Endocrine system

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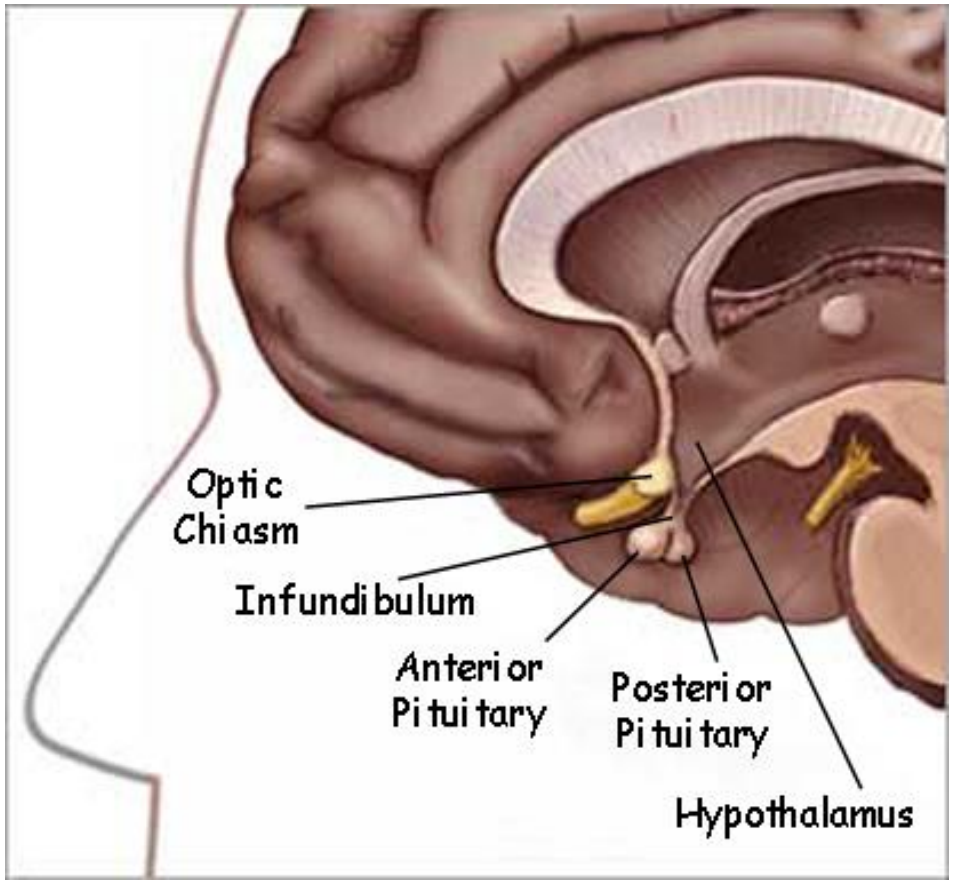
Mechanisms of endocrine disease

1. Primary hyper-function of an endocrine gland
2. Secondary hyper-function of an endocrine gland
3. Primary hypo-function of an endocrine gland
4. Secondary hypo-function of an endocrine gland
5. Endocrine hyperactivity secondary to diseases of other organs
6. Hyper-secretion of hormones or hormone like substances by non-endocrine tumours
7. Abnormal degradation of hormone
8. Failure of target cell response
9. Iatrogenic syndromes of hormone excess

I. PITUITARY GLAND

Pituitary gland



Hormone secretion from the anterior pituitary is regulated by hormones secreted from the hypothalamus.

Anterior pituitary

- This constitutes about 80% of the gland.
- Under the influence of the hypothalamus, it produces and secretes several peptide hormones that regulate many physiological processes, including stress, growth and reproduction

Hypothalamus	Pituitary	Target	Effect
CRH, CRF	ACTH	Adrenal gland	glucocorticoids
GnRH	LH & FSH	Ovaries/testes	Reproductive, sex H
SS, GHIH, SRIF ↓	GH	Liver, adipose	Growth
TRH, TRF	TSH	Thyroid	T3, T4
ADH, Vassopressin	ACTH	Adrenal gland	glucocorticoids
Dopamine ↓	PRL	ovaries, mammary	E2, P4, milk

Posterior pituitary

- The posterior lobe is connected to the hypothalamus via the infundibulum (pituitary stalk).
- Hormones are made in nerve cell bodies positioned in the hypothalamus.
- These hormones are then transported down the nerve cell's axons to the posterior pituitary.

Hormone	Target	Effect
Oxytocin	Uterus, mammary glands	Uterine contraction, lactation
Vasopressin ADH	Kidneys or Arterioles	Stimulates water retention raises blood pressure, induces male aggression

A. Hyperpituitarism

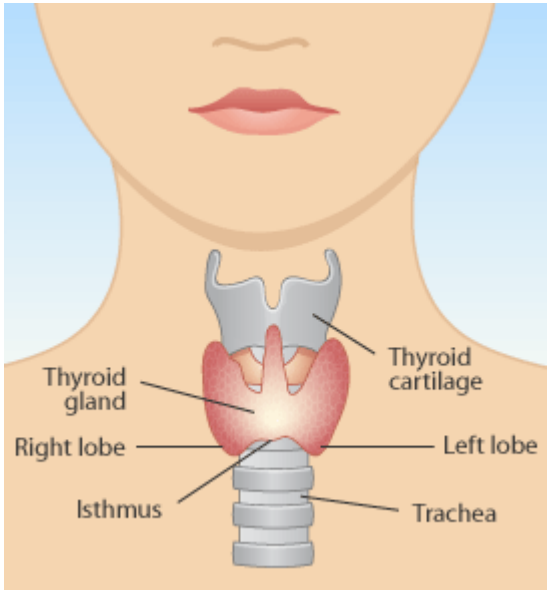
- In many instances, excess production of anterior pituitary hormones is caused by the presence of functional adenoma arising in the anterior lobe.
- Other less common causes include:
  - hyperplasias and carcinomas of the anterior pituitary
  - secretion of hormones by some pituitary tumours
  - certain hypothalamic disorders.

- The signs and symptoms of pituitary adenomas include endocrine abnormalities and local mass effects.
- expanding pituitary lesions often compress the nerve fibres in the optic chiasm. This results in visual field abnormalities.
- signs and symptoms of elevated intracranial pressure including headache, nausea and vomiting.
- compress the adjacent non-neoplastic anterior pituitary or pituitary stalk sufficiently to compromise their functions, resulting in hypopituitarism.
- Acute haemorrhage into an adenoma is sometimes associated with a rapid increase into local mass effects, a situation sometimes designated pituitary apoplexy.

b. Hypopituitarism

- This refers to decreased secretion of pituitary hormones, which can result from diseases of the hypothalamus or of the pituitary.
- Hypofunction of the anterior pituitary occurs when approximately 75% of the parenchyma is lost or absent.
- This may be congenital or the result of a variety of acquired abnormalities that are intrinsic to the pituitary.

