      - **GI** - Anorexia, Weight Loss, Vomiting, Diarrhoea
      - **Skin** – Hyperpigmentation (Esp. Sun-Exposed & Pressure Point Areas)
      - **Electrolytes** (↓Aldosterone) – Hyponatraemia & Hyperkalaemia
  - **Diagnosis:**
    - **Synacthen (Synthetic ACTH) Test →** (Measure Cortisol and Aldosterone 30mins after)
    - **Adrenal-Autoantibodies**
    - **UECs – (↑K, ↓Na, ↑Urea ↑Creatinine)**
  - **Treatment:**
    - **Cortisol Replacement (*Hydrocortisone*)**
    - **Correct Electrolytes**
  - **Complication - Addisonian Crisis:**
    - **Why:** Stress → Adrenal Glands Cannot Respond → *Crisis*
    - **Clinical Features:**
      - Fever
      - Intractable Vomiting
      - Abdominal Pain
      - Hypotension
      - Coma
      - Shock (Vascular Collapse)



- **WATERHOUSE-FRIDERICHSEN SYNDROME (Acute Adrenocortical Insufficiency):**
  - **Aetiology:**
    - Overwhelming Sepsis
  - **Pathogenesis:**
    - Acute Haemorrhageic Infarction → Adrenal Necrosis → Acute Adrenal Hypofunction:
      - →↓Aldosterone → Salt & Water Loss → Hypovolaemic Shock
  - **Morphology:**
    - **Macro:**
      - Haemorrhagic Mass (Blood Clot) Completely Obscures the Adrenal Gland
    - **Micro:**
      - Acute Haemorrhagic Necrosis (Starts in Medulla → Spreads to Cortex)
      - Islands of Recognizable Cortical Cells
  - **Clinical Features:**
    - Abrupt & Severe Clinical Course (Death in Hours-Days unless Treated)
    - Typically Meningococcal Septicaemia
      - :. Neck stiffness
      - :. DIC
    - Hypovolaemic Shock (Due to ↓Aldosterone)
  - **Treatment:**
    - Prompt Antibiotic Treatment
    - Fluids



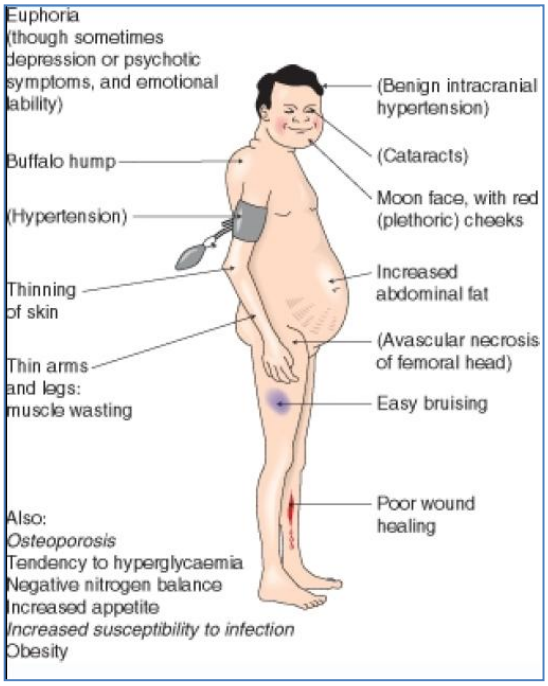
The adrenals from a child dying of meningococcal septicaemia are destroyed by haemorrhage.

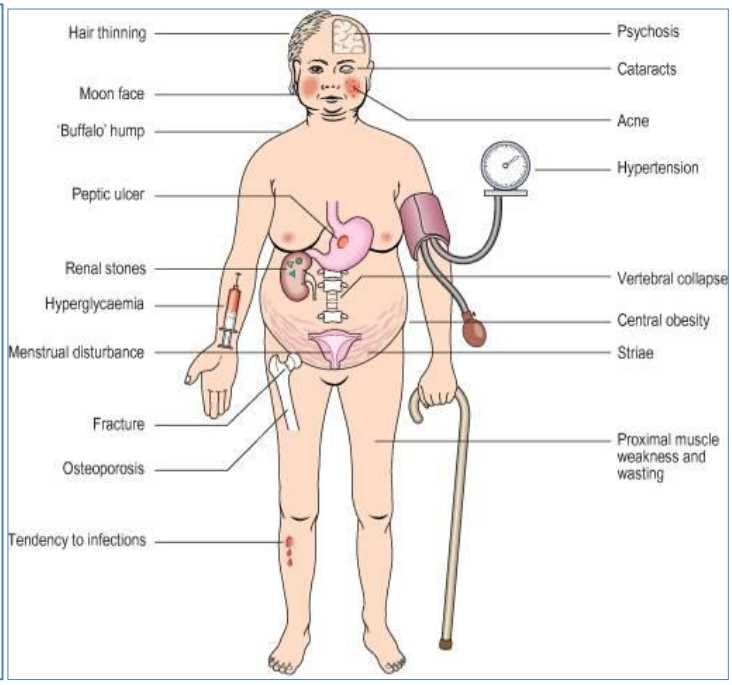
- **CONGENITAL ADRENAL HYPERPLASIA (CAH) - (Adrenogenital Syndromes/Virility Syndromes):**
  - **Aetiology:**
    - Autosomal Recessive 21-Hydroxylase Deficiency
  - **Pathogenesis:**
    - →↓Cortisol/Aldosterone Synthesis → ↑**Androgen Synthesis**
  - **Clinical Features:**
    - **Androgen Excess:**
      - Masculinisation of Females (Clitoral Hypertrophy/Hirsutism/Oligomenorrhoea)
      - Masculinisation of Males (Penile Enlargement/Precocious Puberty/Oligospermia)
      - Neonate with Ambiguous Genitalia
    - **Mineralocorticoid (Aldosterone) Deficiency:**
      - Hypotension & Salt Wasting.

Adrenocortical Hyperfunction (Hyperadrenal) Syndromes:

- **CONN'S SYNDROME (& other Primary Hyper-Aldosteronisms):**
  - NB: Aldosterone = Mineralocorticoid = Produced by the Zona Glomerulosa of the Adrenal Cortex.
  - **Aetiologies:**
    - #1. Idiopathic Hyperplasia of Adrenal Glands
    - **#2. Aldosterone-Producing Adenoma (Conn's Syndrome)**
    - #3.(Rare) Aldosterone-Producing Carcinoma
  - **Pathogenesis:**
    - →Chronic Excess ↑↑ Aldosterone Secretion → Na^+ Retention (& ↓K^+) → Fluid Retention
    - → **Hypertension**
  - **Clinical Features:**
    - ****Universal Sign = Hypertension**
    - **Hypernatraemia** (due to Renal Na Retention)
    - **Hypokalaemia** (due to Renal K Wasting):
  - **Diagnosis:**
    - **Very HIGH Aldosterone**
  - **Treatment:**
    - **Idiopathic Hyperplasia:** Spirinolactone (Aldosterone Antagonist)
    - **Adenomas (Conn's):** Surgical Resection

- **CUSHING'S DISEASE/SYNDROME (Hypercortisolism):**
  - **Aetiology:**
    - **Cushing's Syndrome:** (*Any* cause of Excess Glucocorticoid Levels)
    - **Cushing's Disease: (**Central – ACTH-Secreting Pituitary Adenoma)
  - **Pathogenesis (Cushing's Disease ONLY):**
    - **ACTH-Secreting Pituitary Adenoma → ↑ACTH Levels → ↑Cortisol**
  - **Clinical Features:**
    - Slow onset
    - **Early Features – (**Hypertension & Weight Gain)





  - **Diagnosis:**
    - **Dexamethasone Suppression Test (Central Vs. Primary)**
    - **ACTH Levels**
    - **Cortisol Levels**
    - **CT/MRI Brain (Pituitary Adenoma)**
  - **Treatment – Depends on Aetiology:**
    - **If Exogenous Cortisol** – Wean Pt. off Cortisol.
    - **If Pituitary Tumour (Cushing's Disease) –** Surgical Removal + Temp Cortisol Replacement.
    - **If Adrenal Tumour** – Surgical Removal + Temporary Cortisol Replacement.

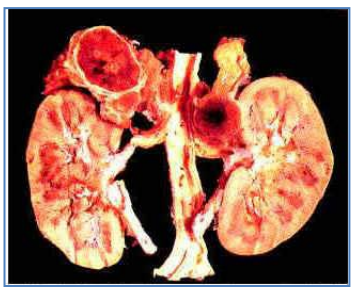
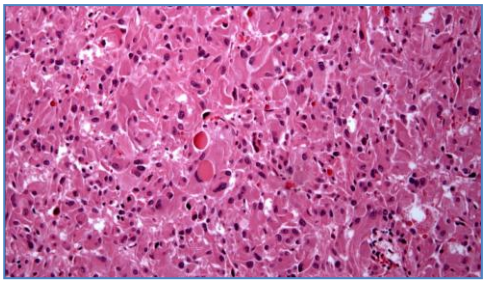
ENDOCRINOLOGY Pathology:
ADRENAL MEDULLA DYSFUNCTION

Phaeochromocytoma:

- ↑Adrenaline & Noradrenaline
- Metabolites of Adrenaline & noradrenaline = Normetadrenalines
- Hypertensive crises
- Worsening pre-existing hypertension
- Episodic white flashes, palpitations
- Young
- diaphoretic

Adrenomedullary Hyperfunction:

- **Phaeochromocytoma (Medullary Adenoma):**
  - **Aetiology:**
    - Idiopathic
    - May be familial (in MEN2 Syndrome)
  - **Pathogenesis:**
    - Tumour of the Medullary Chromaffin Cells (Which produce Catecholamines)
      - →Increased Catecholamines
      - → Secondary Hypertension
  - **Clinical Features:**
    - Young Age
    - 10% Are Malignant
    - **Symptoms:**
      - #1. Paroxysmal Hypertension
      - Palpitations/Tachycardia
      - Headache
      - Sweating/Hot Flushes
      - Tremor
      - Anxiety
      - Nausea/Vomiting
    - (NB: Phaeos are a cause of *Surgically-Correctable Hypertension*)
    - (NB: Phaeos *May be associated with MEN2 Syndromes*)
  - **Diagnosis:**
    - Increased Urinary Catecholamines & VMA (Vanillylmandelic Acid – A Metabolite of Adrenaline & NA)
  - **Treatment:**
    - Preoperative Sympatholytic Drugs (To prevent hypertensive crisis)
    - Surgical Resection
  - **Complications:**
    - **- of Hypertension:**
      - Congestive Heart Failure
      - Pulmonary Oedema
      - Myocardial Infarction
      - Ventricular Fibrillations
      - CVAs

ENDOCRINOLOGY Pathology:
CALCIUM & PHOSPHATE BALANCE DISORDERS

Disorders of Calcium & Phosphate Regulation:

- **Hypercalcaemia:**
  - **Caused By:**
    - Hyperparathyroidism
    - Malignancy (Eg. BRCA, Multiple Myeloma)
    - Vit D Excess
    - Secondary Renal Hyperparathyroidism
- **Hypocalcaemia:**
  - **Caused by:**
    - Vit.D Deficiency/Disorders of Vit.D Metabolism (Activation) → ↓Active Vit.D → ***Rickets***
      - Eg. Lack of sunlight
      - Eg. Lack of Dietary Vit.D
      - Eg. Chronic Kidney Failure
    - Hypoparathyroidism – (Because PTH is required for Vit.D Activation in the Kidneys)
      - Aquired/Congenital
- **Rickets:**
  - **What is it?:**
    - A Vit.D Deficiency → Resulting in a Calcium/Phosphate Deficiency.
    - NB: Clinical Signs occur after a few months (Once the Bone's Ca/P Reservoirs are Depleted)
  - **Effects:**
    - Marked ↑PTH Secretion → Extreme Osteoclastic Activity:
      - → ↑↑Plasma Calcium
      - → ↓↓Plasma Phosphate (Due to ↑Renal Excretion)
    - Tetany – Once the Bone's Ca^+ Reservoir is Depleted, Plasma Ca^+ falls to dangerous levels.
  - **Treatment:**
    - Dietary Calcium Supplements
    - Exogenous Vit.D Administration.
- **Hypoparathyroidism:**
  - **What is it?:**
    - When the Parathyroid Glands don't secrete sufficient PTH.
  - **Effects:**
    - ↓Resorption of exchangeable Calcium → Hypocalcaemia
    - When Ca^+ falls too low, Tetany can develop. (Can occur in larynx → obstructs respiration)
- **Hyperparathyroidism:**
  - **What is it?:**
    - When the Parathyroid Glands secrete an inappropriate excess of PTH.
  - **Effects:**
    - ↑↑Extreme Osteoclastic activity in bones.
      - → Hypercalcaemia
      - → Hypophosphataemia (Due to ↑Renal Excretion)
- **Osteoporosis:**
  - **What is it?:**
    - Decreased Bone ***Matrix*** (Not decreased bone *calcification*)
  - **Possible Causes:**
    - Usually due to poor ***Osteoblastic Activity*** → ↓Osteoid Deposition.
    - Can be due to ↑↑***Osteoclastic Activity*** → ↑Osteoid Resorption.
    - Inactivity → Lack of physical stress on bones
    - Malnutrition
    - Postmenopausal Lack of Oestrogen (Oestrogen normally ↓Osteoclast Activity)
    - Cushing's Syndrome - ↑↑Glucocorticoids cause ↓Protein deposition throughout the body.

Parathyroid Disorders:

Hyperparathyroidism:

- **What is it?:**
  - When the Parathyroid Glands secrete ↑↑PTH.
- **Effects of ↑↑PTH:**
  - ↑↑Extreme Osteoclastic activity in bones → Hypercalcaemia
  - ↑↑Renal Phosphate Excretion → Hypophosphataemia
- **Types:**
  - **Primary Hyperparathyroidism – Autonomous, Spontaneous Overproduction of PTH:**
    - **Aetiologies/Pathogeneses:**
      - **Adenoma(Sporadic or MEN)**/Hyperplasia/Carcinoma → ↑↑PTH
    - **Clinical Features:**
      - **F>>M**
      - **Hypercalcaemia Triad** – ***"Bones, Moans & Abdominal Groans"***:
        - **1. Bone**: Pain/Osteoporosis/Fractures
        - **2. Moans:** Depression/Lethargy/Seizures
        - **3. Abdo:** Constipation/Nausea/Ulcers/Gallstones
        - **+ (Renal:** Renal Stones)
        - **+ (Heart:** Aortic/Mitral Calcification)
    - **Diagnosis:**
      - ↑PTH
      - ↑Serum Calcium
      - ↓Serum Phosphate
    - **Treatment:**
      - Surgical Excision
  - **Secondary Hyperparathyroidism – Secondary to Chronic Renal Insufficiency:**
    - **Aetiology:**
      - Secondary to Renal Failure → HypOcalcaemia
      - (Others incl. Dietary Calcium Deficiency, Vit.D Deficiency)
    - **Pathogenesis:**
      - **Renal Failure** → Hypocalcaemia → ↑PTH to Compensate → Hyperplasia
    - **Clinical Features:**
      - Symptoms of Chronic Renal Failure
      - **Osteoporosis**
    - **Treatment:**
      - Vitamin D + Calcium Supplementation
      - Partial Parathyroidectomy

Hypoparathyroidism:

- **Effects:**
  - ↓Resorption of exchangeable Calcium → Hypocalcaemia
- **Aetiologies:**
  - **Iatrogenic –** Surgery (Eg. Thyroidectomy/Lymphadenectomy/Over-resection in 1^{o}HyperPT)
  - **Genetic –** (Autoimmune/Familial/Congenital Absence of Gland)
- **Clinical Features:**
  - ***Hypocalcaemia**
  - ***Hallmark = *Tetany*:**
    - → Neuromuscular Irritability
    - → Distal Paraesthesias
    - → Carpopedal Spasm
    - → *Laryngospasm (Life-Threatening)
    - → Seizures
  - **CNS:** Confusion/Depression/Hallucinations/Psychosis
  - **Eyes:** Cataracts (Calcification of Lenses)
  - **CVS:** Characteristic Prolonged QT-Interval

ENDOCRINOLOGY Pathology:
DIABETES

Diabetes: General Information:

- **Diagnostic Criteria (The "7-11 Rule"):**
  - ***Fasting BSL ≥ 7.0 mmol/L*** (NB: For Non-Pregnant)
  - ***Random BSL of >11*** (NB: If Fasting BSL = 5.5-7.0 mmol/L → Perform OGTT)
  - ***OGTT*** **– Oral Glucose Tolerance Test** (Fasting) ***>11 @ 2hrs***
  - **Autoantibodies (If Type 1 Diabetes):**
    - ***+ Anti-Islet-Cell Antibodies (Anti-ICAs)***
    - ***+ Anti-Glutamic Acid Decarboxylase Antibodies (Anti-GADs)***
  - (NB: **HbA1c** for monitoring only)
- **Initial Presentation:**
  - **PPP – Polyuria, Polydipsia, Polyphagia**
  - Unexplained Weight Loss/Fatigue/Lethargy
  - Recurrent/Persistent Infections, Delayed Healing & Immunosuppression (Eg. Genital Thrush)
- **Emergency Presentations:**
  - **HYPERs:**
    - **DKA** - Diabetic Ketoacidosis
    - **HONC** - Hyperosmolar Non-Ketotic Coma
  - **HYPOs:**
    - **Eg. Insulin Overdose/Overexercise/Missed Meal**
- **Treatment:**
  - **Lifestyle (Diet + Exercise + Weight Loss)**
  - **Medications:**
    - ***Insulins*** **– (Broad range of Rapid to Long-Acting)**
    - **Oral Hypoglycaemic Agents:**
      - **"Insulin Secretagogues" – (*Sulfonylureas):**
      - **Biguanides - (*Metformin)**
    - **Incretin Mimetics:**
      - **Incretin Analogues – (*Exenatide):**
      - **DPP-4 Inhibitors – (*Sitagliptin)**

Different Types of Diabetes:

- **Type 1 Diabetes – Insulin Deficiency, Juvenile, Rapid Onset:**
  - **Aetiology – (Autoimmune Destruction of the β-Cells of the Pancreatic Islets)**
  - **Clinical Features – (**Juvenile Disease, Rapid Onset)
  - **Diagnosis – (+ Anti-GADs, Anti-Islet-Cell Antibodies (Anti-ICAs) & Insulin Auto Antibodies (IAAs))**
  - **Treatment: - (*Exogenous Insulin*)**
  - **Complications – (*Diabetic Ketoacidosis*)**
- **LADA – Latent Autoimmune Diabetes of Adults:**
  - **Aetiology – (**Delayed Autoimmune Type I in Adults)
  - **Clinical Features – (**Slim Adults with Diabetes Symptoms**)**
  - **Complications – (**HONC, DKA)
  - **Diagnosis – (**Hyperglycaemia, **+ Anti-GADs, Anti-ICAs & Insulin Auto Antibodies)**
  - **Treatment – (Insulin)**
- **Type 2 Diabetes – Insulin Resistance, Adults, Insidious Onset:**
  - **Aetiology – (***Insulin Resistance* And/Or *Relative Insulin Deficiency*)
  - **Clinical Features – (**Adults, Slow Onset +/- ***'Pre-Diabetic State'***)
  - **Diagnosis – (Random BSL >11, OGTT >11 @2hrs)**
  - **Treatment – (1.** Diet & Lifestyle, 2. Orals [Metformin/Sulfonylureas/Incretins], 3. Insulin)
- **MODY – Maturity Onset Diabetes of Youth:**
  - **Aetiology – (**Autosomal Dominant**)**
  - **Pathogenesis – (Essentially a Type II DM in a Child)**
  - **Clinical Features – (**Young, Non-Obese, Autosomal Dominant :. FamHx)
  - **Treatment – (**1. Orals [Metformin/Sulfonylureas/Incretins], 2. Insulin)
  - **Complications – (**Like Type II Diabetes (Ie. HONC rather than DKA))

What is Diabetes:

- **Diagnostic Criteria:**
  - Fasting BSL ≥ 7.0 mmol/L
  - 2hr Post Prandial BSL ≥11.1 mmol/L
  - NB: People who have ***Impaired Glucose Tolerance*** and/or ***Impaired Fasting Glucose*** have slightly raised fasting & Post Prandial BSL's, but not high enough for diagnosis of diabetes.
- **Symptoms:**
  - Thirst
  - Polyuria & Nocturia
  - Weight Loss
  - Fatigue
  - Blurring of Vision
  - Infections
  - Nausea, Vomiting, Abdo. Pain.

Insulin & Glucagon in a Nutshell: (For more detail – see previous endo weeks)

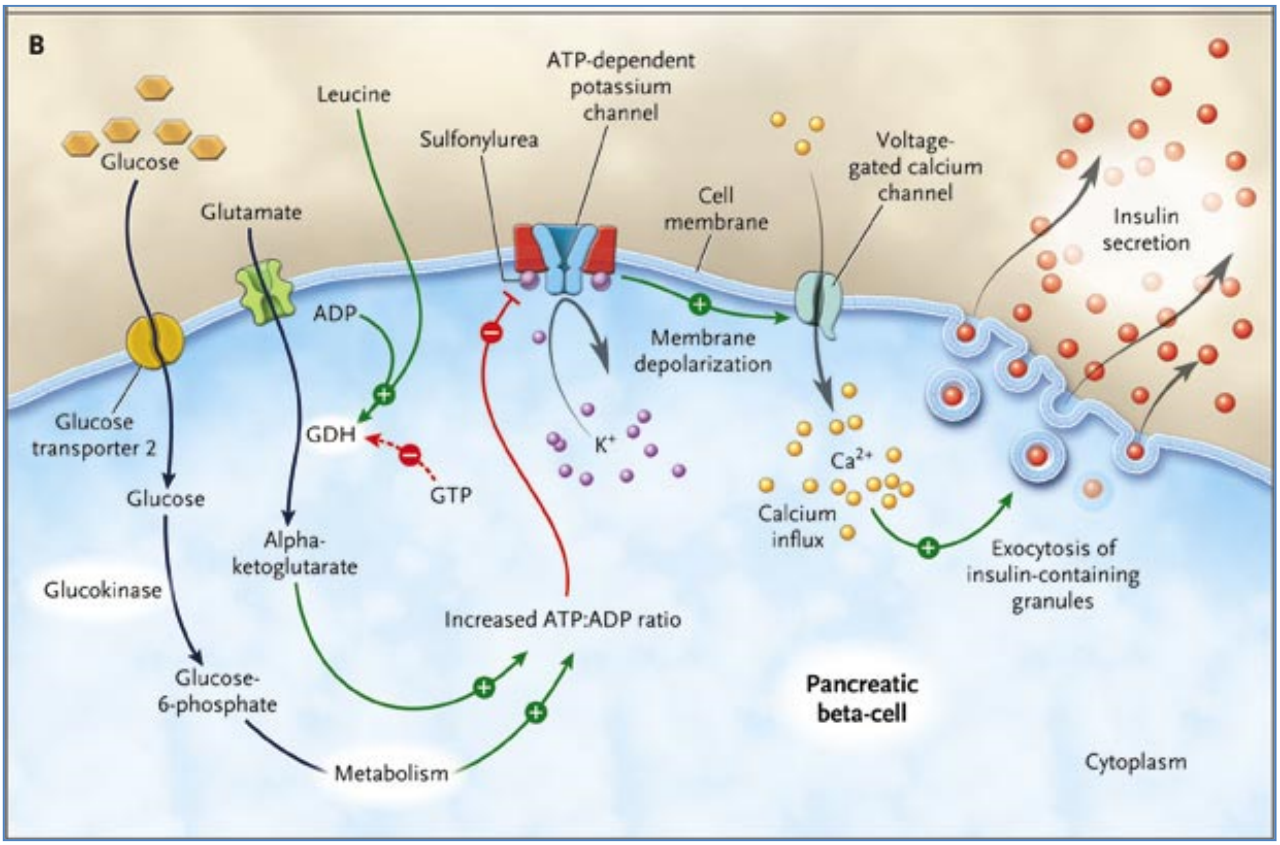
- **Insulin:**
  - **Released Due to:**
    - ↑Blood Glucose
    - ↑Blood Amino Acids
  - **Stimulates:**
    - Glucose Uptake (Fat & Muscle)
    - Lipid Synthesis & Storage (Fat)
    - Protein Deposition (Muscle)
  - **Inhibits:**
    - Ketogenesis
    - Macromolecular Breakdown
- **Glucagon:**
  - **Released Due to:**
    - ↓Blood Glucose
    - ↓Blood Amino Acids (Ie. Fasting)
  - **Stimulates:**
    - Glycogenolysis
    - Gluconeogenesis
    - Lipolysis
    - Ketogenesis
  - **Inhibits:**
    - Macromolecular Synthesis/Storage.

Without Insulin:

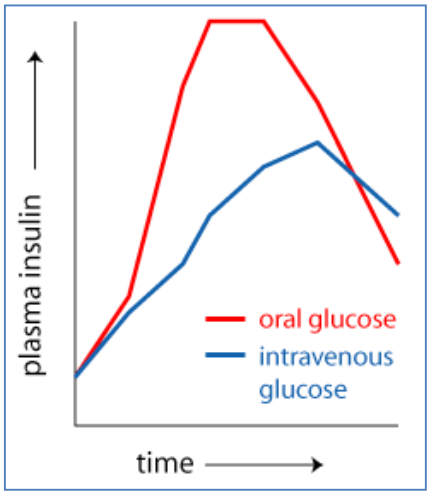
- ↑Gluconeogenesis in Liver
- ↑Glycogenolysis in Liver
- ↑Plasma Glucose → ↑Urine Glucose
- Osmotic Diuresis (Due to ↑Filtrate-[Glucose]) → Dehydration → Circulatory Collapse
- Polydypsia (↑Thirst) due to dehydration.
- ↑Lpolysis
- ↑Ketogenesis → Acidosis →
  - → Myocardial Dysfunction
  - → Cerebral Dysfunction
  - → Venoconstriction
  - → Arterial Dilation
- Fatal if Untreated.

Mechanism of Insulin Release from β-Cells of Pancreas:

1. **↑Blood Glucose → ↑ Uptake of Glucose into Pancreas (Via GLUT-2)**
2. **GLUT-2 + Glucokinase + ATP → ↑Glucose-6-Phosphate**
3. **G-6-P is metabolised via Glycolysis → ↑ATP Production in β-Cell.**
4. **↑ATP Closes the ATP-Gated-K^+ Channels in β-Cell Membrane → Depolarises the β-Cell**
5. **Depolarisation → opens Voltage-Gated Ca^+ Channels → Influx of Ca^+**
6. **Influx of Ca^+ → Ca^+ Mediated Exocytosis of Insulin Vesicles (Similar to ACh Release in Muscles)**

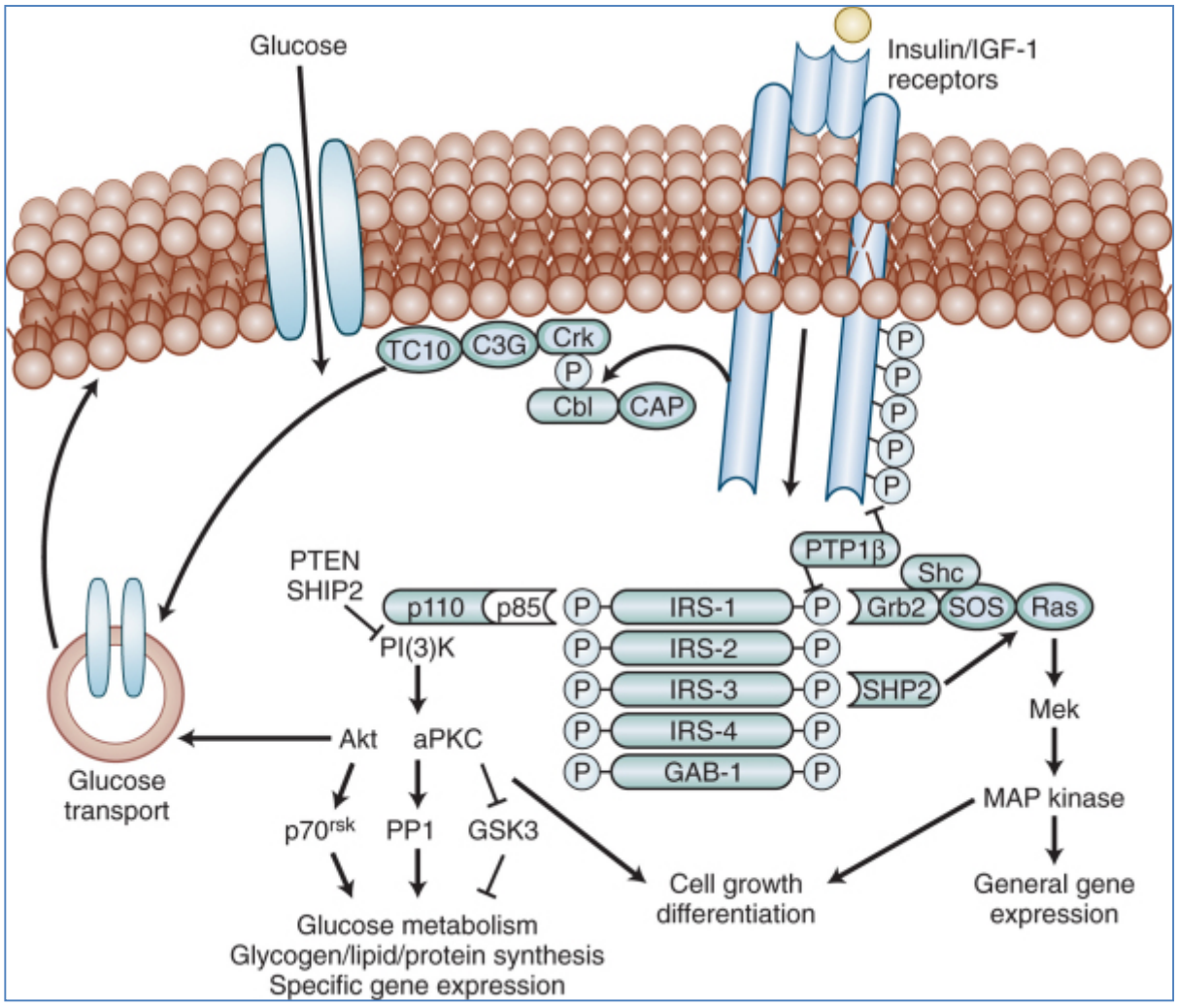


- **NB: "Incretin Effect":**
  - Incretins (Released by GIT after a meal) Further Stimulates Insulin Release from Pancreas.
  - Hence → The Insulin Response to Oral Glucose is much Greater & Quicker than IV Glucose.



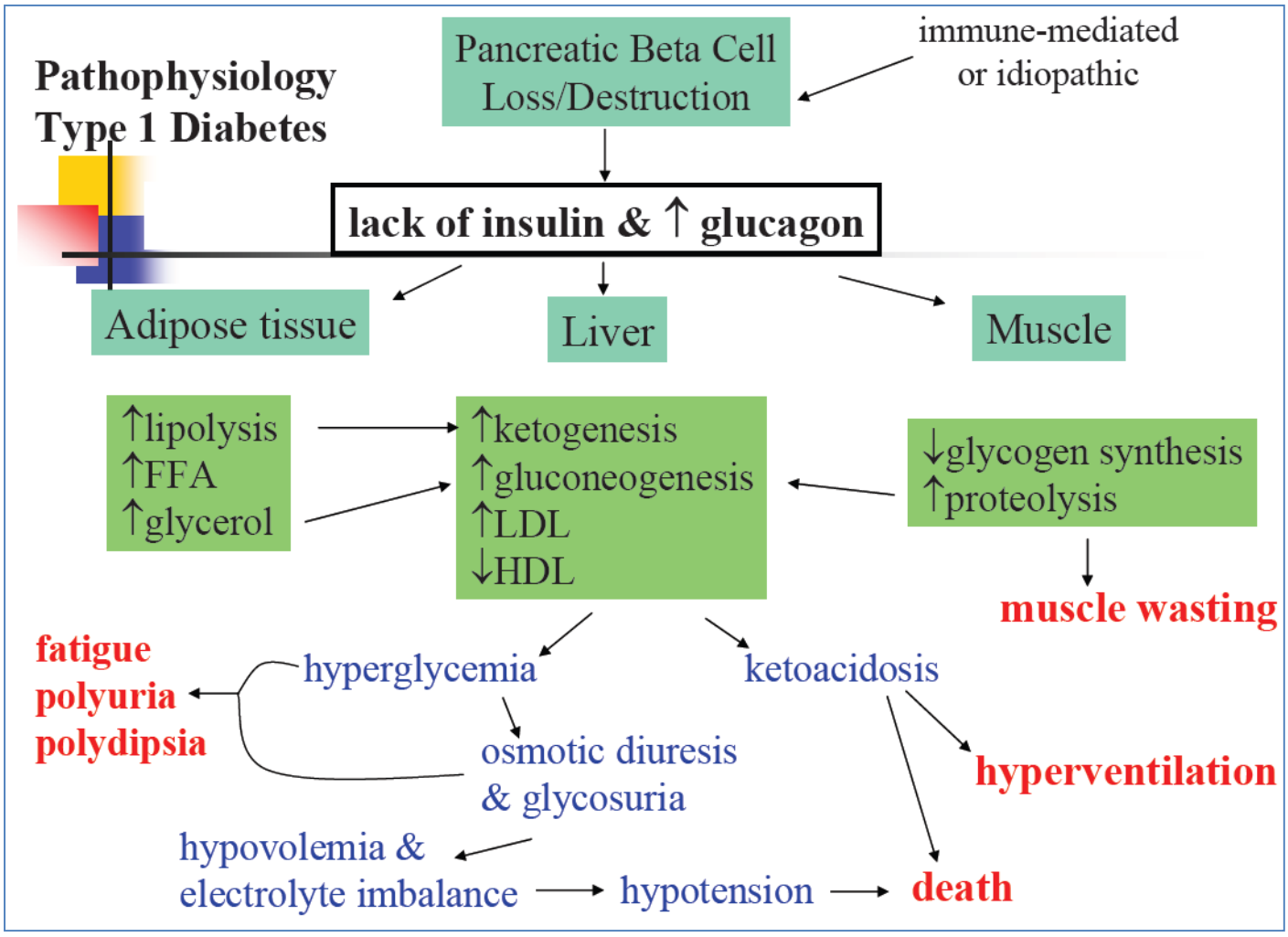
Mechanism of Insulin Action (Glucose Uptake):

- Insulin only affects glucose uptake in tissue that expresses GLUT-4 Transporters (Ie. Are ***Insulin Sensitive***):
  - Muscle
  - Adipose Tissue
- Insulin increases Glucose Uptake in the above tissues by ↑ Expression of GLUT-4 Transporters in the PM.
- **Fasted State:**
  - There will be some GLUT-4 Transporters expressed in the Plasma Membrane.
  - However, most will be found in the membranes of Cytoplasmic Vesicles within the cell.
- **Fed State:**
  - Binding of Insulin to Receptors → Initiates a Signalling Cascade → Movement of GLUT-4 Laden Vesicles to the Cell Surface.
  - Upon reaching the Plasma Membrane, the vesicles fuse with it → ↑Plasma Membrane-[GLUT-4].
  - ↑Plasma Membrane-[GLUT-4] → ↑Glucose Uptake
  - **NB:** Signalling Cascade also Causes→
    - Glucose Metabolism
    - Protein Synthesis
    - Glycogen Synthesis
    - Inhibition of Gluconeogenesis
    - Lipid Synthesis.
    - Cell Growth & Gene Expression

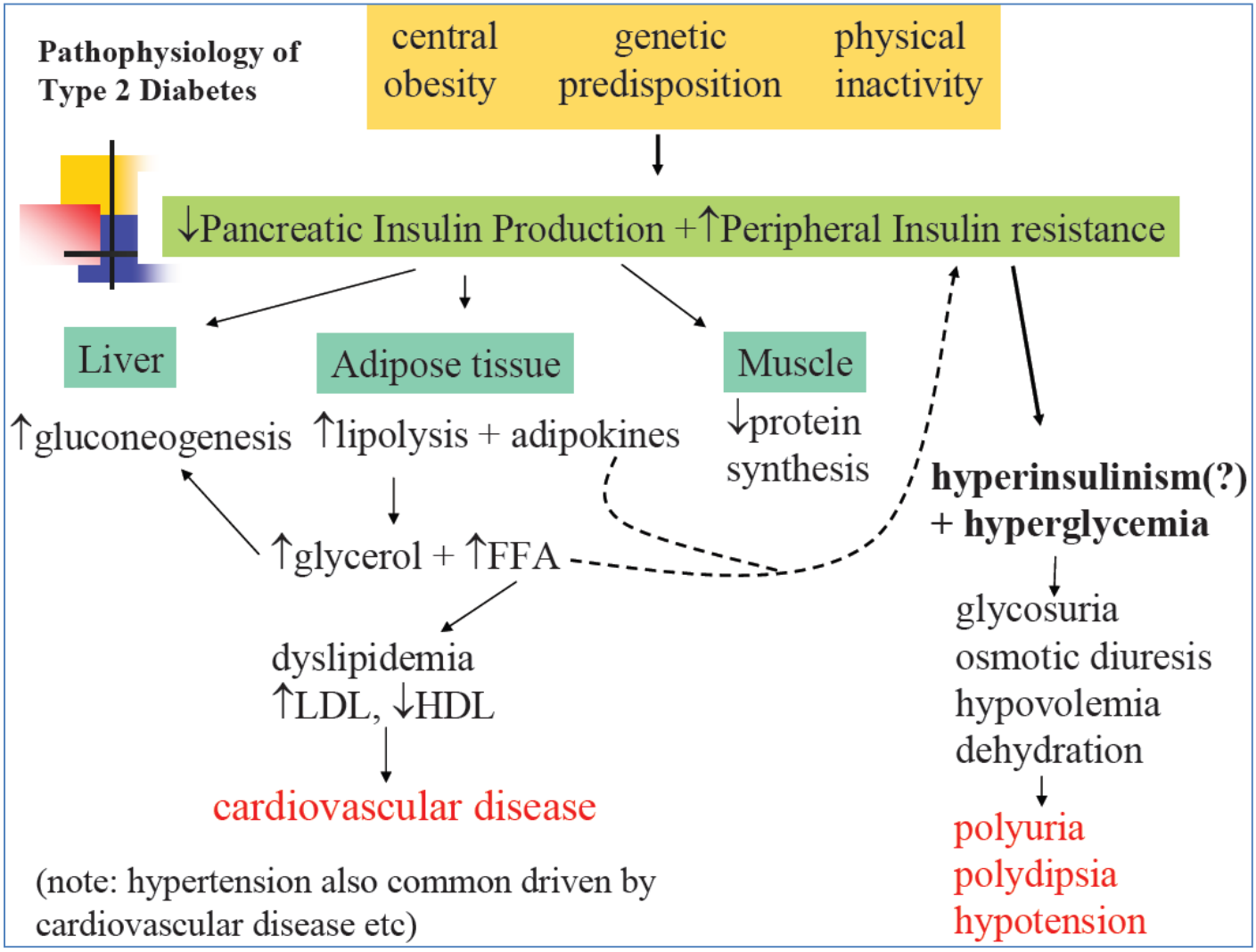


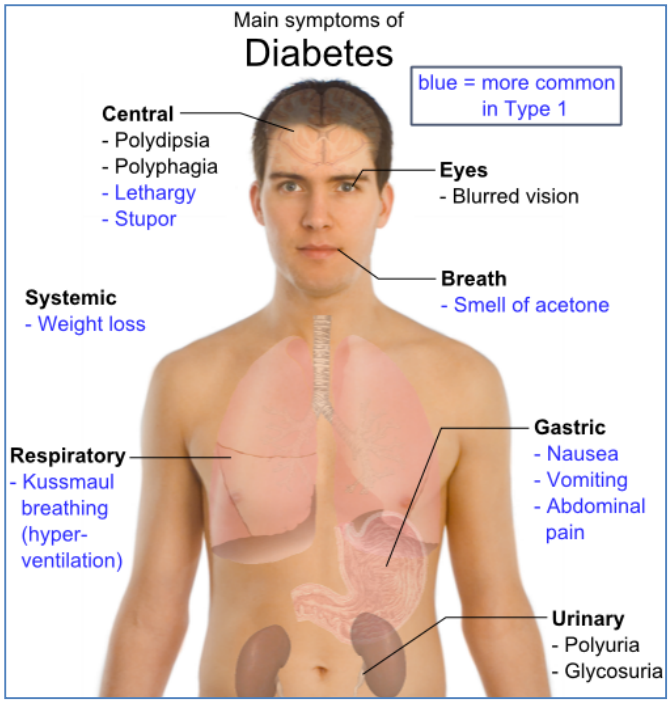
Different Types of Diabetes:

- **Type 1 – Insulin Deficient:**
  - Autoimmune attack on the β-Cells of the Pancreatic Islets.
  - Results in a ***Physical Lack of Insulin Production***
  - Aetiology can be Genetic & Environmental
  - Rapid Onset → Therefore Fewer Complications @ Diagnosis.
  - Presentation:
    - Hyperglycaemia
    - Ketonuria (Ketoacidosis) →
      - Hyperventilation
      - Nausea
      - Vomiting
      - Abdo Pain
    - Rapid Significant Weight Loss
    - Excessive Hunger (Polyphagia)
    - Mental Fatigue
  - Treated with Exogenous Insulin



- **Type 2 – Insulin Resistance:**
  - Results from ***Insulin Resistance*** sometimes combined with ***Relative Insulin Deficiency***.
  - **NB: Obesity** is the #1 Predisposer of Insulin Resistance:
    - Due to Change in Adipose-Release of ***'Adipokines'*** – Hormones that Mediate Insulin Resistance.
      - Incl: Resistin/Leptin/Adipopectin.
  - Peak onset @ ≈50yrs
  - Gradual Onset → Therefore ≈1/4 have Complications @ Diagnosis (Eg. Vascular)
    - NB: Many people spend years in a ***'Pre-Diabetic State'*** – where BSL is higher than normal but not high enough for a diagnosis of Type 2 Diabetes
  - Presentation:
    - Same as Type 1, Except:
      - No Ketonuria
      - Usually Overweight (Central Obesity)
    - ***Metabolic Syndrome*** (Due to Insulin Resistance)**:**
      - ↑Circulating FFA's
      - ↑Insulin
      - ↑Glucose
      - ↓HDL's
      - ↑BP
  - Treated with Diet / Tablets / Exogenous Insulin
    - NB: Over time Insulin Resistance Increases & β-Cell Function Decreases →
      - Therefore the later stages require ↑Amount of Treatment.





