Endocrinology concerns the synthesis, secretion and action of hormones.

Endocrine disease causes clinical syndromes with symptoms and signs involving many organ systems, reflecting the diverse effects of hormone deficiency and excess.

Diabetes mellitus and thyroid disease are the most common endocrine diseases. e.g. thyroid dysfunction occurs in more than 10% of the population in areas with iodine deficiency, such as the Himalayas and 4% of women aged 20-50 years in the UK.

**Functional anatomy and physiology**

Hormones are chemical messengers produced by ductless glands that are transported in the circulation to act on a distant target cells and co-ordinate the activities of different cells in multi-cellular organisms. The hormones mediating those actions on target cells through hormone receptors that are known to involve multiple intracellular mechanisms.

Some hormones such as neurotransmitters may act on adjacent cells (Paracrine system) in which the products of cells diffuse in the ECF to affect neighbor cells that may be some distance away. Or even sometimes the cells secrete hormones that bind to receptors on the same cell, i.e., the cell that secreted the hormone (Autocrine).

**Types of Hormones:**

A wide variety of molecules act as hormones:

- **The amines:** e.g. thyroid hormones and catecholamine, originally from amino acid Tyrosine.
- **Glycoproteins:** e.g. Thyroid stimulating hormone (TSH).
- **Proteins and peptides:** hormone synthesis involves processing of a primary gene transcript called a prohormone: e.g. Growth Hormone (GH) and Insulin.
- **Steroids:** in which cholesterol is the common precursor in this class, e.g. adrenal cortical and reproductive gland hormones and the active metabolites of Vitamin D.

**Hormone Action:**

3 major steps involved in eliciting the response of a target cell to a hormonal stimulus:

- The hormone must be recognized by a specific receptor.
- The hormone receptor complex must be coupled to a signal-generating mechanism.
- The generated signal (2nd messenger) that causes a quantitative change in intracellular processes by altering enzymatic activity or its concentration.

If all 3 steps are intact then a particular hormone effectively stimulates a particular cell.
• There are 2 basic methods to accomplishing these steps:
  o Mainly employed by peptide / protein and catecholamine hormones, the receptor for the hormone and the signal generating system is located within or adjacent to the plasma membrane of the cell. Which signal through G-proteins and/or enzymes on the cytosolic side of plasma membrane. The hormone is essentially only an extra cellular signal. This type of hormone response is elicited within seconds to minutes.
  o Largely employed by steroids and thyroid hormones. The hormone must enter the cell, occupy the receptor and in combination with the receptor, interact with DNA molecules in the nucleus to generate a message. The hormone is a true intracellular signal. This type of hormone action requires minutes to hours or even days for its expression.

• In pituitary gland, the anterior pituitary hormone secretion is controlled by substances produced in hypothalamus and released into portal blood which drains directly down the pituitary stalk. Posterior pituitary hormones are synthesized in the hypothalamus and transported down nerve axons to be released from the posterior pituitary. Hormone release in the hypothalamus and pituitary is regulated by numerous stimuli and through feedback Control by hormones produced by the target glands (thyroid, adrenal cortex and gonads). These integrated endocrine systems are called ‘axes’ while some other endocrine gland, such as the parathyroids and pancreas respond directly to metabolic signals.

| Hormone A → Recognition → Signal Generation → Enzymatic Machinery → Effect A |

### Endocrine pathology

• Pathology arising within the gland is often called ‘primary’ disease (e.g. primary hypothyroidism in Hashimoto’s thyroiditis) while abnormal stimulation of the gland is often called secondary disease (for e.g. ‘secondary’ hypothyroidism in patients with a pituitary tumor and TSH deficiency).

• Two types of endocrine disease affect multiple glands
  o Organ-specific autoimmune disease (which are common)
  o And multiple endocrine neoplasia (MEN) syndromes (which are rare)

### Classification of endocrine disease

- **Hormone excess**
  - Primary gland over production
  - Secondary to excess trophic substance

- **Hormone deficiency**
  - Primary gland failure
  - Secondary to deficient trophic hormone

- **Hormone hypersensitivity**
  - Failure of inactivation of hormone
  - Target organ over-activity/hypersensitivity

- **Hormone resistance**
  - Failure of activation of hormone
  - Target organ resistance

- **Nonfunctioning tumors**
Embryology:

Arise from the fourth pharyngeal pouch. The mature thyroid gland weight (20gm). It’s butterfly-shaped with 2 lateral lobes (2×3cm) partially hidden by sterno cleido mastoid muscle. Connected by isthmus just below cricoid cartilages. A pyramidal lobe is present in 30% of the cases it extends from isthmus upwards lateral to trachea. The gland consists of spherical follicles (acini) lined by epithelial tissue filled with colloid.

Physiology:

The principal hormone secreted by the thyroid gland are thyroxin T4 predominantly & triiodothyronine T3 (small amount). 85% of T3 is produced by monodeiodination of T4 in the periphery such as liver, muscle & kidney. Both hormones are iodine containing amino acids. In thyroid venous blood small amounts of reverse triiodothyronine (rT3) is found, T3 is more active than T4 while reverse T3 is inactive.

The adult requirement for iodine is about 100µg/day. Ingested iodine is converted to iodide & absorbed. Iodide (I⁻) is taken from ECF to thyroid gland & converted to iodine by peroxidase. Iodine incorporated into tyrosine molecules to form mono iodo tyrosine (MIT) & diiodotyrosine (DIT).

One MIT & one DIT molecule are coupled to form T3 & 2 DIT molecules are coupled to form T4 which is mainly converted to T3 peripherally. T3&T4 circulate in plasma 99.9% are bound to transport protein mainly thyroxin binding globulin (TBG). The other remain as free T4&T3. Production of T4&T3 in the thyroid is stimulated by thyrotrophin (thyroid stimulating hormone, TSH) from the anterior pituitary in response to the hypothalamus TRH.