II. THYROID GLAND

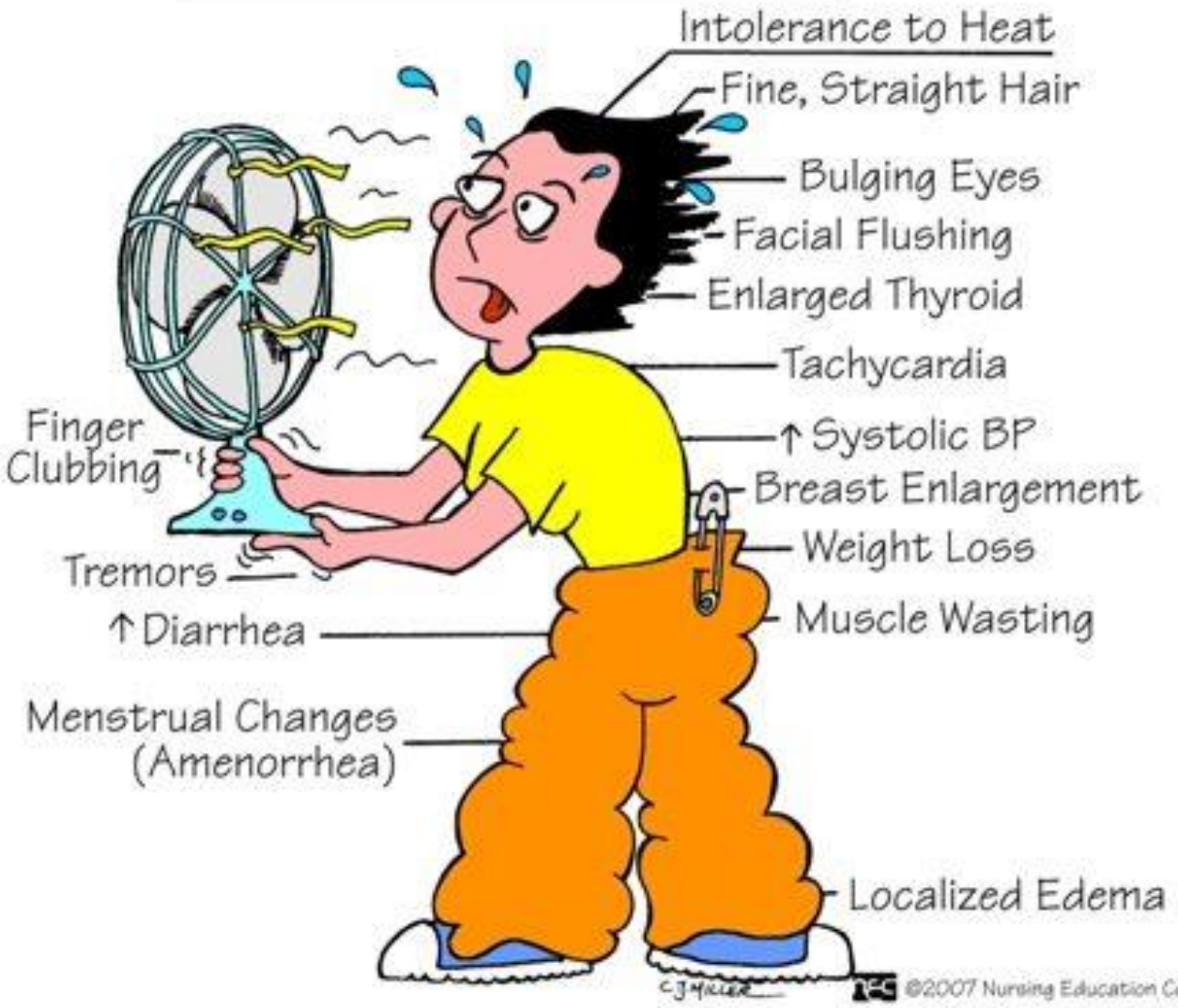

Thyroid cartilage
Thyroid gland
Right lobe
Left lobe
Isthmus
Trachea

Feature	Description
Thyroid epithelial cells (or "follicular cells")	secrete **T3** and **T4**.
Parafollicular cells (or "C cells")	secrete **calcitonin**.

a. Hyperthyroidism

- hypermetabolic state caused by elevated levels of free T3 and T4 caused by hyperfunction of the thyroid gland.
- The clinical manifestations of hyperthyroidism include:
  - changes referable to the hypermetabolic state induced by excess thyroid hormone as well as
  - changes related to over activity of the sympathetic nervous system

HYPERTHYROIDISM



b. Hypothyroidism

- caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone.
- It can be the consequence of 3 general processes

    (i) 1° hypothyroidism

    (ii) hypothyroidism due to surgery, radiation, drugs

    (iii) 2° or 3° hypothyroidism

(i) Primary hypothyroidism

- This accounts for the vast majority of cases.
- The most common cause is chronic autoimmune thyroiditis (Hashimoto thyroiditis)

(ii) Hypothyroidism due to surgery or radiation, drug induced, or as a result of an infiltrative disorder

- Surgery - Total thyroidectomy for the treatment of hyperthyroidism or excision of a primary neoplasm is a common cause of hypothyroidism.
- Radiation – the gland may be ablated by radiation,
- Drugs – drugs given to decrease thyroid secretion can cause hypothyroidism e..g. methimazole and propylthiouracil. Drugs used to treat non thyroid conditions can also cause hypothyroidism e.g. lithium.
- Infiltrative diseases – haemochromatosis, amyloid and sarcoid are rare causes.

(iii) Inadequate secretion of TSH by the pituitary or of TRH by the hypothalamus (secondary and tertiary hypothyroidism).

- 2° - that caused by TSH deficiency.
  - It can result from any of the causes of hypopituitarism.
- 3° - caused by TRH deficiency.
  - It can be caused by any disorder that damages the hypothalamus or interferes with hypothalamic-pituitary portal blood flow, thereby preventing delivery of TRH to pituitary.