Secondary Diabetes:

- **Ie. Diabetes caused by some other disease...For Example:**
  - **Endocrine Disorders:**
    - Cushings (↑Cortisol)
    - Acromegaly (↑GH)
  - **Pancreatic Disorders:**
    - Pancreatitis
    - Surgery
    - Cystic Fibrosis
    - Tumour
  - **Genetic Disorders:**
    - Down's Syndrome
    - Prada Willi
  - **Drugs That Antagonise Insulin's Action:**
    - Some Steroids
    - Some Diuretics
    - β-Blockers

Complications of Diabetes:

Acute Complications – (*METABOLIC*):

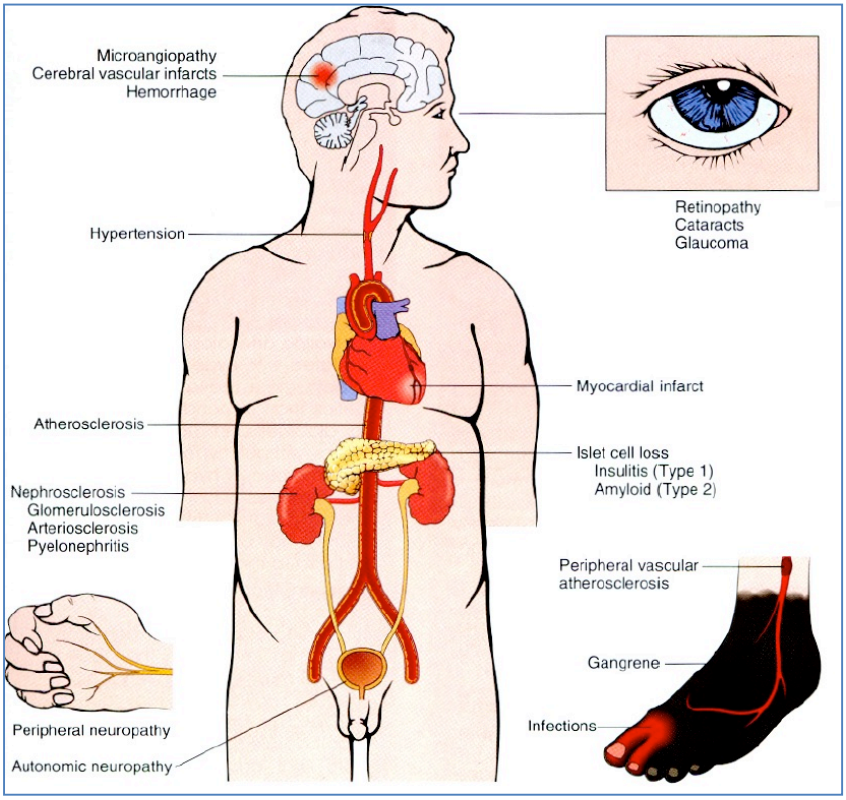
- **Diabetic Keto-Acidosis (DKA):**
  - **Acute life threatening**
  - **Caused By – (***Type I Diabetes* - Lack of Insulin (Eg. Forgotten to take insulin))
  - **Diagnosis:**
    - **Hyperglycaemia:** High Glucose (>15 mmol/L)
    - **Ketoacidosis:** Low pH, Low Bicarbonate (< 15 mmol/L), Sweet Breath, Ketonuria
  - **Symptoms:**
    - **– of Underlying Diabetes – (**Polyuria, Polydipsia, Weight loss)
    - **– of Hyperglycaemia – (**Glycosuria/Osmotic dieresis, **Severe Dehydration**)
    - **– of Hyperketonaemia → KetoAcidosis – (**Vomiting, Acetone Breath, Hyperventilation)
    - **- of Electrolyte Disturbances [↓Na & ↓K] – (**Cardiac Arrhythmia / Bradycardia)
  - **Treatment:**
    - 1. IV access → Correct Dehydration
    - 2. Insulin Infusion → Correct Hyperglycaemia
    - 3. Monitor/Correct Electrolytes – Particularly Potassium
  - **Complications:**
    - 40% mortality – medical emergency
    - Severe Dehydration
- **HONC – Hyperosmolar Non-ketonic Coma:**
  - **Caused By – (***Type II Diabetes* - Relatively Low Insulin/Insulin Insensitivity + Precipitant**)**
  - **Diagnosis:**
    - **Hyperglycaemia**
    - **NO KetoAcidosis**
  - **Symptoms:**
    - Confusion/Coma
    - Marked Dehydration
    - Polyuria (Osmotic Diuresis)
    - Neurology – (Sensory/Motor Impairment, Focal Seizures, Hyporeflexia, Tremors)
  - **Treatment:**
    - IV Fluids
    - Insulin + Potassium (Since Insulin causes K^+ Shift *Into Cells*)
    - Electrolyte Replacement (Esp. Potassium)
  - **Complications:**
    - Fatal if Untreated
- **Hypoglycaemia (BSL < 6.0mmol/L):**
  - **Aetiology – (**Diabetes + Insulin Overdose / Alcohol / Sepsis)**
  - **Diagnosis – (BSL < 3.5 mmol/L)**
  - **Symptoms:**
    - **Autonomic – (**Sweating, Anxiety, Hunger, Tremor, Palpitations, Dizziness)
    - **CNS – (**Confusion, Drowsiness, Visual Disturbances, Seizures, Coma)
  - **Treatment:**
    - #1 – Oral/IV Glucose (Jellybeans/Juice/Biscuits/etc.)
    - OR – IM/IV Glucagon

Chronic Complications:

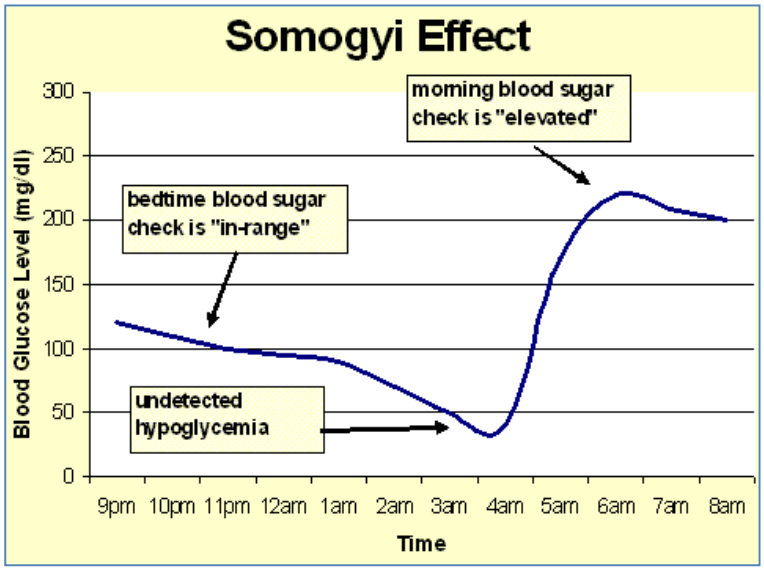
- **Macrovascular (Atherosclerosis)** → IHD / CVA / PVD
- **Microvascular (arteriolosclerosis)** → Retinopathy, Nephropathy, Neuropathy
- **Immunosuppression**
- **Poor Wound Healing**

Chronic Complications:

- **Caused by chronic exposure to Hyperglycaemia & Dyslipidaemia in the Insulin *Insensitive Tissues.***
- **Vascular:**
  - **Macrovascular:**
    - **Heart Disease/Coronary Artery Disease/Atherosclerosis**
    - **Stroke**
    - **Peripheral Vascular Disease**
  - **Microvascular:**
    - **Retinopathy**
    - **Neuropathy**
    - **Nephropathy**

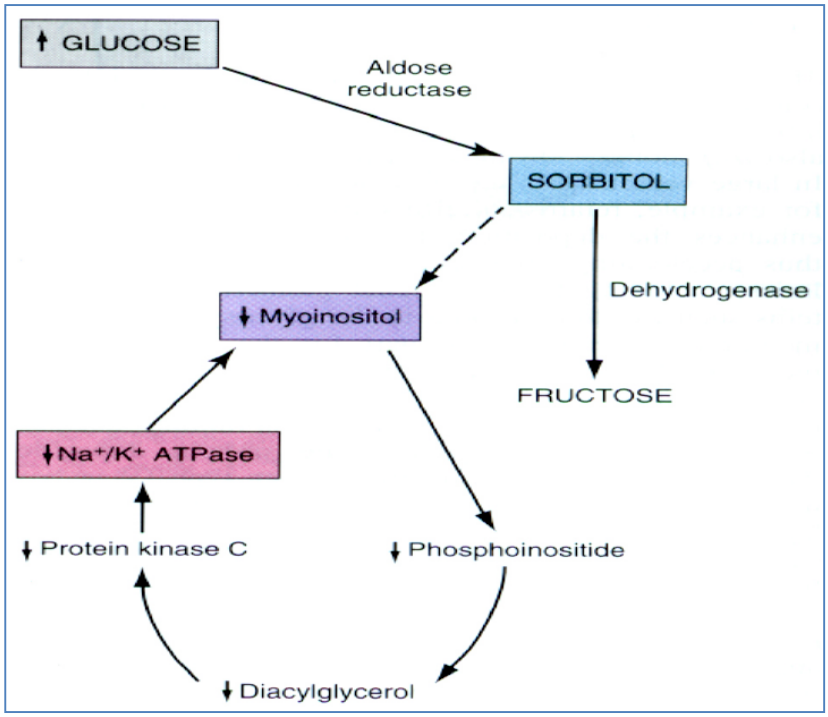


- **The 'Somogyi' Effect:**
  - Where Circadian Elevations in Counter-Regulatory hormones (GH & Cortisol) cause Hyperglycaemia early in the morning → Patient Increases Insulin Dose @ Bedtime → Sustained Hypo all night → Body releases Glucagon, Adrenaline & Cortisol → Hyper @ Dawn.



Possible Causes of Chronic Complications:

- **The 'Polyol Pathway':**
  - Hyperglycaemia → ↑Glucose Accumulation in Insulin *Independent* Tissues.
  - Much Glucose → Converted to **Sorbitol** → Slowly converted to Fructose.
  - However, **Sorbitol** is ***Osmotically Very Active*** → Sorbitol Accumulation →
    - Osmotic Cell Injury
    - Affects Ion Pumps
    - Affects Some Cellular Secondary Messenger Pathways



- **Hyperglycosylation of Proteins:**
  - ↑Glucose → 'Glycosylation' of proteins (Ie. Linkage of Glucose to Free Amino Groups in Proteins)
    - Eg. HbA_{1C} (Glycosylated Haemoglobin)
  - Affects proteins in Blood Vessel Walls & Basement Membranes → Can stimulate Inflammation.
    - Includes Collagen, Fibronectin, etc.
  - Leads to formation of ***'Advanced Glycosylated End-Products' (AGE's)***:
    - Can form cross-linkages between peptides → Forms a "Mesh" → Traps Other Molecules:
      - Eg. LDL Trapping → Cholesterol Deposition → Atherosclerosis
      - Eg. Immunoglobulins & Complement → Inflammation
    - Can form binding-sites for other proteins (eg. Albumin)
    - Inactivate Nitric Oxide → Reduce Vasodilation
    - Stimulate Growth-Factor & Cytokine Secretion
    - ↑Vascular Permeability
    - ↑Clotting Activity → Stroke/Embolus/etc.
    - ↑Extra-Cellular Matrix Deposition.

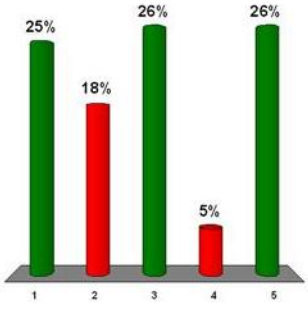
- **Reactive Oxygen Species:**
  - ↑Hyperglycaemia → ↑O_2 Free-Radical Production.
  - Compounded by ↑Immune Cell Activation

Diabetes Qs

Lecture Keypad Questions:

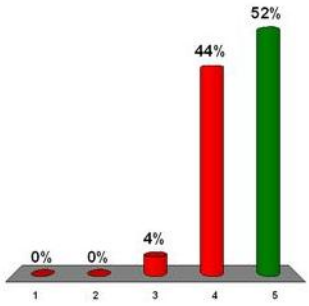
Diagnostic points (for DM2) ?

1. On & off for long time.
2. Always drinking.
3. Put on weight.
4. Recurrent boils.
5. Mom has DM type 2



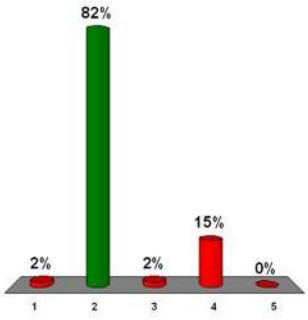
?Pathogenesis: "recurrent multisite infections"

1. Associated AIDS
2. Hyperglycemia
3. Ischemia
4. Immunodeficiency
5. Multifactorial



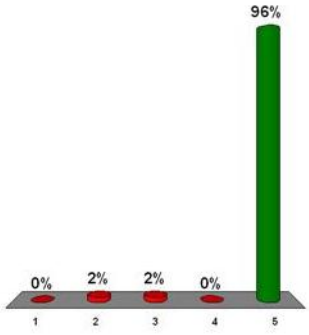
Miss ML: Most likely diagnosis:

1. DM Type 1
2. DM Type 2
3. MODY 1
4. MODY 2
5. Gestational DM



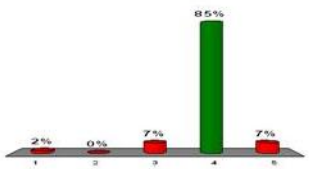
?Pathogenesis: Whitish vaginal discharge.

1. Proteinuria
2. Bacterial infection
3. Glycosuria
4. Trichomoniasis
5. Candidiasis



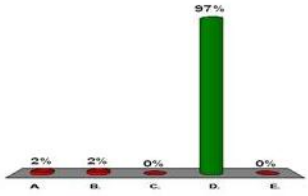
Pathologic mechanism?

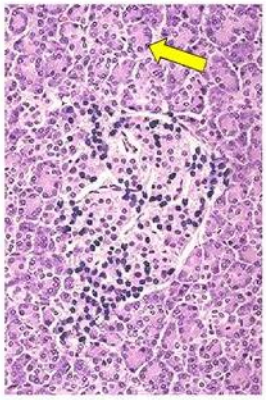
1. Anti-insulin antibodies.
2. Increased insulin uptake.
3. Irregular insulin secretion.
4. Peripheral insulin resistance.
5. Serum Anti GAD-67 antibodies.



DM– Pancreatic Islet- ? Feature shown by arrow?

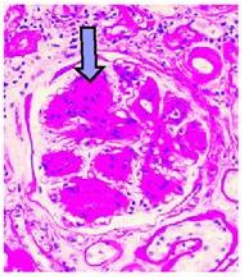
A. B cell exhaution.
B. Amyloid deposits
C. Lymphocytic Insulitis
D. Pancreatic acinus
E. Chronic Pancreatitis

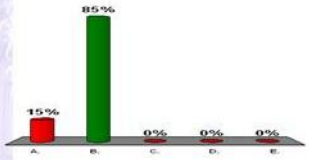




50y, male DM2, kidney biopsy. Likely nature of feature shown by arrow?

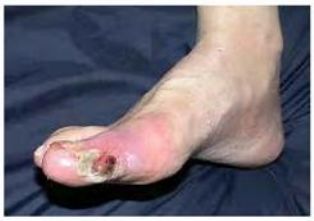
A. Amyloid protein.
B. AGE protein
C. Basement mem protein.
D. Fibrinoid necrosis.
E. Inflammatory cells.

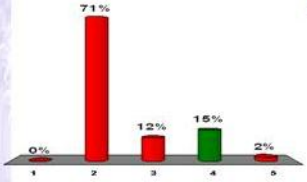




47y F, DM2 - foot ulcer: ? Diagnosis

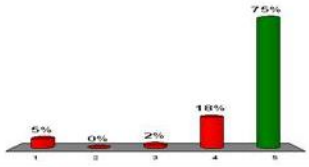
A. Fungal infection
B. Neuropathic ulcer
C. Venous ulcer
D. Arterial ulcer
E. Atypical TB in AIDS





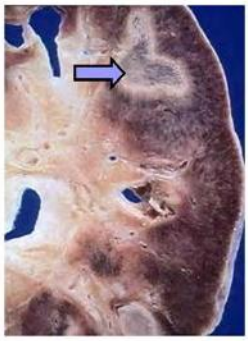
Thickening of small BV in this patient is most likely related which pathologic mechansim?

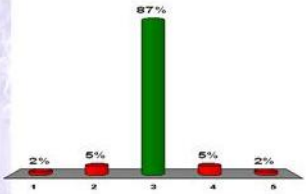
1. Glycosylation of hemoglobin.
2. Inadequate inflammtion resp.
3. Insulin resistance in tissues.
4. Increased Atherosclersis.
5. Microvascular disease.



57y M, DM2: Gross Kidney- arrow ? feature

A. Benign nephrosclerosis.
B. Glomerulonephritis
C. Papillary necrosis
D. Nodular glomerulosclerosis
E. Renal artery Atherosclerosis





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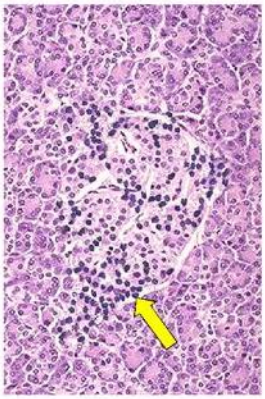
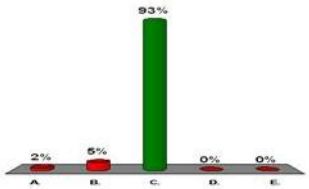
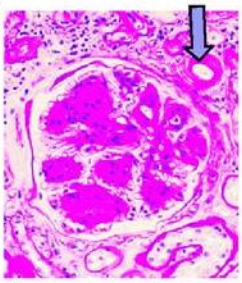
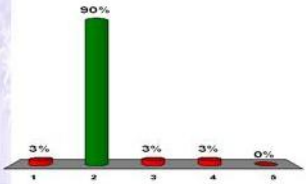




47y F, DM2 – Kidney- arrow ? feature

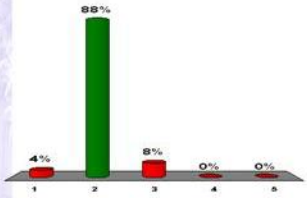
A. Nodular glomerulosclerosis.
B. Artereolosclerosis
C. Atherosclerosis
D. AGE deposition
E. Diffuse glomerulosclerosis

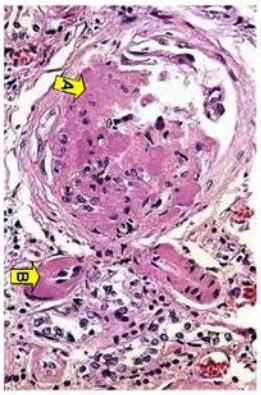




DM Kidney.Microscopy. ? Feature Arrow B

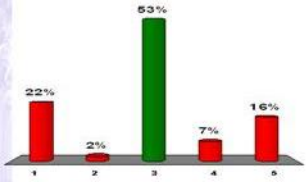
A. Nodular sclerosis
B. Artereolosclerosis
C. Diffuse sclerosis
D. Pyelonephritis
E. Abscess formation

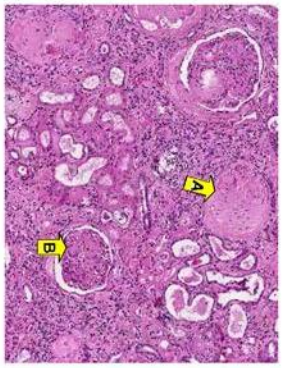




DM Kidney.Microscopy. ? Feature Arrow A

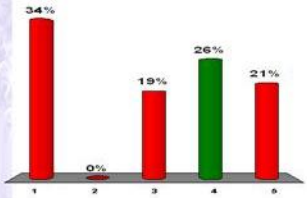
A. Nodular sclerosis
B. Artereolosclerosis
C. Diffuse sclerosis
D. Pyelonephritis
E. Abscess formation

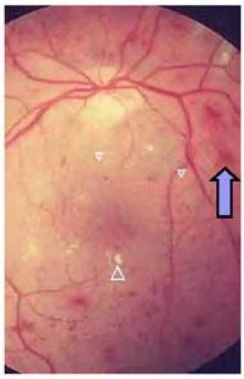




57y M, DM2 – Kidney- arrow ? feature

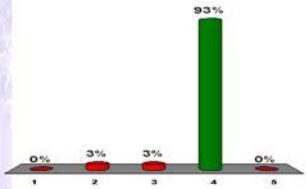
A. Dot hemorrhage
B. Hard exudate
C. Soft cotton wool exudate
D. Neovascularization
E. Micro Aneurysm

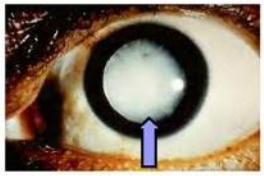




57y M, DM2 – Eye ? Pathogenesis

A. AGE deposition
B. Glycosylation
C. Collagen deposition
D. Osmotic Polyol damage
E. Artereolosclerosis





47y F, DM2 - foot ulcer: ? Diagnosis

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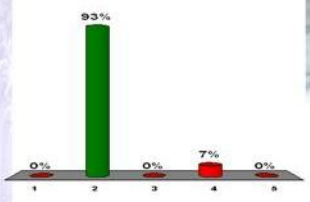
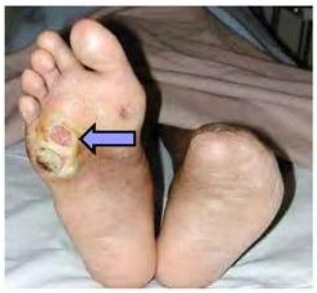
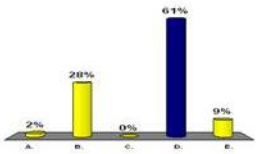
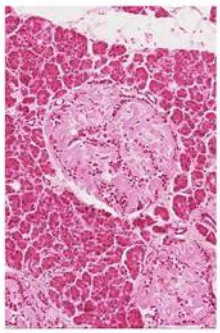




56y Fem, Anterior wall MI. 3+ proteinuria & FBG 19mmol/L. Image shows her pancreas. What complication she may develop?

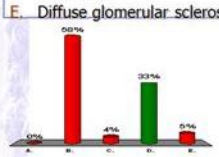
A. Gall stones.
B. Chronic pancreatitis.
C. Uric acid stones.
D. Gangrene of foot.
E. Pancreatic carcinoma

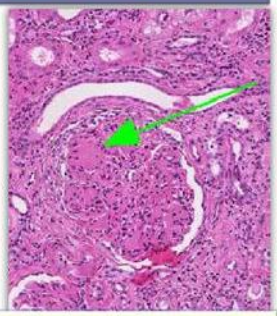




A 65y man, BMI 40, peripheral neuropathy, retinopathy and abdominal aortic aneurysm is now developing renal failure. His FBS is 18.3 mmol/L, microscopic examination of his renal biopsy. What is the microscopic feature shown ?

A. Renal papillary necrosis.
B. Nodular glomerulosclerosis.
C. Hyaline artereolosclerosis.
D. Atrophy + Amyloid deposition.
E. Diffuse glomerular sclerosis.

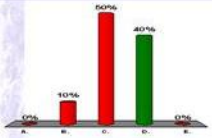


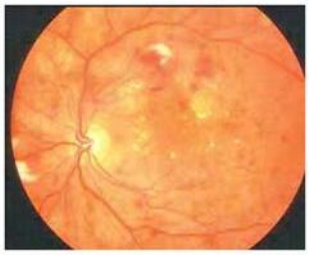


1. What is the chemical nature of nodular deposit within glomerulus?
2. Briefly describe steps in the Pathogenesis of nodular glomerulosclerosis?
3. What other renal pathology are commonly seen in diabetic patients?

A 47 year old man, Hypertensive & DM2 since 6 years for checkup. Complains of his vision as spectacles recently made does not seem to help. Image shows his fundoscopy. What is the most likely diagnosis ?

A. Normal fundus.
B. Mild Hypertensive retinopathy.
C. Non proliferative retinopathy.
D. Proliferative retinopathy.
E. Retinal detachment.

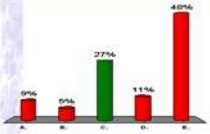


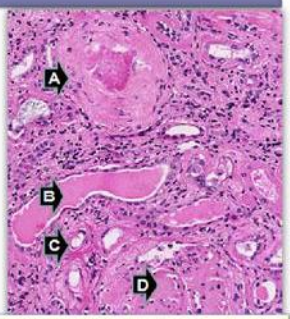


1. Retinopathy – Differences between Hypertensive & Diabetic retinopathy?
2. Briefly describe steps in the Pathogenesis of diabetic retinopathy?
3. Differentiate soft & hard exudates, dots & blots, proliferative & non-proliferative.?

A 65y man, BMI 40, Diabetes since 18 years. His FBS is 18.3 mmol/L, is now developing hypertension since 3 years (BP 186/98 mm of Hg) . Image shows microscopic appearance of his renal biopsy. What microscopic feature shows pathogenesis of high blood pressure?

A. Hyperplastic artereosclerosis
B. Protein cast within tubule.
C. Artereolosclerosis.
D. Nodular glomerulosclerosis.
E. Both A & C.

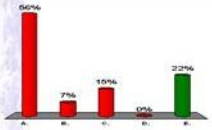


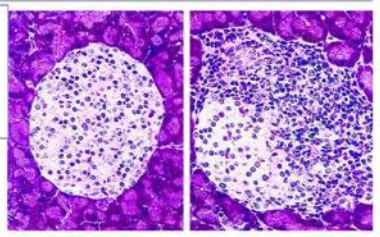


1. What is the pathogenesis of feature A (hyperplastic arterosclerosis) in the image?
2. Briefly describe feature B and its clinical presentation?
3. What is seen in the interstitium of this kidney? Pathogenesis? Clinical feature?

A 42 year female presents with recent onset polyuria, polydypsia and decreasing vision. HbA1c was 16.1%. She is chronic alcoholic with past history of jaundice. Image shows her pancreatic biopsy compared with normal. What is the most likely diagnosis ?

A. Secondary diabetes.
B. Late onset Type 2 diabetes.
C. Chronic cholecystitis.
D. Cushing's syndrome.
E. Type 1 diabetes.

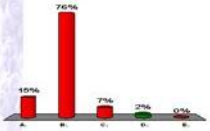




1. Briefly describe features of LADA?
2. What further investigations can be done to confirm the diagnosis?
3. List & briefly describe other types of Diabetes ?

70y man brought from nursing home with progressive confused & disoriented status since 2 weeks. Not eating or drinking well. On steroid therapy for COPD.
What is the most likely diagnosis ?

A. Diabetic ketoacidosis.
B. Non-ketotic hyperosmolar coma.
C. Diabetic lactic acidosis.
D. Respiratory acidosis.
E. Diabetic nephropathy.

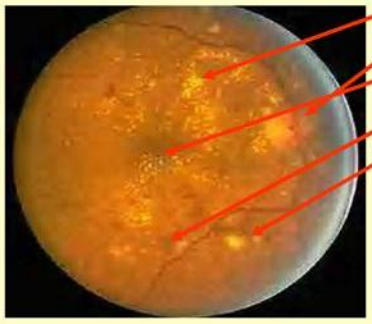


Lab tests:

Na	155 mmol/L
K	5 mmol/L
Cl	110 mmol/L
HCO_3	30 mmol/L
Urea	15 mmol/L
Glucose	50 mmol/L
Arterial pH	7.35

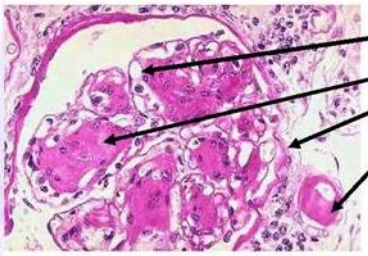
1. List & briefly discuss common metabolic complications of Diabetes?
2. ?
3. ?

Label the diagram.



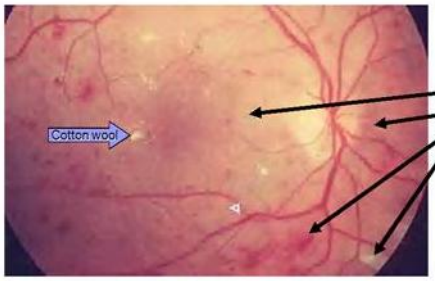
1. Hard/waxy dep
2. Optic disc
3. Macula
4. Blot hem
5. Cotton wool / soft dep.

Label the diagram.



1. Capillary
2. Nodule – AGE
3. Bowman cap.
4. Hyaline arteriolo sclerosis in arteriole.

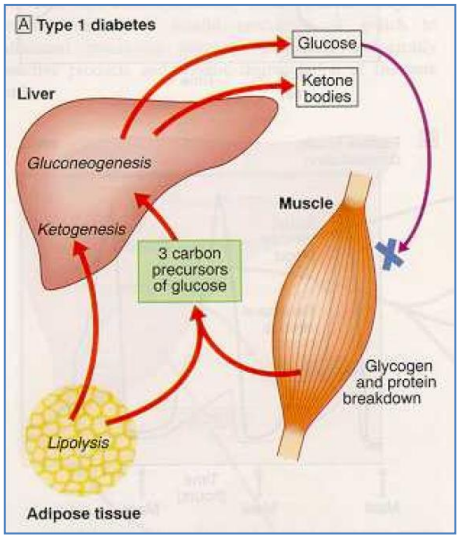
Diabetic Retinopathy



Endocrine Emergencies:
Focus on Diabetic Emergencies

Diabetic Emergencies:

- **Diabetic Ketoacidosis:**
  - **Acute life threatening**
  - **Pathology – Combination of:**
    - **Insulin Deficiency**
      - Cell unable to absorb & metaoblis glucose
    - **Excess Counter-Regulatory Hormones (Eg. Glucagon/Adrenaline)**
      - Glycogen Breakdown
      - Lipolysis → Ketogenesis
      - Protein Catabolism
    - **Resultant Hyperglycaemia**
      - Osmotic dieresis → Dehydration
  - **Presentation:**
    - **– of Underlying Diabetes:**
      - Polyuria
      - Polydipsia
      - Weight loss
    - **– of Hyperglycaemia:**
      - Glycosuria/Osmotic dieresis
      - Salt & Water Depletion
    - **– of Hyperketonaemia → Metabolic Acidosis:**
      - Acetone Breath
      - Hyperventilation (Respiratory Compensation)
      - Peripheral Vasodilation → Hypotension
      - K^+ Depletion



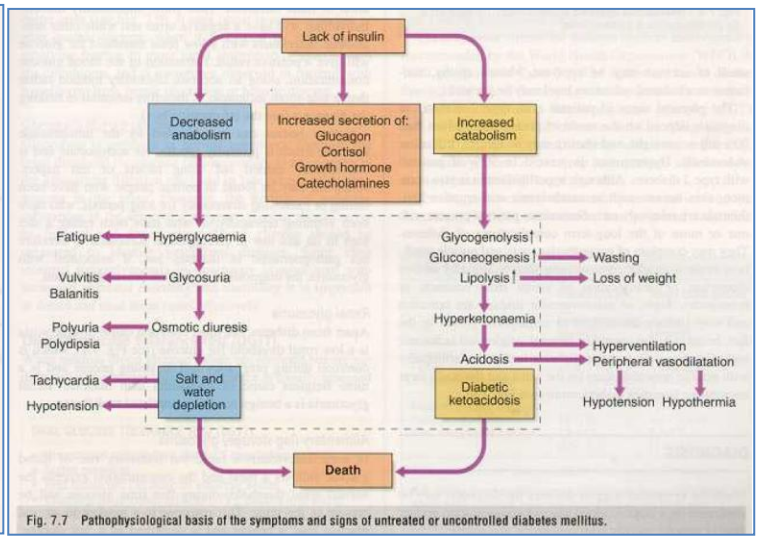


Fig. 7.7 Pathophysiological basis of the symptoms and signs of untreated or uncontrolled diabetes mellitus.

