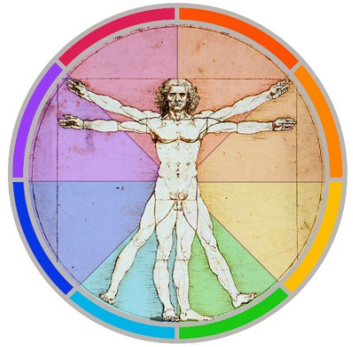
HUBS 191 2025
Lecture 27



Endocrine 3: Thyroid, parathyroids and calcium homeostasis

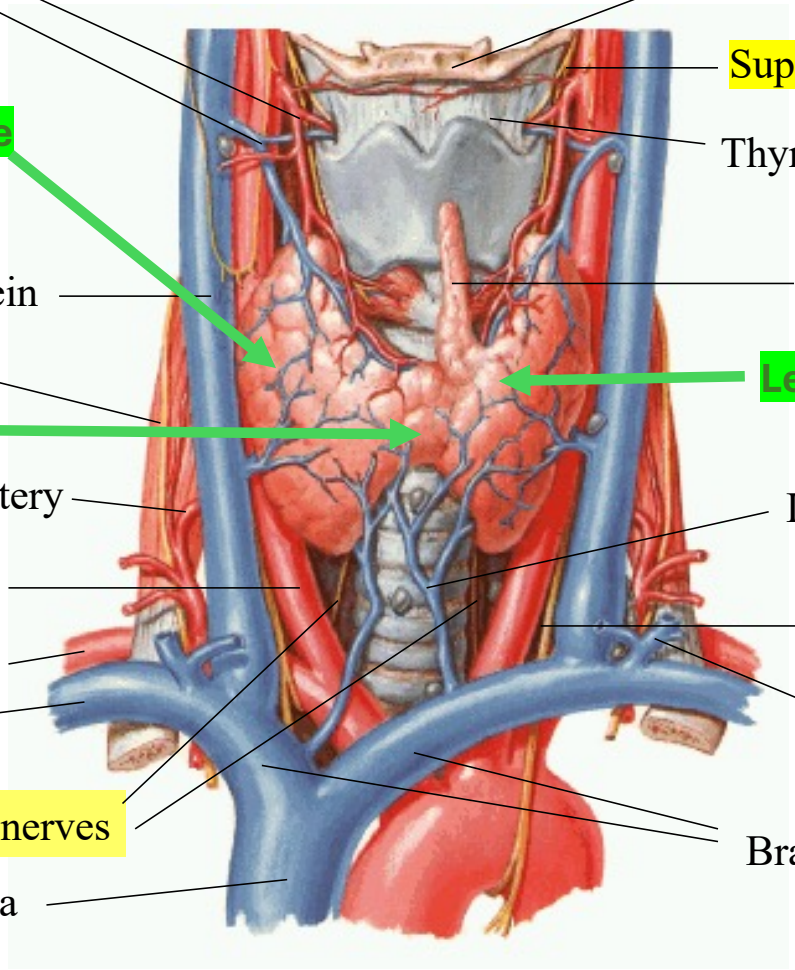
- Thyroid hormones and thyroid gland
- Thyroid disorders
- Parathyroid glands and parathyroid hormone
- Vitamin D and calcitriol
- Disorders of relating to calcium and calcitriol

Philip Kelly
HUBS Professional Practice Fellow

Lecture Objectives (Updated)

- Discuss the location and structure of the thyroid and parathyroids.
- Outline the synthesis and the secretion of thyroid hormones and their effects.
- Explain how thyroid hormone secretion is controlled.
- Outline selected disorders relating to the thyroid.
- Recognise signs and symptoms of hypo and hyperthyroidism
- Outline the importance of plasma calcium (Ca^{2+}) homeostasis and how this is regulated by parathyroid hormone and calcitonin.
- Explain the formation of calcitriol (active Vitamin D) and how this affects calcium homeostasis and bone mineralization.
- Identify the disorders that occur in children and adults if calcitriol is deficient

Thyroid Gland -Location



You don't need to know the names of these blood vessels or nerves yet

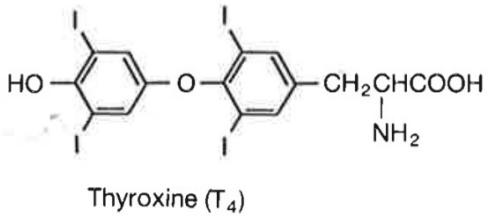
Immediately below larynx, anterior and on each side of trachea

<u>Very vascular</u> and one of the largest endocrine glands

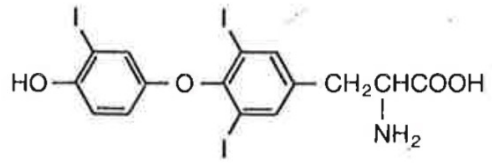
Thyroid Gland

- **Secretes thyroid hormones**
  - Thyroxine (T4) and Triiodothyronine (T3)
  - Iodine attached to tyrosines which then get linked
  - Two benzene rings confers **lipid solubility**
  - > 90% of thyroid hormone in blood is T4
  - Most of the T4 is converted to T3 in the tissues
  - 99% T3 and T4 attached to plasma proteins in blood i.e. thyroid-binding globulins or albumin