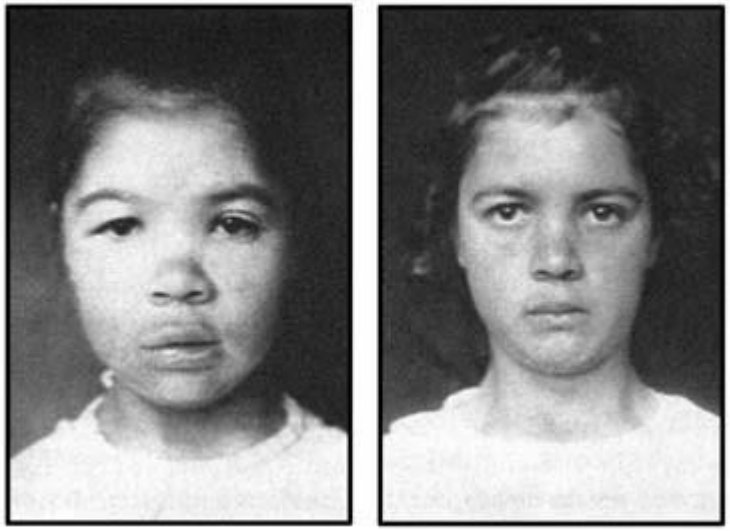
Classical clinical manifestations

Cretinism –

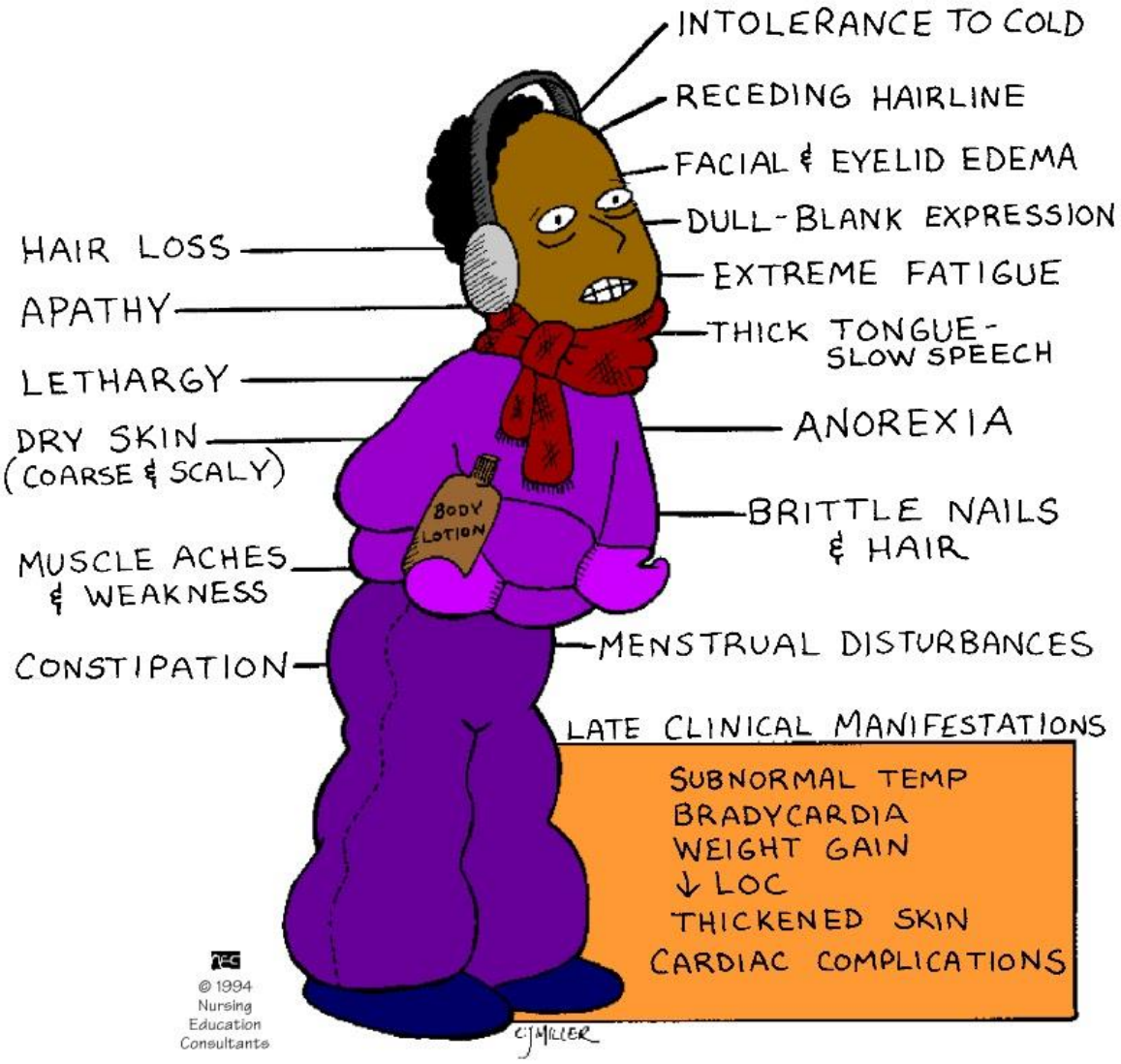
- hypothyroidism developing in infancy or early childhood.
- impaired development of the skeletal system and central nervous system,
  - severe retardation,
  - short stature,
  - coarse facial features,
  - protruding tongue
  - umbilical hernia.

Myxedema-

- hypothyroidism developing in an older child or adult.
- The clinical manifestations vary with age of onset.
- The older child shows signs and symptoms intermediate between those of a cretin and those of an adult with hypothyroidism.
  - slowing of physical and mental activity.
  - generalized fatigue, apathy, mental and sluggishness.
  - oedema, a broadening and coarsening of the facial features
  - Frequently the patients are overweight.



HYPOTHYROIDISM



c. Thyroiditis

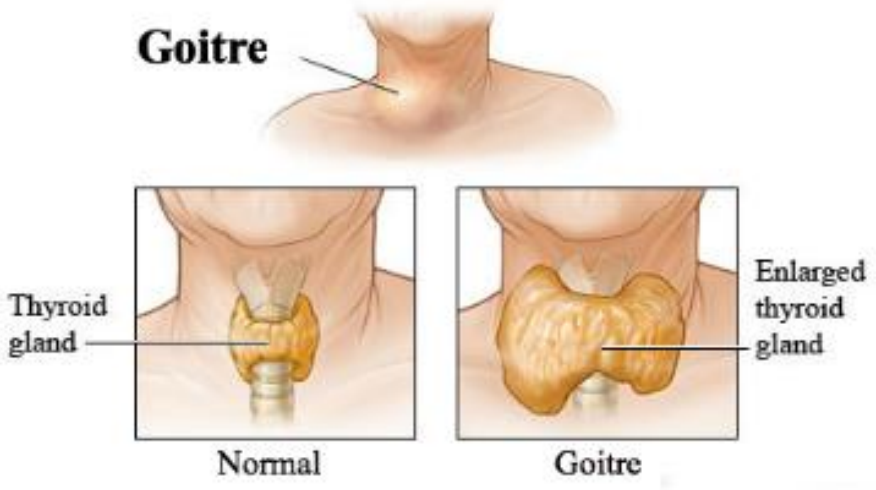
- This encompasses a diverse group of disorders characterised by some form of thyroid inflammation.
- Include:
  - conditions that result in acute illness with severe thyroid pain (e.g. infectious thyroiditis, subacute granulomatous thyroiditis)
  - disorders in which there is relatively little inflammation and the illness is manifested primarily by thyroid dysfunction (subacute Lymphocytic thyroiditis and fibrous thyroiditis).