  - **Treatment:**
    - Supportive (ABCs)
    - Rehydration
      - Replace ½ fluid deficit in 1st 12 hrs
    - Insulin infusion
    - Close monitoring of Electrolytes

- **Hyperosmolar Non-Ketotic Coma:**
  - **Pathophysiology:**
    - Relative Insulin Deficiency
    - Enough to Prevent Lipolysis;
      - → NO Ketosis
    - But *Not* enough to Prevent Hyperglycaemia
      - → Hyperglycaemia
  - **Presentation:**
    - Confusion/Coma
    - Marked Dehydration
  - **Treatment:**
    - Supportive ABCs
    - Rehydration
    - Insulin Infusion

- **Hypoglycaemia:**
  - **Don't Ever Forget Glucose:**
    - Because severe or prolonged hypoglycaemia can cause Brain damage/death.
  - **Causes:**
    - ****Diabetic:**
      - Insulin Overdose (Accidental/Suicide Attempt)
      - Missed Meal
      - Exercise
      - Alcohol
    - **Alcohol Excess**
    - **Sepsis**
  - **Symptoms:**
    - **CNS Glucose Deficiency**
      - Confunsion/Coma/Seiure
      - Drowsiness
      - Incoordination
    - **Autonomic**
      - Anxiety
      - Sweating
      - Tremors
      - Palpitation
    - **Non Specifics**
      - Nausea
      - Headache
      - Fatigue
  - **Diagnosis:**
    - Hypoglycaemia
    - Clinical Symptoms
    - Response to Glucose Administration
  - **Treatment:**
    - Supportive:
      - ABCs
    - Suspect the Diagnosis:
      - Don't ever forget glucose
    - Correct serum Glucose:
      - Glucose Oral/IV
      - Glucagon (if IV Glucose isn't possible)
    - Disposition
      - Oral Hypoglycaemics (Admit to all patients)

Other Endocrine Emergencies:

- **Alcoholic Ketoacidosis:**
  - **Cause:**
    - Alcoholic with recent decreased food intake
  - **Presentation:**
    - Abdo pain, nausea & vomiting
    - Metabolic Acidosis & Possible Ketoneuria
  - **Treatment:**
    - Supportive ABCs
    - Rehydration

- **Thyroid:**
  - **Hyperthyroidism:**
    - **Cause:**
      - High free T4 & low TSH
        - Eg. Graves Disease: goitre, exopthalmos, pretibial myxoedema
    - **Presentation:**
      - →Nervousness, irritability, mental disturbance, tachycardia,
      - →palpitations, heat intolerance, weight loss, goiter
    - **Treatment:**
      - Supportive ABCs
      - Block Effects of T4 (Thyroid Blocking Drugs)
  - **Hypothyroidism:**
    - **Cause:**
      - Low free T4 & high TSH
    - **Presentation:**
      - →Fatigue, weakness, constipation, cold intolerance & depression
      - → Goitre, menstrual irregularities
    - **Treatment:**
      - Supportive ABCs
      - T4 Replacement (Thyroxine)

- **Adrenocortical Insufficiency:**
  - **Causes:**
    - **Primary:**
      - Adrenal Failure
    - **Secondary:**
      - Pituitary Failure
      - Adrenopituitary Suppression by Steroids
  - **Presentation:**
    - →Hypotension, abdominal pain, confusion, weakness, & pigmentation
    - →Hyponatraemia
    - →Hyperkalaemia
  - **Treatment:**
    - Corticosteroid Replacement (Hydrocortisone)

ENDOCRINOLOGY Pathology:
GONADAL DYSFUNCTION

Male Hypogonadism:

- **What is it?**
  - A deficiency in Testosterone due to problems with either:
    - 1) Testes, or - Primary
    - 2) Hypothalamus/Pituitary - Secondary
- ***Primary Hypogonadism (Hypergonadotrophic)***
  - Ie. Problem with the Leydig Cells in the Testes → ↓↓Testosterone Production → ↑↑Hypothalamo-Pituitary release of Gonadotropins (FSH/LH).
  - **Causes:**
    - Trauma/Irradiation of Testes.
    - Mumps
    - Klinefelter's Syndrome (XXY)
    - Androgen Resistance
    - Autoimmune
    - Congenital
- ***Secondary Hypogonadism (Hypogonadotrophic)***
  - Ie. Problem with the Hypothalamo-Pituitary Axis → ↓↓Gonadotropin Release (FSH/LH) → ↓↓Testosterone Production
  - **Causes:**
    - Developmental
    - Pituitary Tumour/Trauma/Pituitary Irradiation/Autoimmune
    - Genetic Syndromes

- **Effects of ↓↓Testosterone:**
  - Infertility (Low Sperm Count)
  - ↓Libido
  - ↓Muscle Mass
  - ↓Beard/Body Hair
  - Erectile Dysfunction
  - ↑Breast Tissue
  - ↓Bone Mass
  - ↑Body Fat
- **Range of Treatments – Testosterone Replacement Therapy:**
  - Buccal
  - Oral
  - Trans-Cutaneous (patch/gel)
  - IM Injection
  - Implant

ENDOCRINOLOGY Pathology:
GROWTH DYSFUNCTION

Defects in Endocrine Control of Growth:

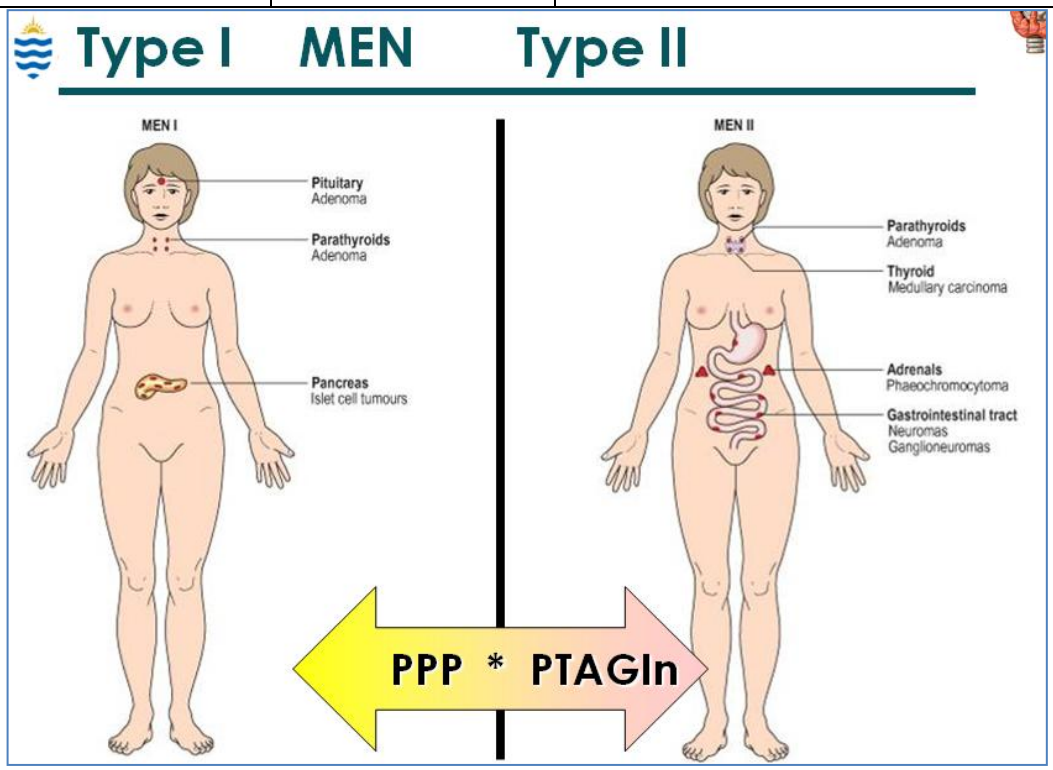
- **Hyper:**
  - **Too Much Growth Hormone &/or Growth Factors (Rare):**
    - Eg. Childhood Gigantism
    - Eg. Adults - Acromegaly
  - **Non-GH Causes:**
    - Eg. Precocious Puberty
- **Hypo:**
  - **Defective Growth Hormone Axis:**
    - **GH-Deficiency:**
      - **Primary GH Deficiency:**
        - Hypothalamic Defect
        - And/Or Pituitary Defect
      - **Secondary Pituitary Deficiency:**
        - Eg. Tumour & other Destructive Diseases.
        - Eg. Psychosocial Deprivation (Ie. Kids in abusive/non-supportive environments → GH-Deficiency → exhibit slowed growth)

ENDOCRINOLOGY Pathology:
MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES

Familial Endocrine Neoplasias – MEN Syndromes:

- **Multiple Endocrine Neoplasia** = Genetic Disorders where 2/More Tumours are found in Endocrine Glands (Parathyroid, Pituitary, Thyroid, & Adrenal Medulla).
- MEN Disorders → Greatly ↑the risk of developing multiple cancerous and noncancerous tumors in glands such as the parathyroid, pituitary, and pancreas.

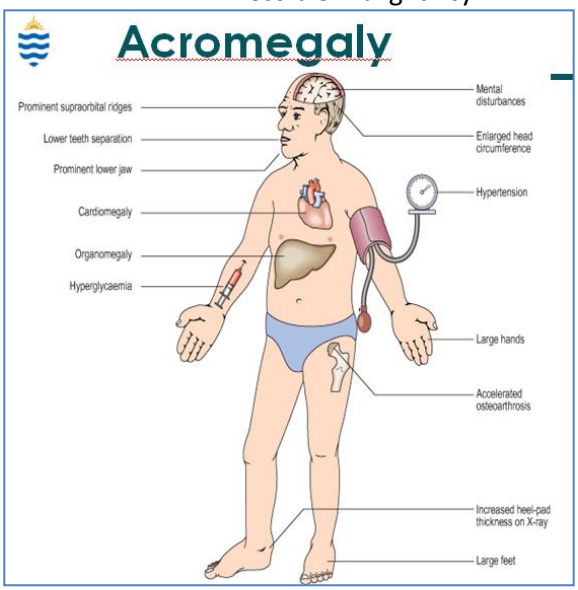
Multiple Endocrine Neoplasm Classifications			
Type	**Aetiology**	**Organs Involved**	**Clinical Features**
MEN1: Wermer's Syndrome	**Autosomal Domimant** Genetic Mutation in MEN1 Tumour Suppressor Gene on Chromosome 11	1. Pituitary 2. Parathyroid 3. Pancreas (Top 2/3 of Body)	**60% of Wermer's Pts have >2x of the Following:** -Pituitary Adenoma → Eg. Prolactinomas/GH - Can also → Bilateral Hemianopia -Parathyroid Adenomas → Hyperparathyroidism -Pancreatic Gastrinoma → Peptic Ulcer Disease -Pancreatic Insulinoma → Hypoglycaemia -Pancreatic VIPomas → ↑VIP→ Secretory Diarrhoea
MEN2a: Sipple's Syndrome	**Autosomal Domimant** Genetic Mutation in MEN2 Tumour Suppressor Gene on Chromosome 10	1. Thyroid 2. Parathyroid 3. Adrenal Medulla (Lower 2/3 of Body)	100% of Pts → Medullary Thyroid Cancer 50% of Pts → Phaeochromocytoma → ↑Adrenaline 30% of Pts → Parathyroid Hyperplasia → ↑PTH
MEN2b:	**Autosomal Domimant** Genetic Mutation in MEN2 Tumour Suppressor Gene on Chromosome 10	1. Thyroid 2. Adrenal Medulla (Lower 2/3 of Body)	100% of Pts → Medullary Thyroid Cancer 50% of Pts → Phaeochromocytoma → ↑Adrenaline (Other: Mucosal Neuromas, Marfanoid Features)

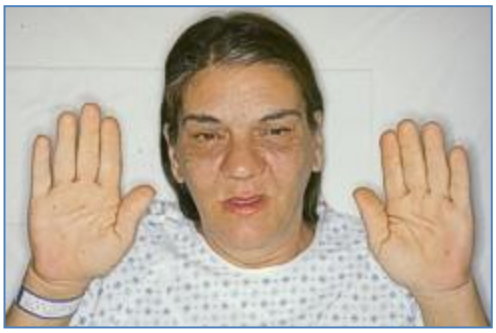


ENDOCRINOLOGY Pathology:
PITUITARY DYSFUNCTION

Hyperpituitarism:

- **Anterior Pituitary:**
  - **Cushing's Disease (Already Covered)**
  - **Primary Central Hyperthyroidism (Already Covered)**
  - **Gigantism/Acromegaly:**
    - **Aetiology:**
      - Pituitary Adenoma
    - **Pathogenesis:**
      - Pituitary Adenoma → Secretes Excess GH
    - **Morphology:**
    - **Clinical Features:**
      - Insidious Onset
      - Mostly Middle-Aged Adults
      - **Symptoms:**
        - Severe Disfigurement
        - Soft-Tissue Swelling (Hands, Feet, Nose, Lips, Ears, Skin, Carpal Tunnel)
        - Prominent Jaw & Supra-Orbital Ridges
        - Hypertension
        - **Compressive Pituitary Adenoma** → Headache + Visual Field Defect
    - **Diagnosis:**
      - IGF1 & GH Levels
      - Brain MRI
    - **Treatment:**
      - Surgical Removal of Pituitary Adenoma
      - Somatostatin Analogues
    - **Complications:**
      - Hypertrophic Cardiomyopathy & Heart Failure
      - Hypertension & Kidney Failure
      - Hyperglycaemia & Diabetes Mellitis
      - Accelerated Osteoarthosis
      - Possible Malignancy





- **Posterior Pituitary:**
  - **SIADH – (Syndrome of Inappropriate ADH Secretion):**

Hypopituitarism:

- **Anterior Pituitary:**
  - **Sheehan's Disease; AKA: *Postpartum Hypopituitarism* (Pituitary Infarction):**
- **Posterior Pituitary:**
  - **Diabetes Insipidus:**

ENDOCRINOLOGY Pathology:
THYROID DYSFUNCTION

Abnormalities of Thyroid Function:

- **Classic Common symptoms;**
  - Weight change
  - Sleep change
  - Mood change
  - Bowel function change
  - Skin change
  - Menstrual bleeding change
  - Infertility

Hypothyroidism (Most Common):

- **"Under-Secretion of Thyroid Hormone"**
- **Causes:**
  - ****Autoimmune: '*Hashimoto's Disease*'**
    - **– Anti-Thyroid Peroxidase Antibodies (Anti-TPO-Abs) → ↓T3/T4 Production**
    - **- or Anti-Thyroglobulin Antibodies** → Destroy T3/T4.
    - Classically Women >60yrs
  - *******Dietary: - Insufficient Iodine intake*** – (Worldwide greatest cause)
  - ***Hypothalamic-Pituitary Disorder***
- **Effects of Hypothyroidism:**
  - ↓Metabolic Rate
  - ↓Body Temerature & Cold Intolerance
  - ↓Sympathetic Sensitivity
  - If Extreme → *"Cretinism"* – Severely stunted physical growth & mental development.

Hyperthyroidism:

- **"Excessive Secretion of Thyroid Hormone"**
- **Causes:**
  - ****Auto-Immune:** ***'Grave's Disease'*** – where **TsAb's (Thyroid-Stimulating Antibodies)** mimic TSH → ↑T3/T4 Production
  - *******Toxic Multinodular Goitre***
  - ****Post-URTI Subacute ("De-Quervain's") Thyroiditis*** **(→ Transient ↑→↓→ Eu-Thyroid)**
- **Effects of Hyperthyroidism:**
  - ↑Metabolic Rate
  - ↑Body Temperature (→ Heat Intolerance. Ie can't stand hot environments)
  - ↑Sympathetic Sensitivity
  - **If Grave's Disease:** Exophthalmos (Eye Protrusion) & Goitre (Thyroid Enlargement)

Goitre:

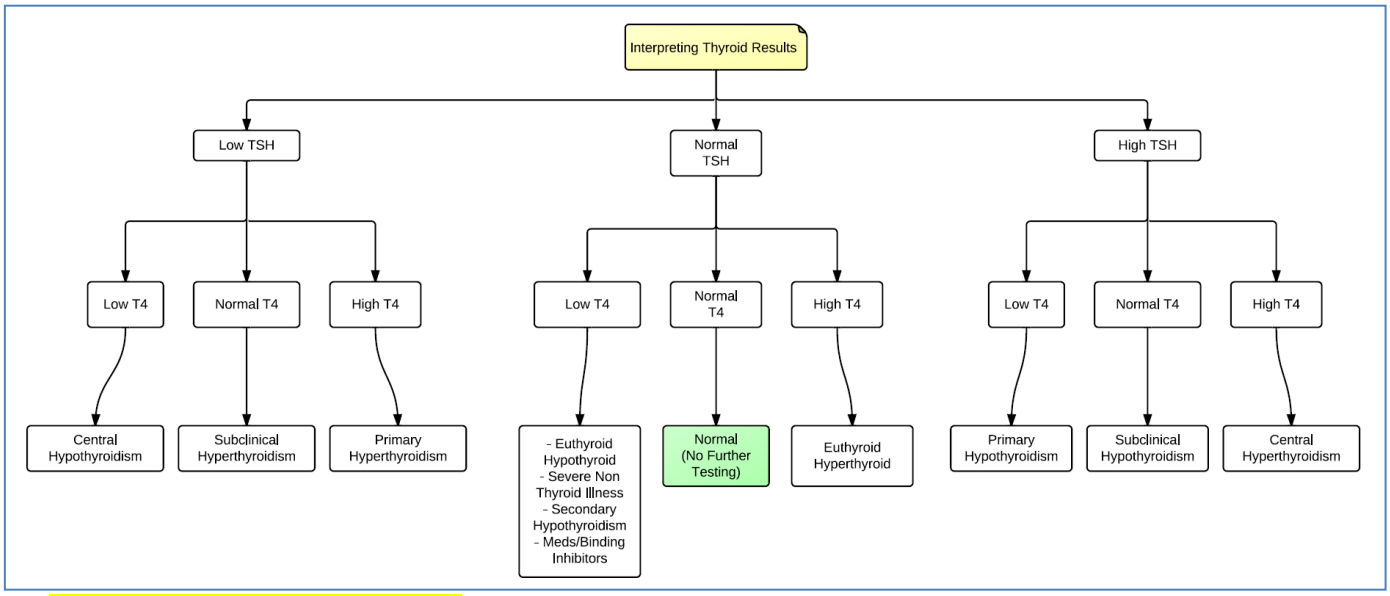
- **"Enlarged Thyroid Gland"**
- **Occurs in the Following Conditions:**
  - **Normal Physiological Conditions (Adolescence, Pregnancy, Lactation)**:
    - – ie. Conditions requiring ↑Metabolism.
  - **Hyperthyroidism:**
    - Why? – Increased stimulation (eg. From TsAb's) → Hypertrophy
  - **Hypothyroidism:**
    - Why? – Increased stimulation (eg. From Pituitary due to Iodine deficiency) → Hypertrophy
  - **Dietary:**
    - Eg. Iodine Deficiency
  - **Tumours:**
    - Those secreting Thyroid Hormones regardless of TSH Levels.

Where is the Problem?

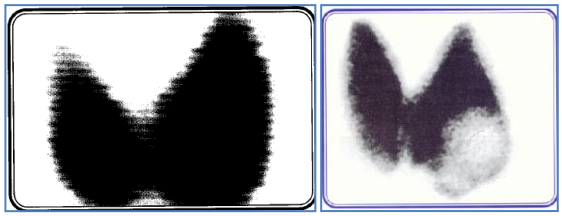
- **Primary ↓/↑-Thyroidism – (*Glandular Level*)**
  - **Eg. Primary Hyperthyroidism = Graves Disease**
  - **Eg. Primary Hypothyroidism = Hashimoto's Disease**
- **Secondary ↓/↑-Thyroidism:**
  - **Problem with the Pituitary Gland or Hypothalamus (Ie. ↓TRH / TSH)**

Diagnosing Thyroid Problems:

- **TFTs Interpretation:**



- **Thyroid Autoantibody Assays:**
  - **Grave's** – Presence of **TsAb's (Thyroid-Stimulating Antibodies)**
  - **Hashimoto's** – Presence of **Anti-Thyroid Peroxidase Antibodies (Anti-TPO-Abs)**
    - or **Anti-Thyroglobulin Antibodies**
- **TRH Stimulation Test (Dynamic Testing)**
  - Investigates Pituitary-TSH Deficiency
- **Imaging:**
  - **Ultrasound** – for sizing.
  - **RadioIsotope Methods (Nuclear Medicine)** – (Radioactive Iodide) to measure activity of the gland.
    - Can distinguish Inactive (Cold) & Overactive (Hot) Nodules.



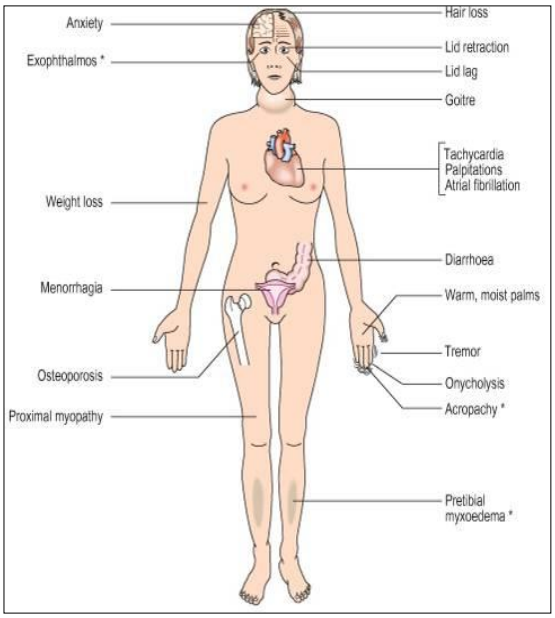
- **Histopathology:**
  - Ie. Biopsy.

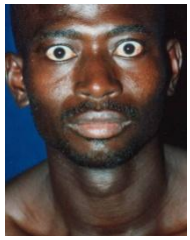
Treatment of Thyroid Problems:

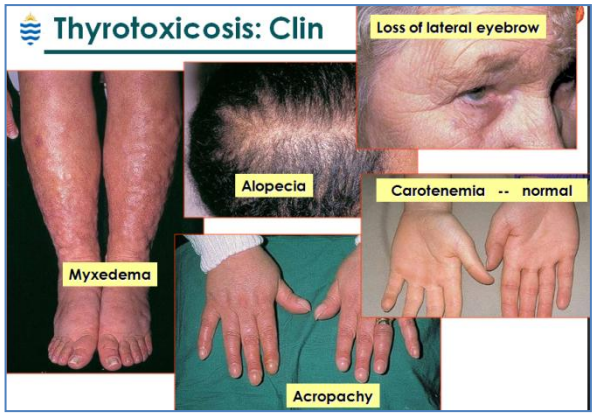
- **Hypothyroidism:**
  - **Thyroid Hormone Replacement:**
    - ****Thyroxine*** /levothyroxine (T4)
- **Hyperthyroidism:**
  - **Surgery (Thyroidectomy):**
    - ***Total Vs Partial***
  - **Radioactive Iodine - Destroy Thyroid Follicular Tissue:**
    - ***Radioactive Iodine (I^{125})***
    - NB: Can kill too much thyroid tissue→ Hypothyroidism.
  - **Anti-Thyroid Agents:**
    - ****Carbimazole***

Hyperthyroidism Clinical Features:

- **General:**
  - Fatigue
  - *Heat* Intolerance
- **CVS:**
  - Tachycardia
  - Palpitations
    - AF (Suspect Thyrotoxicosis if New-Onset AF in elderly)
  - Cardiomegaly
  - Congestive Heart Failure (In Elderly)
- **GI:**
  - Weight Loss *Despite INCREASED Appetite*
  - Thirst
  - Hypermotility (↑Frequency of Bowel Movements, Diarrhoea)
- **Neuro:**
  - Overactive Sympathetic NS
    - Fine Tremor
    - Irritability
    - Anxiety
    - Insomnia
  - Proximal Myopathy (Muscle Weakness) & Wasting.
- **Eye:**
  - Exophthalmos (Wide, Staring Gaze)
  - Lid Lag
  - (NB: Proptosis only in Graves)
- **Dermatology:**
  - Acropachy (Digital Clubbing & Swelling; Fingers & Toes)
  - **Hair:** Fine, Allopecia
  - **Skin:** Soft, Warm, Flushed, Sweaty.
  - Vitiligo (Pigmentation)
  - Soft Nails with Onycholysis (Plummer's Nails)
- **MSK:**
  - ↑Bone Resorption → Osteoporosis
- **Haem:**
  - Lymphadenopathy (esp. Graves Disease)
- **Others:**
  - Menorrhagia
  - Pretibial Myxoedema





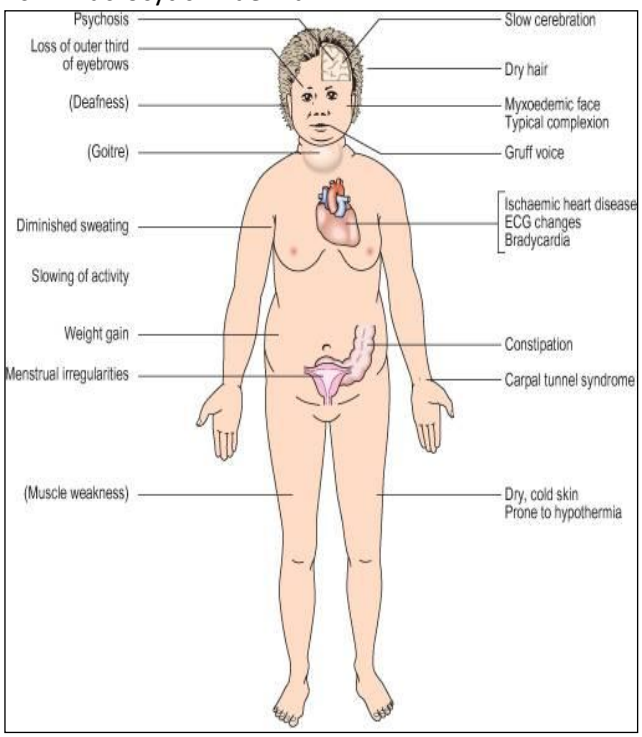


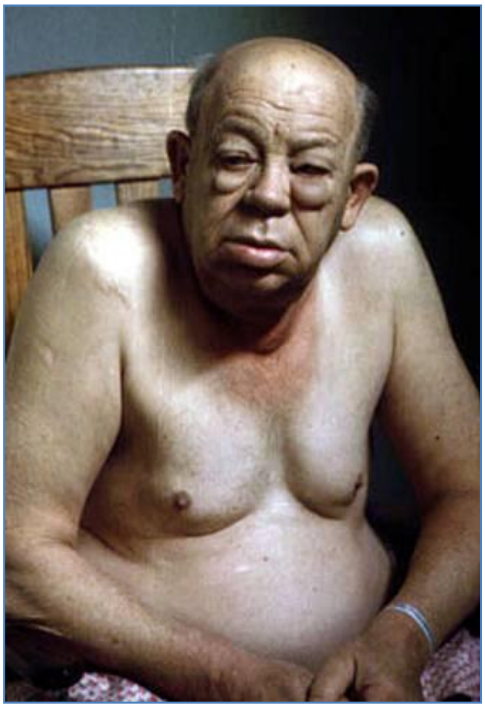
Complications:

- ***Thyrotoxic Storm:***
  - **Aetiology:**
    - Precipitated by Infection/Trauma/Surgery/etc. In a Hyperthyroid Patient.
  - **Pathogenesis:**
    - Pre-existing Hyperthyroidism → ↑Sympathetic Sensitivity
      - + Precipitant → ↑Catecholamine Levels → Sympathetic Symptoms.
  - **→SEVERE Clinical Features – 50% MORTALITY:**
    - Extreme Fever
    - Tachycardia/Arrhythmias
    - Vascular Collapse (Hypotension)
    - Congestive Heart Failure/Pulmonary Oedema
    - Vomiting/Diarrhoea
    - Confusion/Delerium/Coma
  - **Differentials:**
    - Sepsis
    - Phaeochromocytoma
    - Malignant Hyperthermia
  - **Lab Findings:**
    - ↑↑↑T3/T4
    - ↓↓↓TSH
    - (Leukocytosis, Hypercalcaemia, ↑LFTs)
  - **Treatment:**
    - Fluid & Electrolyte Maintenance
    - Vasopressors → Regain Blood Pressure
    - Cooling Blanket/Paracetamol → Control Fever
    - Dexamethasone → ↓Conversion of T4 to T3
    - **& Treat Precipitating Factor**

Clinical Features:

- **General:**
  - Fatigue
  - *Cold* Intolerance
  - Apathetic Face
  - Droopy Eyes
  - Hoarseness
  - Menstrual Irregularities
  - Muscle Weakness
- **CVS:**
  - Bradycardia
  - Pericardial Effusion
  - ↓Cardiac Output
- **GI:**
  - Weight Gain *Despite* Poor Appetite
  - Constipation
- **Neuro:**
  - Paresthesia
  - Slow Speech
  - Mental Sluggishness
- **Dermatology:**
  - **Skin:**
    - Pale, Cool, Dry (Due to ↓Blood Flow)
    - NON-Pitting Oedema (Due to Accumulation of Hyaluronic Acid & Glycosaminoglycans)
      - Face & Periorbital Oedema
  - **Hair:** Dry, Coarse, Loss of Lateral 1/3 Eyebrow
- **MSK:**
  - Muscle Cramps
  - "Hung Reflexes" – Delayed Relaxation in deep tendon reflexes.
- **Haem:**
  - Macrocytic Anaemia





Dx:

- TSH Levels
- T4/T3 Levels
- **Hashimotos:**
  - + Anti-Thyroid Peroxidase Antibodies (Anti-TPO-Abs)
  - + Anti-Thyroglobulin Antibodies

Complications:

- ***"Cretinism":***
  - **Terminology:**
    - = "Hypothyroidism that develops in Infancy or Early Childhood → Severely stunted physical growth & mental development"
  - **Aetiology:**
    - Maternal Hypothyroidism (Typically Iodine Deficiency)
  - **Clinical Features:**
    - Short Stature
    - Severe Mental Retardation
    - Coarse Facial Features
    - Protruding Tongue
    - Umbilical Hernia
    - (NB: Severity of Disease depends on *When* Maternal Hypothyroidism occurred during Pregnancy)
- **Generalised Atherosclerosis:**
  - Due to ↑↑Cholesterol, LDL & Triglycerides
- ***Myxoedema Coma!:**
  - – Most Severe Complication
  - **Aetiology:**
    - *Longstanding Undiagnosed Hypothyroidism + Precipitant (Infection/Surgery/MI/CHF)*
  - **Clinical Features:**
    - Hypothermia
    - Hypoventilation
    - Bradycardia
    - Hypertension
    - Hypoglycaemia
    - Stupor
  - **Lab Findings:**
    - ↓↓↓T3/T4
    - ↑↑↑TSH
    - Hypoglycaemia
    - Check ACTH & Cortisol for ?Concomitant Adrenal Insufficiency?.
  - **Treatment:**
    - Emergency management (ABCs)
    - Keep Pt Warm
    - Loading Dose Thyroxine
    - Treat Precipitant

Treatment:

- **Thyroid Hormone Replacement:**
  - **L-Thyroxine** (Thyroid Hormone Replacement)
  - NB: Thyroxine is the preferred agent as it is the least biologically active – (Longer Half-life), and can be Deiodinated by the body to T3 (Thyronine) when needed.

Non-Toxic Goitres – (Diffuse & Multinodular Goitres):

Terminology:

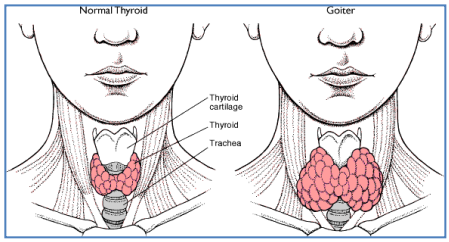
- **Goitre =** "Enlargement of the Thyroid"
- **Non-Toxic Goitre** = "Enlargement of the Thyroid Gland in a *EUTHYROID* Individual that is *NOT DUE TO* Inflammatory, or Neoplastic Changes"

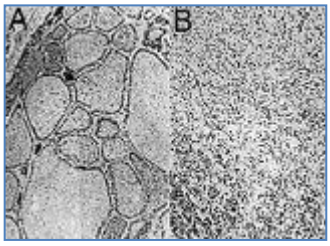
Epidemiology:

- Adolescents
- Pregnancy
- Lactation
- 3rd World Countries

(*Simple*) Diffuse Goitre (Early):

- **Aetiologies:**
  - **Normal Physiological Conditions** (Adolescence, Pregnancy, Lactation):
  - **Iodine Deficiency** – Most Common:
- **Pathogenesis:**
  - **NB: Hyperplasia; *NOT* Neoplastic –** (Due to ↑TSH Stimulation)
- **Morphology:**
  - Goitre is Mild, Diffuse & Symmetrical
- **Clinical Features:**
  - **Most Pts are Euthyroid**
- **Ix:**
  - ↑↑TSH
  - Normal T3/T4 (Unless Severe - ↓T3/T4)
- **Complications:**
  - Mechanical (Dysphagia, Airway Obstruction)
  - Endocrine (Toxic Nodule → Hyperthyroidism)

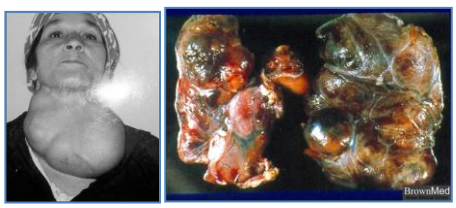




(A = Normal; B = Diffuse Goitre)

Non-Toxic Multinodular Goitre (Late):

- **Aetiology:**
  - Prolonged Hyperplasia of a Diffuse Goitre due to Iodine Deficiency
- **Pathogenesis:**
  - **1. Simple *Diffuse Goitre* due to Iodine Deficiency**
  - **2. Prolonged Hyperplasia of a Diffuse Goitre →→*Multinodular Goitre*.**
- **Morphology:**
  - Asymmetrical, Multinodular, Multilobulated, Goitres
  - Can be MASSIVE
  - Nodules are ***Un*-Encapsulated**, & Contain Variable amounts of Colloid (Brown, Gelatinous)
- **Clinical Features:**
  - Massive Goitre
  - **Most Pts are Euthyroid**
- **Complications:**
  - Toxic Adenoma/Toxic Nodule.



Thyroid Neoplasms – (Adenomas & Carcinomas):

Terminology:

- **Hot Nodules** - Those secreting Thyroid Hormones regardless of TSH Levels.
- **Cold Nodules** – Those that are Hypofunctioning regardless of TSH Levels

Clinical Features:

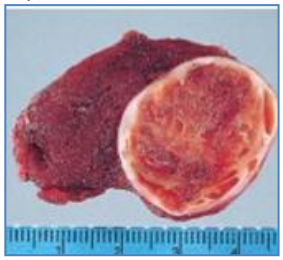
- **Mostly Asymptomatic**
- Palpable (sometimes visible) lump in throat
- **Red Flags:**
  - Rapid Growth
  - Firm/Hard
  - Immobile
  - Voice Hoarseness
  - Dyspnoea
  - Dysphagia
  - Lymphadenopathy
- **Green Flags:**
  - Mobile, Painful & Inflammation – Non Neoplastic.

Universal Investigations of Thyroid Neoplasms (Despite Patterns):

- **1. Imaging**
- **2. TFTs**
- **3. FNA + Biopsy**
- **4. Surgical Resection & Histology.**

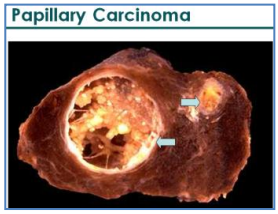
Thyroid Adenoma: "*Follicular Adenoma*" (Benign Neoplasms) – 90%:

- **Cold or Hot Adenomas**
- **Morphology:**
  - Solitary, Spherical Mass
  - Well-Defined, *Intact* Fibrous Capsule
  - ≈3cm Diameter
  - Colour:
    - **Cold Adenoma** = Grey-White colour (Due to ↓Colloid)
    - **Hot (Toxic) Adenoma** = Red-Brown colour (Due to ↑Colloid Content)
  - Areas of Haemorrhage, Fibrosis & Calcification (Similar to MNG)
- **Clinical Features:**
  - Unilateral Painless Mass
  - **Cold Adenomas** = Euthyroid
  - **Hot (Toxic) Adenomas** = Hyperthyroid
- **Investigations:**
  - As above
- **Complications:**
  - Excellent Prognosis (post surgery) – No Recurrence or Metastasis.

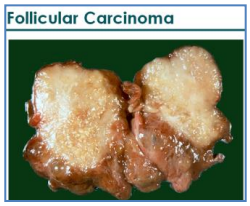


Thyroid Carcinomas (Malignant Neoplasms) – 10%:

- **4x Types – (NB: ALL begin as Follicular Cells *Except* Medullary Carcinomas, which are Parafolicular Cells):**
- **Papillary Carcinoma of the Thyroid – MOST COMMON:**
    - **Clinical Features:**
        - Asymptomatic, Mobile Thyroid Nodule (Indistinguishable from Benign Nodule)
        - NB: Presenting Symptom is often Cervical Lymphadenopathy.
        - Symptoms of Severe Disease: Dysphagia, Hoarseness, Cough.
    - **Investigations:**
        - As above
    - **Treatment:**
        - Surgical Excision
    - **Prognosis:**
        - Malignant, but *Clinically Benign* – Ie. High survival rate (98% @ 10yrs).
        - Rarely extends outside the thyroid capsule or to other structures.