The characteristic metabolic changes produced by thyroid hormones are:

1. Protein synthesis during growth.
2. Increase metabolic rate with increase oxygen consumption
3. Increase sensitivity to catecholamine with proliferation of β-adrenoceptors (partially important in the C.V.S)

Factors ↑TBG:

Pregnancy, estrogen therapy & genetic factors.

Factors ↓TBG:

Nephrotic syndrome, cirrhosis and androgen therapy.
HYPERTHYROIDISM

The clinical, physiologic / biochemical findings that result when the tissues are exposed to and respond to an excess supply of thyroid hormone. It denotes only those conditions in which sustained hyper function of the thyroid leads to thyrotoxicosis. It’s a common disorder with a prevalence of about 20/1000. males are affected 5 times less frequently.

Etiology:

Grave’s disease 76%.
Multinodular goiter 14%.
Autonomously functioning solitary thyroid nodule 5%.
Thyroiditis.
---- Sub acute (de Quervian’s) 3%.
---- Post partum 0.5%.
Iodine induced.
---- Drugs (amiodarone) 1%.
---- Radiographic contrast media.
---- Iodine – prophylaxis program.
Extrathyroidal source of thyroid hormone
---- Factitious hyperthyroidism 0.2%
---- Struma ovarii (Ovarian teratoma containing Thyroid tissue)
TSH- induced
----- TSH- secreting pituitary adenoma 0.2%.
----- Choriocarcinoma & hydatidiform mole.
Follicular carcinoma ± metastasis 0.1%.

Clinical features:

Usually develops insidiously & most patients have had symptoms for at least 6 months before presentations. Almost every system is affected.

There is great individual variations in the dominant features. for e.g; the initial presentation may be to a cardiologist on account of palpitations or to a G.I.T clinic with diarrhea. Particularly are AF, heart failure, bulbar myopathy and apathy.

The listed clinical features are:

1. Goiter diffuse with bruit or nodular
2. G.I.T: weight loss despite normal or ↑ appetite, hyper defecation, diarrhea or steatorrhea, anorexia, vomiting.
3. Cardio respiratory: Palpitation, sinus tachycardia, AF, ↑ pulse pressure, ankle edema in absence of cardiac failure. angina, cardio myopathy & cardiac failure, dyspnea on exersion, exacerbation of asthma.
4. Neuromuscular: Nervousness, irritability, emotional liability, psychosis, tremor, hyper reflection, ill-sustained clonus, muscular weakness, proximal myopathy, bulbar myopathy (particularly found in elderly patients).
5. Dermatological: ↑ Sweating, pruritis, palmer erythema, spider naevi, onycholysis, alopecia, pigmentation, vitiligo, finger clubbing, pretibial myxoedema.

7. Ocular: Lid retraction, lid lag, grittiness, excessive lacrimation, chemosis, exophthalmus, corneal ulceration,

8. Ophthalmologic: common eye muscle to be affected is inferior rectus, 2nd common muscle will be medial rectus. Papilloderma & loss of visual acuity.


10. Features found in elderly patients particularly are AF, heart failure, bulbar myopathy and apathy.

**Thyroid acropachy:**

Clubbing of fingers & toes with characteristic boney changes that differs from those of hypertrophic pulmonary osteoarthritis may accompany dermal changes. This disorder is usually self limited.

**Apathic thyrotoxicosis:**

In a few patients usually elderly the clinical picture may be one of apathy rather than hyperactivity & evidence of hyper metabolism may be slight in such patients myopathic features may be profound. More often cardiovascular manifestations predominate since mild hyperthyroidism may produce severe disability in patients with underlying heart disorder.

So all patients with cardiac failure & AF & resistance to the usual dose of digitalis should be confirmed by lab diagnosis for thyrotoxicosis.
Clinical features of Graves’ disease:

It is distinguished from other forms by:
1. Diffuse thyroid enlargement & bruit.
2. Ophthalmopathy.
3. Rarely pretibial myxodema.
4. Commonly occurs between 30-50 year & unusual before puberty.

Graves’ disease - Pathogenesis

It’s the major immunologically mediated form of hyperthyroidism. The other one is post partum thyroiditis.

Grave’s disease results from production of IgG antibodies directed against the TSH – receptors on the thyroid follicular cells, which stimulate thyroid hormone production & proliferation of follicular cells, leading to goiter formation, the antibody termed thyroid stimulating Ig or TSH receptor antibody (TRAb) and can be detected in the serum of 80-95% of patients with Graves disease. Usually the cause is not known but there is genetic and environmental roles.

In Caucasian there is association with HLAB8, DR3&DR2. In the family study, show that 50% of monozygotic twins are concordant for hyperthyroidism as opposed to 5% of dizygotic twins.

Graves’ disease - Clinical features

1. Goite:
The diffusely enlarged gland is usually 2-3 times the normal volume with a thrill or a bruit. In some patients particularly the elderly no thyroid enlargement is palpable or the gland may be nodular. The largest goiters tend to occur in young men.

2. Ophthalmopathy:
Only present in 50% of patients at 1st look, it may be unilateral and it may appear after treatment, or precede hyperthyroidism by many years (exophthalmic Grave’s disease), it is more common in cigarette smokers. The mechanism is by cytokine-mediated proliferation of fibroblast within the orbit, marked swelling of extraocular muscle & ↑ in retrobulbar pressure results from ↑ interstitial fluid content & chronic inflammatory cell infiltrate. The eye is displaced forward (proptosis, exophthalmoses), & in more severe cases there is optic nerve compression, pain occur from conjunctivitis & corneal ulceration, diplopia from extraocular muscle involvement.

3. Pretibial myxodema:
This infiltrative dermopathy occurs in fewer than 10% of patients with Graves’ disease, it takes the form of raised pink colored or purplish plaques on the anterior aspect of the leg extending on to the dorsum of the foot, the lesion may be itchy.

Investigations:

T3&T4 ↑ in the majority. T4 in the upper part of normal & T3 elevated (T3 thyrotoxicosis) this occurs in 5% of patients. Particularly in those with recurrent hyperthyroidism following surgery or antithyroid drug.