- Infectious thyroiditis may be either acute or chronic.
- Acute infections may reach the thyroid via haematogenous spread or through direct seeding of the gland; such as via a fistula from the piriform sinus adjacent to the larynx.
- Other infections of the thyroid, including mycobacterial, fungal and *Pneumocystis* infections, are more chronic and frequently occur in immunocompromised patients.

- The inflammatory involvement may cause sudden onset of neck pain and tenderness in the area of the gland and is accompanied by fever, chills, and other signs on infection.
- Infectious thyroiditis can be self limiting or controlled therapeutically.
- Thyroid function is usually not significantly affected

d. Goitre

- Enlargement of the thyroid or goitre is the most common manifestation of thyroid disease.
- Diffuse and multinodular goitres reflect impaired synthesis of thyroid hormone, most often caused by dietary iodine deficiency.
- Impaired thyroid hormone synthesis → compensatory rise in serum TSH level, → hypertrophy and hyperplasia of thyroid follicular cells → gross enlargement of the thyroid gland.

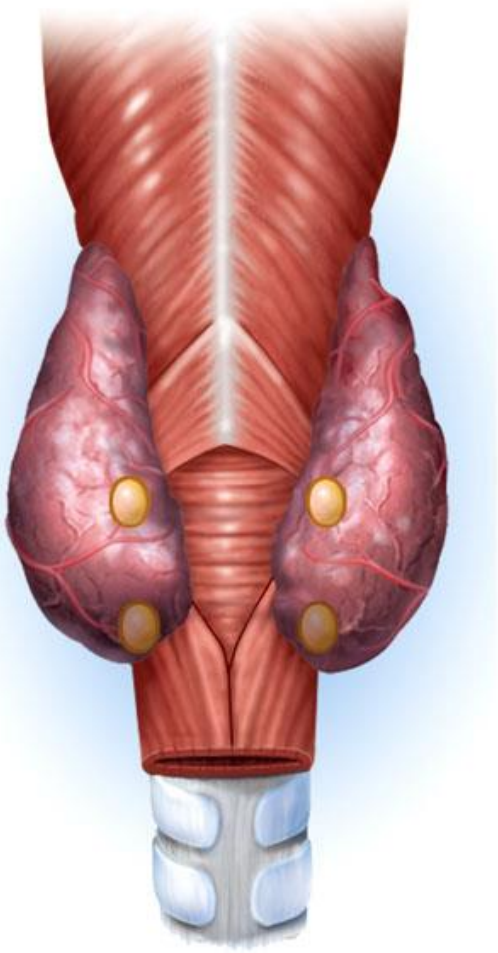


- The dominant clinical features of goitre are those caused by the mass effects of the enlarged gland.
- They may cause airway obstruction, dysphagia and compression of the large vessels of the neck and upper thorax.
- Most patients are euthyroid but in a small number of patients a hyperfunctioning nodule may develop within the gland resulting in hyperthyroidism.
- This condition is known as Plummer syndrome.
- Less commonly, goitre may be associated with hypothyroidism

e. Thyroid neoplasms

- The possibility of neoplastic disease is of a major concern in patients who present with thyroid nodules. Thyroid nodule is a palpable discrete swelling within an otherwise apparently normal gland.
- The overwhelming majority of solitary nodules prove to be benign lesions, either follicular adenomas or localized non-neoplastic conditions (e.g. nodular hyperplasia, simple cysts, or foci of thyroiditis).
- When such nodules prove to be neoplastic, in well over 90% of instances, they are adenomas.
- Carcinomas of the thyroid are uncommon, accounting for well under 1% of solitary thyroid nodules.

III. PARATHYROID GLAND



- Maintains the body's calcium level within a very narrow range, so that the nervous and muscular systems can function properly.
- The activity of the parathyroid glands is controlled by the level of free calcium in the blood, rather than by trophic hormones secreted by the hypothalamus and pituitary.
- When blood calcium levels drop below a certain point, calcium-sensing receptors in the parathyroid gland are activated to release hormone into the blood.

- Parathyroid hormone has effects antagonistic to those of calcitonin.
- The metabolic functions of PTH in supporting serum calcium level can be summarized as follows:
  - it activates osteoclasts, thereby mobilizing calcium from bone
  - It increases the renal tubular resorption of calcium, thereby conserving free calcium
  - It increases the conversion of vitamin D to its active dihydroxy form in the kidneys.
  - It increases urinary phosphate excretion, thereby lowering serum phosphate level
  - It augments gastrointestinal calcium absorption

- Parathyroid hormone (PTH, also known as parathormone) is a small protein that takes part in the control of calcium and phosphorus homeostasis, as well as bone physiology
- The net result of these activities is an increase in the level of free calcium, which in turn, inhibits further PTH secretion in a classic feed back loop.