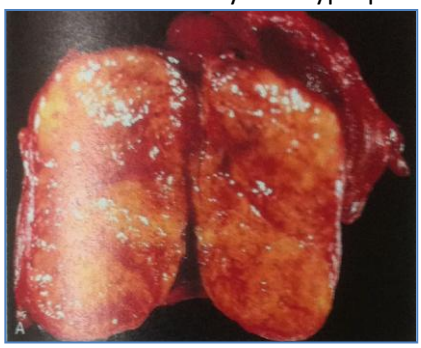


- **Follicular Carcinoma of the Thyroid:**
    - **Morphology:**
        - Single Nodules
        - May be Well-Demarcated (Similar to Follicular Adenoma) or Infiltrative
        - Grey-Tan Colour
        - Central Fibrosis & Calcification
    - **Clinical Features:**
        - Slow-Growing, Painless Nodules
        - Follicular Carcinoma prefers Haematogenous Metastasis rather than Lymphatic
            - :. No Lymphadenopathy
            - Aggressive - Spreads Early to Bone (May present as a pathological fracture)
    - **Treatment:**
        - Total Thyroidectomy
        - + Radioactive Iodine Ablation for ?Metastases.
        - + Supportive Thyroid Hormone Replacement



- **Anaplastic Carcinoma of the Thyroid:**
    - **Pathogenesis:**
        - Typically arise due to **De-Differentiation** of a ***Papillary*** or ***Follicular Carcinoma***
    - **Morphology:**
        - Invasion out of the Thyroid Capsule & Into Adjacent Structures (Eg. Trachea & Jugular Vein)
    - **Clinical Features:**
        - Typically Elderly
        - Rapid-Growing Nodule.
        - Compressive Symptoms: Dysphagia, Dyspnoea, Hoarseness, Cough.
    - **Treatment/Prognosis:**
        - Highly Aggressive – Local Invasion & Metastasis @ Presentation.
        - **No Treatments**
        - **100% Mortality @ 1yr.**

- **Medullary Carcinoma of the Thyroid:**
  - **Aetiology:**
    - **70% Sporadic Proto-oncogene Mutation.**
    - **30% Occur in *Multiple Endocrine Neoplasia Syndrome Type 2* (MEN-2a & 2b)**
  - **Morphology:**
    - Solitary if Sporadic; Multiple/Bilateral if MEN-2a/b.
    - Firm, Pale Grey-Tan, Areas of Haemorrhage & Necrosis
    - Invasion outside the Thyroid Capsule
  - **Clinical Features:**
    - **Sporadic:**
      - Thyroid Nodule + Dysphagia or Hoarseness
      - NB: NO Hypocalcaemia, despite ↑Calcitonin.
    - **MEN-2 Also Involves:**
      - (Thyroid Gland – Medullary Carcinoma of the Thyroid)
      - Adrenal Medulla – Phaeochromocytoma
      - Parathyroid Gland – Parathyroid Hyperplasia



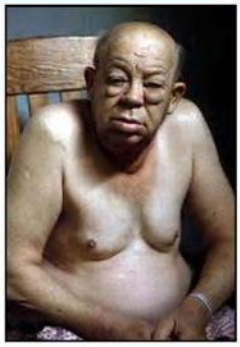
Summary:

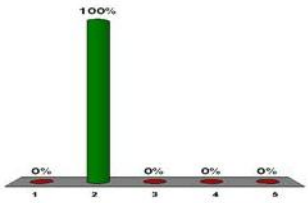
Carcinoma of Thyroid

Type	(%)	age	spread	Prognosis
Papillary	60-70	young adults 20-40 (<45y)	Lymphatic, to local nodes	Excellent
Follicular	20-25	Young-middle 40-50 (>45)	Blood stream, especially to bone	Good with radio-iodine therapy.
Anaplastic	10-15	Elderly	Aggressive local extension	Very poor
Medullary (C-cells)	5-10	Usually elderly, but familial cases occur	Local, lymphatic, blood stream	Variable. More aggressive in familial cases

68y M, lethargy, puffy eyes - ? diagnosis

A. Hyperthyroidism
B. Hypothyroidism
C. Papillary carcinoma
D. Multinodular goitre
E. Follicular carcinoma

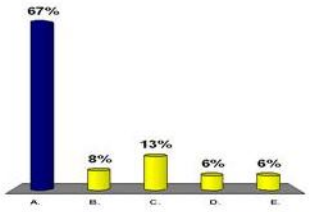




Thyroid Function ? diagnosis

TSH	Decreased,
Free T3	High
Free T4	High/Norm
Anti Thy. Ab.	High/Norm

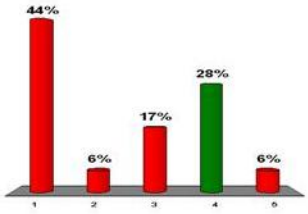
A. Primary hyperthyroidism
B. Primary Hypothyroidism
C. Central Hyperthyroidism
D. Central Hypothyroidism
E. Primary T3 toxicosis



Thyroid Function ? diagnosis

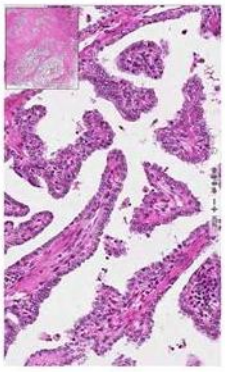
TSH	Decreased,
Free T3	Decreased
Free T4	Decreased
Anti Thy. Ab.	Norm

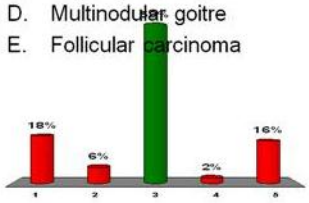
A. Primary hyperthyroidism
B. Primary Hypothyroidism
C. Central Hyperthyroidism
D. Central Hypothyroidism
E. T3 toxicosis



45y female progressive hoarseness of voice, SOB, stridor 3 weeks. 4 kg weight loss. Small tender mass right thyroid lobe immobile extending into posterior trachea. Image is taken from biopsy of the mass. ? diagnosis

A. Graves Disease
B. Hashimoto's disease
C. Papillary carcinoma
D. Multinodular goitre
E. Follicular carcinoma

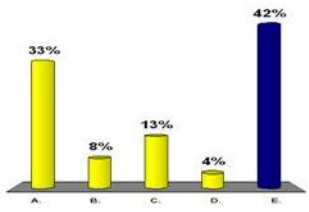




Thyroid Function ? diagnosis

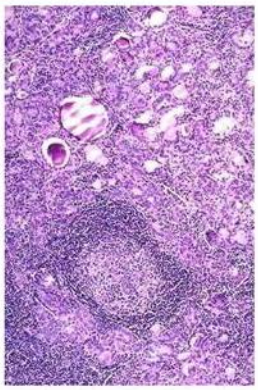
TSH	Decreased
Free T3	High
Free T4	Normal
Anti Thy. Ab.	High

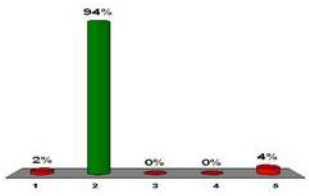
A. Primary hyperthyroidism
B. Primary Hypothyroidism
C. Central Hyperthyroidism
D. Central Hypothyroidism
E. Primary T3 toxicosis



67y F, weight gain, lathargy - ? diagnosis

A. Graves Disease
B. Hashimoto's disease
C. DeQuervain's Disease
D. Multinodular goitre
E. Follicular carcinoma





28y F, Hypertension - ? diagnosis

A. Primary hyperthyroidism
B. Primary Hypothyroidism
C. Central Hyperthyroidism
D. Central Hypothyroidism
E. Sub clinical hyperthyroidism

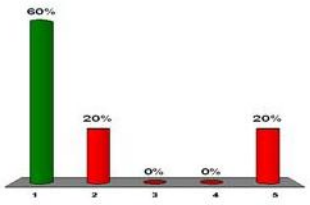
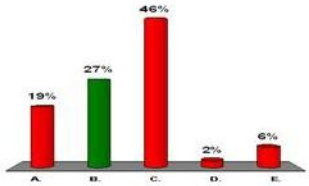


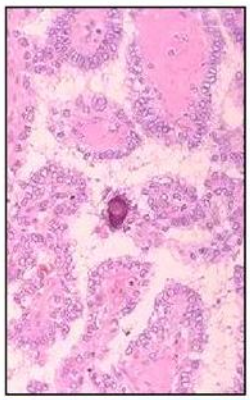
Image shows ca thyroid, compressing and infiltrating the trachea. Most correct statement?

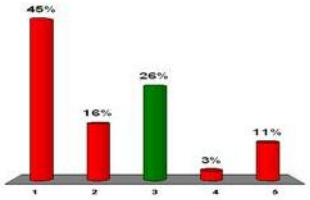
A. Papillary carcinoma
B. Anaplastic carcinoma
C. Follicular carcinoma
D. Elderly patient…
E. Metastasis in bone.



47y F, weight loss, lethargy Thyroid ? diagnosis

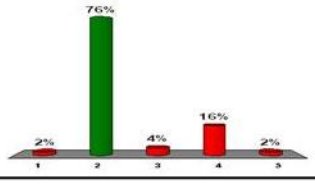
A. Graves Disease
B. Hashimoto's disease
C. Papillary carcinoma
D. Multinodular goitre
E. Follicular carcinoma





29y woman, nervousness, muscle weakness 6m, heat intolerance, wt loss, Physical examination reveals warm and moist skin and bulging eyes, Laboratory studies will likely reveal which of the following endocrine abnormalities in this patient?

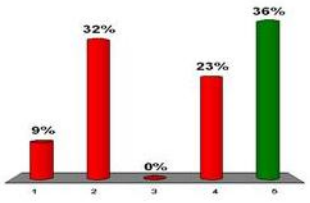
1. Antithyroid DNA antibodies
2. Anti-TSH receptor antibodies
3. Decreased uptake of radioactive iodine in the thyroid
4. Increased serum TSH
5. Low serum T3



Thyroid Function ? diagnosis

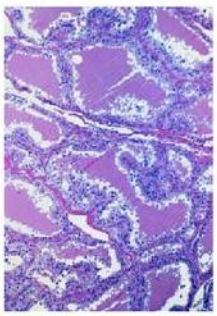
TSH	Decreased
Free T3	Normal
Free T4	Normal
Anti Thy. Ab.	Positive

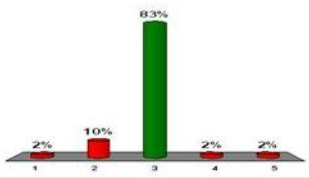
A. Primary Hypothyroidism
B. Euthyroid state
C. Central Hypothyroidism
D. Subclinical hypothyroidism
E. Subclinical Hyperthyroidism



A thyroid biopsy obtained from her is shown. Which of the following best describes the pathologic findings?

1. Atrophy and fibrosis
2. Dense lymphoid infiltrate with germinal centers
3. Follicular hyperplasia & scalloping of colloid
4. Necrotizing parenchymal granulomas
5. Papillary hyperplasia with psammoma bodies

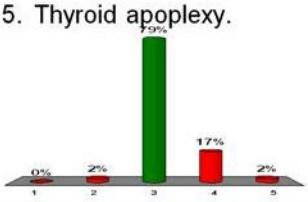




Read: Graves disease

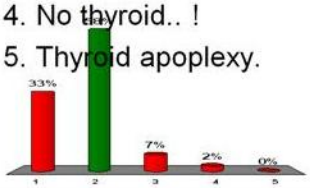
Oprah - What is her Thyroid function status?

1. Euthyroid.
2. Hyperthyroid
3. Hypothyroid
4. No thyroid.
5. Thyroid apoplexy.



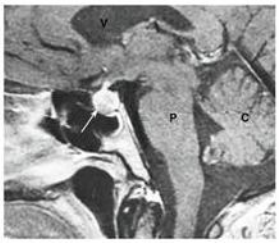
68y Man, What is his Thyroid function status?

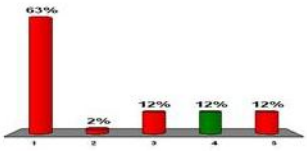
1. Euthyroid.
2. Hypothyroid
3. Hyperthyroid
4. No thyroid.. !
5. Thyroid apoplexy.



57y 6m h/o severe headaches & visual problems. Past h/o bilateral adrenalectomy 15y ago. CT scan shows pituitary macroadenoma (shown). What is the most likely diagnosis?

1. Corticotrope adenoma
2. Gonadotrope adenoma
3. Lactotrope adenoma
4. Null cell adenoma
5. Somatotrope adenoma

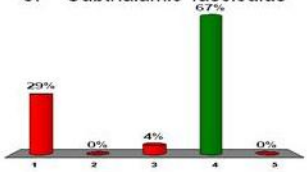




Read Nelson Syndrome *

25y man 3m polyuria & thirst. The patient suffered trauma to the base of the skull in a motorcycle accident 4 months ago. A 24-hour urine collection shows polyuria. No hematuria, glucosuria, or proteinuria. The pathogenesis of polyuria in this patient is most likely caused by a lesion in which of the following areas of the brain?

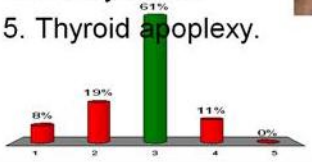
1. Adenohypophysis
2. Brain stem
3. Mammillothalamic tract
4. Neurohypophysis
5. Subthalamic fasciculus



Read: Diabetes insipidus

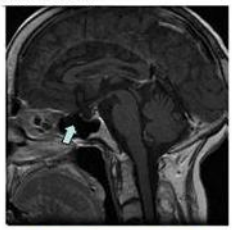
Oprah, What is her Thyroid function status?

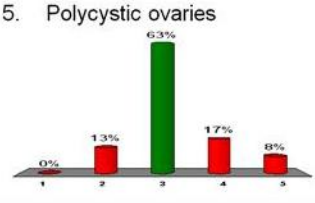
1. Euthyroid.
2. Hypothyroid
3. Hyperthyroid
4. No thyroid.. !
5. Thyroid apoplexy.



A 21y woman experiences abruptio placentae with severe bleeding during the delivery of a term fetus. Five months later, she presents with profound lethargy, pallor, muscle weakness, failure of lactation, and amenorrhea. Which of the following pathologic findings best explains cause of her symptoms & signs?

1. Atrophy of the endocrine pancreas
2. Autoimmune destruction of the adrenal cortex
3. Infarction of the pituitary
4. Pituitary prolactinoma
5. Polycystic ovaries

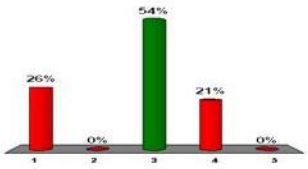




Read: Sheehan's sy

Physical examination of a neonate shows peculiar genitalia (shown). Cytogenetic studies reveal a 46,XX karyotype. Laboratory studies will most likely reveal a deficiency of which of the following?

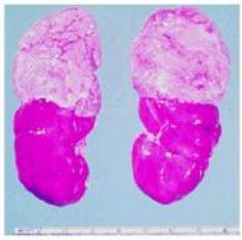
1. Androstenedione
2. Corticotropin
3. 21-Hydroxylase
4. Progesterone
5. Prolactin

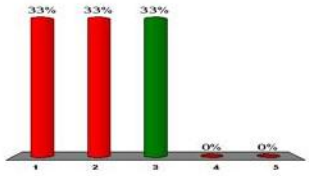


Read: **Adrenogenital syndrome**

A 7-week-old infant develops severe dehydration and hypotension and expires. The kidneys and adrenal glands at autopsy are shown. Hypovolemic shock in this infant was most likely caused by inadequate synthesis of which of the following hormones?

1. Androstenedione
2. Corticotropin
3. 21-Hydroxylase
4. Progesterone
5. Prolactin

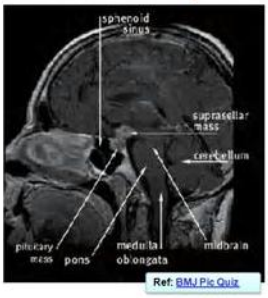


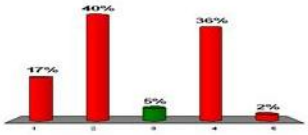


Read: **Adrenogenital syndrome**

A 43y woman, progressive malaise 3m, intermittent headache 2wk, polyuria & polydipsia 1wk. Low cortisol levels, Normal synthacten response. Past H. mastectomy & chemo for breast cancer 8y. Image shows MRI. **? Polyuria**

1. Sheehan's syndrome.
2. Posterior pituitary adenoma.
3. Cushing's disease.
4. Diabetes insipidus.
5. Secondary diabetes.





Read: **head injury & D. insipidus**

Continue Reading For Bonus Supplementary Study Materials…

Endocrinology

Tara Justice and **Ilia Makedonov,** chapter editors
Hart Stadnick and **Kevin Yau,** associate editors
Alex Cressman, EBM editor
Dr. Alice Cheng and **Dr. Adam Millar,** staff editors

Acronyms

[ ]	concentration
Ab	antibody
ACR	albumin-creatinine ratio
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AG	anion gap
BG	blood glucose
BMD	bone mineral density
BMI	body mass index
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CHO	carbohydrates
CK	creatine kinase
CMV	cytomegalovirus
CrCl	creatinine clearance
CRH	corticotropin releasing hormone
CVD	cardiovascular disease
DDAVP	desmopressin (1-deamino-8-D-arginine vasopressin)
DHEA	dehydroepiandrosterone
DI	diabetes insipidus
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DXM	dexamethasone
ECF	extracellular fluid
EtOH	ethanol
FBG	fasting blood glucose
FFA	free fatty acids
FNA	fine needle aspiration
FSH	follicle stimulating hormone
GFR	glomerular filtration rate
GH	growth hormone
GHIH	growth hormone inhibiting hormone
GnRH	gonadotropin releasing hormone
Hb	hemoglobin
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HHS	hyperosmolar hyperglycemic state
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HPA	hypothalamic pituitary adrenal
hs-CRP	highly sensitive C-reactive protein
ICF	intracellular fluid
IDL	intermediate density lipoprotein
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LCAT	lecithin-cholesterol acyltransferase
LDL	low density lipoprotein
LH	luteinizing hormone
MEN	multiple endocrine neoplasia
MMI	methimazole
MTC	medullary thyroid cancer
NS	normal saline
OGTT	oral glucose tolerance test
PAD	peripheral arterial disease
PCOS	polycystic ovarian syndrome
POMC	pro-opiomelanocorticotropin
PRL	prolactin
PTH	parathyroid hormone
PTU	propylthiouracil
RAAS	renin-angiotensin-aldosterone system
RH	releasing hormone
T2DM	type 2 diabetes mellitus
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroid binding globulin
TC	total cholesterol
TG	triglycerides
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone
TSI	thyroid stimulating immunoglobulin
VLDL	very low density lipoprotein
WC	waist circumference

Basic Anatomy Review

Major Endocrine Organs

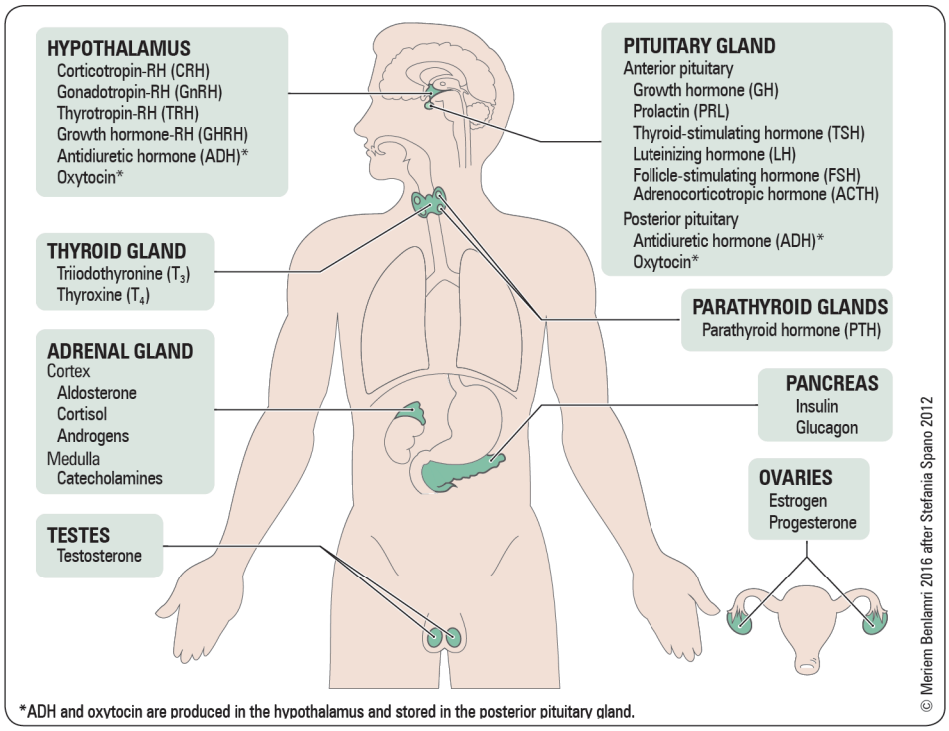


Figure 1. Endocrine system

GENERAL FUNCTION OF ORGANS

The Hypothalamic-Pituitary Axis
Information about cortical inputs, automatic function, environmental cues (light, temperature) and peripheral hormonal feedback is synthesized at the coordinating centre of the endocrine system, the hypothalamus. The hypothalamus then sends signals to the pituitary to release hormones that affect the thyroid, adrenals, gonads, growth, milk production, and water balance

Anatomy ↔ Function
Hypothalamic hormones: small peptides, non-binding protein → rapid degradation
High [ ] in pituitary-portal blood system
Low [ ] in peripheral circulation
Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons

Thyroid
Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system

Adrenal
Each gland, 6-8 g, has 1) a cortex with 3 layers that act like independent organs (zona glomerulosa → aldosterone, fasciculata → cortisol, reticularis → androgen and estrogen precursors), and 2) a medulla that acts like a sympathetic ganglion to store/synthesize adrenaline and noradrenaline

Gonads
Bifunctional: sex steroid synthesis and gamete production
Sex steroids control sexuality and affect metabolic and brain functions

Parathyroid
Synthesize and secrete PTH, a principle regulator of ECF Ca^{2+}, regulated by $[Ca^{2+}]$, $[Mg^{2+}]$, $1,25(OH)_2D$ (active metabolite of vit D), and phosphate

Pancreas
Endocrine islet β-cells produce insulin: oppose glucose production (glycogenolysis, gluconeogenesis), increase glucose uptake into muscle and fat. Glucagon, epinephrine, cortisol, and GH are the counterregulatory hormones

Dyslipidemias

Definition

- metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol

Overview of Lipid Transport

- lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apoproteins, and phospholipids
- lipoproteins transport lipids within the body
- apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle

Table 1. Lipoproteins

Lipoprotein	Apolipoproteins	Function
Exogenous Pathway		
Chylomicron	B-48, C, E, A-I, A-II, A-IV	• Transports dietary TG from gut to adipose tissue and muscle
Endogenous Pathway		
VLDL	B-100, C, E	• Transports hepatic synthesized TG from liver to adipose tissue and muscle
IDL	B-100, E	• Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters
LDL	B-100	• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals)
HDL	A-I, A-II, C, E	• Transports cholesterol from peripheral tissues to liver • Acts as a reservoir for apolipoproteins

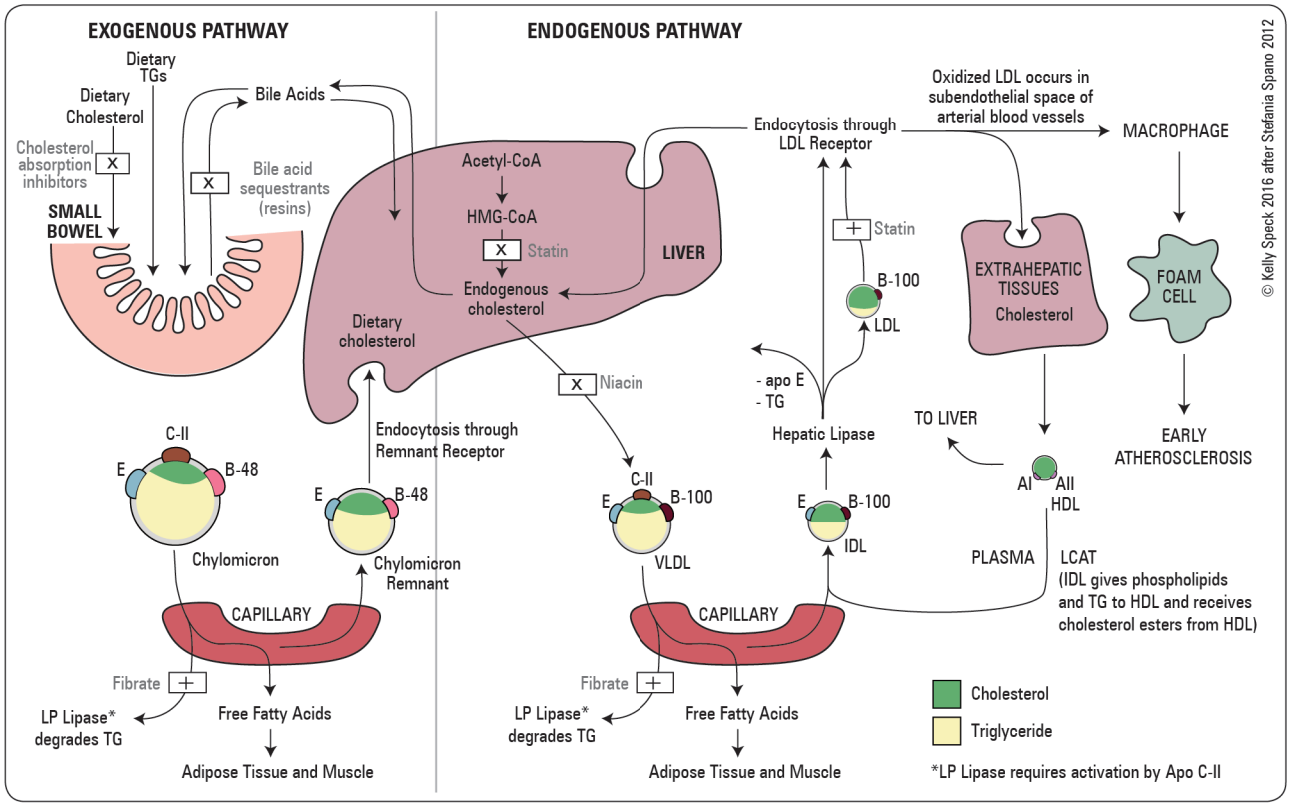


Figure 2. Exogenous and endogenous biosynthetic lipid pathways

Hypertriglyceridemia (Elevated Triglycerides)

PRIMARY HYPERTRIGLYCERIDEMIA

Table 2. Primary Hypertriglyceridemias

Hypertriglyceridemia	Etiology/ Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Lipoprotein Lipase Deficiency	• Autosomal recessive deficiency of lipoprotein lipase or its cofactor	↑ TG ↑ Chylomicrons Moderate ↑ in VLDL	• Hepatosplenomegaly • Splenic infarct • Anemia, granulocytopenia, thrombocytopenia 2° to hypersplenism • Pancreatitis • Lipemia retinalis • Eruptive xanthomata	• Decrease dietary fat intake to <10% of total calories • Decrease dietary simple carbohydrates • Cook with medium chain fatty acids • Abstain from EtOH
Familial Hypertriglyceridemia	• Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL	↑ TG ↑ VLDL	• Possible premature CAD • Develop syndrome of obesity, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia in early adulthood	• Decrease dietary simple carbohydrates and fat intake • Abstain from EtOH • Fibrates or niacin

SECONDARY HYPERTRIGLYCERIDEMIA

Etiology

- endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing's syndrome, DM
- renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
- hepatic: chronic liver disease, hepatitis, glycogen storage disease
- drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
- other: pregnancy

Hypertriglyceridemia and Pancreatitis
Serum triglyceride levels >10 mmol/L increases the risk of developing pancreatitis (even some reports of TG >5 mmol/L)

Hypercholesterolemia

PRIMARY HYPERCHOLESTEROLEMIA

Table 3. Primary Hypercholesterolemias

Hypercholesterolemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Hypercholesterolemia	• 1/500 in U.S. population • Autosomal codominant with high penetrance • More prevalent in French Canadian population • Defect in the normal LDL receptor on cell membranes	↑ LDL ↑ TC	• Tendinous xanthomatosis (Achilles, patellar, and extensor tendons of hand) • Arcus cornealis • Xanthelasmata • Heterozygotes: premature CAD, 50% risk of MI in men by age 30 • Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (<20 yr) if untreated	• Heterozygotes: improvement of LDL with HMG-CoA reductase inhibitors, often in combination with ezetimibe or bile acid sequestrants • Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective
Polygenic Hypercholesterolemia	• Most common • Few mild inherited defects in cholesterol metabolism	↑ TC ↑ LDL	• Asymptomatic until vascular disease develops • No xanthomata	• HMG-CoA reductase inhibitors, ezetimibe, niacin, bile acid sequesterant

FH and Cardiovascular Risk Calculators
- Risk calculators such as Framingham and SCORE do not apply to patients with familial hypercholesterolemia
- Consider all adults with FH as "high risk"

SECONDARY HYPERCHOLESTEROLEMIA

Etiology

- endocrine: hypothyroidism
- renal: nephrotic syndrome
- immunologic: monoclonal gammopathy
- hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
- nutritional: diet, anorexia nervosa
- drugs: cyclosporin, anabolic steroids, carbamazepine

Combined Hyperlipidemia

Table 4. Primary Combined Hyperlipidemias

Hyperlipidemia	Etiology/Pathophysiology	Labs	Clinical Presentation	Treatment
Familial Combined Hyperlipidemia	• Over-population of VLDL and associated ↑ LDL 2º to excess hepatic synthesis of apolipoprotein B • Autosomal dominant	↑ TC + TG ↑ VLDL ↑ LDL	• Xanthelasma • CAD and other vascular disease	• Weight reduction • Decrease simple carbohydrates, fat, cholesterol, and EtOH in diet • HMG-CoA reductase inhibitors (statins) • Niacin, fibrates, ezetimibe
Dysbetalipoproteinemia	• Abnormal apolipoprotein E	↑ TC + TG ↑ VLDL ↑ IDL	• Tuberous, eruptive, palmar xanthomata • Impaired glucose tolerance • CAD and PAD	• Weight reduction • Decrease fat, cholesterol, and EtOH in diet • HMG-CoA reductase inhibitors • Niacin, fibrates

Familial Combined Hyperlipidemia
- A common disorder (1-2% of the population)
- Contributes to 1/3 to 1/2 of familial coronary artery disease

Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk

Screening

- screen men over age 40, women over age 50 or post-menopausal
- if following risk factors present, screen at any age
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90)
  - obesity (BMI >27 kg/m^2)
  - family history of premature CAD
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - evidence of atherosclerosis
  - inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
  - HIV infection on highly active anti-retroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m^2)
  - erectile dysfunction
- screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment

- metabolic syndrome
- apolipoprotein B (apo B)
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- C-reactive protein (hs-CRP) levels
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment

For clinical guidelines see *Can J Cardiol* 2012;29:151-167

- estimate 10 yr risk of CAD using Framingham model
- establish treatment targets according to level of risk

Table 5. Target Lipids by Risk Group

Level of Risk	Definition (10 Yr Risk of CAD)	Initiate Treatment if:	Primary Target LDL-C	Alternate
High	• Risk ≥20% , or • Clinical atherosclerosis • Abdominal aortic aneurysm • DM >15 yr duration and age older than 30 yr • DM with age older than 40 yr • Microvascular disease • High risk kidney disease • High risk HTN	Consider treatment in all patients	≤2 mmol/L or ≥50% ↓ in LDL	apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L
Moderate	Risk 10-19%	• LDL >3.5 mmol/L • For LDL-C<3.5 consider if: apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L	≤2 mmol/L or ≥50% ↓ in LDL	apo B <0.80 g/L or non-HDL-C ≤2.6 mmol/L
Low	Risk <10%	• LDL ≥5.0 mmol/L • Familial hypercholesterolemia	≥50% ↓ in LDL	

Treatment Effect
Each 1.0 mmol/L decrease in LDL corresponds to 20-25% relative risk reduction in cardiovascular disease

6% Rule
If the dose of a statin is doubled there is approximately a 6% increase in the LDL lowering efficacy

For Statin Follow-Up
- Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment then once after therapy initiated. Lipids (once stabilized) measured annually. Order both if patient complains of jaundice, RUQ pain, dark urine
- CK at baseline and if patient complains of myalgia
- D/C statin if CK >10x upper limit of normal or patient has persistent myalgia

Intensive Lipid Lowering in CAD: TNT
NEJM 2005;352:1425-1435
Study: Multicentre, randomized, double-blinded trial with median follow-up of 4.9 yr.
Patients: 10,001 patients with CAD and LDL-C <3.4 mmol/L.
Intervention: 80 mg vs. 10 mg atorvastatin daily.
Main Outcomes: Death from CAD, MI, cardiac arrest, or stroke.
Results: A primary event occurred in 8.7% of the patients receiving intensive therapy, compared to 10.9% of patients receiving standard therapy (RR 0.78, p<0.001). There was no difference in overall mortality. Incidence of persistent transaminase elevations was higher in the intensive therapy group (1.2% vs. 0.2%, p<0.001).
Conclusion: Intensive statin therapy is associated with lower rates of CAD events than standard therapy, but also a higher rate of transaminase elevation.

Simvastatin to Lower CAD Risk – The Heart Protection Study (HPS)
Lancet 2002;360:7-22
Study: Randomized, double-blind, placebo-controlled trial (median follow-up 5.0 yr).
Patients: 20,536 patients with coronary disease, other occlusive arterial disease or DM (aged 40-80 yr) who had a total cholesterol level of ≥3.5 mmol/L.
Intervention: Simvastatin 40 mg/d or placebo.
Main Outcomes: Mortality, fatal or non-fatal vascular events.
Results: The use of simvastatin significantly decreased total mortality (12.9 vs. 14.7, p=0.0003) and the first event rate of any cardiovascular event by 25% (p<0.0001).
Conclusion: Treatment with simvastatin improved survival and cardiovascular outcomes in high-risk CAD patients.

Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia

Treatment of Hypercholesterolemia	Treatment of Hypertriglyceridemia

• **Conservative:** 4-6 mo trial unless high risk group, in which case medical treatment should start immediately
  • Diet
  • Decrease fat: <30% calories
  • Decrease saturated fat: <10% calories
  • Decrease cholesterol: <200 mg/d
  • Increase fibre: >30 g/d
  • Decrease alcohol intake to ≤1-2 drinks/d
  • Smoking cessation
  • Aerobic exercise: ≥150 min/wk in bouts of ≥10 min
  • Weight loss: target BMI <25
• **Medical**
  • HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see *Common Medications*, E53)
	• **Conservative:** 4-6 mo trial
	  • Diet
	  • Decrease fat and simple carbohydrates
	  • Increase omega-3 polyunsaturated fatty acid
	  • Control blood sugars
	  • Decrease alcohol intake to ≤1-2 drinks/d
	  • Smoking cessation
	  • Aerobic exercise: ≥150 min/wk in bouts of ≥10 min
	  • Weight loss: target BMI <25
	• **Medical:** fibrates, niacin (see *Common Medications*, E53)
	  • Indications:
	  • Failed conservative measures
	  • TG >10 mmol/L (885 mg/dL) to prevent pancreatitis
	  • Combined hyperlipidemia

Disorders of Glucose Metabolism

Overview of Glucose Regulation

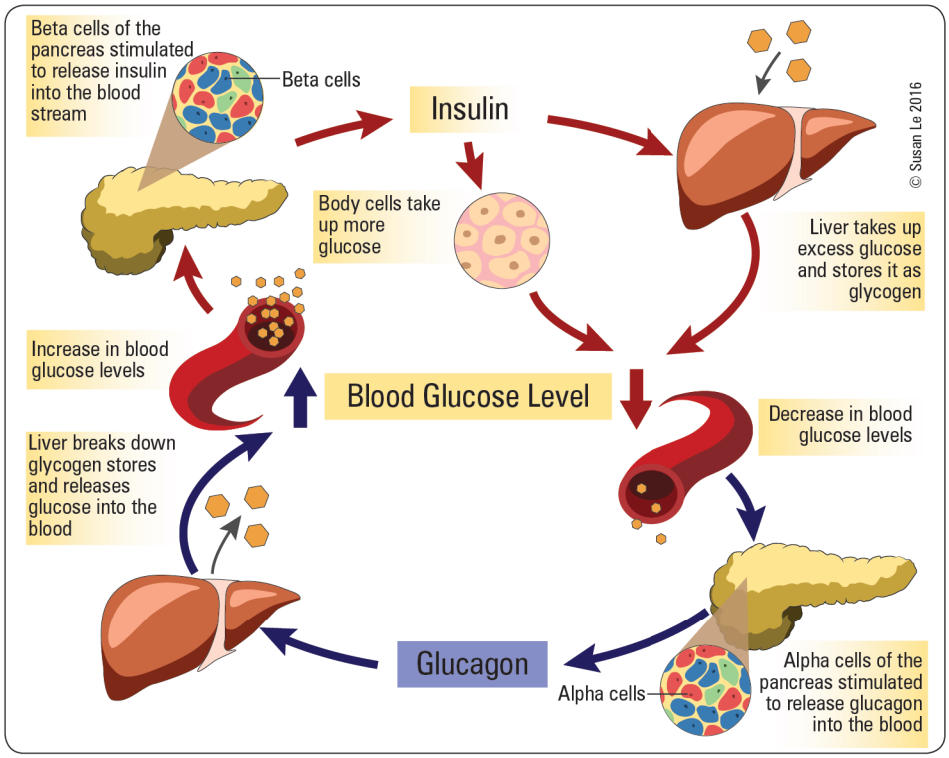


Figure 3. Blood glucose regulation

Glucose Related Emergencies
- DKA
- HHS
- Hypoglycemia

Three Year Efficacy of Complex Insulin Regimens in Type 2 DM: 4T Trial
NEJM 2009;361:1736-1747
Study: Randomized unblinded trial with 3 yr of follow-up.
Population: 708 patients with type 2 DM, not on insulin or thiazolidinedione therapy on maximal metformin and sulfonylurea therapy.
Intervention: Thrice-daily prandial insulin aspart, versus twice-daily biphasic insulin aspart, versus once-daily basal insulin detemir. Sulfonylurea therapy was replaced with a secondary insulin regime specific to each arm if there was persistent hyperglycemia.
Primary Outcome: Three yr hemoglobin HbA1c.
Results: Significant difference in rates of patient withdrawal from the study: 5.1% biphasic, 11.7% prandial, 8.5% basal regimens (p=0.04). There were no significant differences in median HbA1c levels between all three arms from yr 1-3. A smaller proportion of patients reached HbA1c <6.5% or <7.0% in the biphasic arm. The basal arm had least weight gain and least weight circumference increase, but highest rate of secondary insulin requirement. The basal arm had fewest severe hypoglycemic events per patient yr, while the biphasic had the most serious adverse effects.
Conclusion: Basal insulin regime provides the best glycemic control over a 3 yr study; with better HbA1c control, fewer hypoglycemic events, and less weight gain.