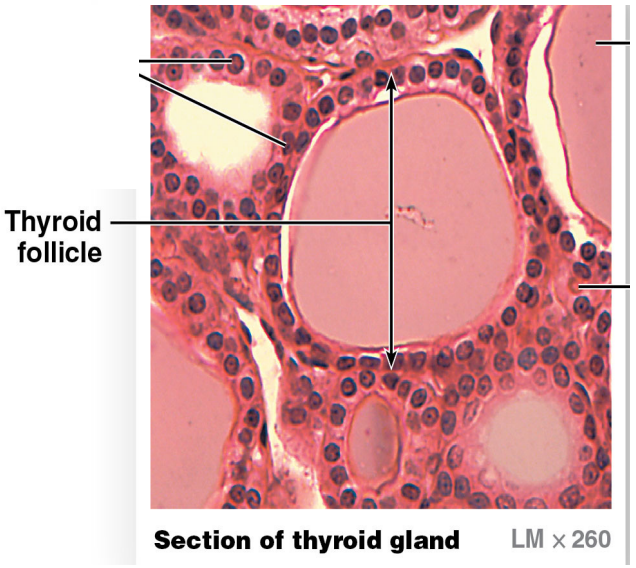
- **Thyroid gland composed of follices**
  - Follicles filled with a large glycoprotein (***thyroglobulin***) secreted by cuboidal cells that comprise the follicular walls
  - Thyroglobulin also referred to as colloid



Thyroxine (T_4)



3,5,3′-triiodothyronine (T_3)



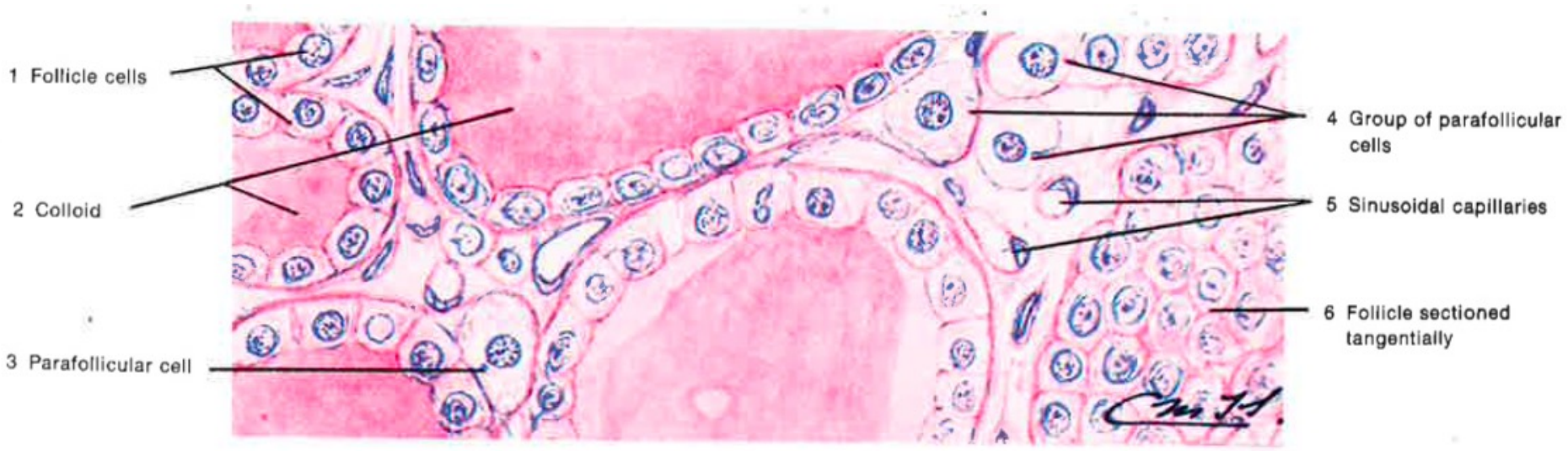


Fig. 3. *Parafollicular cells.*
Stain: hematoxylin-eosin. 600×.

Parafollicular (C-cells) lie between follicles and secrete **calcitonin** (peptide)

- Secretion triggered by increased ECF calcium concentration
- **Reduces osteoclast activity** and shifts balance toward deposition in bone
- **Inhibits reabsorption of calcium by kidney** (so more calcium lost in urine)
- Lowers ECF calcium levels via above 2 mechanisms
- Generally has the opposite effect to PTH (see later) but **much less important.**