TSH is undetectable 0.1 mU/L or less. If this is not available demonstration of absent (TSH) response after 200 µg TRH used.

I¹³¹ uptake ↑ in all forms of thyrotoxicosis while negligible radio – iodine uptake occur in:
---Sub acute thyroiditis & post partum thyroiditis
---Iodine induced thyrotoxicosis
---Factitious hyperthyroidisms.
---Struma ovarii.

If a patient has grave’s disease with absent goiter, exophthalmoses & pretibial myxodema so TRAb measurement done.

**Non specific abnormalities:**
---Hepatic dysfunction TSB ↑. raised alanine aminotransferase .Gamma glutamyl transferase ↑ .↑ alkaline phosphatase derived from bone and liver.
---Mild hyper calcemia 5%
---Glycosuria :
---Associated D.M
---Lag storage

**Graves’ : Management of hyperthyroidism**

1. Antithyroid drug
2. Surgery
3. Radioactive I\(^{131}\)
   ---If single episode was anticipated from the natural history & age below 40 years so anti thyroid drug is used
   ---For experience recurrent disease destructive therapy by I\(^{131}\) or surgery used , which includes:
   ---Young men with large goiter
   ---Sever hyperthyroidism

**1. Antithyroid drugs:**

The most commonly used are carbimazole & its active metabolite methimazole, Propylthiouracil is equally effective. They inhibit deiodination of tyrosine reducing the synthesis of new thyroid hormone.

Carbimazole also has an immunosuppressant action & ↓ s. TRAb. The dose of carbimazole is 15 mg 8 hourly for the first 3 weeks later on 10 mg 8 hourly 4-8 weeks & maintenance dose is 5-20 mg /day. The duration of treatment is 18-24 months.

There is subjective improvement within 10-14 days & the patient is usually clinically & biochemically euthyroid at 3-4 weeks. The maintenance dose is determined by measuring T4&TSH; hyperthyroidism recurs in at least 50% usually within 2 years of stopping treatment.

If T4&TSH levels fluctuate during follow up between that of hyperthyroidism & hypothyroidism so carbimazole & thyroxine 100 -150µg is given. Adverse effects usually develop within 7-28 days of starting treatment, skin rash 2%, agranulocytosis 0.2% (reversible).

So if there is sever sore throat carbimazole should be stopped & measure WBC, rare adverse effects is urticaria .Cross sensitivity between anti thyroid drugs is unusual. Dose of propylthiouracil orally 400-600 mg /day until euthyroid, maintenance dose is 50-150 mg/day.
2. Surgery:

Usually by subtotal thyroidectomy. Patient must be euthyroid for 6 weeks & antithyroid stopped 2 weeks before surgery & for 14 days prior to surgery to give KI (potassium iodide) 60mg 8-hourly orally or 5 drops twice daily to:

↓ Size of the gland & ↓ Vascularity.

Indication for surgery:

1. Recurrent hyperthyroidism after course of antithyroid in patients below 40 years.
2. Male, large goiter & severe thyrotoxicosis T3 > 9.0 nmole/L.
3. Poor drug compliance.

--- Complications of surgery:

1. Recurrent laryngeal nerve palsy 1%.
2. Hypoparathyroidism 1%.

--- Contraindications:

1. Previous thyroid surgery
2. Dependence upon voice e.g. opera singer, lecturer.

After one year from surgery 80% euthyroid, 15% hypothyroid & 5% thyrotoxic. There may be temporary thyroid failure within 6 months of operation. Total thyroidectomy done for severe progressive ophthalmopathy.

3. Radioactive I\textsuperscript{131}:

It will act by (1) destroying functioning thyroid cells or (2) inhibiting their ability to replicate.

5-10 mCi orally depending on size of the gland, it’s effective in 75% of patients. within 4-12 weeks for lag period 160 mg propranolol or 15 mg carbimazole three times daily for 4-6 weeks starting 48 hours after I\textsuperscript{131}. If after 12 weeks thyrotoxicosis persist, further dose of I\textsuperscript{131} is needed.

Indications:

1. Pts. >40 years, Recurrence following surgery irrespective of age.
2. Other serious illness as multiple sclerosis.

--- Contraindications:

Pregnancy or planned pregnancy within 6 months.

Men are also advised against fathering children for 6 months.

Disadvantages:

Hypothyroidism approximately 40% in 1\textsuperscript{st} year, 80% after 15 years.

---- Indications of propranolol:

1. When rapid control is needed.
2. Adjuvant to I\textsuperscript{131}.
3. Thyroidectomy.
4. Thyrotoxic crisis.
5. SVT associated with thyrotoxicosis.

Usually used for 1-2 months 20-40 mg ×2.
Treatment of ophthalmopathy:

The majority of Pts. require no treatment other than reassurance. Lid retraction will usually resolve when the Pt. become euthyroid & exophthalmus usually lessens gradually over a period of 2-3 years.

Methylcellulose eye drops used for gritting dry eye

Lateral Tarsorraphy for corneal ulceration

Prednisolone 60 mg for papilloedema, loss of visual acuity & visual field. If no response in 7-10 days so orbital decompression.

Management of dermopathy:

The pretibial myxodema rarely requires treatment. Local injection of triamcinolone or betamethason ointment under occlusive dressing may be effective.
### Toxic multinodular goiter:

More common in women. The mean age is 60 years. Thyroid hormone levels are usually only slightly elevated but cardiovascular features tend to predominate.

Treatment with $^{131}I$ 15-30mCi, hypothyroidism is less common than after treatment of Grave’s disease. Partial thyroidectomy is indicated for tracheal compression or retrosternal extrusion of goiter.

### Toxic adenoma:

The nodule is a follicular adenoma usually greater than 3 cm in diameter. Autonomously secretes excess thyroid hormones & inhibits endogenous TSH secretion with subsequent atrophy of the rest of the thyroid gland. Most Pts. are ♀ & over 40 years of age. Certain diagnosis is by isotope scanning. In 50% of Pts. the plasma T3 alone is elevated (T3 thyrotoxicosis).