Pre-Diabetes (Impaired Glucose Tolerance/ Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications (IGT >IFG)
- lifestyle modifications decrease progression to DM by 58%

Diagnostic Criteria (CDA Guidelines)

- impaired fasting glucose (IFG): fasting blood glucose (FBG) 6.1-6.9 mmol/L
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L
- HbA1c: 6.0-6.4%

Diabetes Mellitus

Definition

- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

Diagnostic Criteria (CDA Guidelines)

- any one of the following is diagnostic
  - FPG ≥7.0 mmol/L (fasting = no caloric intake for at least 8 h) OR
  - 2h 75 g OGTT ≥11.1 mmol/L OR
  - random PG ≥11.1 mmol/L OR
  - HbA1c ≥6.5% (not for diagnosis of suspected Type 1 DM, children, adolescents, or pregnant women)
- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision,), a confirmatory test is not required
- in the absence of hyperglycemic symptoms, a repeat confirmatory test is required to make the diagnosis of diabetes

Etiology and Pathophysiology

Table 7. Etiologic Classification of Diabetes Mellitus

I. Type 1 DM (immune-mediated β cell destruction, usually leading to absolute insulin deficiency)
II. Type 2 DM (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2º to β cell dysfunction)
III. Other Specific Causes of DM a. Genetic defects of β cell function (e.g. MODY – Maturity-Onset Diabetes of the Young) or insulin action b. Diseases of the exocrine pancreas: • Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes") c. Endocrinopathies: • Acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism d. Drug-induced: • Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, clozapine e. Infections: • Congenital rubella, CMV, coxsackie f. Genetic syndromes associated with DM: • Down's syndrome, Klinefelter's syndrome, Turner's syndrome
IV. Gestational Diabetes Mellitus (see Obstetrics, OB27)

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

	Type 1	Type 2
Onset	• Usually <30 yr of age	• Usually >40 yr of age • Increasing incidence in pediatric population 2º to obesity
Epidemiology	• More common in Caucasians • Less common in Asians, Hispanics, Aboriginals, and Blacks • Accounts for 5-10% of all DM	• More common in Blacks, Hispanics, Aboriginals, and Asians • Accounts for >90% of all DM
Etiology	• Autoimmune	• Complex and multifactorial
Genetics	• Monozygotic twin concordance is 30-40% • Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of type 1 DM • Certain DQ alleles also confer a risk	• Greater heritability than type 1 DM • Monozygotic twin concordance is 70-90% • Polygenic • Non-HLA associated
Pathophysiology	• Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion • Autoimmune process is believed to be triggered by environmental factors (e.g. viruses, bovine milk protein, urea compounds) • Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction • 80% of β cell mass is destroyed before features of DM present	• Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormality), and excess hepatic glucose production

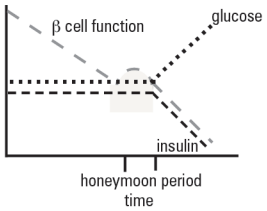
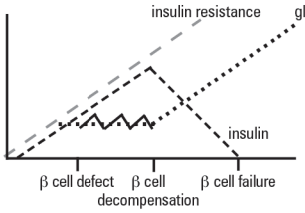
Effects of Intensive Treatment of Type 1 DM on the Development and Progression of Long-Term Complications: The DCCT Study
NEJM 1993;329:977-986.
Study: Multicentre RCT, with 6.5 yr of mean follow-up
Patients: 1,441 patients (aged 13-39 yr) with type 1 DM with no cardiovascular history or severe diabetic complications
Intervention: Intensive therapy (3 or more daily insulin injections or treatment with an insulin pump with dose adjustments as needed, BG monitoring minimum qid, monthly visits, strict BG targets) vs. Conventional therapy (1 or 2 insulin injections per day with no dose adjustments, daily BG monitoring, visits q3 months).
Outcomes: Primary outcome was development or progression of retinopathy. Secondary outcomes were development or progression of renal, neurological, cardiovascular, and neuropsychological outcomes
Results: Intensive treatment of Type 1 DM significantly reduced the risk for the development and progression of retinopathy in the primary- and secondary-intervention cohorts, respectively. Intensive therapy also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy. The chief adverse event associated with intensive therapy was an increase in the occurrence of severe hypoglycemia.
Conclusions: Intensive treatment of Type 1 DM significantly reduces the development and progression of diabetic retinopathy, nephropathy, and neuropathy in patients with Type 1 DM.

Blood Glucose Control in Type 2 DM – UKPDS 33
Lancet 1998;352:837-853
Study: RCT (mean follow-up 10 yr).
Patients: 3,867 patients with newly diagnosed type 2 DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose [FPG] 6.1-15.0 mmol/L). Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.
Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <15 mmol/L without hyperglycemic symptoms).
Main Outcomes: DM-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), DM-related death, and all-cause mortality.
Results: Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

Outcome	RRR % (p value)
DM-related endpoint	12 (0.029)
DM-related death	10 (0.34)
All-cause mortality	6 (0.44)

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.
Conclusion: Intensive blood glucose control reduces microvascular, but not macrovascular complications in type 2 DM.

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)

	Type 1	Type 2
Natural History	 • After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin • Once these cells are destroyed, there is complete insulin deficiency	 • Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production • As insulin resistance and compensatory hyperinsulinism continue, the β cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM
Circulating Autoantibodies	• Islet cell Ab present in up to 60-85% • Most common islet cell Ab is against glutamic acid decarboxylase (GAD) • Up to 60% have Ab against insulin	• <10%
Risk Factors	• Personal history of other autoimmune diseases including Graves', myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia • Family history of autoimmune diseases	• Age >40 yr • Abdominal obesity/overweight • First-degree relative with DM • Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander) • Hx of IGT or IFG • HTN • Dyslipidemia • Medications e.g. 2nd generation antipsychotics • PCOS • Hx of gestational DM or macrosomic baby (>9 lb or 4 kg) • Schizophrenia • Fatty liver • Hyperuricemia
Body Habitus	• Normal to thin	• Typically overweight with increased central obesity
Treatment	• Insulin	• Lifestyle modification • Oral antihyperglycemic agents • Incretin therapy • Insulin therapy
Acute Complication	• Diabetic ketoacidosis (DKA) in severe cases	• Hyperosmolar hyperglycemic state (HHS) • DKA in severe cases
Screening	• Subclinical prodrome can be detected in first and second-degree relatives of those with type 1 DM by the presence of pancreatic islet autoantibodies	• Screen individuals with risk factors

Treatment of Diabetes

Glycemic Targets

- HbA1c reflects glycemic control over 3 mo and is a measure of patient's long-term glycemic control
- therapy in most individuals with type 1 or type 2 DM (especially younger patients) should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications
- more intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia
- less stringent HbA1c targets (7.1-8.5%) may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to attain HbA1c <7.0% despite intensified basal and bolus insulin therapy
- there may be harm associated with strategy to target HbA1c <6.0% (see *ACCORD trial*, E9)

Diet

- daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy
- intake of saturated fats <7% and polyunsaturated fats <10% of total calories each
- limit sodium, alcohol, and caffeine intake
- type 1: carbohydrate counting is used to titrate insulin regimen
- type 2: weight reduction

Targeting Intensive Glycemic Control vs. Targeting Conventional Glycemic Control for Type 2 DM
Cochrane DB Syst Rev 2011;6:CD008143
Study: Systematic review of randomized clinical trials of glycemic control in adults with type 2 DM.
Patients: Twenty trials randomized 16,106 patients with type 2 DM to intensive control and 13,880 patients with type 2 DM to conventional glycemic control.
Intervention: Intensive glycemic control (HbA1c ≤6.5%) versus conventional glycemic control (determined by local guidelines).
Primary Outcomes: All-cause mortality, compositive macrovascular (death from cardiovascular cause, nonfatal MI, nonfatal stroke) and microvascular events (nephropathy, retinopathy).
Results: There was no significant difference between targeting intensive and conventional glycemic control for all-cause mortality or cardiovascular mortality. Targeting intensive glycemic control reduced the risk of amputation, the composite risk of microvascular disease, retinopathy, retinal photocoagulation, and nephropathy. The risks of both mild and severe hypoglycemia were increased with targeting intensive glycemic control.
Conclusions: Intensive glycemic control did not reduce all-cause mortality and cardiovascular mortality compared to conventional glycemic control. Intensive glycemic control reduced the risk of microvascular complications while increasing the risk of hypoglycemia. Intensive glycemic control may also reduce the risk of non-fatal MI in trials exclusively dealing with glycemic control in usual care settings.

Canadian Diabetes Guidelines 2013

	Target
HbA1c	<7.0%
Fasting plasma glucose	4-7 mmol/L (72-126 mg/dL)
2h post-prandial glucose	5-10 mmol/L (90-180 mg/dL) 5-8 mmol/L (90-144 md/dL) if not meeting target A1c and can be safely achieved
Lipids	As per high risk group if age >40 or age >30 if DM duration >15 yr
Blood pressure	<130/80

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 DM: The Look AHEAD Trial
NEJM 2013;369:145-154
Study: RCT, with 9.6 yr of median follow-up.
Population: 5,145 overweight or obese patients with type 2 DM.
Intervention: Intensive lifestyle intervention promoting weight loss through decreased caloric intake and increased physical activity (intervention) or DM support and education (control).
Primary Outcome: First occurrence of death from cardiovascular (CV) causes, non-fatal MI, non-fatal stroke, or hospitalization for angina.
Results: Although the intensive lifestyle intervention produced greater weight loss and reductions in glycated hemoglobin, the intervention did not significantly reduce the risk of CV morbidity or mortality.
Conclusions: An intensive lifestyle intervention focusing on weight loss did not significantly reduce the rate of cardiovascular events in overweight or obese adults with type 2 DM.

Lifestyle
- regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure
- smoking cessation

Medical Treatment: Oral Antihyperglycemic Agents and/or Incretin Therapy (Type 2 DM)
- initiate oral antihyperglycemic therapy and/or incretin therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if HbA1c >8.5%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately
- continue to add additional pharmacologic therapy in a timely fashion to achieve target HbA1C within 3-6 months of diagnosis
- see *Common Medications*, E52 for details on antihyperglycemic agents

Medical Treatment: Insulin (Figure 5)
- used for type 1 DM at onset, may be used in type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin lispro, Insulin glulisine)
- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, Insulin glargine)
- premixed insulins (combination of basal and bolus insulins) available but not used regularly
- estimated total daily insulin requirement: 0.5-0.7 units/kg (often start with 0.3-0.5 units/kg/d)

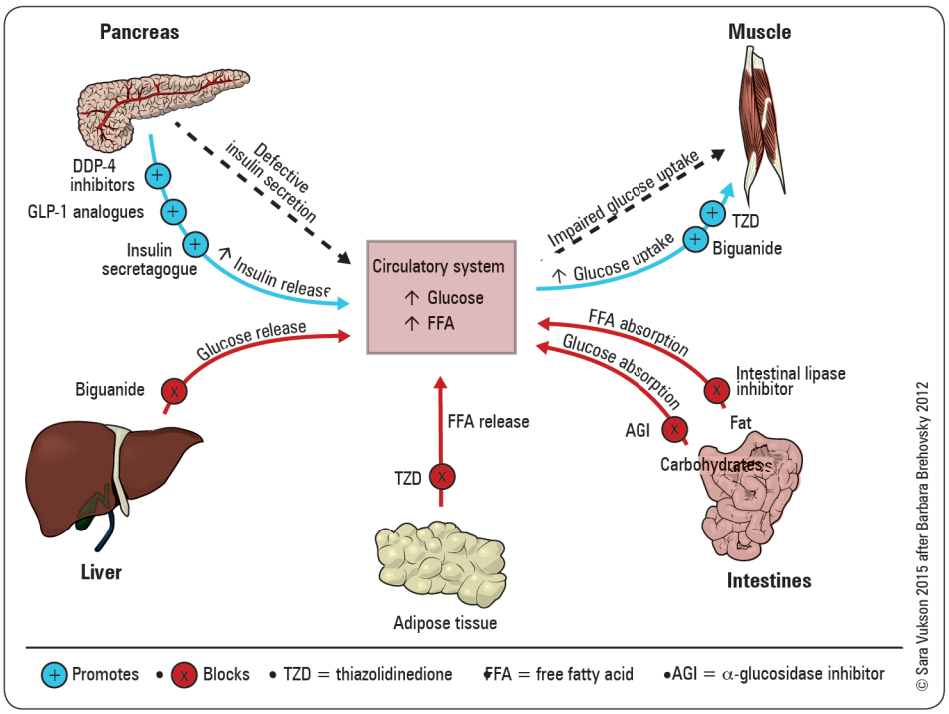


Figure 4. Antihyperglycemic agents

Table 9. Available Insulin Formulations

Insulin Type (trade name)	Onset	Peak	Duration
PRANDIAL (BOLUS) INSULINS			
Rapid-acting insulin analogues			
• Insulin aspart (NovoRapid®)	10-15 min	1-1.5 h	3-5 h
• Insulin lispro (Humalog®)	10-15 min	1-2 h	3.5-4.75 h
• Insulin glulisine (Apidra®)	10-15 min	1-1.5 h	3-5 h
Short-acting insulins			
• Humulin R®	30 min	2-3 h	6.5 h
• Novolin Toronto®			

Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial
NEJM 2008;358:2545-2559
Study: Multicentre RCT.
Patients: 10,251 patients (mean age 62.2) with type 2 DM, and cardiovascular risk factors.
Intervention: Intensive therapy targeting a HbA1c level of less than 6.0% or standard therapy targeting 7.0-7.9%.
Outcomes: First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.
Results: The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hypoglycemic events, any nonhypoglycemic serious adverse events, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (>3 times upper limit) and ACE drug use in the standard therapy group.
Conclusions: Intensive glucose lowering therapy in type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.

Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial
NEJM 2010;362:1575-1585
Study: RCT, unblinded with 4.7 yr of mean follow-up.
Population: 4,733 patients with type 2 DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.
Intervention: sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).
Primary Outcomes: Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).
Results: Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.4-3.5) versus 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, p=<0.001); especially bradycardia or arrhythmia (0.5% vs. 0.13%, p=0.02) and hyperkalemia (0.4% vs. 0.04%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, p=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.
Conclusions: Intensive BP lowering to less than 120 mmHg vs. 140 mmHg in patients with type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

Effects of Combination Lipid Therapy in Type 2 DM: the ACCORD Trial
NEJM 2010;362:1563-1574
Study: RCT, double-blinded trial with 4.7 yr of mean follow-up.
Population: 5,518 patients with type 2 DM.
Intervention: Statin with or without fibrate therapy.
Primary Outcome: Major cardiovascular (CV) event (composite nonfatal MI, nonfatal stroke, or CV-related death).
Results: No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms.
Conclusions: The addition of fibrate therapy to statin therapy in patients with type 2 DM does not reduce major CV event risk.

Table 9. Available Insulin Formulations (continued)

Insulin Type (trade name)	Onset	Peak	Duration
BASAL INSULINS			
Intermediate-acting • Humulin N® • Novolin NPH®	1-3 h	5-8 h	Up to 18 h
Long-acting basal insulin analogues Insulin detemir (Levemir®) Insulin glargine (Lantus®)	90 min	Not applicable	Up to 24 h (glargine 24 h, detemir 16-24 h)
PRE-MIXED INSULINS			
Premixed regular insulin – NPH • Humulin 30/70® • Novolin 30/70® Premixed insulin analogues • Biphasic insulin aspart (NovoMix 30®) • Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)	A single vial or cartridge contains a fixed ratio of insulin (% of rapid acting or short-acting insulin to % of intermediate-acting insulin)		

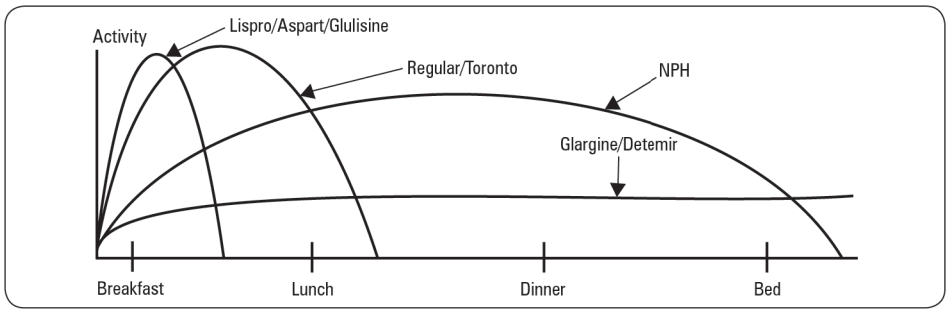


Figure 5. Duration of activity of different insulins

Insulin Regimens

Table 10. Insulin Regimens for Type 2 DM and Type 1 DM

	Regimen	Administration
Type 2 DM	Oral hypoglycemic agent + basal insulin	• Start with 10 units at bedtime of basal insulin • Titrate up by 1 unit until FBG <7.0 mmol/L
Type 1 DM	Multiple daily injections (MDI)	• Estimated total insulin requirement is 0.5-0.7 U/kg • 40% is given as basal insulin at bedtime • 20% is given as bolus insulin before breakfast, lunch, and dinner • Continue metformin but discontinue secretagogue
	Split-mixed	• Estimated total insulin requirement is 0.5-0.7 U/kg • 2/3 dose is given as pre-mixed insulin before breakfast • 1/3 dose is given as pre-mixed insulin before dinner • Continue metformin but discontinue secretagogue

*Bolus insulin: Aspart, Glulisine, Lispro
*Basal insulin: Gargine, Detemir, NPH
*Pre-mixed insulin: Humulin 30/70, Novolin 30/70, Novomix 30, Humalog Mix25, Humalog Mix50

Table 11. Titrating Insulin Doses

Hyperglycemic Reading	Insulin Correction
High AM sugar	Increase bedtime basal insulin
High lunch sugar	Increase AM rapid/regular insulin
High supper sugar	Increase lunch rapid/regular insulin, or Increase AM basal insulin
High bedtime sugar	Increase supper rapid/regular insulin

Variable Insulin Dose Schedule ("Sliding/Supplemental/Correction Scale")

- for patients on Basal-Bolus MDI regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- when used in hospital (including perioperative management of DM) patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia

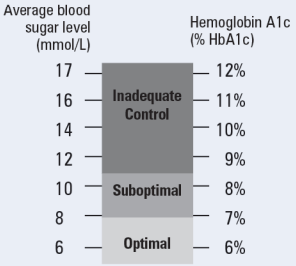
Effects of a Mediterranean Diet in Preventing Cardiovascular Events in Type 2 DM: The PREDIMED Trial
NEJM 2013;368:1279-1290
Study: RCT, with 4.8 yr of median follow-up.
Population: 7,447 patients with type 2 DM or other high cardiovascular risk factors.
Intervention: Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet supplemented with mixed nuts, or control diet with advice to reduce dietary fat.
Primary Outcome: Major cardiovascular (CV) event (MI, stroke, or death from CV causes).
Results: Both Mediterranean diets were associated with a reduced incidence of major CV events compared to the control diet.
Conclusions: A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, stroke, and CV death in those at high risk for CV disease.

DPP-IV Inhibitors
- Antihyperglycemic agents (e.g. sitagliptin, saxagliptin, linagliptin) that inhibit DPP-IV, which is an enzyme that degrades endogenous incretin hormones like GLP-1
- Incretin hormones stimulate glucose-dependent insulin secretion and inhibit glucagon release from the pancreas

GLP-1 Analogues (Incretins)
- Human glucagon-like peptide-1 analogues: exenatide, liraglutide
- These activate GLP-1 causing increased insulin secretion, decreased inappropriate glucagon secretion, increased B-cell growth/replication, slowed gastric emptying, and decreased food intake
- Associated with weight loss
- Subcutaneous formulation

Treatment of DKA/HHS
- Fluids
- Insulin
- Potassium
- Search for and treat precipitant

Conversion Chart for Percentage HbA1c to Average Blood Sugar Control



Conversion chart adapted from Nathan DM, et al. The clinical information value of a glycosylated hemoglobin assay. *NEJM* 1984;310:341-346

The 8 Is Precipitating DKA
Infection
Ischemia or **I**nfarction
Iatrogenic (glucocorticoids)
Intoxication
Insulin missed
Initial presentation
Intra-abdominal process (e.g. pancreatitis, cholecystitis)
Intraoperative/perioperative stress

- construction of a supplemental sliding scale for a patient on anti-hyperglycemics
  - Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
  - BG <4: call MD and give 15 g carbohydrates
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)

- external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected
- coverage available for insulin pumps for individuals with Type 1 DM varies by province

Acute Complications

All Ketonemia is not DKA
Consider starvation or alcohol ketosis

Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
Pathophysiology	• Usually occurs in type 1 DM • Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH) • Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise) • Unopposed hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na^+ (water shift to ECF causing pseudohyponatremia) • Fat mobilization → ↑ FFA → ketoacids → metabolic acidosis • Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria • Total body K^+ depletion but serum K^+ may be normal or elevated 2° to shift from ICF to ECF due to lack of insulin, ↑ plasma osmolality • Total body PO_4^{3-} depletion	• Occurs in type 2 DM • Often precipitated by sepsis, stroke, MI, CHF, renal failure, trauma, drugs (glucocorticoids, immunosuppressants, phenytoin, diuretics), dialysis, recent surgery, burns • Partial or relative insulin deficiency decreases glucose utilization in muscle, fat, and liver while inducing hyperglucagonemia and hepatic glucose production • Presence of a small amount of insulin prevents the development of ketosis by inhibiting lipolysis • Characterized by hyperglycemia, hyperosmolality, and dehydration without ketosis • More severe dehydration compared to DKA due to more gradual onset and ↑ duration of metabolic decompensation plus impaired fluid intake which is common in bedridden or elderly • Volume contraction → renal insufficiency → ↑ hyperglycemia, ↑ osmolality → shift of fluid from neurons to ECF → mental obtundation and coma
Clinical Features	• Polyuria, polydipsia, polyphagia with marked fatigue, N/V • Dehydration (orthostatic changes) • LOC may be ↓ with ketoacidosis or with high serum osmolality (osm >330 mmol/L) • Abdominal pain • Fruity smelling breath • Kussmaul's respiration	• Onset is insidious → preceded by weakness, polyuria, polydipsia • History of decreased fluid intake • History of ingesting large amounts of glucose containing fluids • Dehydration (orthostatic changes) • ↓ LOC → lethargy, confusion, comatose due to high serum osmolality • Kussmaul's respiration is absent unless the underlying precipitant has also caused a metabolic acidosis
Serum	• ↑ BG (typically 11-55 mmol/L, ↓ Na^+ (2° to hyperglycemia → for every ↑ in BG by 10 mmol/L) there is a ↓ in Na^+ by 3 mmol/L) • Normal or ↑ K^+, ↓ HCO_3^-, ↑ BUN, ↑ Cr, ketonemia, ↓ PO_4^{3-} • ↑ osmolality	• ↑ BG (typically 44.4-133.2 mmol/L) • In mild dehydration, may have hyponatremia (spurious 2° to hyperglycemia → for every ↑ in BG by 10 mmol/L there is a ↓ in Na^+ by 3 mmol/L) – if dehydration progresses, may get hypernatremia • Ketosis usually absent or mild if starvation occurs • ↑ osmolality
ABG	• Metabolic acidosis with ↑ AG, possible 2° respiratory alkalosis • If severe vomiting/dehydration there may be a metabolic alkalosis	• Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)
Urine	• +ve for glucose and ketones	• -ve for ketones unless there is starvation ketosis • Glycosuria

Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States (continued)

	Diabetic Ketoacidosis (DKA)	Hyperosmolar Hyperglycemic State (HHS)
Treatment	• ABCs are first priority • Monitor degree of ketoacidosis with AG, not BG or serum ketone level • Rehydration – 1 L/h NS in first 2 h – after 1st 2 L, 300-400 mL/h NS. Switch to 0.45% NaCl once euvolemic (continue NS if corrected sodium is falling faster than 3 mosm/kg water/h) – once BG reaches 13.9 mmol/L then switch to D5W to maintain BG in the range of 12-14 mmol/L • Insulin therapy – critical to resolve acidosis, not hyperglycemia – do not use with hypokalemia (see below), until serum K^+ is corrected to >3.3 mmol/L – use only regular insulin (R) – maintain on 0.1 U/kg/h insulin R infusion – check serum glucose hourly • K^+ replacement – with insulin administration, hypokalemia may develop – if serum K^+<3.3 mmol/L, hold insulin and give 40 mEq/L K^+ replacement – when K^+ 3.5-5.0 mmol/L add KCL 20-40 mEq/L IV fluid to keep K^+ in the range of 3.5-5 mEq/L • HCO_3^- – if pH <7.0 or if hypotension, arrhythmia, or coma is present with a pH of <7.1 give HCO_3^- in 0.45% NaCl – do not give if pH >7.1 (risk of metabolic alkalosis) – can give in case of life-threatening hyperkalemia • ± mannitol (for cerebral edema)	• Same resuscitation and emergency measures as DKA • Rehydration – IV fluids: 1 L/h NS initially – evaluate corrected serum Na^+ – if corrected serum Na^+ high or normal, switch to 0.45% NaCl (4-14 mL/kg/h) – if corrected serum Na^+ low, maintain NS (4-14 mL/kg/h) – when serum BG reaches 13.9 mmol/L switch to D5W • K^+ replacement – less severe K^+ depletion compared to DKA – if serum K^+<3.3 mmol/L, hold insulin and give 40 mEq/L K^+ replacement – if K^+ is 3.3-5.0, give KCl 20-30 mEq/L IV fluid – if serum K^+ ≥5.5 mmol/L, check K^+ every 2 h • Search for precipitating event • Insulin therapy – use only regular insulin (R) – initially load 0.1 U/kg body weight insulin R bolus – maintenance 0.1 U/kg/h insulin R infusion or IM – check serum glucose hourly – in general lower insulin requirement compared to DKA
Prognosis	• 2-5% mortality in developed countries • Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)	• Overall mortality approaches 50% primarily because of the older patient population and underlying etiology/precipitant

Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C26)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in type 2 DM
  - most patients with DM are considered "high risk" under the risk stratification for CAD (see *Dyslipidemias*, E2)
- ischemic stroke (see Neurology, N50)
  - risk of stroke is approximately 2.5x higher in those with DM
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS2)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control (LDL ≤2.0 mmol/L)
  - ACEI or angiotensin receptor blocker in high-risk patients
  - smoking cessation

Average fluid loss runs at 3-6 L in DKA, and 8-10 L in HHS

Laboratory Testing: Ketones
The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:
- Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB.
- As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving.

Microvascular Complications

DIABETIC RETINOPATHY (see Ophthalmology, OP35 for a more detailed description)

Epidemiology
- type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- type 2 DM: 25% affected at diagnosis, 60% at 20 yr
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

Clinical Features
- nonproliferative
- preproliferative
- proliferative

Treatment and Prevention
- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available – see Ophthalmology, OP36 for more details
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of type 2 DM; 5 yr after diagnosis of type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy

DIABETIC NEPHROPATHY (see Nephrology, NP30 for a more detailed description)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with type 1 DM (after 5-10 yr) and 4-20% with type 2 DM have progressive nephropathy

Screening
- serum creatinine
- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all type 2 DM patients at diagnosis, then annually, and for postpubertal type 1 DM patients with ≥5yr duration of DM

Treatment and Prevention
- appropriate glycemic control
- appropriate blood pressure control (<130/80 mmHg)
- use either ACEI or ARB (often used first line for their CVD protection)
- limit use of nephrotoxic drugs and dyes

DIABETIC NEUROPATHY

Epidemiology
- approximately 50% of patients within 10 yr of onset of type 1 DM and type 2 DM

Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

Screening
- 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with type 2 DM and after 5 yr duration of type 1 DM

Effect of a Multifactorial Intervention on Mortality in Type 2 DM: The Steno-2 Study
NEJM 2008;358:580-591
Study: Single centre RCT.
Patients: Patients (n=160) with type 2 DM and persistent microalbuminuria.
Intervention: Random assignment to receive either conventional multifactorial treatment or intensified, target-driven therapy involving a combination of medications and focused behaviour modification. Targets included an HbA1c level of <6.5%, a fasting serum total cholesterol level of <4.5 mmol/L, a fasting serum triglyceride level of <1.7 mmol/L, a sBP of <130 mmHg, and a dBP of <80 mmHg. Patients were treated with blockers of the renin–angiotensin system because of their microalbuminuria, regardless of blood pressure, and received low-dose Aspirin® as primary prevention.
Outcomes: The primary end point was the time to death from any cause. Other endpoints examined were death from CV causes and various CV events along with diabetic neuropathy, nephropathy, and retinopathy.
Results: Twenty-four patients in the intensive-therapy group died, as compared with 40 in the conventional-therapy group (hazard ratio, 0.54; 95% confidence interval [CI] 0.32-0.89; p=0.02). Intensive therapy was associated with a lower risk of death from CV causes (hazard ratio, 0.43; 95% CI 0.19-0.94; p=0.04) and of CV events (hazard ratio, 0.41; 95% CI 0.25-0.67; p<0.001). One patient in the intensive-therapy group had progression to end-stage renal disease, as compared with six patients in the conventional-therapy group (p=0.04). Fewer patients in the intensive-therapy group required retinal photocoagulation (relative risk, 0.45; 95% CI 0.23-0.86; p=0.02).
Conclusions: In at-risk patients with type 2 DM, intensive intervention with multiple drug combinations and behaviour modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from CV causes.

Management of Diabetic Retinopathy: A Systematic Review
JAMA 2007;298:902-916
Purpose: To review the best evidence for primary and secondary interventions in the management of diabetic retinopathy (DR), including diabetic macular edema.
Study Selection: English-language RCTs with more than 12 mo of follow-up and meta-analyses were included.
Results: Forty-four studies (including 3 meta-analyses) met the inclusion criteria. Tight glycemic and blood pressure control reduces the incidence and progression of DR. Pan-retinal laser photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe nonproliferative and proliferative retinopathy. Focal laser photocoagulation reduces the risk of moderate visual loss by 50-70% in eyes with macular edema. Early vitrectomy improves visual recovery in patients with proliferative retinopathy and severe vitreous hemorrhage. Intravitreal injections of steroids may be considered in eyes with persistent loss of vision when conventional treatment has failed.
Conclusions: Tight glycemic and blood pressure control remains the cornerstone in the primary prevention of DR. Pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe DR and macular edema, respectively. There is currently insufficient evidence to recommend routine use of other treatments.

Clinical Features

Table 13. Clinical Presentation of Diabetic Neuropathies

Peripheral Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands Decreased ankle reflex Symptoms may first occur in entrapment syndromes e.g. carpal tunnel May result in neuropathic ulceration of foot	Less common than sensory neuropathy Delayed motor nerve conduction and muscle weakness/atrophy May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex) Some of the motor neuropathies spontaneously resolve after 6-8 wk Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell's palsy) Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors	Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver Gastroparesis and alternating diarrhea and constipation Urinary retention and erectile dysfunction

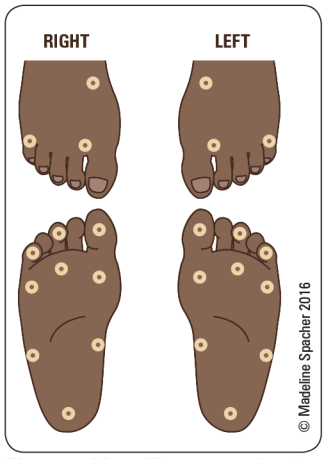


Figure 6. Monofilament testing for diabetic neuropathy

Treatment and Management
- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U30)

Effects of Treatments for Symptoms of Painful Diabetic Neuropathy: Systematic Review
BMJ 2007;335:87
Purpose: To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.
Study Selection: RCTs comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.
Results: 25 included reports compared anticonvulsants (n=1,270), antidepressants (94), opioids (329), ion channel blockers (173), NMDA antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% CI 1.77-16.02) for traditional anticonvulsants, 3.25 (95% CI 2.27-4.66) for newer generation anticonvulsants, and 22.24 (95% CI 5.83-84.75) for tricylic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (95% CI 0.33-6.96) for traditional anticonvulsants, 2.98 (95% CI 1.75-5.07) for newer generation anticonvulsants, and 2.32 (95% CI 0.59-9.69) for tricyclic antidepressants.
Conclusion: Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Tricyclic antidepressants and traditional anticonvulsants are better for short-term pain relief than newer anticonvulsants. Evidence of the long-term effects of antidepressants and anticonvulsants is lacking. Further studies are needed on opioids, NMDA antagonists, and ion channel blockers.

Other Complications

Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as "shin spots", secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren's contracture
- bone demineralization: bone density 10-20% below normal
- adhesive capsulitis ("frozen shoulder")

Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections
- see Infectious Diseases, ID15

Hypoglycemia (BG <4.0 mmol/L or 72 mg/dL)

Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses

Other Players in Glucose Homeostasis
These hormones act to increase blood glucose levels
- Glucagon
- Epinephrine
- Cortisol
- Growth hormone

C-Peptide
A short peptide released into the circulation when proinsulin is cleaved to insulin

Table 14. Common Causes of Hypoglycemia

Fasting		Post-Prandial (Nonfasting, Reactive)
Hyperinsulinism	**Without Hyperinsulinism**	
• Exogenous insulin • Sulfonylurea or meglitinide reaction • Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor) • Pentamidine • Pancreatic β cell tumour – insulinoma	• Severe hepatic dysfunction • Chronic renal insufficiency • Hypocortisolism • Alcohol use • Non-pancreatic tumours • Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme deficiency	• Alimentary • Functional • Noninsulinoma pancreatogenous hypoglycemic syndrome • Occult DM • Leucine sensitivity • Hereditary fructose intolerance • Galactosemia • Newborn infant of diabetic mother

Clinical Features

- Whipple's triad
  1. serum glucose <2.5 mmol/L in males and <2.2 mmol/L in females
  2. neuroglycopenic symptoms
  3. rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations

- electrolytes, creatinine, LFTs, drugs/toxins, cortisol
- if concerned about possible insulinoma
  - blood work to be drawn when patient is hypoglycemic (e.g. during hospitalized 72-h fast) for glucose, serum ketones, insulin, pro-insulin, C-peptide, insulin antibodies

Treatment

- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, ER35
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - may need ongoing glucose infusion once BG >5 mmol/L

Metabolic Syndrome

- several definitions exist
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity

- see Family Medicine, FM7

Use C-peptide Levels to Distinguish between Exogenous and Endogenous Source of Hyperinsulinemia
Increased = endogenous
Decreased or normal = exogenous

Treatment of Acute Hypoglycemic Episode (Blood Glucose <4.0 mmol/L) in the Awake Patient (e.g. able to self-treat)

1) Eat 15 g of carbohydrates (CHO) (e.g. 3 packets sugar dissolved in water; 3/4 cup of juice)
↓
2) Wait 15 min
↓
3) Retest Blood Glucose (BG)
↓
4) Repeat steps 1-3 until BG >5 mmol/L
↓
5) Eat next scheduled meal. If next meal is >1 h away, eat snack including 15 g of CHO and protein.