Synthesis and Release of Thyroid Hormones

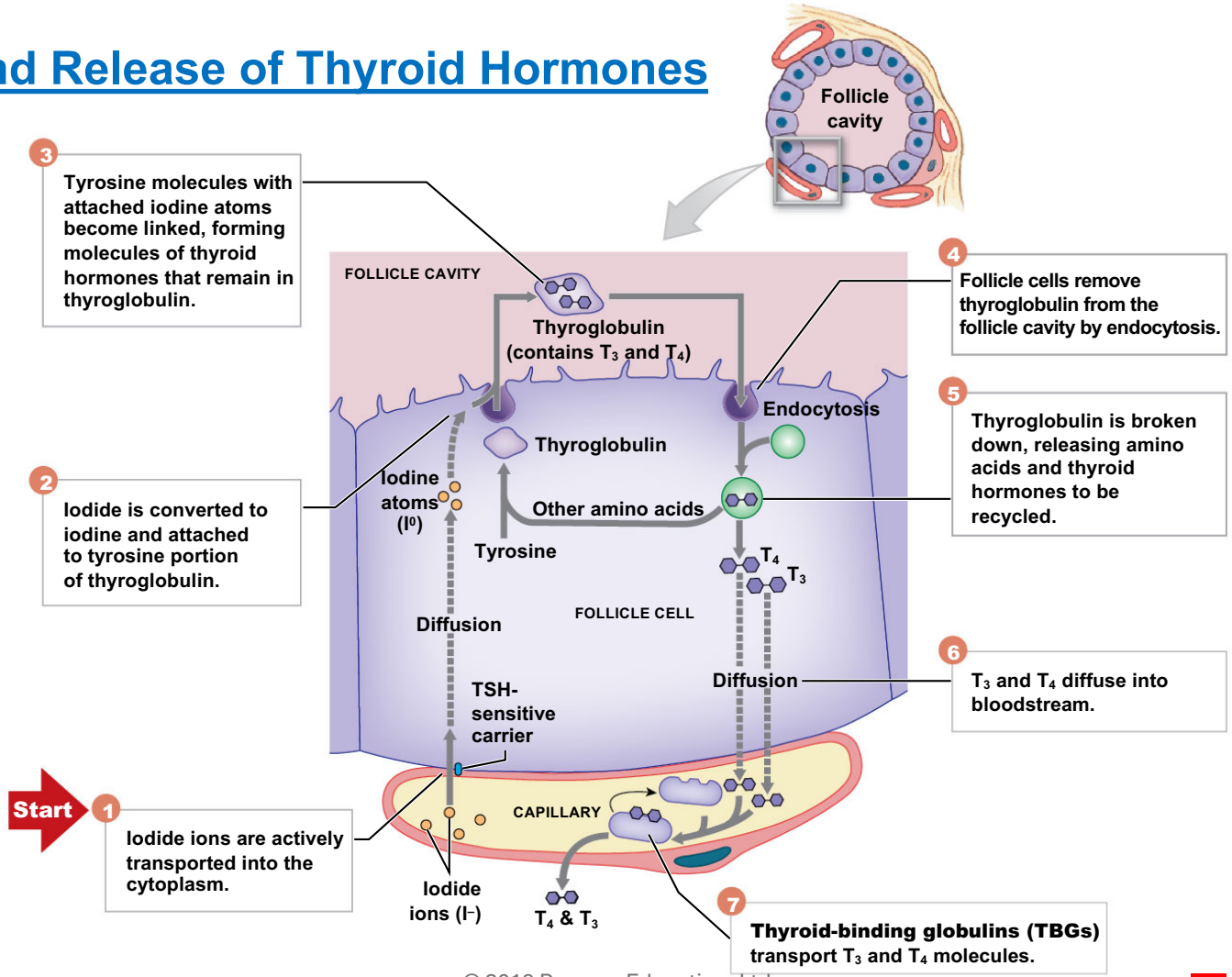


Figure 16.8 3

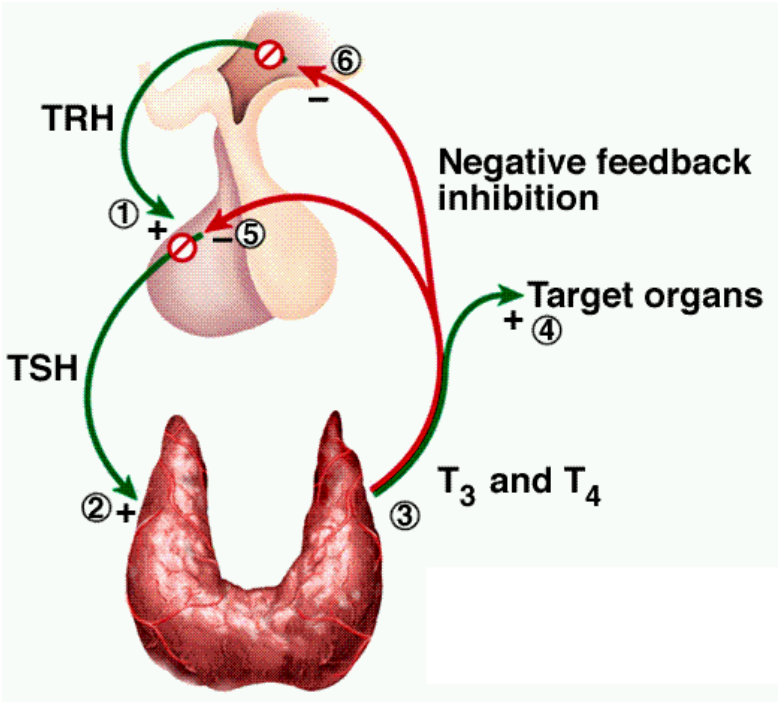
Synthesis and Release of Thyroid Hormones (as per previous diagram)

