The Endocrine System diseases

- The endocrine system consists of a **highly integrated and widely distributed group** of organs that **orchestrate a state of metabolic equilibrium**, or homeostasis, among the various organs of the body.
- Signaling by extracellular secreted molecules can be classified into three types—**autocrine, paracrine, or endocrine**.

Endocrine diseases can be generally classified as

(1) diseases of **underproduction or overproduction** of hormones and their resulting biochemical and clinical consequences

(2) diseases associated with the **development of mass lesions**. Such lesions might be nonfunctional, or they might be associated with overproduction or underproduction of hormones.

PITUITARY GLAND

The pituitary gland is composed of two components: **the anterior lobe (adenohypophysis**) and the **posterior lobe (neurohypophysis**).

The **anterior** pituitary constitutes about **80% of the gland**. Specific antibodies against the pituitary hormones identify five cell types:

1. Somatotrophs, producing growth hormone (GH).
2. Lactotrophs (mammotrophs), producing prolactin.
3. Corticotrophs: These cells produce adrenocorticotropic hormone (ACTH), pro-opiomelanocortin (POMC), melanocyte-stimulating hormone (MSH), endorphins, and lipotropin.
4. Thyrotrophs: These cells produce thyroid-stimulating hormone (TSH).
5. Gonadotrophs: These cells produce both follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Clinical Manifestations of Pituitary Disease

- **Hyperpituitarism**: excess secretion of trophic hormones.
- **Hypopituitarism**: deficiency of trophic hormones.
- **Local mass effects**: pituitary adenomas can produce signs and symptoms of elevated intracranial pressure, including headache, nausea, and vomiting.

Pituitary Adenomas and Hyperpituitarism

- The most common cause is an **adenoma** arising in the anterior lobe.
- Pituitary adenomas are classified on the basis of hormone produced by the neoplastic cells.
- Some pituitary adenomas can secrete **two hormones** (GH and prolactin the most common combination), and rarely, pituitary adenomas are **plurihormonal**. Pituitary adenomas can be **functional or nonfunctioning**.

Morphology

- The typical pituitary adenoma is a soft, well-circumscribed lesion that may be confined to **the sella turcica**. Larger lesions typically extend superiorly through the diaphragm sella into the suprasellar region, where they often compress the optic chiasm and adjacent structures, such as some of the cranial nerves.
- Histologically, typical pituitary adenomas are composed of relatively uniform, polygonal cells arrayed in sheets or cords.

- PROLACTINOMAS
- **GROWTH HORMONE CELL (SOMATOTROPH) ADENOMAS**
- ACTH CELL (CORTICOTROPH) ADENOMAS
- OTHER ANTERIOR PITUITARY ADENOMAS

Hypopituitarism

- Traumatic brain injury and subarachnoid hemorrhage are among the most common causes of pituitary hypofunction.
- Pituitary surgery or radiation
- Pituitary apoplexy.
- Ischemic necrosis of the pituitary and Sheehan syndrome.
- Empty sella syndrome: There are two types: (1) primary empty sella, (2) secondary empty sella.
- Genetic defects.
- Hypothalamic lesions.
- Inflammatory disorders and infections.

THYROID GLAND

- The thyroid gland consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx.
- The thyroid is divided by thin fibrous septae into lobules composed of about 20 to 40 evenly dispersed follicles, lined by a cuboidal to low columnar epithelium, and filled with thyroglobulin.

Hyperthyroidism

Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of free T3 and T4.

The three most common causes of thyrotoxicosis:

- Diffuse hyperplasia of the thyroid associated with Graves disease (accounts for 85% of cases)
- Hyperfunctional multinodular goiter
- Hyperfunctional adenoma of the thyroid

Clinical Course

- Excessive levels of thyroid hormone result in an increase in the basal metabolic rate.
- The skin of thyrotoxic patients tends to be soft, warm, and flushed because of increased blood flow and peripheral vasodilation to increase heat loss.
- Heat intolerance and sweating are common.
- Characteristic weight loss despite increased appetite.
- Tachycardia, palpitations, and cardiomegaly are common.
- Tremor, hyperactivity, emotional lability, anxiety, inability to concentrate, and insomnia. Proximal muscle weakness and decreased muscle mass are common (thyroid myopathy).