Hypoglycemia Unawareness (Type 1 DM >>> Type 2 DM)

Patient remains asymptomatic until severely hypoglycemic levels are reached

Causes:
- Decreased glucagon/epinephrine response
- History of repeated hypoglycemia or low HbA1c
- Autonomic neuropathy
- Not safe to drive

Suggest that patient obtain a Medic-Alert bracelet if at risk for hypoglycermia, especially with hypoglycemia unawareness

Features of Metabolic Syndrome
(≥ 3 measures to make a Dx)

Measure	Men	Women
Abdominal Obesity (Elevated Waist Circumference)		
Canada, USA	≥102 cm (40 inches)	≥88 cm (35 inches)
Europid, Middle Eastern, Sub-Saharan Africa, Mediterranean	≥94 cm (37 inches)	≥80 cm (31.5 inches)
Asian, Japanese, South & Central America	≥90 cm (35 inches)	≥80 cm (31.5 inches)
Triglyceride Level	≥1.7 mmol/L (150 mg/dL)	
HDL-C Level	<1.0 mmol/L (<40 mg/dL)	<1.3 mmol/L (<50 mg/dL)
Blood Pressure	≥130/85 mmHg	
Fasting Glucose Level	≥5.6 mmol/L (>100 mg/dL)	

Drug treatment for any elevated marker is an alternate indicator

Pituitary Gland

Pituitary Hormones

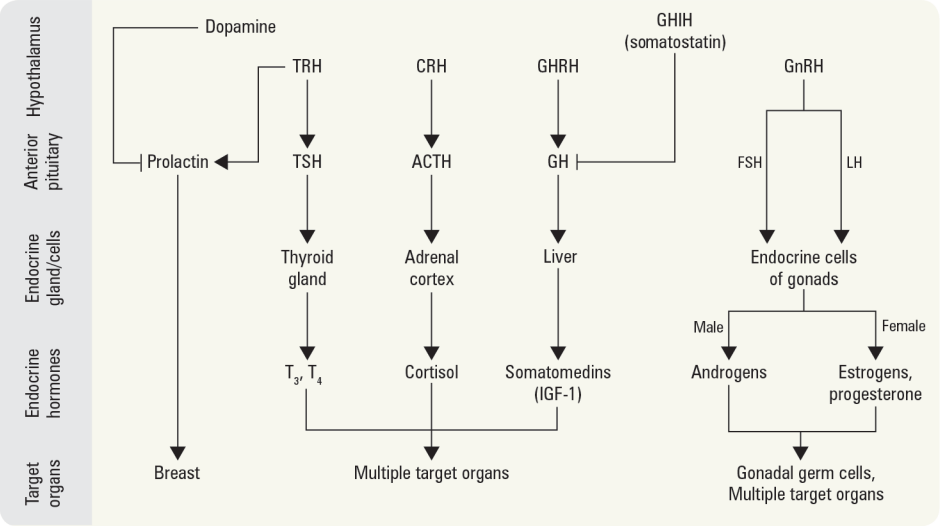


Figure 7. Hypothalamic-pituitary hormonal axes
CRH = corticotropin-releasing hormone; GHIH = growth hormone-inhibiting hormone; GHRH = growth hormone-releasing hormone; GnRH = gonadotropin-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

Hypothalamic Control of Pituitary

- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by SS (somatostatin)
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

Anterior Pituitary Hormones

- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL)

Posterior Pituitary (Hypothalamic) Hormones

- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus these hormones are stored and released from the posterior pituitary

Table 15. The Physiology and Action of Pituitary Hormones

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
ACTH	• Stimulates growth of adrenal cortex and secretion of its hormones	• Polypeptide • Pulsatile and diurnal variation (highest in AM, lowest at midnight)	• Dexamethasone • Cortisol	• CRH • Metyrapone • Insulin-induced hypoglycemia • Vasopressin • Fever, pain, stress
GH	• Needed for linear growth • IGF-1 stimulates growth of bone and cartilage	• Polypeptide • Acts indirectly through serum factors synthesized in the liver: IGF-1 (somatomedin-C) • Serum GH undetectable for most of the day and suppressed after meals high in glucose • Sustained rise during sleep	• Glucose challenge • Glucocorticoids • Hypothyroidism • Somatostatin • Dopamine D2 receptor agonists • IGF-1 (long-loop) • Tonically by dopamine	• GHRH • Insulin-induced hypoglycemia • Exercise • REM sleep • Arginine, clonidine, propranolol, L-dopa

Table 15. The Physiology and Action of Pituitary Hormones (continued)

Hormone	Function	Physiology	Inhibitory Stimulus	Secretory Stimulus
LH/FSH	• Stimulate gonads via cAMP • Ovary: – LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles – FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation • Testes: – LH: production of testosterone (Leydig cells) – FSH: production of spermatozoa (Sertoli cells)	• Polypeptide • Glycoproteins (similar α subunit as TSH and hCG) • Secreted in pulsatile fashion	• Estrogen • Progesterone • Testosterone • Inhibin • Continuous (i.e. non-pulsatile) GnRH infusion	• Pulsatile GnRH
Prolactin	• Promotes milk production • Inhibits GnRH secretion	• Polypeptide • Episodic secretion	• Dopamine	• Sleep • Stress, hypoglycemia • Pregnancy, breastfeeding • Mid-menstrual cycle • Sexual activity • TRH • Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen
TSH	• Stimulates growth of thyroid and secretion of T_3 and T_4 via cAMP	• Glycoprotein	• Circulating thyroid hormones (T_3, T_4) • Opiates, dopamine	• TRH • Epinephrine • Prostaglandins
ADH	• Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine	• Octapeptide • Secreted by posterior pituitary • Osmoreceptors in hypothalamus detect serum osmolality • Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↑ osmolality	• ↓ serum osmolality	• Hypovolemia or ↓ effective circulatory volume • ↑ serum osmolality • Stress, pain, fever, paraneoplastic • Lung or brain pathology
Oxytocin	• Causes uterine contraction • Breast milk secretion	• Not a peptide • Secreted by posterior pituitary	• EtOH	• Suckling • Distention of female genital tract during labor via stretch receptors

Growth Hormone

GH DEFICIENCY

- cause of short stature in children (see Pediatrics, P27)
- controversial significance in adults; often not clinically apparent, may present as fatigue

GH EXCESS

- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyiseal fusion) leads to acromegaly

Etiology

- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

Pathophysiology

- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

Clinical Features

- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, barrel chest, thyromegaly, renal calculi, HTN, cardiomyopathy, obstructive sleep apnea, colonic polyps, erectile dysfunction, menstrual irregularities, and DM

Risks Associated with GH Excess

- Cardiac disease (e.g. CAD, cardiomegaly, cardiomyopathy) in 1/3 of patients, with a doubling of risk of death from cardiac disease
- HTN in 1/3 of patients
- Risk of cancer (particularly GI) increased 2-fold to 3-fold

Signs and Symptoms of Acromegaly

ABCDEF
Arthralgia/**A**rthritis
Blood pressure raised
Carpal tunnel syndrome
DM
Enlarged organs
Field defect (visual)

Investigations
- elevated serum insulin-like growth factor-1 (IGF-1) is usually the first line diagnostic test
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), growth hormone receptor antagonist (pegvisomant), radiation

Prolactin

HYPERPROLACTINEMIA

Etiology
- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H_2-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

Approach to Nipple Discharge
- Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
- If abnormal breast discharge, must rule out a breast malignancy

Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine
- MRI of the sella turcica

Treatment
- long-acting dopamine agonist: bromocriptine, cabergoline, or quinagolide (Norprolac®)
- surgery ± radiation (rare)
- prolactin-secreting tumours are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

Thyroid Stimulating Hormone

- see *Thyroid*, E20

Adrenocorticotropic Hormone

- see *Adrenal Cortex*, E29

Luteinizing Hormone and Follicle Stimulating Hormone

HYPOGONADOTROPIC HYPOGONADISM

Clinical Features
- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

Treatment
- Pergonal® (combined FSH/LH hormone therapy), hCG, rFSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

HYPERGONADOTROPIC HYPOGONADISM
- 2° hypersecretion in gonadal failure (e.g. in menopause)

Antidiuretic Hormone

DIABETES INSIPIDUS

Definition
- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

Etiology and Pathophysiology
- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

Clinical Features
- passage of large volumes of dilute urine, polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism

Diagnostic Criteria
- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

Diagnosing Subtypes of DI with DDAVP Response

Concentrated urine = **C**entral
No effect = **N**ephrogenic

Treatment
- DDAVP/vasopressin for central DI
- chlorpropamide, clofibrate, thiazides, NSAIDs, or carbamazepine as second line or for partial DI
- nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

SYNDROME OF INAPPROPRIATE ADH SECRETION

Diagnostic Criteria
- hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal, or thyroid insufficiency

SIADH vs. Cerebral Salt Wasting (CSW)
CSW can occur in cases of subarachnoid hemorrhage. Na^+ is excreted by malfunctioning renal tubules, mimicking findings of SIADH; hallmark is hypovolemia

Etiology and Pathophysiology
- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (TB, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Presentations of Pituitary Lesions
- Mass effect (visual field deficits, diplopia, ptosis, headaches, CSF leak)
- Hyperfunction
- Hypofunction

Treatment
- treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used) fludrocortisone, furosemide

Pituitary Pathology

PITUITARY ADENOMA (see Neurosurgery, NS19)

Clinical Features
- local mass effects
  - visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
- hypofunction
  - hypopituitarism
- hyperfunction
  - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing's disease = Cushing's syndrome caused by a pituitary tumour)
  - tumours secreting LH, FSH, and TSH are rare

Important Deficiencies to Recognize are:
- Adrenal insufficiency
- Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis

Investigations
- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing
- hypothalamic-pituitary hormonal function

The Pituitary Hormones
Order they are usually lost with compression by a mass:
"Go Look For The Adenoma Please"
GH, **L**H, **F**SH, **T**SH, **A**CTH, **P**RL + posterior pituitary hormones: ADH and oxytocin

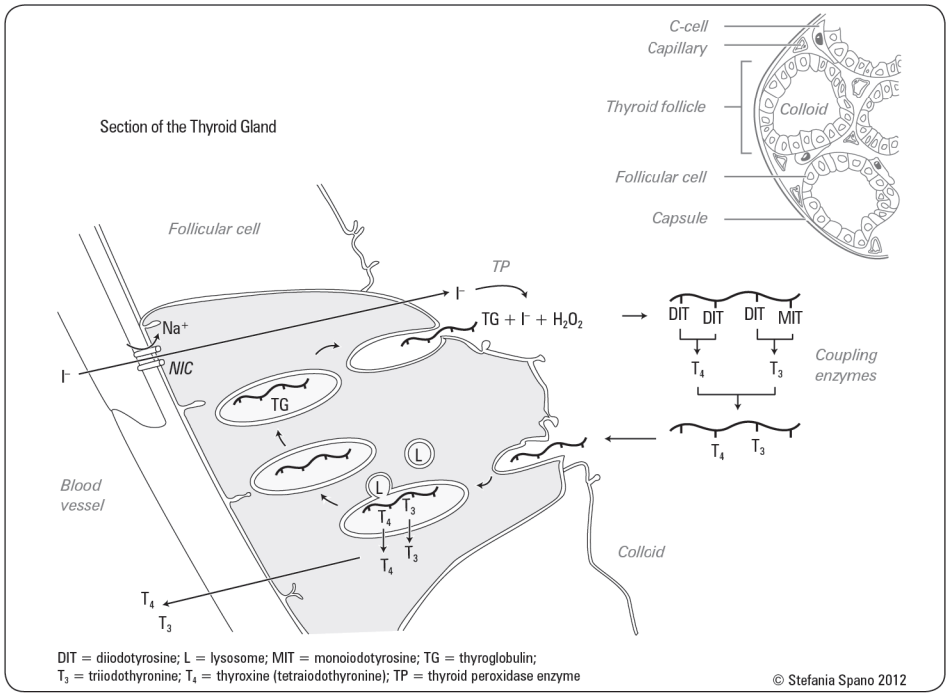
HYPOPITUITARISM

Etiology (The Eight Is)
- **I**nvasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- **I**nfarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered level of consciousness; can be fatal if not recognized and treated early)
- **I**nfiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- **I**nfectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- **I**njury
  - severe head trauma
- **I**mmunologic
  - autoimmune destruction
- **I**atrogenic
  - following surgery or radiation
- **I**diopathic
  - familial forms, congenital midline defects

Investigations
- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH, and TRH
  - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH/cortisol
  - GnRH (100 μg IV push) → increased LH and FSH
  - TRH (200 μg IV push over 120 s) → increased TSH and PRL (no longer available in Canada)

Thyroid

Thyroid Hormones



DIT = diiodotyrosine; L = lysosome; MIT = monoiodotyrosine; TG = thyroglobulin; T_3 = triiodothyronine; T_4 = thyroxine (tetraiodothyronine); TP = thyroid peroxidase enzyme

Figure 8. Thyroid hormone synthesis

Synthetic Function of Thyroid Gland
- the synthesis of thyroid hormones T_4 (thyroxine) and T_3 (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, and release of T_3 and T_4
- free T_4 (0.03%) and free T_3 (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
- T_3 is more biologically active (3-8x more potent), but T_4 has a longer half-life
- 85% of T_4 is converted to T_3 or reverse T3 (RT3) in the periphery by deiodinases
- RT3 is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma T_3 pool is derived from the peripheral conversion of T_4
- calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells
  - it functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones
- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- action of these hormones is diffuse, effecting nearly every organ system
- they produce an increase in basal metabolic rate including: increased Na^+/K^+ATPase activity, increased O_2 consumption, increased respiration, heat generation, and increased cardiovascular activity
- also play crucial role during fetal life in both neurological and somatic development

Regulation of Thyroid Function
- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  - T_3 negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroid (autoregulation)
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T_3 to T_4 in iodide deficiency
  - increased activity of peripheral 5' deiodinase in hypothyroidism increases T_3 production despite low T_4 levels

Patterns of Hormone Levels

	TSH	T_3, T_4
1° Hyper	↓	↑
2° Hyper	↑	↑
1° Hypo	↑	↓
2° Hypo	↓	↓

Thyroid Assessment
- Serum thyroid hormones (TSH, T_3, T_4)
- Antibodies Antibodies (TRAb, TgAb and TPOAb)
- Thyroglobulin (to monitor thyroid cancer)
- Thyroid ultrasound
- Nuclear uptake and scan (for hyperthyroidism)
- Biopsy (FNA)

Tests of Thyroid Function and Structure

TSH
- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating T_3 and T_4
  - secondary: increased TSH results in increased T_3 and T_4
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T_3 and T_4
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T_3 and Free T_4
- standard assessment of thyroid function measures TSH and if necessary free T_4. Free T_3 should only be measured in the small subset of patients with hyperthyroidism and suspected T_3 toxicosis. TSH would be suppressed, free T_4 normal, and free T_3 elevated

Thyroid Autoantibodies
- anti-thyroglobulin antibodies (TgAb), anti-thyroid peroxidase antibodies (TPOAb), anti-TSH receptor antibodies (TRAb) of the blocking variety
  - increased in Hashimoto's disease; normal variant in 10-20% of individuals
- anti-TSH receptor antibodies (TRAb) of the stimulating variety are also referred to as thyroid stimulating immunoglobulins (TSI)
  - increased in Graves' disease

Plasma Thyroglobulin
- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- normal or elevated levels may suggest persistent, recurrent, or metastatic disease

Serum Calcitonin
- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes
  - used to monitor for residual or recurrent medullary thyroid cancer

Does this Patient have a Goitre?
From The Rational Clinical Examination
JAMA 2009; http://www.jamaevidence.com/content/3480618

Study: Systematic review of articles assessing the accuracy and precision of the clinical exam in the diagnosis of a goitre.

Results: Clinical diagnosis was based on degree of lateral prominence, visibility, and palpability of the thyroid gland. No evidence exists to support the superiority of any one method.

The combined results of 4 studies detail the predictive utility of assessing grades of thyroid gland weight:

Weight	Reference	LR+	95% CI
0-20 g	normal	0.15	(0.10-0.21)
20-40 g	1-2x	1.9	(1.1-3.0)
>40 g	>2x	25.0	(2.6-175)

Alternatively, defining a goitre as mass larger than the distal phalanx of the thumb has been shown to have an LR+ of 3.0 (95% CI 2.5-3.5) and LR- of 0.30 (95% CI 0.24-0.37) in children, and an LR+ of 4.7 (95% CI 3.6-6.0) and LR- of 0.08 (95% CI 0.02-0.27) for the presence of a goitre.

Conclusions: Use of weight of thyroid tissue is an appropriate method of diagnosing a goitre, while comparing the size of thyroid mass to the distal phalanx of the thumb may be a useful alternative.

Thyroid Imaging/Scans

- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
- radioisotope thyroid scan (Technetium-99)
  - *test of structure*: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  - differentiates between hot (functioning → excess thyroid hormone production) and cold (non-functioning) nodules
    - hot nodule → very low chance malignancy; treat hyperthyroidism
    - cold nodule → ~5% chance malignancy; further workup required (U/S and FNAB)
- radioactive iodine uptake (RAIU)
  - *test of function*: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland *in vivo*
  - if ↑ uptake (i.e. incorporated) → gland is overactive (hyperthyroid)
  - if ↓ uptake (i.e. not incorporated) → gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)
- see Figure 9, *Approach to the Evaluation of a Thyroid Nodule*, E29 for further information regarding the utility of these scans

Thyroid Biopsy

- fine needle aspiration (FNA) for cytology
  - differentiates between benign and malignant disease
  - best done under U/S guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

Caution with Amiodarone

Amiodarone-Induced Hypothyroidism (AIH): AIH occurs more often in iodine-sufficient areas, and is more common in populations with a higher prevalence of autoimmune thyroid disease, such as women and the elderly. AIH can also occur in patients without pre-existing thyroid dysfunction.

Amiodarone-Induced Thyrotoxicosis (AIT): AIT occurs more often in iodine-deficient areas. It may occur in patients with pre-existing thyroid deficiencies, as an iodine load on an already dysfunctional thyroid may result in excessive thyroid hormone synthesis and release. AIT may also occur in patients without thyroid abnormalities through a cytotoxic mechanism that results in leakage of thyroid hormone into the systemic circulation.

Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

	Hyperthyroidism	Hypothyroidism
TSH	• Decreased in 1° hyperthyroidism • Increased in 2° hyperthyroidism	• Increased in 1° hypothyroidism • Decreased in 2° hypothyroidism
Free T_4	• Increased in 1° hyperthyroidism • Increased in 2° hyperthyroidism	• Decreased in 1° hypothyroidism • Decreased in 2° hypothyroidism
Antibodies	Graves': thyroid stimulating Ig (TSI)	Hashimoto's: antithyroid peroxidase (TPO)
RAIU	Increased uptake • Graves' • Toxic multinodular goitre • Toxic adenoma Decreased uptake • Subacute thyroiditis • Recent iodine load • Exogenous thyroid hormone	
Radioisotope Thyroid Scan	• Graves': homogenous diffuse uptake • Multinodular goitre: heterogeneous uptake • Toxic adenoma: single intense area of uptake with suppression elsewhere	

Signs and Symptoms of HYPERthyroidism

Tremor
Heart rate up
Yawning (fatigued)
Restlessness
Oligomenorrhea/amenorrhea
Intolerance to heat
Diarrhea
Irritability
Sweating
Muscle wasting/weight loss

Thyrotoxicosis

Definition

- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology

- 1% of general population have hyperthyroidism
- F:M = 5:1

Etiology and Pathophysiology

Table 17. Differential Diagnosis of Thyrotoxicosis

Disorder	TSH	Free T_4/T_3	Thyroid Antibodies	RAIU	Other
HYPERTHYROIDISM					
Graves' Disease	Decreased	Increased	TSI	Increased	Heterogeneous uptake on scan
Toxic Nodular Goitre	Decreased	Increased	None	Increased	Heterogeneous uptake on scan
Toxic Nodule	Decreased	Increased	None	Increased	Intense uptake in hot nodule on scan with no uptake in the rest of the gland
THYROIDITIS					
Subacute, Silent, Postpartum	Decreased	Increased	Up to 50% of cases	Decreased (becomes increased once entering hypothyroid phase, when TSH rises	In classical subacute painful thyroiditis, ESR increased

Common Etiologies

Thyrotoxicosis	Hypothyroidism
Graves' Disease	Hashimoto's
Toxic Nodular Goitre	Congenital
Toxic Nodule	Iatrogenic (thionamides, radioactive iodine, or surgery)
Thyroiditis	Hypothyroid phase of thyroiditis

Table 17. Differential Diagnosis of Thyrotoxicosis (continued)

Disorder	TSH	Free T_4/T_3	Thyroid Antibodies	RAIU	Other
EXTRATHYROIDAL SOURCES OF THYROID HORMONE					
Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)	Decreased	Increased	None	Decreased	
Exogenous (drugs)	Decreased	Increased (T_4 would be decreased if taking T_3)	None	Decreased	
EXCESSIVE THYROID STIMULATION					
Pituitary thyrotrophoma	Increased	Increased	None	Increased	
Pituitary thyroid hormone receptor resistance	Increased	Increased	None	Increased	
Increased hCG (e.g. pregnancy)	Decreased	Increased	None	Increased DO NOT DO THIS TEST IN PREGNANCY	

Clinical Features

Table 18. Clinical Features of Thyrotoxicosis

General	Fatigue, heat intolerance, irritability, fine tremor
CVS	Tachycardia, atrial fibrillation, palpitations Elderly patients may have only cardiovascular symptoms, commonly new onset atrial fibrillation
GI	Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)
Neurology	Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)
GU	Oligomenorrhea, amenorrhea, decreased fertility
Dermatology	Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritis Graves' disease: clubbing (acropachy), pretibial myxedema (rare)
MSK	Decreased bone mass, proximal muscle weakness
Hematology	Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)
Eye	Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjuctival injection

Treatment

- thionamides: PTU or MMI; MMI recommended (except in first trimester pregnancy)
- β-blockers for symptom control
- radioactive iodine thyroid ablation for Graves' disease
- surgery in the form of hemi, sub-total, or complete thyroidectomy

Graves' Disease

Definition

- an autoimmune disorder characterized by autoantibodies to the TSH receptor that leads to hyperthyroidism

Epidemiology

- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F>M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology

- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds and stimulates the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) a result of increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and displacement of the eye ball forward
- dermopathy may be related to cutaneous glycosaminoglycan deposition

Graves' Ophthalmopathy

NO SPECS (in order of changes usually)
No signs
Only signs: lid lag, lid retraction
Soft tissue: periorbital puffiness, conjuctival injection, chemosis
Proptosis/exophthalmos
Extraocular (diplopia)
Corneal abrasions (since unable to close eyes)
Sight loss

Clinical Features
- signs and symptoms of thyrotoxicosis
- diffuse thyroid goitre ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity if Graves' (plus signs of hyperthyroidism: lid retraction, characteristic stare)
- dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as *non-pitting* edema)
- acropachy: clubbing and thickening of distal phalanges

Investigations
- low TSH
- increased free T_4 (and/or increased T_3)
- positive for TSI
- increased radioactive iodine (I-131) uptake
- homogeneous uptake on thyroid scan (only do this test in the presence of nodule)

Treatment
- thionamides
  - propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of T_4 to T_3
  - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
  - small goitre and recent onset are good indicators for long-term remission with medical therapy
  - major side effects: hepatitis, agranulocytosis, and fever/arthralgias
  - minor side effects: rash
  - iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of T_4 to T_3 and are especially effective in combination with MMI
  - MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
  - MMI contraindicated in pregnancy (teratogenic), use PTU
- symptomatic treatment with β-blockers
- thyroid ablation with radioactive ^{131}I if PTU or MMI trial does not produce disease remission
  - high incidence of hypothyroidism after ^{131}I requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy
- subtotal or total thyroidectomy (indicated rarely for large goitres, suspicious nodule for CA, if patient is intolerant to thionamides and refusing RAI ablation)
  - risks include hypoparathyroidism and vocal cord palsy
- ophthalmopathy/orbitopathy
  - smoking cessation is most important
  - prevent drying
  - high dose prednisone in severe cases
  - orbital radiation, surgical decompression

Prognosis
- course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
- lifetime follow-up needed
- risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Other Medications Used in the Treatment of Graves'

Glucocorticoids have been useful in the treatment of severe Graves' hyperthyroidism and thyroid storm, by inhibiting the conversion of peripheral T_4 to T_3

Lithium is also used to treat Graves' hyperthyroidism. It acts by blocking thyroid hormone release, but its toxicity has limited its use in practice

Caution with Thionamides

These drugs are effective in controlling hyperthyroidism and induce permanent remission in 20-30% of patients with Graves' disease. They inhibit thyroid hormone synthesis. They are most often employed to achieve a euthyroid state before definitive treatment. Adverse effects include teratogenicity, agranulocytosis, hepatotoxicity, and ANCA-positive vasculitis

Radioiodine Therapy for Graves' Disease and the Effect on Ophthalmopathy: A Systematic Review

Clin Endocrinol 2008;69:943-950

Purpose: To assess whether radioiodine therapy (RAI) for Graves' disease (GD) is associated with increased risk of ophthalmopathy compared with antithyroid drugs (ATDs) or surgery. To assess the efficacy of glucocorticoid prophylaxis in the prevention of occurrence or progression of Graves' ophthalmopathy (GO), when used with RAI.

Study Selection: RTCs regardless of language or publication status.

Results: RAI was associated with an increased risk of GO compared with ATD (Relative Risk (RR) 4.23, 95% confidence interval (CI 2.04-8.77) but compared with thyroidectomy, there was no statistically significant increased risk (RR 1.59, 95% CI 0.89-2.81). The risk of severe GO was also increased with RAI compared with ATD (RR 4.35, 95% CI 1.28-14.73). Prednisolone prophylaxis for RAI was highly effective in preventing the progression of GO in patients with pre-existing GO (RR 0.03; 95% CI 0.00-0.24). The use of adjunctive ATD with RAI was not associated with any significant benefit on the course of GO.

Conclusions: RAI therapy for GD is associated with a small but definite increased risk of development or worsening of GO compared with ATDs. Steroid prophylaxis is beneficial for patients with pre-existing GO.

Subacute Thyroiditis (Thyrotoxic Phase)

Definition
- acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
- two subtypes: painful and painless

Etiology and Pathophysiology
- acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
- disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
- painful = viral (usually preceded by URTI), De Quervain's (granulomatous thyroiditis)
- painless = postpartum, auto-immune, lymphocytic
  - occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

Clinical Features
- two forms
  - painful ("De Quervain's") thyroid, ears, jaw, and occiput
  - painless ("Silent")
- fever and malaise may be present, especially in De Quervain's
- postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo postpartum
- may be mistakenly diagnosed as postpartum depression

Laboratory Investigations
- initial elevated free T_4, T_3, low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses values consistent with hypothyroidism may appear

Treatment
- painful – high dose NSAIDs, prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of T_4 to T_3
- β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid, may treat short-term with thyroxine

Prognosis
- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

Toxic Adenoma/Toxic Multinodular Goitre

Etiology and Pathophysiology
- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T_3 and T_4
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer's disease])

Clinical Features
- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- seen most frequently in elderly people, often with presentation of atrial fibrillation

Investigations
- low TSH, high T_3 and T_4
- thyroid scan with increased uptake in nodule(s) and suppression of the remainder of the gland

Treatment
- initiate therapy with PTU or MMI to attain euthyroid state
- use high dose radioactive iodine (I-131) to ablate hyperfunctiong nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

Thyrotoxic Crisis/Thyroid Storm

Definition
- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- rare, but serious with mortality rate between 10-30%

Etiology and Pathophysiology
- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- tachyarrhythmia, CHF, shock
- mental status changes ranging from delirium to coma

Laboratory Investigations
- increased free T_3 and T_4, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or similar agents for β-adrenergic blockade is used, which additionally causes decreased peripheral conversion of T4 → T3
- use with caution in CHF patients as it may worsen condition

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses
- Give iodide, which acutely inhibits the release of thyroid hormone, one hour after the first dose of PTU is given
  - Sodium iodide 1 g IV drip over 12h q12h
    OR
  - Lugol's solution 2-3 drops q8h
    OR
  - Potassium iodide (SSKI) 5 drops q8h
- dexamethasone 2-4 mg IV q6h for the first 24-48 hours lowers body temperature and inhibits peripheral conversion of T4 → T3

Prognosis
- probably <20% mortality rate if rapidly recognized and treated

Hypothyroidism

Definition
- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

Epidemiology
- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T_4, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative (^{131}I or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves'
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4,000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
  - insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 19. Interpretation of Serum TSH and Free T_4 in Hypothyroidism

	Serum TSH	Free T_4
Overt Primary Hypothyroidism	Increased	Decreased
Subclinical Primary Hypothyroidism	Increased	Normal
Secondary Hypothyroidism	Decreased or not appropriately elevated	Decreased

Thyroid Hormone Replacement for Subclinical Hypothyroidism
Cochrane DB Syst Rev 2007;3:CD003419
Purpose: To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.
Study Selection: RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.
Results: No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood, and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.
Conclusions: In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

Clinical Features

Table 20. Clinical Features of Hypothyroidism

General	Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia
CVS	Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart
Respiratory	Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia
GI	Weight gain despite poor appetite, constipation
Neurology	Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes ("hung reflexes"), carpal tunnel syndrome, asymptomatic increase in CK, seizures
GU	Menorrhagia, amenorrhea, impotence
Dermatology	Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discolouration (carotenemia)
Hematology	Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis

Signs and Symptoms of Hypothyroidism

HIS FIRM CAP
Hypoventilation
Intolerance to cold
Slow HR
Fatigue
Impotence
Renal impairment
Menorrhagia/amenorrhea
Constipation
Anemia
Paresthesia

Treatment
- L-thyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 μg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism
  - monitor via measurement of free T_4 (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM
- see Pediatrics, P29

Hashimoto's Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

Etiology and Pathophysiology
- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na^+/I^- symporter

Risk Factors
- female gender
- genetic susceptibility: increased frequency in patients with Down's syndrome, Turner's syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations
- high TSH, low T_4 (not necessary to measure T_3 as it will be low as well)
- presence of anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin antibodies (TgAb) in serum

Treatment
- if hypothyroid, replace with L-thyroxine (analog of T_4)

Myxedema Coma

Definition
- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare, high level of mortality when it occurs (up to 40%, despite therapy)

Clinical Features
- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

Investigations
- decreased T_4, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider T_3 therapy
- supportive measures: mechanical ventilation, vasopressor drugs, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

Sick Euthyroid Syndrome

Definition
- changes in circulating thyroid hormones amongst patients with serious illness, trauma, or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free T_3 may be followed by low TSH and if severe illness low free T_4
- with recovery of illness, TSH may overshoot and become transiently high

Pathophysiology
- abnormalities include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself
  - may be protective during illness by reducing tissue catabolism

Labs
- initially decreased free T_3 followed by decreased TSH and finally decreased free T_4

Treatment
- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goitre

Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone

Treatment
- remove goitrogens
- radioiodine therapy (need very high doses, low iodine uptake, used as last resort)
- suppression with L-thyroxine (rarely done)
- surgery may be necessary for severe compressive symptoms

Complications
- compression of neck structures causing stridor, dysphagia, pain, and hoarseness
- multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition
- clearly defined discrete mass, separated from the thyroid parenchyma
- palpable nodules are found in approximately 5% of women and 1% of men

Etiology
- benign tumours (e.g. colloid nodule, follicular adenoma)
- thyroid malignancy
- hyperplastic area in a multinodular goitre
- cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations

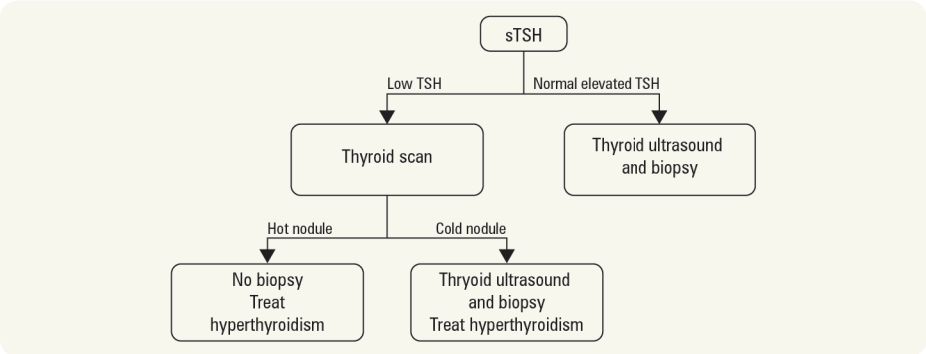


Figure 9. Approach to the evaluation of a thyroid nodule
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

Thyroid Malignancies

- see Otolaryngology, OT38

Adrenal Cortex

Adrenocorticotropic Hormone

- a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
- secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
- stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
- some melanocyte stimulating activity

Adrenocortical Hormones

Aldosterone
- a mineralocorticoid which regulates extracellular fluid (ECF) volume through Na^+ (and Cl^-) retention and K^+ (and H^+) excretion (stimulates distal tubule Na^+/K^+ ATPase)
- regulated by the renin-angiotensin-aldosterone system (Figure 12)
- negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone → volume expansion) and short loop (angiotensin II → peripheral vasoconstriction)

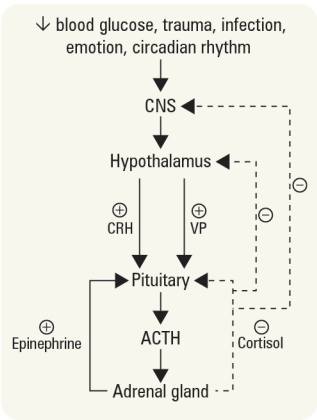


Figure 10. Regulation of CRH-ACTH-adrenal gland axis

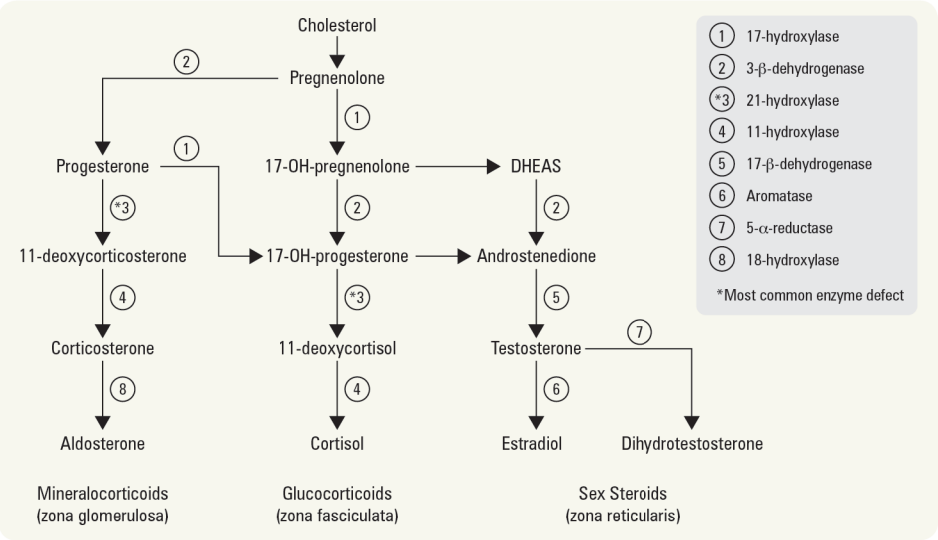


Figure 11. Pathways of major steroid synthesis in the adrenal gland and their enzymes

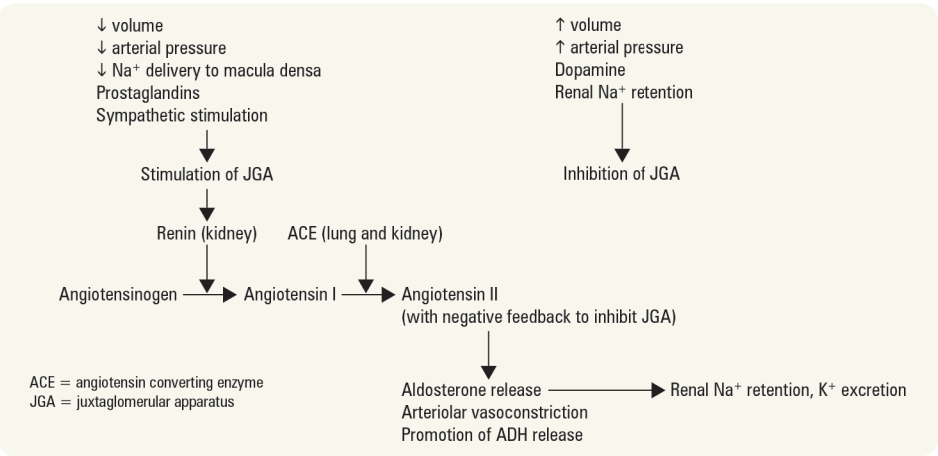


Figure 12. Renin-angiotensin-aldosterone axis (see Nephrology, NP4)

Layers of the Adrenal Cortex

OUTSIDE

Zona Glomerulosa produces **mineralocorticoids (aldosterone)**

Zona Fasciculata produces **glucocorticoids (cortisol)**

Zona Reticularis produces **androgens (DHEA, androstenedione)**

INSIDE

Cortisol

- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behaviour and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

Stimulatory Effects	Inhibitory Effects
Stimulate hepatic glucose production (gluconeogenesis)	Inhibit bone formation; stimulate bone resorption
Increase insulin resistance in peripheral tissues	Inhibit fibroblasts, causing collagen and connective tissue loss
Increase protein catabolism	Suppress inflammation; impair cell-mediated immunity
Stimulate leukocytosis and lymphopenia	Inhibit growth hormone axis
Increase cardiac output, vascular tone, Na^+ retention	Inhibit reproductive axis
Increase PTH release, urine calcium excretion	Inhibit vitamin D_3 and inhibit calcium uptake

Androgens

- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age

Adrenocortical Functional Workup

Principles of Diagnosing Adrenal Disorders
- Is the suspected hormone ↑ or ↓?
- Can it be suppressed/stimulated?
- Is the stimulating hormone ↑ or ↓? (primary vs. secondary)

STIMULATION TEST
- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

1. Tests of Glucocorticoid Reserve
- Cosyntropin (ACTH analogue) Stimulation Test
  - give 1 μg or 250 μg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
  - physiologic response: stimulated plasma cortisol of >500 nmol/L
  - inappropriate response: inability to stimulate increased plasma cortisol
- insulin tolerance is the gold standard test used to diagnose adrenal insufficiency (see *Pituitary Gland*, E16)