- Iodides in blood actively transported into the cells of the follicles
- Iodide oxidised to iodine which then binds to tyrosine residues of large thyroglobulin glycoprotein synthesized and secreted by cuboidal epithelial cells of follicular walls.
- Iodotyrosine residues become coupled to each other to produce T3 and T4
- Thyroid hormones stored within follicles in association with thyroglobulin
- Iodinated thyroglobulin taken up into follicle cells.
- Lysosymes in cytoplasm fuse with vesicles and digest thyroglobulin molecules to release T3 and T4
- T3 and T4 then diffuse into surrounding capillaries
- Thyroid hormones transported in blood bound to plasma proteins

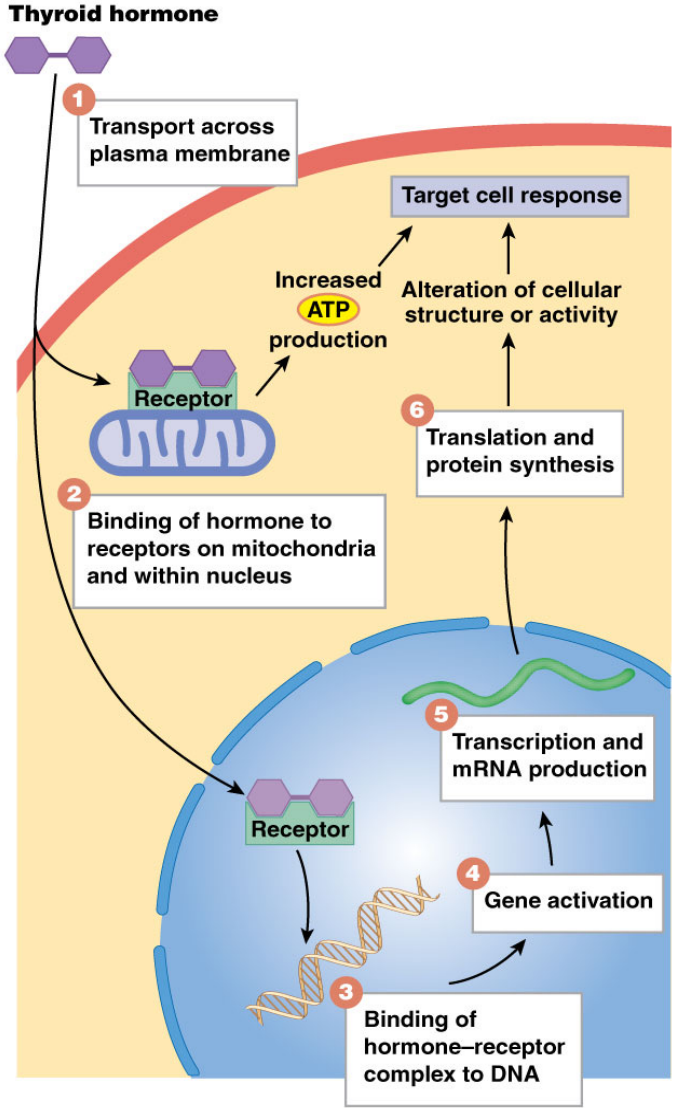
Control of thyroid hormone secretion

Factors stimulating TRH release:

- Low levels of thyroid hormones
- Low metabolic rate
- Prolonged cold exposure
- Other signals relating to metabolism and growth



- Thyrotropin releasing hormone (TRH) is secreted by hypothalamic neurons and enters the hypothalamic-hypophyseal-portal capillaries
- TRH travels to anterior pituitary to cause release of Thyroid Stimulating Hormone (TSH)
- TSH released by anterior pituitary which stimulates synthesis and secretion of thyroid hormones (+ number of thyroid cells and size)
- Thyroid hormones exert negative feedback control of TSH (anterior pituitary) and TRH (hypothalamus)



Actions of Thyroid Hormones

- 'Free' thyroid hormone diffuses into cells and binds to thyroid hormone receptors in mitochondria and nucleus
- Increase mitochondrial numbers and activity.
- Initiates transcription of specific genes and the production of new proteins and enzymes
- **Increases Basal Metabolic Rate (BMR)**
  - the amount of energy per unit time required to keep the body functioning at rest
  - ↑ oxygen consumption and ATP production
  - ↑ activity of Na-K-ATPase (increases heat production)

- Increased heart rate, cardiac output and systolic BP
- Stimulatory effects on the CNS

- **Neural development in fetal and infant life**
- **Normal growth** (in conjunction with other hormones)

Thyroid hormones are essential during fetal and infant life for normal brain development and overall growth (in conjunction with other hormones)