Clinical Course

- Hypermotility, malabsorption, and diarrhea.
- Thyroid hormone stimulates bone resorption, increasing porosity of cortical bone and reducing the volume of trabecular bone.
- Thyroid storm is used to designate the abrupt onset of severe hyperthyroidism. Patients are often febrile and present with tachycardia out of proportion to the fever. Thyroid storm is a **medical emergency.**

Hypothyroidism

- ***Hypothyroidism*** is caused by any structural or functional derangement that interferes with the production of adequate levels of thyroid hormone.
- It can result from a defect anywhere in the hypothalamic-pituitary-thyroid axis.
- is divided into *primary* and *secondary* categories.
- Primary hypothyroidism accounts for the vast majority of cases of hypothyroidism, and can be accompanied by an enlargement in the size of the thyroid gland (goiter).
- Primary hypothyroidism can be **congenital, acquired, or autoimmune**.

Hypothyroidism

- Worldwide, congenital hypothyroidism is most often the result of endemic iodine deficiency in the diet.
- In rare instances there may be complete absence of thyroid parenchyma (thyroid agenesis), or the gland may be greatly reduced in size (thyroid hypoplasia).

Hypothyroidism

- Acquired hypothyroidism can be caused by surgical or radiation-induced ablation of thyroid parenchyma.
- A large resection of the gland for the treatment of hyperthyroidism of a primary neoplasm can lead to hypothyroidism.
- Drugs given intentionally to decrease thyroid secretion can cause acquired hypothyroidism.

Hypothyroidism

- Autoimmune hypothyroidism is the most common cause of hypothyroidism in iodine-sufficient areas of the world.
- The vast majority of cases of autoimmune hypothyroidism are due to Hashimoto thyroiditis.
- Circulating autoantibodies, including anti-microsomal, anti-thyroid peroxidase, and anti-thyroglobulin antibodies, are found in this disorder, and the thyroid is typically enlarged.
- Autoimmune hypothyroidism can occur in isolation or in conjunction with autoimmune polyendocrine syndrome (APS), types 1 and 2.

Hypothyroidism

- Classic clinical manifestations of hypothyroidism include cretinism and myxedema.

CRETINISM

- Cretinism refers to hypothyroidism that develops in infancy or early childhood.
- In the past this disorder occurred fairly commonly in areas of the world where dietary iodine deficiency is endemic.
- Clinical features of cretinism include impaired development of the skeletal system and central nervous system, manifested by severe mental retardation, short stature, coarse facial features, a protruding tongue, and umbilical hernia.
- Normally, maternal hormones, including T3 and T4, cross the placenta and are critical to fetal brain development. If there is maternal thyroid deficiency before the development of the fetal thyroid gland, mental retardation is severe.

MYXEDEMA

- The term myxedema is applied to hypothyroidism developing in the older child or adult. The clinical manifestations vary with the age of onset of the deficiency.
- In the adult the condition appears insidiously and may take years to reach the level of clinical suspicion.
- Clinical features of myxedema are characterized by a slowing of physical and mental activity. The initial symptoms include generalized fatigue, apathy, and mental sluggishness, which may mimic depression in the early stages of the disease. Speech and intellectual functions become slowed. Patients with myxedema are listless, cold intolerant, and frequently overweight.

Thyroiditis

- Thyroiditis, or inflammation of the thyroid gland, encompasses a diverse group of disorders characterized by some form of thyroid inflammation.
- These diseases include conditions that result in acute illness with severe thyroid pain and disorders in which there is relatively little inflammation and the illness is manifested primarily by thyroid dysfunction—subacute lymphocytic thyroiditis and fibrous (Reidel) thyroiditis.

HASHIMOTO THYROIDITIS

- Hashimoto thyroiditis is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.
- Hashimoto thyroiditis is characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland.
- This disorder is most prevalent between 45 and 65 years of age and is more common in women than in men.
- Hashimoto thyroiditis has a strong genetic component.