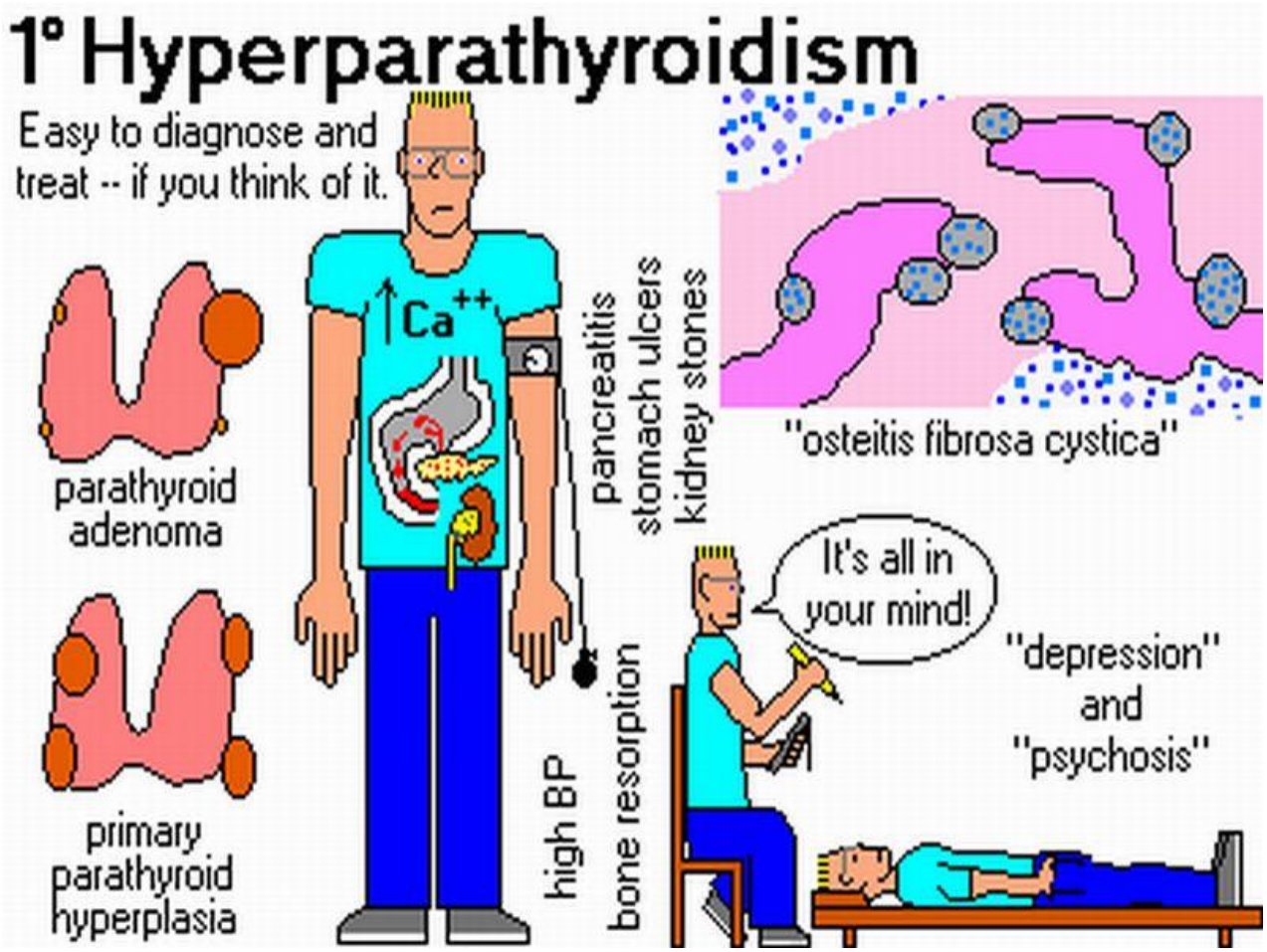
(i) Primary Hyperparathyroidism

- This is an autonomous, spontaneous overproduction of PTH.
- It is usually a disease of adults, more common in women than in men.
- Parathyroid lesions underlying the hyper function are:
  - Adenoma (75-80%)
  - Primary hyperplasia: diffuse or nodular (10-15%)
  - Parathyroid carcinoma (<5%)

Symptomatic

The signs and symptoms reflect the combined effects of **increased PTH secretion** and **hypercalcaemia**:

- Bone disease – bone pain secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica
- Nephrolithiasis (renal stones
- Gastrointestinal disturbances – constipation, nausea, peptic ulcers, pancreatitis, gall stones
- CNS alterations – depression, lethargy and eventually seizures
- Neuromuscular abnormalities – complaints of weakness and fatigue
- Cardiac manifestations – aortic or mitral valve calcification or both


1° Hyperparathyroidism
Easy to diagnose and treat -- if you think of it.
parathyroid adenoma
primary parathyroid hyperplasia
Ca++
high BP
bone resorption
pancreatitis
stomach ulcers
kidney stones
"osteitis fibrosa cystica"
It's all in your mind!
"depression" and "psychosis"

(ii) Secondary hyperparathyroidism
(2°to disease of other organs)

- This is caused by any condition associated with a chronic depression in serum calcium level,
- low serum calcium levels lead to compensatory over activity of the parathyroid glands

Causes include:

- Renal failure – most common cause. Chronic renal insufficiency is associated with decreased phosphate excretion, which results in hyperphosphataemia. The elevated serum phosphate levels directly depress serum calcium levels and thereby stimulate parathyroid gland activity.
- Inadequate dietary intake of calcium
- Steatorrhoea
- Vitamin D deficiency

Clinical features:

- Usually dominated by those associated with chronic renal failure.
- Renal osteodystrophy and other changes associated with PTH excess are in generally less severe than those seen in primary hyperparathyroidism.
- Vascular calcification may occasionally result in significant ischaemic damage to the skin and other organs, a process sometimes referred to as calciphylaxis.

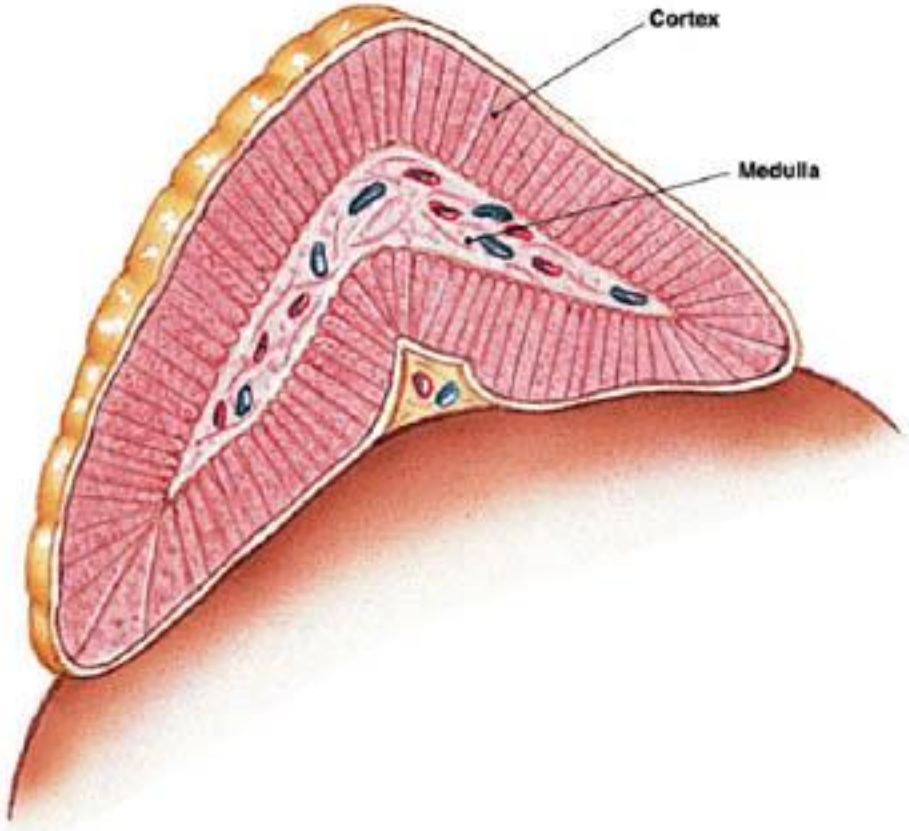
b. Hypoparathyroidism

- Surgically induced hypoparathyroidism
- Congenital absence of the glands
- Primary (idiopathic) atrophy of the glands most likely an autoimmune disease
- Familial hypoparathyroidism

The major clinical manifestations are related to severity and chronicity of hypocalcaemia:

- Tetany – neuromuscular irritability due to decreased serum ionozed calcium concentrations.
- Mental status changes – emotional instability, anxiety and depression, confusional states, hallucinations and frank psychosis
- Intracranial manifestations – parkinsonian-like movement disorders
- Ocular disease – calcification of the lens leading to cataract formation
- Cardiovascular manifestations – conduction defect
- Dental abnormalities – occurs when hypocalcaemia present during early development.