SUPPRESSION TESTS
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. Tests of Pituitary-Adrenal Suppressibility
- Dexamethasone (DXM) Suppression Test
  - principle: DXM suppresses pituitary ACTH → plasma cortisol should be lowered if HPA axis is normal
  - *Screening Test*: Overnight DXM Suppression Test
    - oral administration of 1 mg DXM at midnight → measure plasma cortisol levels the following day at 8 am
    - physiologic response: plasma cortisol <50 nmol/L, with 50-140 nmol/L being a "grey zone" (cannot be certain if normal or not)
    - inappropriate response: failure to suppress plasma cortisol
    - <20% false positive results due to obesity, depression, alcohol, other medications
  - *Confirmatory Test*: Other testing is used to confirm the diagnosis, such as:
    - 24 h urine free cortisol (shows overproduction of cortisol)
    - midnight salivary cortisol (if available), shows lack of diurnal variation
    - inappropriate response: remains high (normally will be low at midnight)

2. Tests of Mineralocorticoid Suppressibility
- principle: expansion of extracellular fluid volume (ECFV) → plasma aldosterone should be lowered if HPA axis were normal
- ECFV Expansion with Normal Saline (NS)
  - IV infusion of 500 mL/h of NS for 4 h → then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L is consistent with primary hyperaldosteronsim, <140 pmol/L is normal
  - inappropriate response: failure to suppress plasma aldosterone

Mineralocorticoid Excess Syndromes

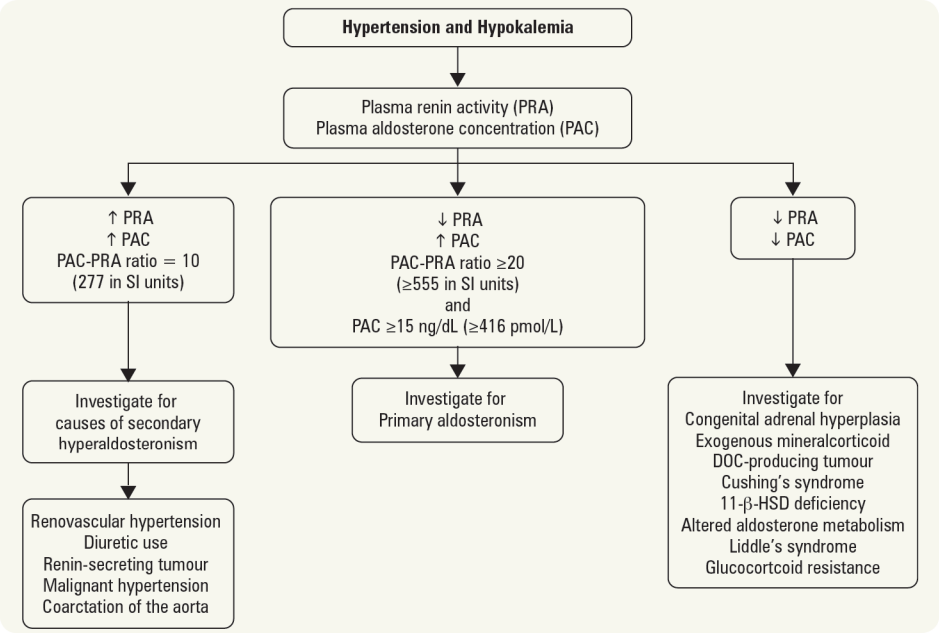


Figure 13. Approach to mineralocorticoid excess syndromes

Definition

- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism (SH): aldosterone production in response to excess RAAS (extra-adrenal cause)

Etiology

- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn's syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism

Clinical Features

- HTN
- hypokalemia (may have mild hypernatremia), metabolic alkalosis
- normal K^+, low Na^+ in SH (low effective circulating volume leads to ↑ ADH release) → edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

Diagnosis

- investigate plasma aldosterone to renin ratio in patients with HTN and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECFV expansion)
- imaging: CT adrenal glands

Table 22. Diagnostic Tests in Hyperaldosteronism

Test	Primary Hyperaldosteronism	Secondary Hyperaldosteronism
Plasma aldosterone to renin ratio (PAC/PRA)	Elevated (↑ aldo, ↓ renin)	Normal (↑ aldo, ↑ renin)
Salt loading test A) Oral test B) IV saline test	 ↑ urine aldosterone ↑ plasma aldosterone	Not performed if normal PAC/PRA

Treatment

- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause

Cushing's Syndrome

Definition
- results from chronic glucocorticoid excess (endogenous or exogenous sources)

Etiology
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing's disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumours)
- ACTH-independent (15%)
  - long-term use of exogenous glucocorticoids
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia

Clinical Features
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent

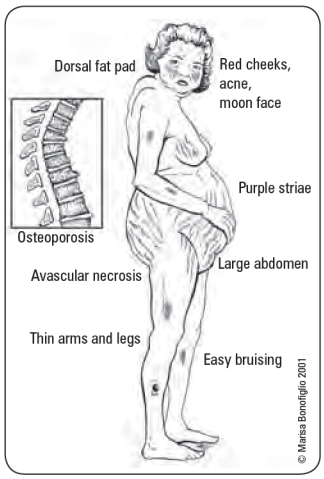


Figure 14. Clinical features of Cushing's syndrome

Diagnosis
- complete a drug history to exclude iatrogenic Cushing's
- perform one of: 1. 24 h urine free cortisol, 2. dexamethasone suppression test, or 3. late night salivary cortisol
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM)
- confirm with one of the remaining tests if necessary (do not rely on random cortisol, insulin tolerance, loperamide, or urinary 17-ketosteroid tests)

Treatment
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation post-operatively
  - carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  - medical treatment: mitotane, ketoconazole to reduce cortisol
- pituitary
  - trans-sphenoidal resection, with glucocorticoid supplement post-operatively
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
  - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole

Congenital Adrenal Hyperplasia

- see Pediatrics, P30

Hyperandrogenism

Definition
- state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

Constitutional/Familial	Family history, predisposing ethnic background Premature adrenarche
Medications Androgen-Mediated	Anabolic steroids, ACTH, androgens, progestational agents
Ovarian	PCOS Ovarian hyperthecosis Theca cell tumours Pregnancy: placental sulfatase/aromatase deficiency
Adrenal	Congenital adrenal hyperplasia (CAH, late-onset CAH) Tumours (adenoma, carcinoma)
Pituitary	Cushing's disease – high ACTH Hyperprolactinemia

Clinical Features

Females

- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
- virilization
  - masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  - increase in musculature
- defeminization
  - loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males

- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production, and spermatogenesis

Conditions that do NOT Represent True Hirsutism

- Androgen-independent hair (e.g. lanugo hair)
- Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)
- Topical steroid use

Investigations

- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose, lipids, 75 g OGTT

Treatment

- discontinue causative medications
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase SHBG, which binds androgens>estrogens; reduce ovarian production of androgens)
- surgical resection of tumour
- low dose glucocorticoid ± mineralocorticoid if CAH suspected
- treat specific causative disorders, e.g. tumours, Cushing's, etc.
- cosmetic therapy (laser, electrolysis)

Adrenocortical Insufficiency

Definition

- a state of inadequate cortisol and/or aldosterone production by the adrenal glands

Etiology

PRIMARY (ADDISON'S DISEASE)

Table 24. Etiology of Primary Adrenocortical Insufficiency

Autoimmune (70-90%)	Isolated adrenal insufficiency Polyglandular autoimmune syndrome type I and II Antibodies often directed against adrenal enzymes and 3 cortical zones
Infection	TB (7-20%) (most common in developing world) Fungal: histoplasmosis, paracoccidioidomycosis HIV, CMV Syphilis African trypanosomiasis
Infiltrative	Metastatic cancer (lung>stomach>esophagus>colon>breast); lymphoma Sarcoidosis, amyloidosis, hemochromatosis
Vascular	Bilateral adrenal hemorrhage (risk increased by heparin and warfarin) Sepsis (meningococcal, *Pseudomonas*) Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children Thrombosis, embolism, adrenal infarction
Drugs	Inhibit cortisol: ketoconazole, etomidate, megestrol acetate Increase cortisol metabolism: rifampin, phenytoin, barbiturates
Others	Adrenoleukodystrophy Congenital adrenal hypoplasia (impaired steroidogenesis) Familial glucocorticoid deficiency or resistance

SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see *Hypopituitarism*, E20), including withdrawal of exogenous steroids

Clinical Features

Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

	Primary AI (Addison's or Acute AI)	Secondary AI
Skin and Mucosa	Dark (palmar crease, extensor surface)	Pale
Potassium	High	Normal
Sodium	Low	Normal or Low
Metabolic Acidosis	Present	Absent
Associated Diseases	Primary hypothyroidism, type 1 DM, vitiligo, neurological deficits	Central hypogonadism or hypothyroidism, growth hormone deficiency, DI, headaches, visual abnormalities
Associated Symptoms	Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia GI: N/V, abdominal pain, diarrhea	Same except: NO salt craving GI less common
Diagnostic Test	Insulin tolerance test Cosyntropin Stimulation Test High morning plasma ACTH	Insulin tolerance test Cosyntropin Stimulation Test Low morning plasma ACTH

Adapted from: Salvatori R. *JAMA* 2005;294:2481-2488

Treatment

- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

Adrenal Medulla

Catecholamine Metabolism

ABC of Adrenaline

Adrenaline activates
β-receptors, increasing
Cyclic AMP

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinehprine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine

Pheochromocytoma

Definition

- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

Etiology and Pathophysiology

- most cases sporadic (80%)
- familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB) (50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5.7% penetrance)
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines

Clinical Features
- 50% suffer from paroxysmal HTN; the rest have sustained HTN
- classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
- other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia
- other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
- symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)

Investigations
- urine catecholamines
  - increased catecholamine metabolites (metanephrines) and free catecholamines
  - plasma metanephrines if available (most sensitive)
    - cut-off values will depend on assay used
- CT abdomen
  - if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment
- surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
- adequate pre-operative preparation
  - α-blockade for BP control: doxazosin or calcium channel blockers (10-21 d pre-operative), IV phentolamine (perioperative, if required)
  - β-blockade for HR control once α blocked for a few days
  - metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
  - volume restoration with vigorous salt-loading and fluids
- rescreen urine 1-3 mo post-operatively
- screen urine in first degree relatives; genetic testing in patients <50 yr old

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasm

- neoplastic syndromes involving multiple endocrine glands
- tumours of neuroectodermal origin
- autosomal dominant inheritance with variable penetrance
- genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II
  - early cure and prevention of medullary thyroid cancer

MEN I – Wermer's Syndrome Affects the 3 Ps

Pituitary
Parathyroid
Pancreas

Table 26. MEN Classification

Type	Tissues Involved	Clinical Manifestations
MEN I (chromosome 11)		
Wermer's Syndrome	Pituitary (15-42%) Anterior pituitary adenoma	Headache, visual field defects, often non-secreting but may secrete GH (acromegaly) and PRL (galactorrhea, erectile dysfunction, decreased libido, amenorrhea)
	Parathyroid (≥95%) Primary hyperparathyroidism from hyperplasia	Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia
	Entero-pancreatic endocrine (30-80%) Pancreatic islet cell tumours Gastrinoma Insulinomas Vasoactive intestinal peptide (VIP)-omas Glucagonoma Carcinoid syndrome	Epigastric pain (peptic ulcers and esophagitis) Hypoglycemia Secretory diarrhea Rash, anorexia, anemia, diarrhea, glossitis Flushing, diarrhea, bronchospasm
MEN II (chromosome 10)		
1. IIa Sipple's Syndrome	Thyroid (>90%) Medullary thyroid cancer (MTC)	Physical signs are variable and often subtle
	Adrenal medulla (40-50%) Pheochromocytoma (40-50%)	Neck mass or thyroid nodule; non-tender, anterior lymph nodes HTN, palpitations, headache, sweating
	Parathyroid (10-20%) 1° parathyroid hyperplasia	Symptoms of hypercalcemia
	Skin Cutaneous lichen amyloidosis	Scaly skin rash

Table 26. MEN Classification (continued)

Type	Tissues Involved	Clinical Manifestations
2. Familial Medullary Thyroid Ca (a variant of IIa)	Thyroid MTC (≥95%)	MTC without other clinical manifestations of MEN IIa or IIb
3. IIb	Thyroid MTC Adrenal medulla Pheochromocytoma (≥50%) Neurons Mucosal neuroma, intestinal ganglioneuromas (100%) MSK (100%)	MTC: most common component, more aggressive and earlier onset than MEN IIa HTN, palpitations, headache, sweating Chronic constipation; megacolon Marfanoid habitus (no aortic abnormalities)

Investigations

- MEN I
  - laboratory
    - may consider genetic screening for MEN-1 mutation in index patients
      - if a mutation is identified, screen family members who are at risk
    - gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
    - insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels
    - glucagonoma: elevated blood glucose and glucagon levels
    - pituitary tumours: assess GH, IGF-1, and prolactin levels (for over-production), TSH, free T_4, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)
    - hyperparathyroidism: serum Ca^{2+} and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumours, gastrinoma, insulinoma
- MEN II
  - laboratory
    - genetic screening for RET mutations in all index patients
      - if a mutation is identified screen family members who are at risk
    - calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum Ca^{2+}, albumin, and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules → cytology
  - imaging
    - CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
    - octreoscan and/or radionuclide scanning for determining the extent of metastasis

Treatment

- MEN I
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress prolactin secretion
    - somatostatin for symptomatic carcinoid tumours
  - surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (if medical treatment fails for the latter)
    - trans-sphenoidal approach with prn external radiation
- MEN II
  - surgery for MEN IIa with pre-operative medical therapy
    - prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
    - α-blocker for at least 10-21 d for pheochromocytoma pre-operatively
    - hydration, calcitonin, IV bisphosphonates for hypercalcemia

Calcium Homeostasis

- normal total serum Ca^{2+}: 2.2-2.6 mmol/L
- ionic/free Ca^{2+} levels: 1.15-1.31 mmol/L
- serum Ca^{2+} is about 40% protein bound (mostly albumin), 50% ionized, and 10% complexed with PO43- and citrate
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney

Table 27. Major Regulators in Calcium Homeostasis

Major Regulators	Source	Regulation	Net Effect
PTH	Parathyroid glands	Stimulated by low serum Ca^{2+} and high serum PO_4^{3-}; inhibited by chronic low serum Mg^{2+}, high serum Ca^{2+}, and calcitriol	↑ Ca^{2+} ↑ Cacitriol ↓ PO_4^{3-}
Calcitriol ($1,25\text{-}(OH)_2D_3$)	Dietary intake Synthesized from cholesterol: UV on skin makes cholecalciferol ($vitD_3$) → liver makes calcidiol ($25\text{-}(OH)D_3$) → kidneys make calcitriol	Renal calcitriol production is stimulated by low serum PO_4^{3-} and PTH; inhibited by high serum PO_4^{3-} and calcitriol in negative feedback	↑ Ca^{2+} ↑ PO_4^{3-}
Calcitonin	Thyroid C cells	Stimulated by pentagastrin (GI hormone) and high serum Ca^{2+}; inhibited by low serum Ca^{2+}	↓ Ca^{2+} (in pharmacologic doses) ↓ PO_4^{3-}
Mg^{2+}	Major intracellular divalent cation	See section on *Magnesium* (E42)	Cofactor for PTH secretion
PO_4^{3-}	Intracellular anion found in all tissues	See section on *Phosphate* (E41)	↓ Ca^{2+}

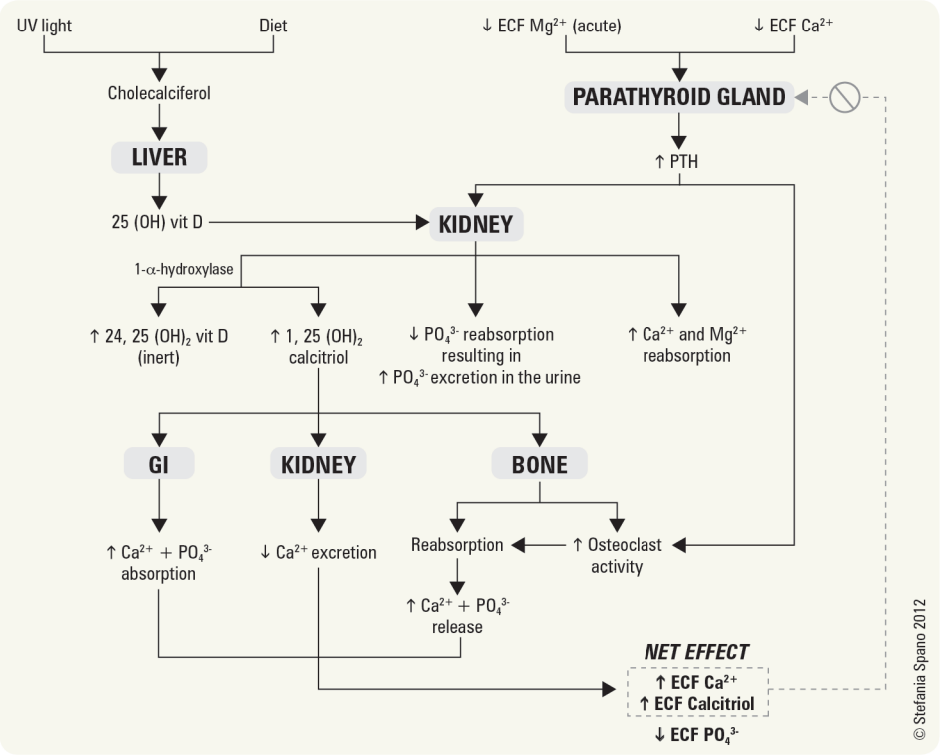


Figure 15. Parathyroid hormone (PTH) regulation

Hypercalcemia

Definition

- total corrected serum Ca^{2+} >2.6 mmol/L OR ionized Ca^{2+} >1.35 mmol/L
- hypercalcemia often diagnosed incidentally

Approach to Hypercalcemia

1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?

Primary Hyperparathyroidism
Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often parathyroid carcinoma or parathyroid hyperplasia

Secondary Hyperparathyroidism
Partial resistance to PTH action leads to parathyroid gland hyperplasia and increased PTH secretion, often in patients with renal failure and osteomalacia (due to low or low normal serum calcium levels)

Tertiary Hyperparathyroidism
Irreversible clonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis

Primary Hyperparathyroidism is the most common cause of hypercalcemia in healthy outpatients. Most commonly related to a solitary adenoma or less commonly multiple gland hyperplasia. Surgical excision acts as a definitive treatment and is recommended for patients who are symptomatic. For mild asymptomatic disease medial surveillance may be appropriate with annual serum calcium, creatinine, and BMD.

For asymptomatic patients surgery is recommended for those who meet ≥1 of the following criteria:

- Serum calcium concentration more than 0.25 mmol/L (1.0 mg/dL) above the upper limit of normal
- Creatinine clearance <60 mL/min
- BMD T-score <-2.5 at hip, spine, or distal radius, and/or previous fragility fracture
- Age <50 yr

Pseudohypercalcemia: increased protein binding leading to an elevation in serum total Ca^{2+} without a rise in the ionized/free form, e.g. hyperalbuminemia from severe dehydration

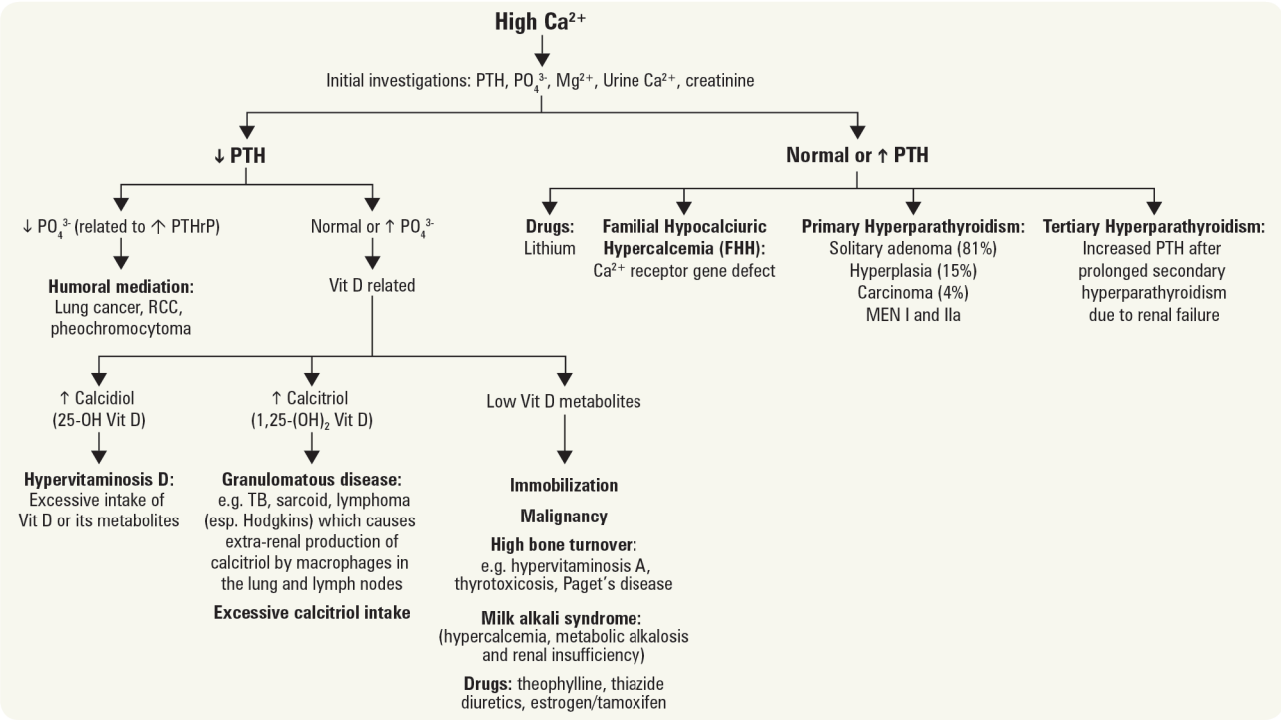


Figure 16. Differential diagnosis of hypercalcemia

Clinical Features

- symptoms depend on the absolute Ca^{2+} value and the rate of its rise (may be asymptomatic)

Table 28. Symptoms of Hypercalcemia

Cardiovascular	GI	Renal	Rheumatological	MSK	Psychiatric	Neurologic
HTN Arrhythmia Short QT Deposition of Ca^{2+} on valves, coronary arteries, myocardial fibres	Constipation Anorexia Nausea Vomiting **(groans)** PUD pancreatitis	Polyuria (Nephrogenic DI) Polydipsia Nephrolithiasis **(stones)** Renal failure (irreversible) Dehydration	Gout Pseudogout Chondrocalcinosis	Weakness Bone pain **(bones)**	>3 mmol/L (12 mg/dL) Increased alertness Anxiety Depression Cognitive dysfunction Organic brain syndromes >4 mmol/L (16 mg/dL) **Psychosis (moans)**	Hypotonia Hyporeflexia Myopathy Paresis

** **Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL):** primary symptoms include oliguria/anuria and mental status changes (including somnolence and eventually coma) → this is a medical emergency and should be treated immediately!

Corrected Ca^{2+} (mmol/L) = measured Ca^{2+} + 0.02 (40 – albumin)

For every decrease in albumin by 10, increase in Ca^{2+} by 0.2

Benign (less likely malignant): Ca^{2+} <2.75 mmol/L)

Pathologic (more likely malignant): Ca^{2+} >3.25 mmol/L

The symptoms and signs of hypercalcemia include: **"Bones, stones, groans, and psychic overtones"**

Treatment

- treatment depends on the Ca^{2+} level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively
- treat the underlying cause of the hypercalcemia

The most common cause of **hypercalcemia in hospital** is **malignancy-associated hypercalcemia**

- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

Mechanisms:

- Secretion of parathyroid hormone-related protein (PTHrP) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma
- Osteolytic bone metastases direct effect
- Excess PTH in parathyroid cancer

Table 29. Treatment of Acute Hypercalcemia/Hypercalcemic Crisis

Increase Urinary Ca^{2+} Excretion	Isotonic saline (4-5 L) over 24 h ± loop diuretic (e.g. furosemide) but only if hypervolemic (urine output >200mL/h) Calcitonin: • 4 IU/kg IM/SC q12h • 8 IU/kg IM/SC q6h • Only works for 48 h • Rapid onset within 4-6 h
Diminish Bone Resorption	Bisphosphonates (treatment of choice) • Inhibits osteoclastic bone resorption and promotes renal excretion of calcium • Acts rapidly but often transient response (decreased by 0.3-0.5 mmol/L beginning within 4-6 h) max effect usually in 7 d • Combination of calcitonin and steroids may prolong reduction in calcium • Tachyphylaxis may occur • Indicated in malignancy-related hypercalcemia (IV pamidronate is most commonly used, zoledronic acid also now used in CA patient) Mithramycin (rarely used) – effective when patient cannot tolerate large fluid load • Dangerous – hematotoxic and hepatotoxic
Decrease GI Ca^{2+} Absorption	Corticosteroids in hypervitaminosis D and hematologic malignancies • Anti-tumour effects → decreased calcitriol production by the activated mononuclear cells in lung and lymph node • Slow to act (5-10 d); need high dose
Dialysis	Treatment of last resort • Indication: severe malignancy-associated hypercalcemia and renal insufficiency or heart failure

Differential Diagnosis of Hypercalcemia
- **Primary hyperparathyroidism**
- **Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)**
- Renal disease: tertiary hyperparathyroidism
- Drugs: calcium carbonate, milk alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
- Familial hypocalciuric hypercalcemia
- Granulomatous disease: sarcoidosis, TB, Hodgkin's lymphoma
- Thyroid disease: thyrotoxicosis
- Adrenal disease: adrenal insufficiency, pheochromocytoma
- Immobilization

Watch Out for:
- Volume depletion via diuresis
- Arrhythmias

Acute Management of Hypercalcemia/ Hypercalcemic Crisis
- Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
- Calcitonin: transient, partial response
- Bisphosphonate: treatment of choice
- Corticosteroid: most useful in vit D toxicity, granulomatous disease, some malignancies
- Saline diuresis + loop diuretic (for volume overload): temporary measure

Hypocalcemia

Definition
- total corrected serum Ca^{2+} <2.2 mmol/L

Table 30. Clinical Features of Hypocalcemia

Acute Hypocalcemia	Chronic Hypocalcemia
Paresthesia Laryngospasm (with stridor) Hyperreflexia Tetany Chvostek's sign (tap CN VII) Trousseau's sign (carpal spasm) ECG changes Delirium Psychiatric Sx: emotional instability, anxiety, and depression	CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson's, dystonia, hemiballismus, papilledema, pseudotumour cerebri CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia) GI: steatorrhea ENDO: impaired insulin release SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition OCULAR: cataracts MSK: generalized muscle weakness and wasting

Hypomagnesmia can impair PTH secretion and action

Approach to Hypocalcemia
1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the Mg^{2+} level low?

Differential Diagnosis of Tetany
- Hypocalcemia
- Metabolic alkalosis (with hyperventilation)
- Hypokalemia
- Hypomagnesemia

Approach to Treatment
- correct underlying disorder
- mild/asymptomatic (ionized Ca^{2+} >0.8 mmol/L)
  - treat by increasing dietary Ca^{2+} by 1000 mg/d
  - calcitriol 0.25 µg/d (especially in renal failure)
- acute/symptomatic hypocalcemia (ionized Ca^{2+} <0.7 mmol/L)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary
  - goal is to raise Ca^{2+} to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion
- if PTH recovery not expected, requires long-term therapy with calcitriol and calcium
- **do not correct hypocalcemia if asymptomatic and suspected to be transient**

Signs and Symptoms of Acute Hypocalcemia
- **Paresthesias:** perioral, hands, and feet
- **Chvostek's sign:** percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
- **Trousseau's sign:** inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia

Transient hypoparathyroidism (resulting in hypocalcemia) common after subtotal thyroidectomy (permanent in <3% of surgeries)

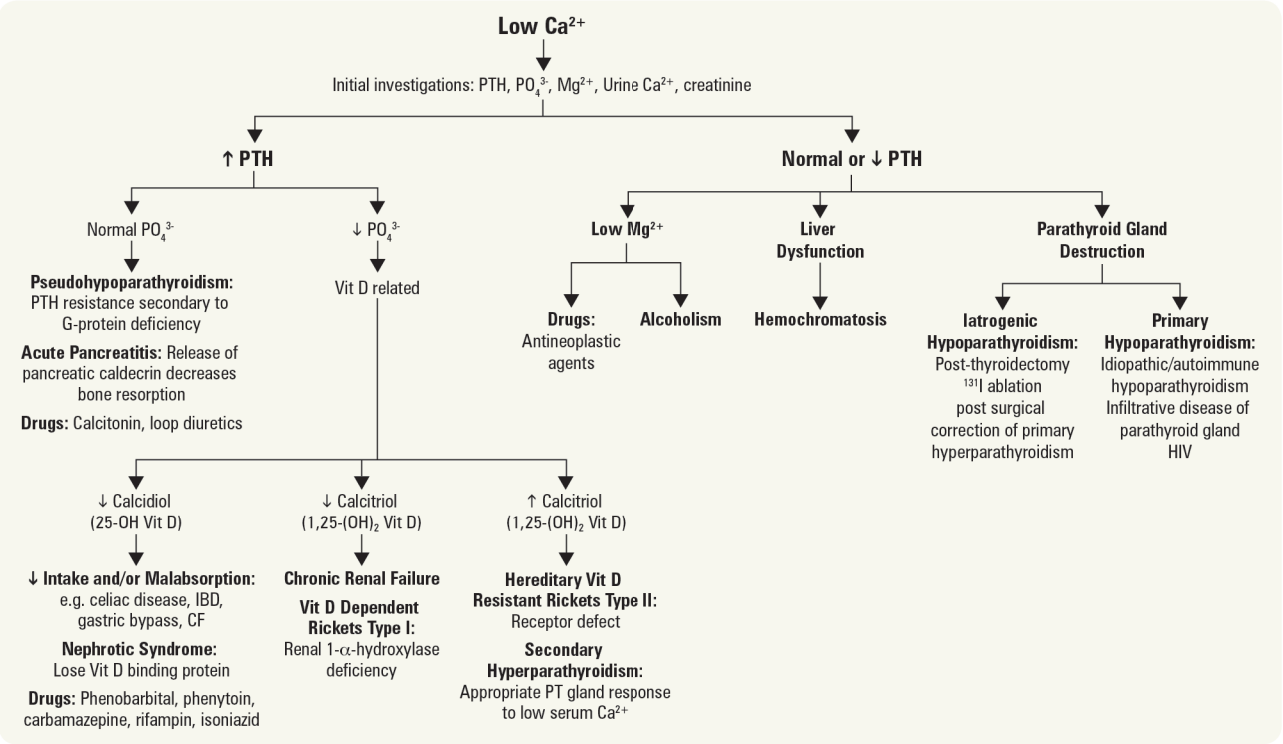


Figure 17. Etiology and clinical approach to hypocalcemia

Hyperphosphatemia

Definition

- serum phosphate >1.45 mmol/L
- critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced CKD and on dialysis

Table 31. Etiology of Hyperphosphatemia

Increased Phosphate Load	Reduced Renal Clearance	Pseudohyperphosphatemia
GI intake (rectal enema, GI bleeding) IV phosphate load (K-Phos®, blood transfusion) Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)	Acute/chronic renal failure Hypoparathyroidism Acromegaly Tumour calcinosis (ability of kidney to specifically clear phosphate is defective)	Hyperglobulinemia Hyperlipidemia Hyperbilirubinemia

Clinical Features

- non-specific, include ectopic calcification, renal osteodystrophy

Treatment

- acute: hemodialysis if symptomatic
- chronic: low PO_4^{3-} diet, phosphate binders (e.g. $CaCO_3$ or lanthanum carbonate with meals)

Hypophosphatemia

Definition

- serum phosphate <0.85 mmol/L

Symptoms usually present when phosphate <0.32 mmol/L (1.0 mg/dL)

Treat asymptomatic patients if phosphate <0.64 mmol/L (2.0 mg/dL)

Table 32. Etiology of Hypophosphatemia

Inadequate Intake	Renal Losses	Excessive Skeletal Mineralization	Shift into ICF
Starvation Malabsorption (diarrhea, steatorrhea) Antacid use Alcoholism	Hyperparathyroidism Diuretics X-linked or AD hypophosphatemic rickets Fanconi syndrome Multiple myeloma	Osteoblastic metastases Post parathyroidectomy (referred to as 'hungry bone syndrome')	Recovery from metabolic acidosis Respiratory alkalosis Starvation refeeding (stimulated by insulin)

Severe burns can cause hypophosphatemia due to PO_4^{3-} losses through the skin

Clinical Features
- non-specific (CHF, coma, hypotension, weakness, defective clotting)

Treatment
- treat underlying cause
  - Oral PO_4^{3-}: 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)
  - IV PO_4^{3-}: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia

Definition
- serum magnesium >0.85 mmol/L

Etiology
- AKI/CRF
- Mg^{2+}-containing antacids or enemas
- IV administration of large doses of $MgSO_4$ (e.g. for preeclampsia; see Obstetrics, OB25)

Clinical Features
- rarely symptomatic
- drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest, hypotension

Treatment
- discontinue Mg^{2+}-containing products
- IV calcium (Mg^{2+}-antagonist) for acute reversal of magnesium toxicity
- dialysis if renal failure

Hypomagnesemia

Definition
- serum magnesium <0.70 mmol/L

Etiology
- GI losses
  - starvation/malabsorption
  - vomiting/diarrhea
  - alcoholism
  - acute pancreatitis
- excess renal loss
  - 2° hyperaldosteronism due to cirrhosis and CHF
  - hyperglycemia
  - hypokalemia
  - hypercalcemia
  - loop and thiazide-type diuretics
  - nephrotoxic medications
  - proton-pump inhibitors

Clinical Features
- seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de pointes

Treatment
- treat underlying cause
- oral Mg^{2+} salts unless patients have seizures or other severe symptoms
- Mg^{2+} IM/IV; cellular uptake of Mg^{2+} is slow, therefore repletion requires sustained correction
- discontinue diuretics
  - in patients requiring diuretics, use a K^+-sparing diuretic to minimize magnesuria

You will be unable to correct hypokalemia or hypocalcemia without first supplementing magnesium if patient hypomagnesemic

Metabolic Bone Disease

Osteoporosis

Definition
- a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture
- bone mineral density (BMD) ≥2.5 standard deviations below the peak bone mass for young adults (i.e. T-score ≤–2.5)
- osteopenia: BMD with T-score between -1.0 and -2.5

Online Clinical Tools
CAROC
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf
FRAX
www.shef.ac.uk/FRAX/tool.aspx

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Osteoporosis (95% of osteoporosis in women & 80% in men)
- primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age
- primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency

Secondary Osteoporosis

- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g. celiac disease)
  - chronic liver disease
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - DM
  - hypogonadism
- malignancy
  - secondary to chemotherapy
  - myeloma
- drugs
  - corticosteroid therapy
  - phenytoin
  - chronic heparin therapy
  - androgen deprivation therapy
  - aromatase inhibitors
- other
  - rheumatologic disorders
    - rheumatoid arthritis
    - SLE
    - ankylosing spondylitis
  - renal disease
  - poor nutrition
  - immobilization
- COPD (due to disease, tobacco, and glucocorticoid use)

Corticosteroid Therapy is a Common Cause of Secondary Osteoporosis
Individuals receiving ≥7.5 mg of prednisone daily for over 3 mo should be assessed for bone-sparing therapy
Mechanism: increased resorption + decreased formation + increased urinary calcium loss + decreased intestinal calcium absorption + decreased sex steroid production

Clinical Features

- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist
  - fragility fractures: fracture with fall from standing height
  - Dowager's hump: collapse fracture of vertebral bodies in mid-dorsal region
  - x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign (weakening of subchondral plates and expansion of intervertebral discs)
- pain, especially backache, associated with fractures

Approach to Osteoporosis

1. Assess risk factors for osteoporosis on history and physical
2. Decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men and women ≥65 yr or younger if presence of risk factors
3. Initial investigations
   - all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis, celiac workup, and 24 h urinary Ca^{2+} excretion to rule out additional secondary causes
   - **25-OH-Vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved**
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture
4. Assess 10-yr fracture risk by combining BMD result and risk factors (only if ≥50 yr)
   1) WHO Fracture Risk Assessment Tool (FRAX)
   2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
      - approach to management guided by 10-yr risk stratification into low, medium, high risk
5. For all patients being assessed for osteoporosis, encourage appropriate lifestyle changes (see Table 35)

Use of Calcium or Calcium in Combination with Vitamin D Supplementation to Prevent Fractures and Bone Loss in People Aged 50 Years and Older: A Meta-Analysis
Lancet 2007;370:657-666
Purpose: To determine whether supplementation with calcium or calcium in combination with vitamin D reduces fractures of all types and percentage change of bone-mineral density from baseline.
Study Selection: RCTs that recruited people aged 50 yr or older.
Results: In trials that reported fracture as an outcome (17 trials, n=52,625), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0.88, 95% CI 0.83-0.95; p=0.0004). In trials that reported bone-mineral density as an outcome (23 trials, n=41,419), the treatment was associated with a reduced rate of bone loss of 0.54% (0.35-0.73; p<0.0001) at the hip and 1.19% (0.76-1.61%; p<0.0001) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0.0001). The treatment effect was better with calcium doses of 1200 mg or more (0.80 vs. 0.94; p=0.006), and with vitamin D doses of 800 IU or more (0.84 vs. 0.87; p=0.03).
Conclusion: Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 yr or older. For best therapeutic effect, use doses of 1200 mg of calcium, and 800 IU of vitamin D.