Treatment is by hemithyroidectomy or by $^{131}I$ (15-30 mCi). Permanent hypothyroidism does not occur following surgery & is unusual after $^{131}I$.

### Hyperthyroidism associated with a low iodine uptake:

### Sub acute (de Quervian’s) thyroiditis:

It is virus induced (Coxsackie, mumps, adenovirus). Affected Pts. are usually females aged 20-40 years. There is pain in the region of thyroid gland usually which may radiate to the angle of jaw & the ears & made worse by swallowing, coughing & movement of the neck.

There is tender enlarged nodes. Systemic upset is common. The condition can also be precipitated by drugs, including interferone-α & lithium. ESR ↑, there is low titer thyroid autoantibody transiently in the serum.

Thyroid hormone levels are raised for 4-6 weeks, the hyperthyroidism is followed by a period of hypothyroidism which is usually asymptomatic & finally by full recovery of thyroid function within 4-6 months.

Treatment of pain & systemic illness is by aspirin or other NSAIDs. Occasionally prednisolone 40 mg daily for 3-4 weeks. The hyperthyroidism is mild & treatment with propranolol 160mg/day is usually adequate, antithyroid drugs are of no benefit.

### Post-partum thyroiditis:

It has immunological base occur in 5-10% of women within 6 months of delivery lasting a few weeks. In early pregnancy there is antithyroid peroxidase (microsomal) antibodies & thyroid biopsy show lymphocytic thyroiditis with negligible $^{131}I$ uptake.

Treatment: β adrenoceptor antagonist. post-partum thyroiditis tends to recur after subsequent pregnancies and eventually patients progress over a period of years to permanent hypothyroidism.

### Iodine induced hyperthyroidism:

Iodine in prophylactic iodination programmes, radiographic contrast media or drugs as amiodarone has structure that is analogous to thyroxine and contains huge amount of iodine; a200mg dose amiodarone contains 75mg iodine, it has a cytotoxic effect on thyroid follicular cells and inhibits conversion of T4 to T3, up to 20% develop hypothyroidism or thyrotoxicosis, hyper thyroidism which is usually difficult to treat, antithyroid drugs may be effective in high dose, potassium perchlorate & prednisolone advocated.
**Factitious hyperthyroidism:**

This uncommon condition occurs when an emotionally disturbed person taking excessive amount of thyroxin, the exogenous T4 suppress TSH & Iodine uptake.

T4:T3 ratio in conventional hyperthyroidism is 30:1. In this condition increased approximately to 70:1, also there is ↓ thyroglobulin & negligible radio-iodine uptake test.

**Hyperthyroidism during pregnancy:**

Almost always caused by Grave’s disease. Fully suppressed TSH with high free thyroid hormone indicates TT. It should be treated with antithyroid drug PTU may be preferable to carbimazole which might be associated with a skin defect in the child, known as aplasia cutis.

Use smallest dose of popylthiouracil (less than 150 mg /day), because it crosses placenta & treat the fetus also whose thyroid gland exposed to TRAb, high dose cause fetal hypothyroidism & goit.

Patient reviewed every 4 weeks & discontinues the drug 4 weeks before the expected date of delivery to avoid any probability of fetal hypothyroidism at the time of maximum brain development.

For breast feeding PTUl is the drug of choice, for poor drug compliance & or hypersensitivity, surgery is performed middle trim. Radioactive iodine is absolutely contraindicated because invariably lead to hypothyroidism.

**THYROTOXIC CRISIS (THYROID STORM):**

It is sudden acute exacerbation of all of the symptoms of thyrotoxicosis, presenting as a life-threatening syndrome.

C/F: variable in intensity, fever often associated with flushing & sweating, tachycardia is common with AF. High pulse pressure & occasionally heart failure.

C.N.S symptoms include marked agitation, restlessness, delirium & coma.

G.I.T include nausea, vomiting, diarrhea & jaundice, death may occur from H.F.

Precipitating cause includes infection in an untreated hyperthyroidism or in ill prepared patient for thyroidectomy or within few days of I$_{131}$ therapies.

The mortality is 10% despite early recognition and treatment.

**Management:**

Propranolol 1-5 mg starting I.V or 80 mg orally /6 h, to control C.V.S symptoms if it is contraindicated because of heart failure & asthma, diltiazim 90-120 mg orally 3-4 times daily or 50-150 mg/ hr by I.V infusion or with reserpin orally 1 mg every 6-12 hr will control H.T & tachycardia.

Release of thyroid hormone from the gland is retarded by KI solution 10 drop orally /day or Na iopodate 500 mg orally /day will restore serum T3 to normal in 48-72 hr. This wills also ↓ T4→T3.

Oral carbimazole 40-60mg daily inhibits synthesis of new thyroid hormone & in unconscious Patient 25 mg every 6 hr rectally is given with good effect. Dexamethason 2mg every 6 hr. I.V is used.

Na iopodate & inderal withdrawal after 10-14 days & continue on carbimazole. Supportive measure to ↓ fever by cooling blankets & paracetamol. Aspirin is contraindicated, also supportive measure to heart failure is given if no response do plasmapheresis or PD.
Atrial fibrillation in thyrotoxicosis:

Thyrotoxicosis is an important cause of AF. Accounts for 26% of the causes while AF is present in about 10% of all patients with thyrotoxicosis.

The incidence increases with age, characteristically the ventricular rate is little influenced by digoxin but respond to the addition of a β-blocker, and anticoagulation with warfarin is required as thrombo-embolic complications are common.

In 50% AF reverts to sinus rhythm when thyroid function have been returned to normal in the other 50% cardioversion will restore sinus rhythm.
Hypothyroidism: Primary hypothyroidism

This is an intrinsic disorder of the thyroid gland, prevalence is 10/1000 if patients with sub clinical hypothyroidism are included. the ♀:♂ is approximately 6:1.