IV. ADRENAL GLANDS


Cortex
Medulla

I. Adrenal cortex

- synthesis of corticosteroid hormones from cholesterol.
- Some cells belong to the hypothalamic-pituitary-adrenal axis and are the source of cortisol synthesis.
- Other cortical cells produce androgens such as testosterone, while some regulate water and electrolyte concentrations by secreting aldosterone.
- the cortex is regulated by neuroendocrine hormones secreted by the pituitary gland and hypothalamus, as well as by the renin-angiotensin system.

a. Hypercorticism (Cushing syndrome)

- caused by any condition that produces an elevation in glucocorticoid levels.

(i) Administration of exogenous glucocorticoids

Iatrogenic Cushing syndrome – the most common cause

(ii) Primary hypothalamic-pituitary diseases associated with hyper-secretion of ACTH

- In most cases, the pituitary gland contains a small ACTH-producing adenoma that does not produce mass effects on the brain.
- In most of the remaining cases, the anterior pituitary contains areas of corticotroph cell hyperplasia without a discrete adenoma.
  - appears to result from excessive stimulation of ACTH release by the hypothalamus.
- The adrenal glands undergo bilateral cortical hyperplasia.

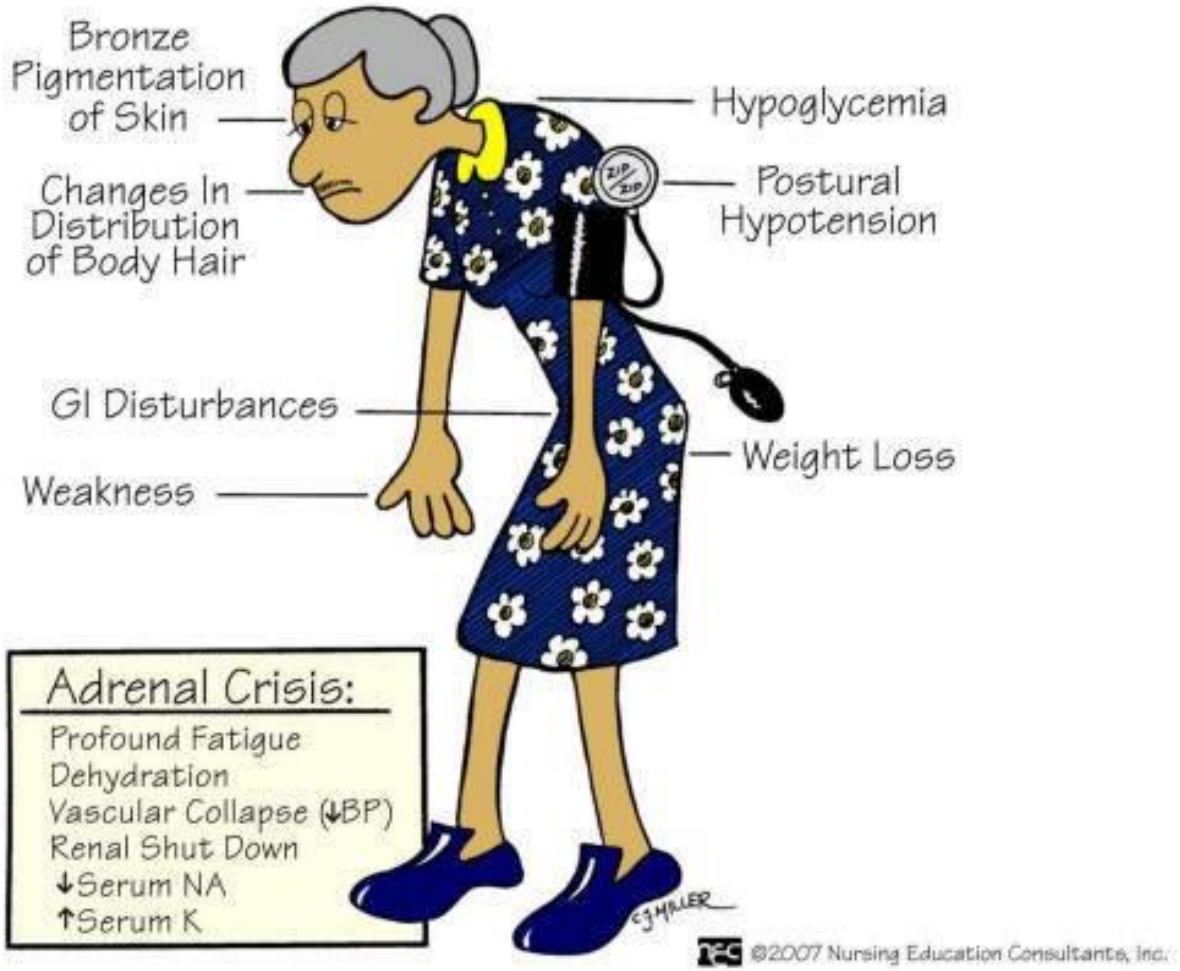
(iii) Hyper-secretion of cortisol by an adrenal adenoma, carcinoma or nodular hyperplasia – ACTH independent Cushing syndrome

- The adrenals function autonomously.
- In cases with a unilateral neoplasm, the uninvolved adrenal cortex and that in the opposite gland undergo atrophy because of suppression of ACTH secretion.
- This is marked by elevated levels of cortisol and low serum levels of ACTH.

(iv) Secretion of ectopic ACTH by a non endocrine neoplasm

- In most cases the responsible tumour is a small cell carcinoma of the lung, although other neoplasms including carcinoid tumours, medullary carcinomas of the thyroid, and islet tumours of the pancreas have been associated with the syndrome.
- These tumours elaborate ectopic ACTH.
- An occasional neoplasm produces ectopic corticotrophin releasing factor (CRF), which in turn causes ACTH secretion and hypercorticism.
- The adrenal glands undergo bilateral cortical hyperplasia.
- This is more common in men (40-50 yrs).

b. Hypocorticism



(i) Primary acute adrenocortical insufficiency

- As a crisis in patients with chronic adrenocortical insufficiency precipitated by any form of stress that requires an immediate increase in steroid output from glands incapable of responding.
- In patients maintained on exogenous corticosteroids, in whom rapid withdrawal of steroids, or failure to increase steroid doses in response to acute stress, may precipitate an adrenal crisis, owing to the inability of the atrophic adrenal glands to produce glucocorticoid hormones.
- As a result of massive adrenal haemorrhage, which destroys the adrenal cortex sufficiently to cause acute adrenocortical insufficiency.