Table 33. Indications for BMD Testing

Older Adults (age ≥50 yr)	Younger Adults (age <50 yr)
All women and men age ≥65 yr Menopausal women, and men aged 50-64 yr with clinical risk factors for fracture: • Fragility fracture after age 40 • Prolonged glucocorticoid use • Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy) • Parental hip fracture • Vertebral fracture or osteopenia identified on x-ray • Current smoking • High alcohol intake • Low body weight (<60 kg) or major weight loss (>10% of weight at age 25 yr) • Rheumatoid arthritis • Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing's disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. inflammatory bowel disease)	Fragility fracture • Prolonged use of glucocorticoids • Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants) • Hypogonadism or premature menopause • Malabsorption syndrome • Primary hyperparathyroidism • Other disorders strongly associated with rapid bone loss and/or fracture

Clinical Signs of Fractures or Osteoporosis
- Height loss >3 cm (Sn 92%)
- Weight <51 kg
- Kyphosis (Sp 92%)
- Tooth count <20 (Sp 92%)
- Grip strength
- Armspan-height difference >5 cm (Sp 76%)
- Wall-occiput distance >0 cm (Sp 87%)
- Rib-pelvis distance ≤2 finger breadth (Sn 88%)

Table 34. Osteoporisis Risk Stratification

Low Risk 10-yr fracture risk <10%	Unlikely to benefit from pharmacotherapy; encourage lifestyle changes Reassess risk in 5 yr
Medium Risk 10-yr fracture risk 10-20%	Discuss patient preference for management and consider additional risk factors Factors that warrant consideration for pharmacological therapy: • Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray • Previous wrist fracture in individuals ≥65 or with T-score ≤-2.5 • Lumbar spine T-score much lower than femoral neck T-score • Rapid bone loss • Men receiving androgen-deprivation therapy for prostate cancer • Women receiving aromatase-inhibitor therapy for breast cancer • Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use • Recurrent falls (defined as falling 2 or more times in the past 12 mo) • Other disorders strongly associated with osteoporosis Repeat BMD and reassess risk every 1-3 yr initially
High Risk 10-yr fracture risk >20%; OR Prior fragility fracture of hip or spine; OR More than one fragility fracture	Start pharmacotherapy

Treatment of Osteoporosis

Table 35. Treatment of Osteoporosis in Women and Men

Treatment for Both Men and Women	
Lifestyle	Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d Exercise: 3x30 min weight-bearing exercises/wk Cessation of smoking, reduce caffeine intake Stop/avoid osteoporosis-inducing medications
Drug Therapy	
Bisphosphonate: inhibitors of osteoclast binding	1st line in prevention of hip, nonvertebral, and vertebral # (Grade A): alendronate, risedronate, zoledronic acid 2nd line (Grade B): etidronate
RANKL Inhibitors	Denosumab: 1st line in prevention of hip, nonvertebral, vertebral # (Grade A)
Parathyroid Hormone	YES fragility #: 18-24 mo duration
Calcitonin (2nd line) osteoclast receptor binding	YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 μg bid
Treatment Specific to Post-Menopausal Women	
SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast	Raloxifene: 1st line in prevention of vertebral # (Grade A) • +ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk • -ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps
HRT: combined estrogen + progesterone (see Gynecology, GY35)	1st line in prevention of hip, nonvertebral, and vertebral # (Grade A) For most women, risks > benefits • Combined estrogen/progestin prevents hip, vertebral, total # • Increased risks of breast cancer, cardiovascular events, and DVT/PE

Alendronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women
Cochrane DB Syst Rev 2008;1:CD001155

Etidronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women
Cochrane Database Syst Rev. 2008;(1):CD003376

Risedronate for the Primary and Secondary Prevention of Osteoporotic Fractures in Postmenopausal Women
Cochrane Database Syst Rev. 2008;(1):CD004523

Purpose: To assess the efficacy of three bisphosponates in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.
Study Selection: Women receiving at least one yr of bisphosphonates for postmenopausal osteoporosis were compared to those receiving placebo or concurrent calcium/vitamin D or both. The outcome was fracture incidence.
Results: Levels of evidence: http://www.cochranemsk.org/review/writing/
%RRR and %ARR for 5 yr fracture incidence reduction.

Aledronate (10 mg/d)

1° Prevention – Vertebral (Gold)	45% RRR, 2% ARR
1° Prevention – Hip	Not significant
1° Prevention – Wrist	Not significant
2° Prevention – Vertebral (Gold)	45% RRR, 6% ARR
2° Prevention – Hip (Gold)	53% RRR, 1% ARR
2° Prevention – Wrist (Gold)	50% RRR, 2% ARR

Etidronate (400 mg/d)

1° Prevention – Vertebral	Not significant
1° Prevention – Hip	Not significant
1° Prevention – Wrist	Not significant
2° Prevention – Vertebral (Silver)	47% RRR, 5% ARR
2° Prevention – Hip	No benefit
2° Prevention – Wrist	No benefit

Risedronate (5 mg/d)

1° Prevention – Vertebral	Not significant
1° Prevention – Hip	Not significant
1° Prevention – Wrist	Not significant
2° Prevention – Vertebral (Gold)	39% RRR, 5% ARR
2° Prevention – Hip (Silver)	26% RRR, 1% ARR
2° Prevention – Wrist	Not significant

Before prescribing Calcitonin, remember to ask about fish allergies

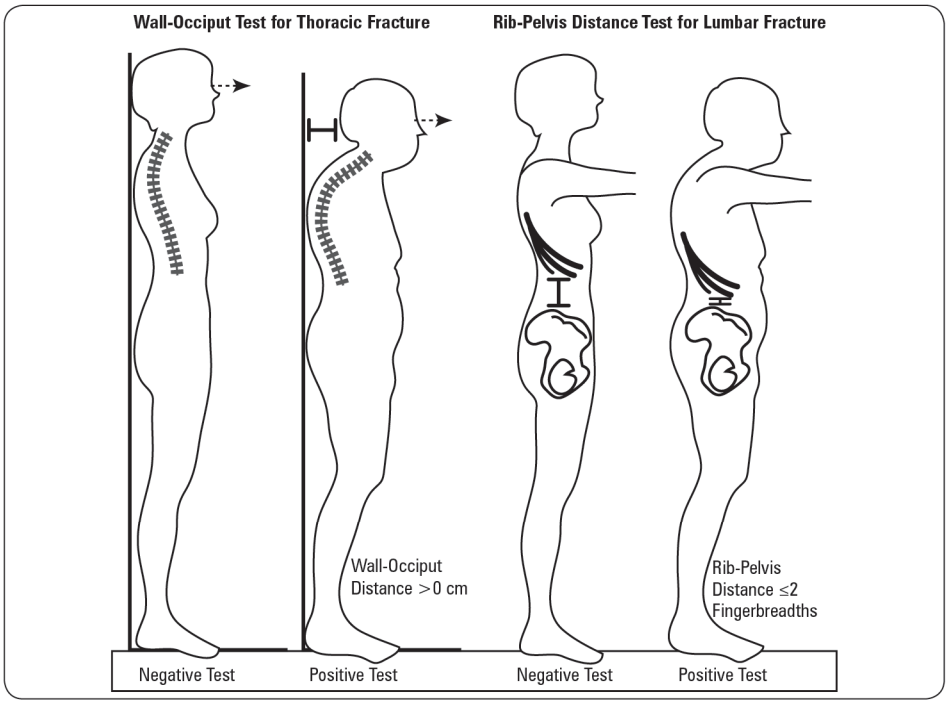


Figure 18. Physical examination test

Osteomalacia and Rickets

- **rickets:** osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *prior* to epiphyseal closure (in childhood)
- **osteomalacia:** osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *after* epiphyseal closure (in adulthood)

Etiology and Pathophysiology

Vitamin D Deficiency

- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- defective 1-α-25 hydroxylation
  - hypoparathyroidism
  - renal failure
- pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

Mineralization Defect

- abnormal matrix
  - osteogenesis imperfecta
  - fibrogenesis imperfecta
  - axial osteomalacia
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - bisphosphonates, aluminum, high dose fluoride, anticonvulsants

Factors Necessary for Mineralization
- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification

Table 36. Clinical Presentations of Rickets and Osteomalacia

Rickets	Osteomalacia
• Skeletal pain and deformities, bow legged • Fracture susceptibility • Weakness and hypotonia • Disturbed growth • Ricketic rosary (prominent costochondral junctions) • Harrison's groove (indentation of lower ribs) • Hypocalcemia	• Not as dramatic • Diffuse skeletal pain • Bone tenderness • Fractures • Gait disturbances (waddling) • Proximal muscle weakness • Hypotonia

Investigations

Table 37. Laboratory Findings in Osteomalacia and Rickets

Disorder	Serum Phosphate	Serum Calcium	Serum ALP	Other Features
Vitamin D deficiency	Decreased	Decreased to normal	Increased	Decreased calcitriol
Hypophosphatemia	Decreased	Normal	Decreased to normal	
Proximal RTA	Decreased	Normal	Normal	Associated with hyperchloremic metabolic acidosis
Conditions associated with abnormal matrix formation	Normal	Normal	Normal	

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profundus hip deformity
- bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO_4^{3-} supplements if low serum PO_4^{3-}, Ca^{2+} supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology
- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits $1,25(OH)_2$-Vit D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features
- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations
- serum Ca^{2+} corrected for albumin, PO_4^{3-}, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy

Treatment
- prevention
  - maintenance of normal serum Ca^{2+} and PO_4^{3-} by restricting PO_4^{3-} intake to 1 g OD
  - Ca^{2+} supplements; PO_4^{3-} binding agents (calcium carbonate, aluminum hydroxide)
  - vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

Paget's Disease of Bone

Definition
- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
- a common disease: 5% of the population, 10% of population >80 yr old
- consider Paget's disease of bone in older adults with ↑ ALP but normal GGT

Etiology and Pathophysiology
- postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis
- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Bones Most Often Affected in Paget's Disease (in decreasing order)
- Pelvis
- Femur
- Skull
- Tibia
- Vertebrae
- Clavicle
- Humerus

Clinical Features
- usually asymptomatic (routine x-ray finding or elevated ALP)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- skull involvement: headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
- high output CHF
- hypercalcemia with immobilization
- osteosarcoma

Investigations
- laboratory
  - ↑↑ serum ALP (unless burnt out), Ca^{2+} normal or ↑, PO_4^{3-} normal
  - urinary hydroxyproline ↑ (indicates resorption)
- imaging
  - bone scan to evaluate the extent of disease
  - confirmation on x-ray required to establish the diagnosis
  - skeletal survey: involved bones are denser and expanded with cortical thickening
    - initial lesion may be destructive and radiolucent
    - multiple fissure fractures in long bones

Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget's Disease
NEJM 2005;353:898-908
Study: Two identical, randomized, double-blind, actively controlled trials (combined for analysis).
Patients: 357 men and women who were older than 30 yr of age and had radiologically confirmed Paget's disease. All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.
Intervention: One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (30 mg/d) with follow up at 6 mo.
Primary Outcome: Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75% in the total alkaline phosphatase excess.
Results: At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171, $p<0.001$). Alkaline phosphatase levels normalized in 88.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group ($p<0.001$). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 d, $p<0.001$). Quality of life increased significantly from baseline at both 3 and 6 mo in the zoledronic acid group and differed significantly from those in the risedronate group at 3 mo. Pain scores improved in both groups. During post-trial follow-up (median, 190 d), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group ($p<0.001$).
Conclusions: A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget's disease than does daily treatment with risedronate.

Complications
- local
  - fractures; osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions and sudden increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output CHF due to increased vascularity

Treatment
- symptomatic therapy (pain management)
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if ALP >3x normal
  - bisphosphonates, e.g. alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo OR zoledronic acid 5 mg IV per yr
  - calcitonin 50-100 U/d SC
- surgery for fractures, deformity, degenerative changes

Male Reproductive Endocrinology

Androgen Regulation

- negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

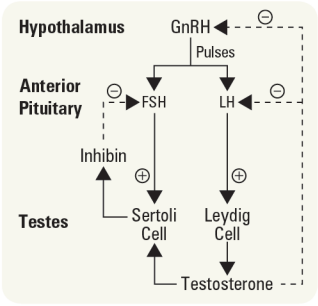


Figure 19. Hypothalamo-pituitary-gonadal axis

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total, bioavailable, and/or free testosterone
- human chorionic gonadotropin (hCG) stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

- see Urology, U34
- deficiency in gametogenesis or testosterone production

Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic
- primary hypogonadism is more common than secondary

Table 38. Classification and Features of Hypogonadism

	Hypergonadotropic Hypogonadism (Primary Hypogonadism)	Hypogonadotropic Hypogonadism (Secondary Hypogonadism)
Definition	Primary testicular failure ↑ LH and FSH, ↑ FSH:LH ratio ↓ testosterone and sperm count	Hypothalamic-pituitary axis failure ↓ LH + FSH (LH sometimes inappropriately normal) ↓ testosterone and sperm count
Etiology	Congenital: • Chromosomal defects (Klinefelter's, Noonan) • Cryptorchidism • Disorders of sexual development (DSD) • Bilateral anorchia (vanishing testicle syndrome) • Myotonic dystrophy • Mutation of FSH or LH receptor gene • Disorders of androgen synthesis Germ cell defects • Sertoli cell only syndrome • Leydig cell aplasia/failure Infection/Inflammation • Orchitis – TB, lymphoma, mumps, leprosy • Genital tract infection Physical factors • Trauma, heat, irradiation, testicular torsion, varicocele Drugs • Marijuana, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone Autoimmune (antisperm antibodies) Chronic systemic diseases (AIDS) Idiopathic	Congenital • Kallman's syndrome • Prader-Willi syndrome • Abnormal subunit of LH or FSH Infection • Tuberculosis, meningitis Endocrine • Adrenal androgen excess • Cushing's syndrome • Hypo or hyperthyroidism • Hypothalamic-pituitary disease (tumour, hyperprolactinemia, hypopituitarism) Drugs • Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/estrogen/progestin use, chronic narcotic use Chronic illness • Cirrhosis, chronic renal failure, AIDS • Sarcoidosis, Langerhan's cell histiocytosis hemochromatosis Critical illness • Surgery, MI, head trauma Obesity Idiopathic
Diagnosis	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone hCG stimulation (mainly used in pediatrics) Karyotype	**Testicular size and consistency (soft/firm)** Sperm count LH, FSH, total, and/or bioavailable testosterone Prolactin levels MRI of hypothalamic-pituitary region

Two Distinct Features of Primary Hypogonadism
- The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
- Likely to be associated with gynecomastia

Two Features of Secondary Hypogonadism
- Associated with an equivalent decrease in sperm count and serum testosterone
- Less likely to be associated with gynecomastia

Treatment
- testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - contraindicated if history of prostate cancer, severe LUTS associated with BPH, uncontrolled or poorly controlled CHF
- GnRH agonist to restore fertility, if hypothalamic dysfunction with intact pituitary
  - administered SC in pulsatile fashion using an external pump
- hCG ± recombinant follicular stimulating hormone (rFSH) can be used to restore fertility in cases of either hypothalamic or pituitary lesions
- testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

Other Causes of Male Infertility
- hereditary disorders: Kartagener syndrome, cystic fibrosis
- anatomy: hypospadias, retrograde ejaculation
- obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- surgery: TURP, radical prostatectomy, orchiectomy

DEFECTS IN ANDROGEN ACTION

Etiology
- complete androgen insensitivity (CAIS)
- partial androgen insensitivity (PAIS)
- 5-α-reductase deficiency
- mixed gonadal dysgenesis
- defects in testosterone synthesis
- infertile male syndrome
- undervirilized fertile male syndrome

Clinical Features
- depends on age of onset

Table 39. Effects of Testosterone Deficiency

First Trimester *in utero*	Incomplete virilization of external genitalia (ambiguous genitalia) Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphrodism)
Third Trimester *in utero*	Micropenis Cryptorchidism (failure of normal testicular descent)
Prepuberty	Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair) Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones) Poor muscle development, reduced peak bone mass
Postpuberty	Decrease in energy, mood, and libido Fine wrinkles in corners of mouth and eyes Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD

Adapted from: UpToDate, 2010; *Cecil's Essentials of Medicine*

Treatment
- appropriate gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

Approach to Male Infertility

Infertility: failure of a couple to conceive after 12 mo of regular intercourse without use of contraception in women <35 yr of age; and after 6 mo of regular intercourse without use of contraception in women ≥35 yr

History
- Partner status re: infertility
- Length of time for attempt to conceive
- Prior successes with other partners
- Ejaculation problems
- Frequency of intercourse
- Prev Surg, Med Hx, STI Hx
- Hx orchitis? Cryptorchidism?
- Hx toxic exposure?
- Medications
- Alcohol and illicit drug use
- Heat exposure: bath, sauna, whirlpool
- Smoking

P/E
- General (height, weight, gynecomastia, masculine)
- Testicular size and consistency
- Varicocele?
- Pituitary disease?
- Thyroid disease?

Investigations

Should be considered for couples unable to conceive after 12 mo of unprotected and frequent intercourse. Consider earlier evaluation if suggestive medical Hx and physical, and in women ≥35 yr of age
- Semen analysis x 2 (sperm count, morphology, motility)
- Scrotal/testicular U/S (look for varicocele)
- Blood work: LH, FSH, testosterone, prolactin, thyroid function tests, DNA fragmentation of sperm, karyotype, Y chromosome deletion
- Test female partner (see Gynecology, GY23)

Treatment
- No specific therapy for majority of cases
- Treat specific causes
- Consider: intrauterine insemination, IVF, therapeutic donor insemination, testicular aspiration of sperm, adoption

Erectile Dysfunction

- see Urology, U30

Gynecomastia

Definition
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

Etiology

Physiologic
- puberty
- elderly (involutional)
- neonatal (maternal hormone)

Pathologic
- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter's syndrome, androgen insensitivity
- other: idiopathic, familial

Pubertal Gyencomastia
- this benign condition peaks between 13-14 years of age and spontaneously regresses in 90% of cases within 2yr
- waiting is often the best approach

Causes of Gynecomastia

DOC TECH
Drugs
Other
Congenital
Tumour
Endocrine
CHronic disease

Pathophysiology
- hormonal imbalance due to increased estrogen activity (increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen) or decreased androgen activity (decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage)

History
- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

Occurrence of Gynecomastia

3 Peaks	% Affected
Infancy	60-90
Puberty	4-69
Ages 50-80	24-65

Physical Exam
- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard, or fixed mass, skin dimpling or retraction, and nipple discharge or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue, and no discrete mass is palpable
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations
- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated need to locate the primary tumour)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region if pituitary adenoma suspected

Treatment
- initial observation for most men with gynecomastia
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen, clomiphene
- surgical
  - usually required for macromastia; gynecomastia present for >1 yr (fibrosis is unresponsive to medication); or failed medical treatment and for cosmetic purposes

Female Reproductive Endocrinology

• see Gynecology, GY4

Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 40. Clinical Presentation

Syndrome Class	Symptoms/Syndrome	Associated Malignancies	Mechanism
Endocrine	Cushing's syndrome	Small-cell lung cancer Pancreatic carcinoma Neural tumours Thymoma	Ectopic ACTH and ACTH-like substance secretion
	SIADH	Small-cell lung cancer CNS malignancies	Antidiuretic hormone secretion
	Hypercalcemia	Lung cancer Breast carcinoma Renal cell carcinoma Multiple myeloma Ovarian carcinoma	PTH-related protein, TGF-α, TNF secretion
	Hypoglycemia	Hepatocellular carcinoma Fibrosarcoma	Insulin or insulin-like substance secretion
	Carcinoid	Pancreatic carcinoma Gastric carcinoma	Serotonin, bradykinin secretion
Neurologic	Lambert-Eaton myasthenic syndrome (LEMS) • muscle weakness in limbs	Small-cell lung cancer	Ab interferes with ACh release
	Myasthenia gravis • fluctuating muscle weakness and fatiguability	Thymoma	Ab interferes with ACh release
	Paraneoplastic limbic encephalitis • depression, seizures, short-term memory loss	Small-cell lung cancer	Unknown
Renal	Hypokalemic nephropathy	Small-cell lung cancer	Ectopic ACTH and ACTH-like substance secretion
	Nephrotic syndrome	Lymphoma Melanomas	Immunocomplex sedimentation in nephrons
GI	Watery diarrhea	Medullary thyroid carcinomas	Prostaglandin secretion
Hematologic	Erythrocytosis	Renal cell carcinoma Hepatocellular carcinoma	EPO production
Rheumatologic	SLE	Lymphomas Lung cancer Breast carcinoma Gonadal carcinoma	Anti-nuclear Ab production
	Scleroderma	Breast carcinoma Lung cancer Uterine cancer	Anti-nuclear Ab production

Investigations

- CBC, electrolytes, creatinine, LFTs, ALP, ESR, CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- ± endoscopy

Treatment

- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IVIg, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)

Diabetes Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects	Comments
Biguanide	• Sensitizes peripheral tissues to insulin → increases glucose uptake • Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK)	metformin	Glucophage® Glumetza®		500 mg OD titrated to 2000 mg/d maximum	• Useful in obese type 2 DM • Improves both fasting and postprandial hyperglycemia • Also↓ TG	ABSOLUTE: • Moderate to severe liver dysfunction • Moderate renal dysfunction GFR <30 mL/min • Cardiac dysfunction	• GI upset (abdo discomfort, bloating, diarrhea) • Lactic acidosis • Anorexia	↓ HbA1c 1.0-1.5% Weight neutral
Insulin Secretagogue	• Stimulates insulin release from β cells by causing K^+ channel closure → depolarization → Ca^{2+} mediated insulin release • Use in nonobese type 2 DM	sulfonylureas: glyburide	Diabeta® Euglucon®	Micronase® Glynase PreTab®	2.5-5.0 mg/d titrated to >5 mg bid Max: 20 mg/d		ABSOLUTE: • Moderate to severe liver dysfunction RELATIVE (glyburide and glimepiride): • Adjust dose in mild to moderate kidney dysfunction and avoid in severe kidney dysfunction • Avoid glyburide in the elderly INTERACTIONS: • Do not combine with a non-sulfonylurea insulin secretagogue or preprandial insulin	• Hypoglycemia • Weight gain	↓ HbA1c 0.8% Glicalazide lowest incidence of hypoglycemia
		gliclazide	Diamicron® Diamicron® MR		40-160 mg bid 30-120 mg OD				
		glimepiride	Amaryl®		1-8 mg OD				
		non-sulfonylureas: repaglinide	GlucoNorm®		0.5-4 mg tid	• Short $t_{1/2}$ of 1 h causes brief but rapid ↑in insulin, therefore effective for post-prandial control	ABSOLUTE: • Severe liver dysfunction INTERACTIONS: • Do not combine with a non-sulfonylurea or pre-prandial insulin	• Hypoglycemia • Weight gain	↓ HbA1c 0.7% for repaglinide and 0.5-1.0% for nateglinide
		nateglinide	Starlix®		60-120 mg tid				
Insulin Sensitizers (thiazolidinedione)	• Sensitizes peripheral tissues to insulin → increases glucose uptake • Decreases FFA release from adipose • Binds to nuclear receptor PPAR-γ	rosiglitazone	Avandia®		2-8 mg OD	• Rosiglitazone – indicated only in patients with type 2 DM for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance	ABSOLUTE: • NYHA > class II CHF INTERACTIONS: • Do not combine with insulin	• Peripheral edema • CHF • Anemia • Fluid retention and CHF • Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing) • Increased risk of bladder cancer with pioglitazone • Fractures	↓ HbA1c 0.8%
		pioglitazone	Actos®		15-45 mg OD				
α-Glucosidase Inhibitor	• ↓ carbohydrate GI absorption by inhibiting brush border α-glucosidase	acarbose	Glucobay®		25 mg OD titrated to 100 mg tid	• ↓ postprandial hyperglycemia	ABSOLUTE: • Inflammatory bowel disease • Severe liver dysfunction	• Flatulence • Abdominal cramps • Diarrhea	↓ HbA1c 0.6% Not recommended as initial therapy in patients with A1c>8.5%
Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor	• Inhibits degradation of endogenous antihyperglycemic incretin hormones • Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emtyping	sitagliptan	Januvia®		100 mg OD		ABSOLUTE (sitagliptin): • Type 1 DM • DKA RELATIVE (sitagliptin and saxagliptin): • Use with dose reduction in kidney dysfunction	• Nasopharyngitis • URTI • Headache • Pancreatitis • Stevens-Johnson syndrome	↓ HbA1c 0.7% Weight neutral
		saxagliptin	Onglyza™		2.5-5 mg OD				
		linagliptin	Trajenta®		5 mg OD				
Glucagon-Like Peptide (GLP)-1 Analogue	• Binds to GLP-1 receptor to promote insulin release • Insulinotropic effect suppressed as plasma glucose <4 mmol/L • Slows gastric emptying, suppresses inappropriately elevated glucagon levels • Causes β-cell regeneration and differentiation *in vitro*	Exenatide		Byetta®	5-10 μg SC bid 1 h before meals		ABSOLUTE: • Type 1 DM • DKA • Acute pancreatitis Hx RELATIVE: • Gastroparesis • ESRD • Personal or family history of medually thyroid cancer (MTC)	• N/V, diarrhea • Dizziness, headache • Muscle weakness • Anti-exantide antibodies • Pancreatitis	↓ HbA1c 1.0%
		Liraglutide		Victoza®	0.6-1.8 mg OD SC				

For insulin formulations see Table 9, E9

Dyslipidemia Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
HMG-CoA Reductase Inhibitor	• Inhibits cholesterol biosynthesis, ↓ LDL synthesis, ↑LDL clearance, modest ↑HDL, limited ↓ VLDL	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin simvastatin	Lipitor® Lescol® Mevacor® Pravachol® Crestor® Zocor®		10-80 mg/d 20-80 mg/d 20-80 mg/d 10-40 mg/d 5-40 mg/d 10-80 mg/d	• 1st line monotherapy • Used for ↑LDL, ↑TG	• Active liver disease • Persistent ↑ in AST, ALT unexplained	• GI symptoms • Rash, pruritus • ↑liver enzymes • Myositis (↑risk if combined with fibrates) • Rhabdomyolysis
Fibrates	• Upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑HDL	bezafibrate fenofibrate gemfibrozil	Bezalip® Lipidil® Lopid®		400 mg/d 48-200 mg/d 600-1200 mg/d	• Used for ↑TG, hyperchylomicronemia	• Hepatic disease • Renal disease	• GI upset • Skin rashes • ↑risk of gallstone formation • ↑risk of rhabdomyolysis when combined with statins
Niacin	• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL	nicotinic acid	Niaspan® generic niacin	Niacor®	0.5-2 g/d 1-3 g/d	• Used for ↑LDL, ↑VLDL	• Hypersensitivity • Hepatic dysfunction • Active PUD • Hyperuricemia	• Generalized flushing • Abnormal liver enzymes • Pruritus • IGT • Watch glucose control with overt DM
Bile Acid Sequestrants	• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL	cholestyramine colestipol	Questran® Colestid®		2-24 g/d 5-30 g/d	• Used for ↑LDL • Use as adjunct with statins or fibrates	• Complete biliary obstruction • Pregnancy, lactation • TG >3.5 mmol/L • GI motility disorder	• Constipation • Nausea • Flatulence • Bloating • Rise in TG
Cholesterol Absorption Inhibitors	• Inhibits cholesterol absorption at the small intestine brush border	ezetimibe	Ezetrol®	Zetia®	10 mg/d	• Used for ↑LDL, apo B	• Hypersensitivity • Hepatic dysfunction • Do not combine with fibrates or bile acid resins	• Fatigue • Pharyngitis • Sinusitis • Abdominal pain • Diarrhea • Arthralgia

Thyroid Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Antithyroid Agent (thionamides)	• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T_4 and T_3 • PTU also interferes with conversion of T_4 to T_3	propylthiouracil (PTU) methimazole (MMI)	Propyl-Thyracil® Tapazole®		Start 100 mg PO tid, then adjust accordingly Thyroid storm: start 200-300 PO qid, then adjust accordingly Start 5-20 mg PO OD, then adjust accordingly Up to 60 mg OD may be required	• Hyperthyroidism	• Hypersensitivity • Relative: renal failure, liver disease • PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester • Lactation: safe with PTU <300 mg/day and MMI <20-30 mg/d	• N/V • Rash • Drug-induced hepatitis • Agranulocytosis • Hepatitis with PTU • Cholestasis with MMI
Thyroid Hormone	• Synthetic form of thyroxine (T_4)	levothyroxine l-thyroxine	Synthroid® Eltroxin®	Levoxyl®	0.05-2.0 mg/d, usually 1.6x weight (kg) is dose in micrograms In elderly patients start at 0.025 mg/d	• Hypothyroidism	• Recent MI, thyrotoxicosis	• If wrong dosing: symptoms of hypothyroidism or hyperthyroidism • Skin rash from dye in pill
Antithyroid Agent Radiopharmaceutical	• Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue	sodium iodide I-131	Iodotope®		Dose corrected for 24 h radioactive iodine uptake Hyperthyroidism 4-12 mCi Thyroid Ca 50-150 mCi	• Hyperthyroidism • Thyroid malignancy	• Hypersensitivity • Concurrent antithyroid medication • Pregnancy, lactation	• N/V • Bone marrow suppression • Sialadenitis • Thyroiditis

Metabolic Bone Disease Medications

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Bisphosphonates	• Inhibits osteoclast-mediated bone resorption	alendronate	Fosamax®		Osteoporosis: 5-10 mg OD 70 mg once weekly Paget's: 40 mg OD for 6 mo	• Prevention of postmenopausal osteoporosis • Treatment of osteoporosis • Glucocorticoid-induced osteoporosis • Paget's disease	• Esophageal stricture or achalasia (oral) • Unable to stand or sit upright for >30 min (oral) • Hypersensitivity • Hypocalcemia • Renal insufficiency	• GI • MSK pain • Headache • Osteonecrosis of the jaw
		risedronate	Actonel®		Osteoporosis: 5 mg OD 35 mg once weekly 150 mg once monthly Paget's: 30 mg OD for 2 mo	• Treatment and prevention of postmenopausal osteoporosis • Treatment and prevention of glucocorticoid-induced osteoporosis • Paget's disease		
		etidronate	Didronel®		Paget's: 5-10 mg /kg OD x 6 mo	• Symptomatic Paget's disease • Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury		
		ibandronate	Boniva®		2.5 mg OD or 150 mg once monthly	• Treatment and prevention of postmenopausal osteoporosis (US only)		
		pamidronate	Aredia®		Hypercalcemia of malignancy 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment	• Hypercalcemia of malignancy • Paget's disease • Osteolytic bone metastases of breast cancer • Osteolytic lesions of multiple myeloma		
		zoledronate	Zometa® Aclasta®		5 mg IV once yearly IV	• Treatment of osteoporosis • Hypercalcemia of malignancy • Treatment and prevention of skeletal complications related to cancer		
Selective Estrogen Receptor Modulators	• Decreases resorption of bone through binding to estrogen receptors	raloxifene	Evista®		60 mg OD	• Treatment and prevention of postmenopausal osteoporosis (2nd line)	• Lactation • Pregnancy • Active or past history of DVT, PE, or retinal vein thrombosis	• Hot flashes • Leg cramps • Increased risk of fatal stroke, venous thromboembolism
Calcitonin	• Inhibits osteoclast-mediated bone resorption	calcitonin	Miacalcin®		One spray (200 IU) per day, alternating nostrils	• Treatment of postmenopausal osteoporosis, greater than 5 yr postmenopause	• Clinical allergy to salmon-calcitonin	• Rhinitis • Epistaxis • Sinusitis • Nasal dryness
Anti-RANKL Monoclonal Ab	• Inhibits RANKL (osteoclast differentiating factor) → inhibit osteoclast formation and decrease bone resorption	denosumab	Prolia™	Xgeva™	60 mg SC q6mo	• Treatment of postmenopausal women at high risk of fracture • Prevent skeletal-related events in patients with bone metastasis from solid tumours	• Hypocalcemia	• Fatigue/headache • Dermatitis/rash • Hypophosphatemia/Hypocalcemia • Hypercholesterolemia • GI discomfort
PTH	• Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity	teriparatide	Forteo®		20 µg SC OD x 18-24 mo	• Treatment of postmenopausal women with osteoporosis who are at high risk for fracture • Treatment of men with primary or hypogonadal osteoporosis who are at high risk for fracture	• Paget's disease • Prior external beam or implant radiation therapy involving the skeleton • Bone metastases • Metabolic bone diseases other than osteoporosis	• Orthostatic hypotension • Hypercalcemia • Dizziness • Leg cramps

Metabolic Bone Disease Medications (continued)

Drug Class	Mechanism of Action	Generic Drug Name	Canada Name	US Name (if different)	Dosing	Indications	Contraindications	Side Effects
Calcium	• Inhibits PTH secretion				1200 mg/d (including diet) Divided in 3 doses	• Osteopenia • Osteoporosis • Prevention of metabolic bone disease	• Caution with renal stones	• Vomiting • Constipation • Dry mouth
Vitamin D	• Regulation of calcium and phosphate homeostasis	cholecalciferol (vitamin D3)			800 -2000 IU/d	• Osteopenia • Osteoporosis • Prevention of metabolic bone disease	• Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)	• Hypercalcemia • Headache • N/V • Constipation
		ergocalciferol (vitamin D2)	Drisdol® Erdol®		50,000 IU/wk	• Osteoporosis in patients with liver dysfunction, refractory rickets, hypoparathyroidism	• Hypercalcemia • Malabsorption syndrome • Decreased renal function	
		calcitriol ($1,25(OH)_2$-D)	Rocaltrol® Calcijex®		Start 0.25 μg/d Titrate up by 0.25 μg/d at 4-8 wk intervals to 0.5-1 μg/d Start 0.25 μg/d Titrate up by 0.25 μg/d at 2-4 wk intervals to 0.5-2 μg/d	• Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis • Hypoparathyroidism	• Hypercalcemia • Vitamin D toxicity	

Adrenal Medications

Drug Class	Mineralocorticoid Activity	Generic Drug Name	Potency (Relative to Cortisol)	Equivalent Dose (mg)	Duration of Action ($t_{1/2}$ in h)	Dosing	Comments
Hydrocortisone	Yes	Cortef Solu-Cortef	1.0	20	8	Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h) PO once stable (50 mg q8h x 48 h, then taper over 14 d) Chronic AI: 15-20 mg PO OD (2/3 AM, 1/3 PM)	• In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K^+ metabolic alkalosis)
Cortisone Acetate	Yes	Cortisone Acetate	0.8	25	oral = 8 IM = 18+	Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h Chronic AI: 25 mg/d	• Pro-drug which is converted to active form as hydrocortisone • High doses can result in mineralocorticoid side effects (see above)
Prednisone	No	Prednisone	4	5	16-36	Adrenal Crisis: 15-60 mg/d PO qd or divided bid/qid Chronic AI: 5 mg daily	• Pro-drug which is converted to active form as prednisolone
Dexamethasone	No	Dexamethasone	30	0.7	36-54	Adrenal Crisis: 4 mg IV; repeat q2-6h if necessary	• Used for undiagnosed adrenal insufficiency (does not interfere with measurement of serum cortisol levels)

Landmark Endocrinology Trials

Trial	Reference	Results
DIABETES		
ACCORD	*NEJM* 2008; 358:2560-72	Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (<6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events
ADVANCE	*NEJM* 2008; 358:2545-59	Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause; hypoglycemia was more common in the intensive control group
BARI-2D	*NEJM* 2009; 360:2503-15	In patients with both type 2 DM and CAD no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin
DCCT	*NEJM* 1993; 329:977-86	Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in type 1 DM
EDIC	*NEJM* 2005; 353:2644-53	Compared with conventional therapy intensive DM therapy early on without macrovascular disease (goal HbA1c <6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 DM
Look AHEAD	*NEJM* 2013; 369:145-54	Moderate weight loss (<7% BW) and increased exercise are not associated with reduction in CVD and its complications among overweight or obese patients with type 2 DM
NAVIGATOR	*NEJM* 2010; 362:1463-90	In patients with impaired glucose tolerance, nateglinide did not reduce progression to DM or risk of cardiovascular events while valsartan only reduced progression to DM
PREDIMED	*NEJM* 2013; 368:1279-90	A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, CVA, or CV death in those at high risk for CV disease (outcome was driven by reduction in rates of CVA)
Steno-2	*NEJM* 2008; 358:580-91	In at-risk patients with type 2 DM intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality; multifactorial intervention is critical in the management of type 2 DM
UKPDS	*Lancet* 1998; 352:837-53	Intensive blood glucose control reduces microvascular but not macrovascular complications in type 2 DM
UKPDS Extension	*NEJM* 2008; 359:1577-89	Continued risk reduction in microvascular risk and emergent risk reductions for MI and death from any cause 10 yr post UKPDS trial follow up in type 2 DM
VADT	*NEJM* 2009; 360:1-11	In patients with longstanding poorly controlled type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications; adverse events, predominantly hypoglycemia, were more common in the intensive control group
LIPIDS		
4S	*Lancet* 1994; 344:1383-89	In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty
FIELD	*Lancet* 2005; 366:1849-61	In patients with type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events; it did reduce non-fatal MI and revascularizations
HPS	*Lancet* 2002; 360:7-22	In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events
Jupiter	*NEJM* 2008; 359:2195-207	Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity CRP levels and no hyperlipidemia
TNT	*NEJM* 2005; 352:1425-35	Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d

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