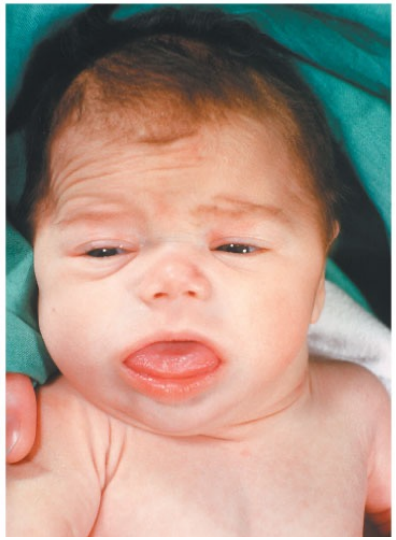
Infantile Hypothyroidism can be due to:

- absent or poorly functioning thyroid gland
- poorly functioning pituitary
- lack of iodine in mother's diet

Effects:

- Low Metabolic rate
- Delayed growth and neural development
- swelling around eyes and tongue

Treatment involves early diagnosis and administration of thyroxine



A 44 yr. old man
Severe intellectual disability
100cm tall,
Very thick, dry skin.
Thick tongue & a saddle nose
He still has his primary teeth

http://www.hsc.missouri.edu/

Adult Hypothyroidism

Simple Goitre

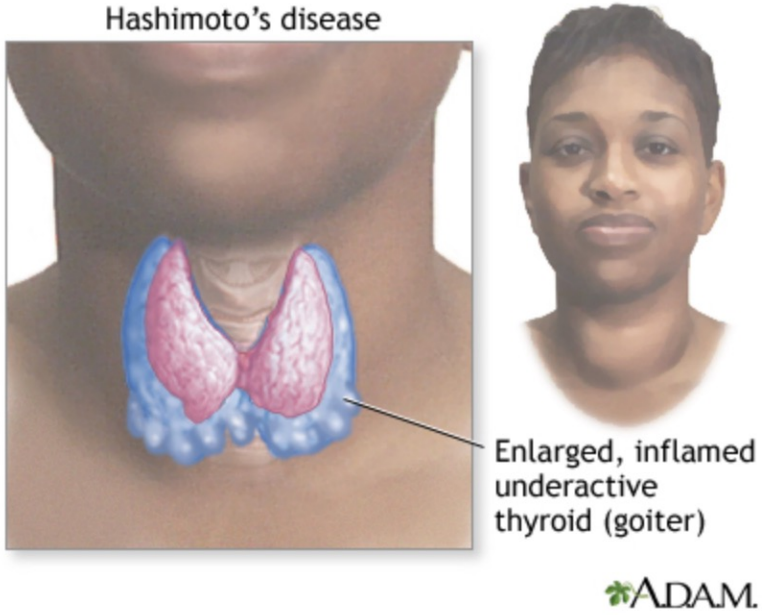
- i.e. not associated with any other disease process e.g. cancer or autoimmune process
- May be due to Iodine deficiency
- Low levels of thyroid hormones
- High TSH

  >> excessive growth of thyroid tissue

http://www.endocrineweb.com/goiter.html

Autoimmune disease

- where immune cells attack own thyroid gland e.g. **Hashimoto's thyroiditis.**
- Thyroid swollen but produces less thyroid hormone than usual



Adult Hypothyroidism – Signs and Symptoms

- Reduced metabolic rate
- slowed heart and cardiac output
- Fatigue and sluggishness (both mental and physical)
- Depression
- Weight gain
- Increased sensitivity to the cold
- Muscle weakness
- Constipation
- Goitre (depending on cause)

You don't need to list all of these signs and symptoms (there are others too) but the ones shown here should make sense if you understand how thyroid hormones work to increase basal metabolic rate, etc

Picture courtesy of Dr Herbert Langford

In severe cases there can be an edematous (swollen) appearance throughout the body = **myxedema** which can lead to coma and death if not treated

Hyperthyroidism

- There are several causes of hyperthyroidism, but the most common cause of is **Graves' disease**
- Autoimmune disease whereby antibodies attach to TSH receptors and act to stimulate (rather than destroy) the thyroid cells
- This leads to overproduction of thyroid hormones

  HYPERthyroidism as well as an associated goitre
- The antibodies can also cause swelling of tissues around/behind they eyes >> **exopthalmus**

Marty Feldman
1933-1982

Hyperthyroidism: Signs and Symptoms

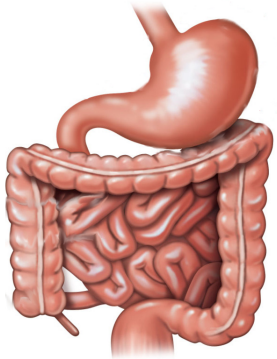
- Increased heart rate and BP
- Palpitations
- Heat intolerance
- Weight loss
- Nervousness
- Tremor
- Insomnia
- Breathlessness
- Increased bowel movements

- You don’t need to list all of these signs and symptoms (there are others too) but the ones shown here should make sense if you understand how thyroid hormones work to increase basal metabolic rate, etc