(ii) Primary chronic adrenocortical insufficiency (Addison disease)

- results from progressive destruction of the adrenal cortex.
- In general clinical manifestations of adrenocortical insufficiency do not appear until at least 90% of the adrenal cortex has been compromised.

Causes

- More than 90% of all cases are attributable to autoimmune adrenalitis, tuberculosis or metastatic cancers.
- Other diseases that may attack the adrenal cortex include lymphomas, amyloidosis, sarcoidosis, hemochromatosis, fungal infections and adrenal haemorrhages.

(iii) Secondary adrenocortical insufficiency

- Any disorder of the hypothalamus and pituitary that reduces the output of ACTH leads to a syndrome of hypoadrenalism having many similarities with Addison disease.
- Prolonged administration of exogenous glucocorticoids suppresses the output of ACTH and adrenal function.
- The adrenal glands are moderately to markedly reduced in size.

II. Adrenal medulla

- The chromaffin cells of the medulla are the body's main source of the catecholamine hormones adrenaline (epinephrine) and noradrenaline (norepinephrine).
- The adrenal medulla can be considered specialized ganglia of the sympathetic nervous system, lacking distinct synapses, instead releasing secretions directly into the blood.

- The most important diseases of the adrenal medulla are neoplasms
  - neoplasms of chromaffin cells (pheochromocytomas) and
  - neuronal neoplasms (including neuroblastomas and more mature ganglion cell tumours).

a. Pheochromocytoma

- The predominant clinical feature is hypertension
- These episodes may be associated with pain in the abdomen or chest, nausea and vomiting.
- In about two thirds of the patients, the hypertension occurs in the form of chronic, sustained elevation in blood pressure.
- The elevations of pressure are induced by the sudden release of catecholamines that may acutely precipitate congestive heart failure, pulmonary oedema, myocardial infarction, ventricular fibrillation and cerebrovascular accidents (stroke).

- In some cases the tumours secrete other hormones like ACTH and somatostatin and may therefore be associated with clinical features related to the secretion of these or other peptide hormones.

V. MULTIPLE ENDOCRINE NEOPLASM (MEN) SYNDROMES

- The MEN syndromes are a group of familial diseases associated with hyperplasias or neoplasms (or both) of several endocrine organs.
- The disorders are inherited as autosomal dominant traits.

a. MEN I

- Primary hyperparathyroidism is the most common manifestation of MEN I. Parathyroid abnormalities include both hyperplasia and adenomas.
- The pancreatic lesions include islet cell tumours which may secrete a wide range of peptide hormones including insulin, glucagons, gastrin, somatostatin, and vasoactive intestinal peptide (VIP).
- The most common type of anterior pituitary tumour is prolactinoma, although other types of tumours can occur.

b. MEN II

- This is subclassified into 3 distinct syndromes:
  - MEN IIA,
  - MEN IIB, and
  - familial medullary thyroid cancer.

(i) MEN IIA

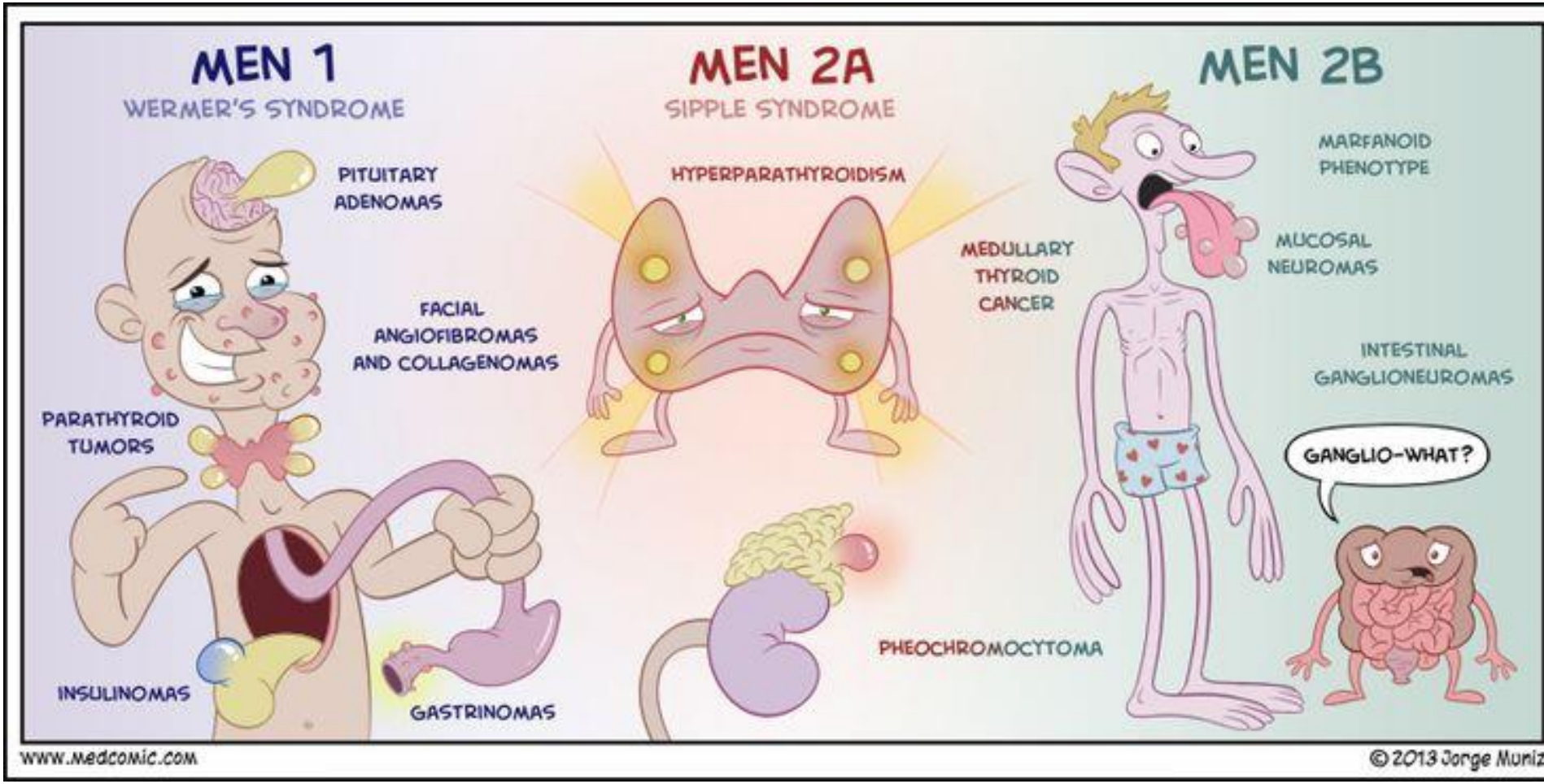
- Medullary carcinomas of the thyroid occur in almost 100% of the patients.
  - They are usually multifocal and virtually always associated with foci of C cell hyperplasia.
  - They may elaborate calcitonin and other active products and are usually clinically aggressive.
  - This is a life threatening disease.
- 40 to 50% of patients have pheochromocytomas which may be malignant or benign.
- Ten to 20% of the patients have parathyroid hyperplasia and evidence of hypercalcaemia or renal stones