Classification of primary hypothyroidism:

Spontaneous atrophic.
Goitrous:
Hashimoto’s thyroiditis
Drug –induced
Iodine deficiency
Dyshormogenesis
Post ablative following I 131 or surgery
Transient Sub clinical Congenital

Spontaneous atrophic, post ablative & Hashimoto’s thyroiditis account for over 90% of cases in the non –iodine deficient areas.

Spontaneous atrophic hypothyroidism:

It ↑ in incidence with age, it is an organ specific autoimmune disorder. There is destructive lymphoid infiltration of the thyroid leads to fibrosis & atrophy there is also evidence for the presence of TRAb which blocks the effect of endogenous TSH.

In some Pts. There is history of Grave’s disease treated 10-20 years earlier & occasionally Pts. With this form of hypothyroidism develop Grave’s disease .There is evidence of other autoimmune conditions as type1 D.M ,pernicious anemia ,Addison’s disease & autoimmune is not uncommon in 1st &2nd degree relatives.

Hypothyroidism: Clinical features

Depends on severity &duration of hypothyroidism

Many of the features are consequence of prolonged hypothyroidism by infiltration of many body tissues by the mucopolysaccharides, hyaluronic acid resulting in a low piched voice , poor hearing , slurred speech due to large tongue & there may be compression of the median nerve at the wrist.

Infiltration of the dermis gives rise to non-pitting edema or myxodema ,most marked in the skin of the hands, feet & eye lids .The resultant peri orbital puffiness & facial pallor due to vasoconstriction & anemia or a lemon yellow tint to the skin due to carotenemia ,purplish lip & malar flush make the diagnosis clear.

General: Tiredness, wt.gain, cold intolerance, hoarseness, goiter.

CV: Bradycardia, HT, angina, heart failure, xanthelasma, Pericardial & pleural effusion.

Neuromuscular: Muscle stiffness, delay relaxation of tendon reflex, carpal tunnel syndrome, deafness, depression, psychosis, cerebellar ataxia, myotonia.

Hematological: Macrocytosis, anemia Fe deficiency (pre menopausal women) normochromia, pernicious anemia.
Dermatological: Dry flaky skin & hair, alopecia, purplish lips & malar flush, carotenemia, vitiligo, erythema ab igne (Granny tartan), and myxodema.

Reproductive: Menorrhage, infertility, galactorrhea, impotence

G.I.T: constipation, ileus, ascitis.

**Investigations:**

T4 is low & TSH is ↑ in excess of 20 mu/L, no need for T3 because it does not discriminate between euthyroid & hypothyroid Pts.

Non –specific abnormalities are ↑ LDH & CpK. ↑ cholesterol & triglyceride & low serum Na.

ECG: in severe prolonged hypothyroidism classically shows sinus bradycardia with low voltage complexes & ST-T wave abnormalities.

**Hypothyroidism: Management**

Thyroxin tab. 25, 50,100 µg, starting by 50 µg for 3 weeks, increase to 100µg for another 3 weeks & finally 150 µg /day. In the elderly & Pts. With IHD should start by 25 µg used as single daily dose as it has h ½ of 7 days .The correct dose of thyroxin is that which restore TSH to normal.

Even if there is normal T4 with undetectable TSH indicates over trt. Patients feel better within 2-3 weeks, reduction in wt. & periorbital puffiness occurs quickly, but the restoration of skin texture & resolution of any effusions may take 3-6 months.

*IHD: 5% of Pts. With long standing hypothyroidism complain of angina at time of presentation , or develop it with thyroxin treatment & although angina may remain unchanged in severity or paradoxically disappear with restoration of metabolic rate , exacerbation of myocardial ischemia & infarction & sudden death are well recognized complications , even using dose of thyroxin low as 25 µg/day.

Approximately 40% of Pts. With angina can not tolerate full replacement therapy despite the use of β– blockers & vasodilators. Coronary artery surgery & balloon angioplasty can safely be performed & if successful allow full replacement dosage of thyroxin in the majority.

**Hypothyroidism in pregnancy:**

Most pregnant women with primary hypothyroidism require an increase in the dose of thyroxin of some 50µg daily .because of ↑ in serum thyroxine binding globulin during pregnancy.

During each trimester serumTSH and free T4 should be measured, the dose of thyroxin is adjusted to maintain a normal TSH. Inadequate maternal T4 therapy is associated with impaired cognitive development in their offspring.

**Myxodema coma**

A rare presentation of hypothyroidism with depress level of consciousness usually in elderly Pts. Who appears myxodematous.

Body temperature? May be low as 25 C◦. convulsion are not uncommon & C.S.F pressure & protein ↑ Mortality rate 20-50 % & depend on early recognition & other factors contributing to the condition e.g: drugs such as phenothiazine , cardiac failure , chest infection , dilutional hyponatremia , hypoxia & hypercapnea due to hypoventilation .

Treatment: 300 µg I.V thyroxin over 5-10 minutes initially followed by 50-100 µg orally until T4 therapy can be started .Alternative is tri-iodo thyroxin (T3) I.V 10 µg every 4 hr. until there is sustained clinical improvement & oral therapy can be resumed . T3 is preferred than
T4, improvement occur by 24 hours by rising body temp. & after 48-72 hr, oral thyroxine 50µg can be given. Hydrocortisone Na succinate 100mg I.M every 8 hourly is given in secondary hypothyroidism.

Other measures are re-warming by wrapping the Pt. in a space blanket. I.V fluid, broad spectrum antibiotic & high oxygen flow. Ensuring compliance: Every 1-2 years do thyroid function test, some time T4 is high & TSH also is high when the patient is taking drug diligently or few days prior to the clinic visit excessively taking the drug.

**Goitrous hypothyroidism:**

They are not always leading to hypothyroidism & should be included in differential diagnosis of euthyroid & goiter

**Hashimoto’s thyroiditis:**

Most common cause of goitrous hypothyroidism, age incidence is 20-60 years in ♀ with small or moderately sized diffuse goiter & characteristically firm or rubbery in consistency or may be soft & difficult to differentiate it from simple goiter.