Calcium Regulation

ECF calcium concentration tightly regulated

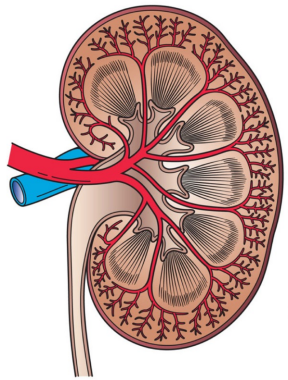
- Normal adult range is approx. 2.2 to 2.6 mmol/L



- Bone acts as a 'reservoir' for calcium
- Calcium absorbed from **intestines**, enters blood and can be deposited in bone tissue by the action of **osteoblasts**
- Calcium into blood if needed via the action of **osteoclasts**

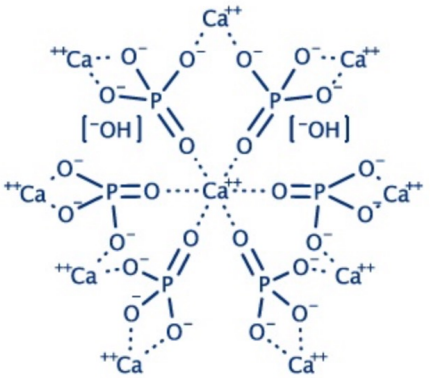
Ca^{++}

- The **kidneys** can adjust the amount of calcium lost in the urine, or reabsorb more calcium from urine if required
- Most (99%) of the calcium stored in bones is in the form of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$

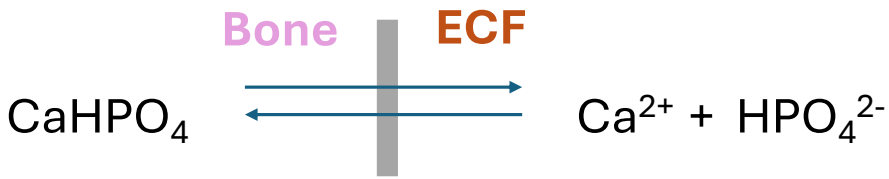


Short term calcium exchange between bone and ECF

- Some calcium in bone (<1%) is stored in form of readily mobilizable salts such as $CaHPO_4$ (as opposed to hydroxyapatite)
- such salts in reversible equilibrium with calcium and phosphate ions in ECF



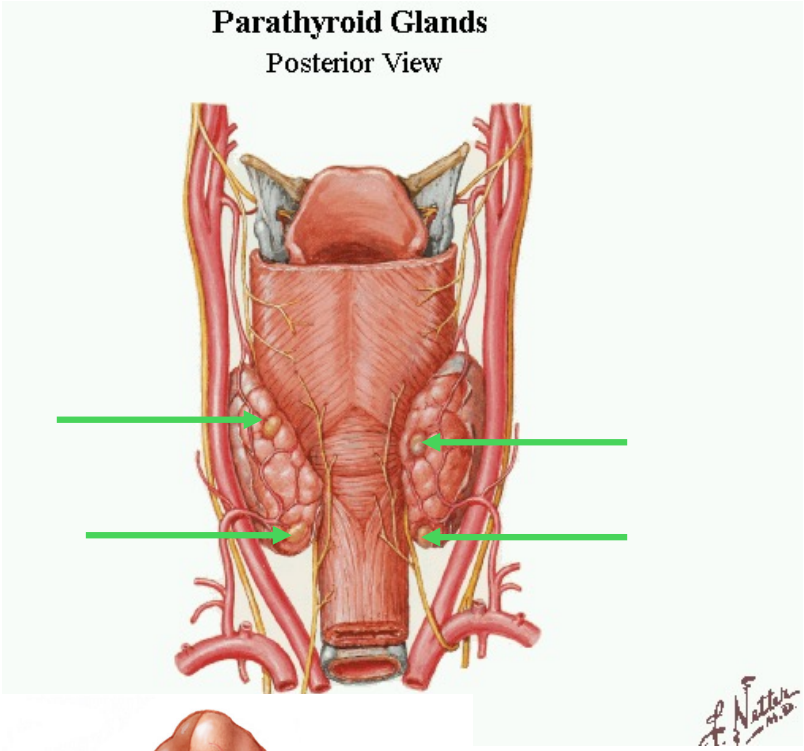
hydroxyapatite

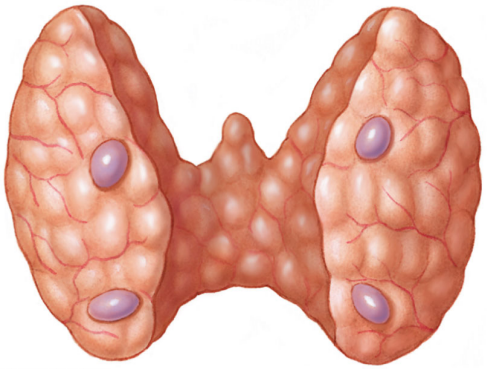


- This is readily exchangeable with the ECF and acts a quick acting 'buffer' to minor short term fluctuations in calcium ion concentrations
- The 'exchangeable' pool of calcium is very limited and longer lasting alterations in calcium levels require an endocrine response....