(ii) MEN IIB

- This is also known as MEN III.
- It is clinically similar to MEN IIA but is genetically distinct.
- In addition to medullary carcinomas and pheochromocytomas, it is also accompanied by neuromas or ganglioneuromas involving the skin, oral mucosa, eyes, respiratory tract and gastrointestinal tract.

(iii) Familial medullary thyroid cancer

- This is a variant of MEN IIA
- there is a strong disposition to medullary thyroid cancer but not other clinical manifestations of MEN IIA or MEN IIB.


MEN 1
WERMER'S SYNDROME
PITUITARY ADENOMAS
FACIAL ANGIOFIBROMAS AND COLLAGENOMAS
PARATHYROID TUMORS
INSULINOMAS
GASTRINOMAS
MEN 2A
SIPPLE SYNDROME
HYPERPARATHYROIDISM
PHEOCHROMOCYTOMA
MEN 2B
MARFANOID PHENOTYPE
MUCOSAL NEUROMAS
MEDULLARY THYROID CANCER
INTESTINAL GANGLIONEUROMAS
GANGLIO-WHAT?
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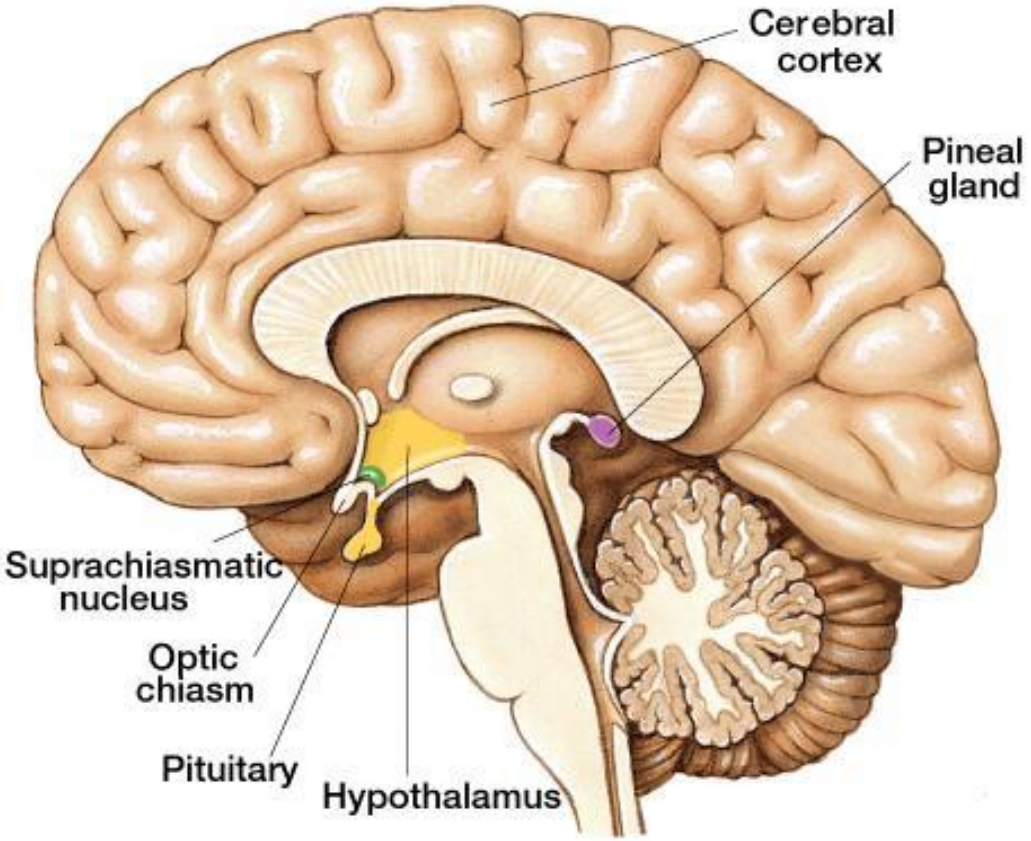
VI. PINEAL GLAND

- The pineal gland is a minute, pine cone shaped organ, weighing 100 to 180mg and lying between the superior colliculi at the base of the brain.
- It produces melatonin, a hormone that affects the modulation of wake/sleep patterns and photoperiodic (seasonal) functions.
- The only clinically significant lesions are tumours.
- All tumours involving the pineal gland are rare.


Cerebral cortex
Pineal gland
Suprachiasmatic nucleus
Optic chiasm
Pituitary
Hypothalamus

a. Germ neoplasms

- 50 to 70% arise from sequestered embryonic germ cells.
- They most commonly take the form of germinomas (replicating testicular seminoma or ovarian dysgerminoma).
- Other lines of germ cell differentiation include embryonal carcinomas; choriocarcinomas; mixtures of germinoma; and uncommonly typical teratomas

b. Pinealomas

- These are tumours arising from pineocytes.
- They are divided into two categories; pineoblastomas and pineocytomas based on their level of differentiation, which in turn correlates with their neoplastic aggressiveness
- Excision is difficult owing to location.

Pineoblastomas

- Pineoblastomas are encountered mostly in young people and appear as soft friable grey masses, punctuated with areas of haemorrhage and necrosis.
- They invade surrounding structures.
- The enlarging mass may compress the aqueduct of Sylvius giving rise to internal hydrocephalus.
- Survival beyond one or two years is rare.

Pineocytomas

- occur mostly in adults and are much slower growing.
- They are well circumscribed grey or haemorrhagic masses that compress but do not infiltrate surrounding structures.
- The clinical course is long, averaging 7 years.
- Clinical manifestations are a consequence of their pressure effects and consist of visual disturbances, headache, mental disorientation and sometimes dementia like behaviour