Thyroid status depends on relative degree of lymphocytic infiltration, fibrosis & follicular cell hyperplasia within the gland & about 25% of Pts are hypothyroid at time of presentation in remainder T4 & TSH are normal but there are chance of hypothyroidism in the future years.

In 90% of Pts thyroid microsomal antibodies are present in the serum. In those below 20 years ANA may be present. Thyroxine is indicated not only for hypothyroidism but also for goiter shrinkage (usually 150µg but sometimes 200µg /day).

**Drug induced:**

Lithium carbonate inhibits thyroid hormone release.

Iodine for long time e.g: in expectorant or amiodarone.

Iodine deficiency

In certain parts of the world such as Andes, Himalayas, with dietary iodine deficiency, thyroid enlargement is common (more than 10% of the population), & is known as endemic goiter, most Pts. Is euthyroid. In general the more sever the iodine deficiency, the greater the incidence of hypothyroidism.

**Dyshormogenesis:**

This is unusual genetically determined defect in thyroid hormone synthesis, it is autosomal recessive, and the most common one is from deficiency of intrathyroidal peroxidase enzyme. Combination of dyshormogenesis & deafness known as pendred’s syndrome.

**Transient hypothyroidism:**

1. during the 1st 6 months after subtotal thyroidectomy or I 131 treatment of Grave’s disease.

2. Post thyrotoxic phase of subacute thyroiditis & post partum thyroiditis.

3. In some neonates of autoimmune thyroid disease mothers the Pt. usually asymptomatic & thyroxine treatment should not be necessary.

**Congenital hypothyroidism:**

By routine TSH estimation test obtained 5-7 days after birth the incidence approximately was 1/1000 from thyroid agenesis, ectopic or hypo plastic gland or dyshormogenesis. Tx: within 2 weeks of birth. The children will have macroGLOSSIA.
**Secondary hypothyroidism:**

It is much less common than primary hypothyroidism. There is atrophy of thyroid gland from failure of TSH secretion in Pts.with hypothalamic or anterior pituitary disease. In hypothalamic disease there is associated diabetes insipidus & in pituitary disease there is deficiency of other anti. Pituitary hormones, recently it may be from an autoimmune lymphoid hypophysitis.

**Subclin hypothyroidism:**

These are euthyroid Pts. With lower end of the reference range of thyroid hormone but raised serum TSH. Usually occur after l\textsuperscript{131} or surgical treatment of hyperthyroidism & may persist for many years.there is a risk of progression to overt thyroid failure particularly if antibodies to thyroid peroxidase are present in the serum or if the TSH rises above 10mU/l, thyroxine should be given in a dose of 50-150 µg /day sufficient to restore TSH to normal.

These are clinically euthyroid patients In whom thyroid hormone concentration is normal but in upper part of reference range in the absence of non-thyroid illness .The TSH is undetectable, it occur most often in Pts.

With exophthalmic grave’s disease 50% , multinodular goiter 25% & following surgery of hyperthyroidism ,usually no treatment instituted, they need follow up for risk of overt hyperthyroidism which increase by 5% each year .but in old patient with multinodular goiter are at increased risk of AF and osteoporosis and usually require therapy with l\textsuperscript{131}.

**Non –thyroid illness:**

In ill Pts. e.g: in M.I or pneumonia not only there is a ↓ in peripheral conversion of T4→T3 but also ulcerations in the concentrations of the binding proteins & in there affinity for thyroid hormones in addition TSH level may be subnormal.

In these cases thyroid function test assessment may be difficult & should not be undertaken unless there is strong clinical evidence of thyroid disease requiring urgent treatment.

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Simple goiter:
It is sporadically occurrence of diffuse or multinodular enlargement of the thyroid of unknown etiology. but may be due to sub optimal iodine intake, minor degree of dyshormonogenesis.

Stimuli as growth stimulating Ig are important in the development of simple goiter. Affected Pts. Are euthyroid ♀ & often with family history of goiter.

Simple diffuse goiter:
Age usually 15-25 years, usually during pregnancy with tight sensation in neck; the goiter is soft symmetrically enlarged .T3, T4, TSH normal .no treatment, in some cases the unknown stimuli persist with changes to simple multinodular goiter within 10-20 years.

Simple MN goiter:
Rare before middle age, signs & symptoms of compression mediastinally on trachea, esophagus & superior vena cava. The goiter is nodular or lobulated & may extend retrosternally, hoarseness may occur due to recurrent laryngeal nerve palsy. T3, T4 normal & TSH normal in majority. 25% may have sub clinical hyperthyroidism; radiographs of the thoracic inlet may show:

1. Tracheal displacement or compression.
2. Intrathyroid calcification.
3. The extent of retro sternal extension.

Simple MN goiter:
If the goiter is small no treatment is necessary, partial thyroidectomy is indicated for large goiter which cause mediastinal compression or for cosmotical reason. Dietary goitrogens are a rare cause of goiter & of this iodide itself. Large dose of I as in Tx of chronic pulmonary disease may in susceptible individual lead to goiter & hypothyroidism.

Other goitrogens Lithium CO3 in manic depressive psychosis. Some vegetable food stuffs such as thioglucoside found in cabbage & goitrin found in certain roots & seeds .menarche, pregnancy & use of oral contraceptive drugs, due to chronic lymphocytic thyroiditis.

Solitary thyroid nodule:
Palpable thyroid nodules occur in approximately 5% of females. It is important to determine whether the nodule is benign e.g: colloid nodule or malignant.