Parathyroid Glands

- Partially embedded in the posterior surface of the lateral lobes of the thyroid gland.
- Usually 4, (2 superior and 2 inferior) although may be more – up to 8 in some people
- approx. pea shaped and sized
- Secrete parathyroid hormone (protein hormone) in response to **LOW ECF calcium concentration**





Parathyroid gland Histology

Two types of cells:

1. **Chief cells or principal cells** which produce parathyroid hormone (PTH)

2. **Oxyphil cells**
   - Not normally present before puberty may be modified or depleted chief cells as numbers increase with age
   - help with identification of parathyroid tissue

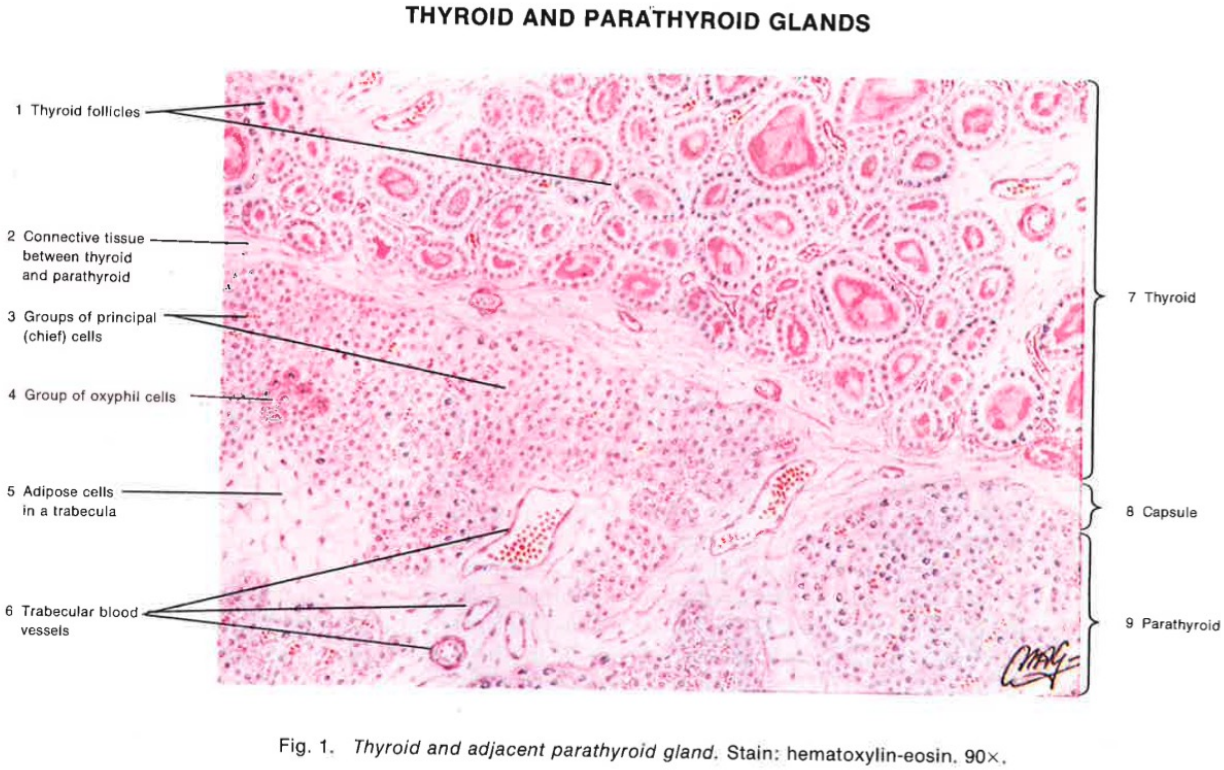
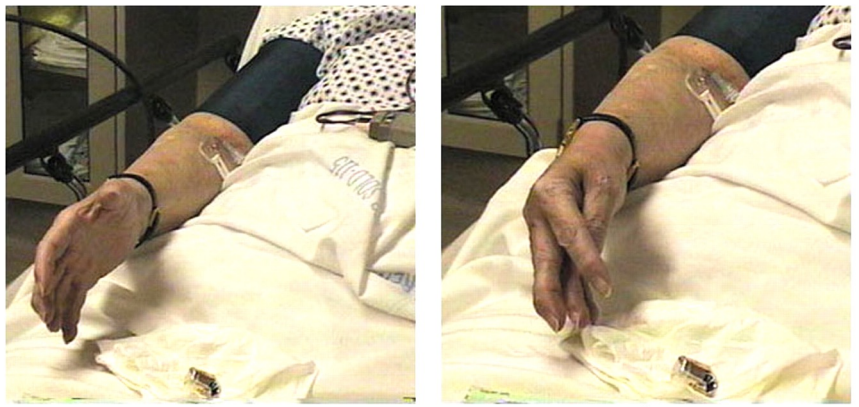


Fig. 1. *Thyroid and adjacent parathyroid gland.* Stain: hematoxylin-eosin, 90×.