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly ♀</td>
<td>Child , young ♂</td>
</tr>
<tr>
<td>Rapid pain due to hemorrhage in cyst with rapid ↑ in size</td>
<td>Recent growth with history of head &amp; neck irradiation</td>
</tr>
<tr>
<td>Family history of benign cyst</td>
<td>Family history of medullary carcinoma, history of hoarsness, dysphagia or obstruction.</td>
</tr>
<tr>
<td>Soft nodule</td>
<td>Firm or dominant nodule on palpation , +ve cervical L.N vocal cord paralysis</td>
</tr>
</tbody>
</table>
Investigations:
The most useful is fine needle aspiration of the nodule. In 80% it is benign & 20% malignant
the limitation of the method is that it can not differentiate between follicular adenoma &
carcinoma. It is important to measure T4, T3, & TSH in all Pts. With history of thyroid nodule
as autonomously functioning thyroid adenoma which can only be confirm by thyroid isotope
scanning is always benign.

T99 thyroid scan
1. Hot
   Follicular adenoma (T3, T4)
   Agenesis of lobe (use a shield)
2. Cold:
   Do u/s:
   Cystic: aspirate & give T4 if recurrences occur 4-5 times do surgery.
   Solid : FNA: this include -:follicular adenoma needs (T4 suppression)
   Follicular carcinoma (surgery).

THE PARATHYROID GLAND

PTH is synthesized by the chief cells of the parathyroid gland it acts on the followings.
1. Renal function: it ↑ reabsorption of calcium but ↓ po4 & bicarbonate reabsorption.
2. Vit. D 1, 25 DHCC → ↑ ca & po4 absorption from intestine & in combination with PTH, to
   mobilize ca from bone.
3. Bone (bone contains 99% of total body ca)
   Initially there is ↑ osteolysis (ca from bone to ECF). On prolonged exposure it → ↑
   osteoclastic activity.

Calcium homeostasis:
Normal total serum calcium 9-11mg/dl, calcium in serum exists as 50% ionized (ca++), the
normal response to ↓ ionized calcium (ca++) leads to PTH stimulation → it act on bone & vit.
D leading to ↑ ca++ conversely once ca++ is elevated leads to PTH suppression & calcium
secretion this cause opposing the action of PTH on renal tubular reabsorption of ca & po4 &
on bone resorption.

Hyperparathyroidism:
Primary: (serum ca high, serum PTH high)
   -single adenoma 90%
   -multiple adenoma 4%
   -nodular hyperplasia 5%
   -carcinoma 1%
Secondary : (serum ca low, PTH high)
   -CRF
   -malabsorption
   -osteomalacia & rickets
Tertiary :( serum ca high, serum PTH high).
Primary hyperparathyroidism:

Commonest parathyroid disorder, prevalence 1/800 2-3 times more common in ♂ &90% are above 50 year of age.

C/F: half of cases with biochemical evidence of hyperparathyroidism are asymptomatic. Many has non specific symptoms as anorexia nausea, vomiting, wt loss, constipation, polyuria & polydipsia, weakness, tiredness, & Lassitude, drowsiness, poor conc. & memory loss.

Calculus formation 5% of 1st stone formation & 15% of recurrent stone formation. Nephrocalcinosis due to ca salt deposition in renal parenchyma other causes of nephrocalcinosis (chronic pyelonephrosis, renal tubular acidosis, vit.D intoxication & heeled renal T.B).

Renal function may be affected: uremia, hyperuricaemia, hyperchloremic acidosis, poor urine concentration ability.

Investigations:

A. Biochemical:

- Primary: ↑ ca, ↑ PTH.
- Secondary: ↓ ca, ↑ PTH.
- Tertiary: ↑ ca, ↑ PTH.

Serum calcium: fasting, no tournique, supine measure albumin.

Serum phosphorus low, Cl ↑, alkaline phosphatase may be ↑ according to degree of bone involvement.

Other causes of hypercalcemia:

1. Malignancy of bone metastasis or PTH –like peptide production. (Breast, kidney, lung, thyroid, ovary & colon)
2. Multiple myeloma
3. Vit. D intoxication
4. Milk −alkali syndrome
5. Hyperthyroidism
6. Hypothyroidism
7. Sarcoidosis, T.B
8. Untreated Addison’s dis
9. Long period of immobilization in Pt. with Paget’s disease
   a. Soft tissue calcification.
10. Drugs (thiazides, frusemide, and vit. D, calcium, vit. Lithium)
11. Familial hypocalciuric hypercalcemia (FHH) is rare autosomal dominant disorder caused by an inactivating mutation in one of the alleles of the calcium sensing receptor, which reduces the ability of the parathyroid gland to sense ionized calcium concentrations.

B. Radiological:

1. Demineralization & subperiosteal erosion ↑ radial surface of middle finger.
2. Pepper-pot appearance on lateral skull x-ray (extensive area of demineralization alternate with area of ↑ bone density)
3. Absent dental lamina dura
5. Soft tissue calcification.
Localization of parathyroid tumor:

In 90% localization done without difficulty, otherwise US, selective neck vein catheter with PTH measurement. CT scanning with subtraction imaging (thallium 201 taken up by thyroid & parathyroid while Te99 taken by thyroid only by computer subtraction of the 2 images leaves a parathyroid image if adenoma is present).

Treatment of primary hyperparathyroidism:

The only long term treatment for primary hyperparathyroidism is surgery. The selection of Pts. Who require surgery is difficult, they include those with clear-cut symptoms or documented complications such as peptic ulcer, renal stone, renal impairment or osteopenia, for cases with vague symptoms or are asymptomatic they should be reviewed every 6-12 months with assessment of symptoms, renal function, S. ca & perhaps bone mineral density.

For adenoma surgical removal & for hyperplasia all 4 glands are removed & transplant some of the excised tissue to the forearm. Complications of the surgery is transient hypocalcemia during the 1st 2 weeks it is treated by 80 mmole calcium / day. Pts are liable to get prolong symptomatic hypocalcemia if there is: High pre operative S. calcium or Obvious bone & renal damage.

Treatment is by 1 αOH D3 2µg / day for 48 hours before surgery & continue for 1-2 weeks after operation I.V calcium gluconate as 10 ml of 10% solution every 3-4 h. & oral calcium may be necessary.

Acute sever hypercalcemia -malignant hypercalcemia:

There is dehydration, hypotension, abdominal pain, vomiting, pyrexia & altered conscious level. Tx: 1. admission with no immobilization. 2. Rehydration with NS. In very ill patient forced diuresis with 4-6 liter N.S +20-100 mg frusemide every 1-2 hours this will ↑ ca loss in urine by 500-1000mg/day & ↓ S.calcium by 2-6 mg/dl after 24hours.

Some times Bisphosphonates e.g: pamidronate 90mg I.V over 4 hours causes a fall in calcium which is maximal at 2-3 days & lasts a few weeks unless the cause is removed, follow up with an oral bisphosphonate, glucorticoids e.g: pridnisolone 40 mg daily is usually useful in hypercalcemia of malignancy. Other additional therapies include calcitonine & haemodialysis.

In rare instance when S. calcium is greater than 18mg/dl the life threatening hypercalcemia can be rapidly but transiently lowered by 500ml 0.1 M neutral phosphate I.V every 6-8 hours.
Malignant tumors:

- Primary thyroid malignancy is rare less than 1% of all carcinoma. Tumors are more common in ♀ except medullary carcinoma
- In most of the cases presents with palpable solitary nodule.

<table>
<thead>
<tr>
<th>Origin of the tumor</th>
<th>Type of tumor</th>
<th>Frequency%</th>
<th>Usual age of presentation(years)</th>
<th>Approx. 20 –year survival rate%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular cells</td>
<td>Differentiated carcinoma</td>
<td>70</td>
<td>20-40</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>*Papillary (L.N)</td>
<td>10</td>
<td>40-60</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>*follicular blood (bone,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>brain, lung)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Undifferentiated carcinoma</td>
<td>5</td>
<td>&gt;60</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td>*Ana plastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular c- cells</td>
<td>Medullary carcinoma</td>
<td>5-10</td>
<td>&gt;40</td>
<td>50</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>Lymphoma</td>
<td>5-10</td>
<td>&gt;60</td>
<td>10</td>
</tr>
</tbody>
</table>

Treatment of differentiated carcinoma is by total thyroidectomy followed by a large dose of 131I (80mCi) in order to ablate any remaining thyroid tissue, normal or malignant.

Long term treatment with thyroxine in a dose sufficient to suppress TSH (usually 150-200μg daily) is important. Follow-up is by measurement of serum thyroglobulin. Detectable thyroglobulin is suggestive of tumor recurrence or metastasis.

Medullary carcinoma:

- It arises from the Para follicular c-cells of thyroid & it secrets calcitonin & also serotonin, ACTH & prostaglandin .as a consequence carcinoid syndrome & Cushing’s syndrome have been described with medullary carcinoma
- Usually there is a firm thyroid mass & cervical lymphadenopathy is common.
- Tx: by total thyroidectomy.
- Rarely medullary Ca. may be familial with an autosomal dominant mode of inheritance.

Multiple endocrine neoplasia: MEN

- MEN I: parathyroid hyperplasia, pancreatic islet cell tumor secreting insulin or gastrin & pituitary tumor.
- MEN IIa: parathyroid hyperplasia, bilateral pheochromocytoma & medullary Ca.
- MEN IIb: it is type IIa & mucosal neuroma, marfanoid habit, kyphosis & pes cavus.
HYPOPARATHYROIDISM:

Hypocalcaemia is much less common than hypercalcaemia. Biochemically ↓ Ca & ↑ P04 is characteristic of hypoparathyroidism.

Causes:

Postoperative: transient hypocalcemia 10% after thyroid surgery by 12-36 hours & 1% for thyroidectomy.

Infantile hypoparathyroidism: May be transient & with maternal hyperparathyroid it persists in thymic aplasia (DiGeorge syndrome).

Idiopathic hypoparathyroidism: At any age, with autoimmune disease, in addition to tetany, there are other features of prolonged hypocalcemia include psychosis, grandmal epilepsy, cataract, calcification of basal ganglion & papilodema, there is an association with mucocutaneous candidiasis of finger nails, mouth & esophagus.

Pseudohypoparathyroidism: post receptor detective mechanism. No mucocutaneous candidiasis but there may be mental retardation & characteristically there are skeletal abnormality as short stature & short 4th & 5th metacarpals & metatarsals, PTH elevated.

Pseudo –pseudo hypoparathyroidism: The same skeletal abnormality but with normal S. Ca.

Management:

PTH therapy: it is unsatisfactory because they have to be given by injections & soon become ineffective because of Ab formation. In acute phase I.V Ca gluconate.

For persistent hypoparathyroidism 1α OH cholecalciferol (alfacalcidol) 1-3 μg/day, 1,25 dihydroxy cholecalciferol (calcitriol). Monitor S.Ca every 3-6 months, calciferol (sterogyl) 15mg/1.5ml oral use. Ca lactate 300mg, Ca gluconate 600mg.

Tetany

The most common cause of hypocalcemia is low serum albumin concentration which will not lead to tetany.

Other causes:

1. Hypocalcemia:
   a. Malabsorption.
   b. Osteomalacia
   c. Hypoparathyroidism.
   d. Mg deficiency.
   e. CRF (no tetany because of coincidental acidosis).
   f. Acute pancreatitis.

2. Alkalosis:
   b. Primary hyperaldosteronism.

C/F: carpopedal spasm, stridor, convulsion, in adult tingling in hand, feet, mouth,

Latent signs: Trousseau’s sign: Inflation of the sphygmomanometer cuff on the upper arm to more than the systolic B.P is followed by carpal spasm within 3 minutes.

Chvostek sign; Tapping over the branches of the facial nerve as they emerge from the parotid gland produces twitching of the facial muscle.

ECG prolonged Q.T interval.

Management:

Control of tetany: Ca I.V 20 ml 10%, correction of alkalosis, if no response Mg. administration may be required.

Correction of alkalosis: I.V fluid for vomiting, isotonic saline, NH4Cl (ammonium chloride) 2 gm 4 hourly by mouth, inhalation of 5% CO2 in oxygen for hysterical.