Lack of PTH results in low blood calcium (e.g damage to parathyroids)

- **Trousseau's sign.**
  - Compression of the forearm produces spasm in the hand and wrist. The thumb is adducted, the fingers bunched and the wrist flexed.

You don't need to Remember these names



Meininger, M & Kendler, JS,2000, Trousseau's Sign *New England Journal of Medicine* 343(25) p1855.

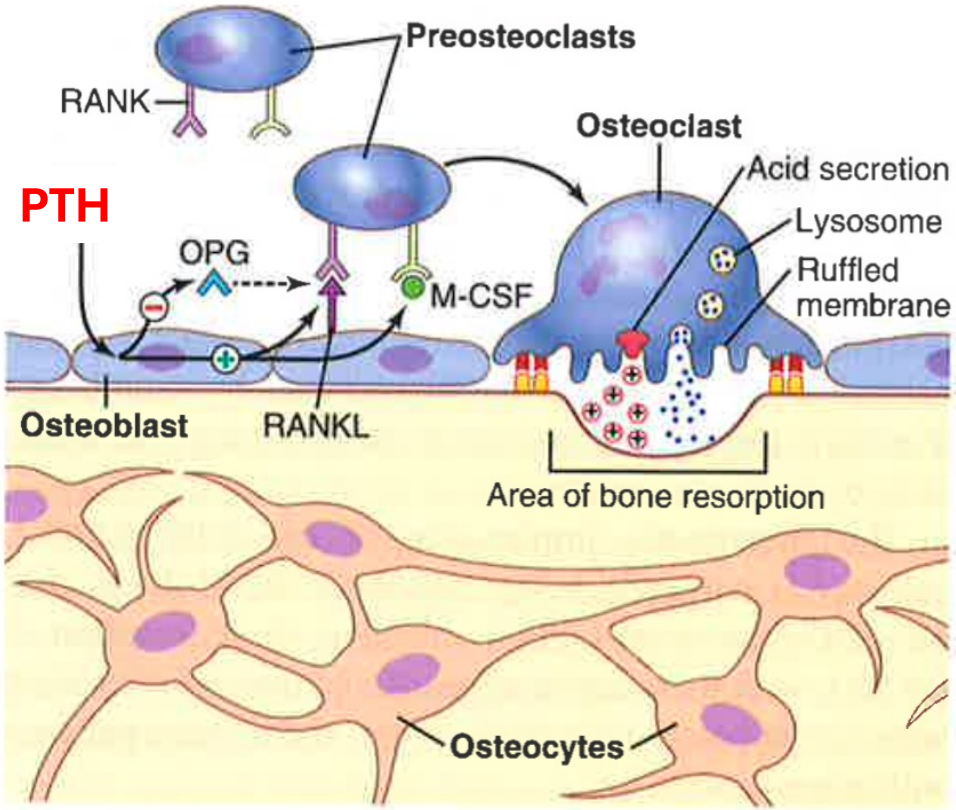
- **Chvostek's sign.**
  - Tapping the face over the facial nerve in front of the tragus of the ear causes spasm of facial muscles, typically a twitch of the nose or lips.

http://www.whonamedit.com/synd.cfm/3073.html

Signs and symptoms of hypocalcemia mostly related to altered excitability of nerve and muscle. Can lead to muscle spasms , tetany and seizures if not treated

http://www.sohnnurse.com/thyroidectomy.html

Action of parathyroid hormone (PTH) on Osteoclast activity



- Osteoclasts don't themselves have membrane receptors for PTH
- PTH binds to receptors on osteoblasts
- Osteoblasts release growth factor **RANKL**
- Stimulates proliferation, development and activity of osteoclasts
- Breakdown of bone and release of calcium into blood

- PTH also act on the **kidney** to increase reabsorption of calcium AND stimulate the formation of **calcitriol** (aka 'active Vitamin D') ....

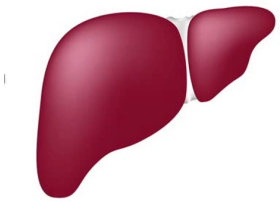
UV

7- dehydrocholesterol in skin

Dietary sources e.g fish oils, egg yolks, red meat, liver

cholecalciferol
(Vitamin D)

Liver



25-hydroxycholecalciferol (25 HCC)

Parathyroid homone (PTH)

1,25-dihydroxycholecalciferol (1.25 DHCC)
(calcitriol = active Vit D)

- **Normal mineralization of bone** via actions on osteoblasts/osteoclasts
- Increased calcium and phosphate reabsorption in renal tubules
- Increased intestinal absorption of calcium and phosphate

PTH stimulates conversion of 25 HCC to **calcitriol** in Kidney

Lack of Vit D and/or dietary calcium in children >> inadequate calcification of new bone. Weakened, bowed lower limb bones and abnormal epiphyseal plates in a child with **Ricketts**

https://radiopaedia.org/articles/rickets

In adults, lack of Vit D and/or calcium can result in abnormal mineralization of mature bone = **osteomalacia**

Bones are weaker and prone to atypical fractures

https://www.radiologymasterclass.co.uk