Morphology

- The thyroid is often diffusely enlarged. The cut surface is pale, yellowtan, firm, and somewhat nodular.
- Microscopic examination reveals extensive infiltration of the parenchyma by a mononuclear inflammatory infiltrate containing small lymphocytes, plasma cells, and well-developed germinal centers. The thyroid follicles are atrophic and are lined in many areas by epithelial cells distinguished by the presence of abundant eosinophilic, granular cytoplasm, termed Hürthle cells.

Clinical Course

- hypothyroidism develops gradually.
- In some cases, however, it may be preceded by transient thyrotoxicosis caused by disruption of thyroid follicles, with secondary release of thyroid hormones (“hashitoxicosis”). During this phase, free T4 and T3 levels are elevated, TSH is diminished, and radioactive iodine uptake is decreased.
- As hypothyroidism supervenes, T4 and T3 levels fall, accompanied by a compensatory increase in TSH.

SUBACUTE (GRANULOMATOUS) THYROIDITIS

- Subacute thyroiditis, which is also referred to as granulomatous thyroiditis or De Quervain thyroiditis, occurs much less frequently than does Hashimoto disease.
- The disorder is most common between the ages of 40 and 50 and, like other forms of thyroiditis, affects women considerably more often than men (4 : 1).

Morphology

- The gland may be unilaterally or bilaterally enlarged and firm, with an intact capsule. On cut section, the involved areas are firm and yellow-white and stand out from the more rubbery, normal brown thyroid substance.
- Histologically, the changes are patchy and depend on the stage of the disease.
- Early in the active inflammatory phase, scattered follicles may be entirely disrupted and replaced by neutrophils forming microabscesses.
- Later, the more characteristic features appear in the form of aggregates of lymphocytes, activated macrophages, and plasma cells about collapsed and damaged thyroid follicles.

Clinical Course

- Granulomatous (de Quervain) thyroiditis is the most common cause of thyroid pain.
- The thyroid inflammation and hyperthyroidism are transient, usually diminishing in 2 to 6 weeks, even if the patient is not treated.
- Nearly all patients have high serum T4 and T3 levels and low serum TSH levels during this phase.
- After recovery, generally in 6 to 8 weeks, normal thyroid function returns.

Graves Disease

Graves disease is the most common cause of endogenous hyperthyroidism.

It is characterized by a triad of clinical findings:

1. Hyperthyroidism due to diffuse, hyperfunctional enlargement of the thyroid
2. Infiltrative ophthalmopathy with resultant exophthalmos
3. Localized, infiltrative dermopathy, sometimes called pretibial myxedema, which is present in a minority of patients

Morphology

- The thyroid gland is usually symmetrically enlarged because of diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells. On cut section, the parenchyma has a soft, meaty appearance resembling normal muscle.
- Histologically, the follicular epithelial cells in untreated cases are tall and more crowded than usual. This crowding often results in the formation of small papillae, which project into the follicular lumen and encroach on the colloid, sometimes filling the follicles. Such papillae lack fibrovascular cores, in contrast to those of papillary carcinoma. The colloid within the follicular lumen is pale, with scalloped margins. Lymphoid infiltrates are present throughout the interstitium; germinal centers are common.
- Changes in extra-thyroidal tissue include generalized lymphoid hyperplasia.
- In patients with ophthalmopathy, the tissues of the orbit are edematous because of the presence of hydrophilic mucopolysaccharides. In addition, there is infiltration by lymphocytes and fibrosis.

Clinical Course

- The clinical findings in Graves disease include changes referable to thyrotoxicosis as well as those associated uniquely with Graves disease, diffuse hyperplasia of the thyroid, ophthalmopathy, and dermopathy.
- Laboratory findings in Graves disease include elevated free T4 and T3 levels and depressed TSH levels. Because of ongoing stimulation of the thyroid follicles by thyroid-stimulating immunoglobulins, radioactive iodine uptake is increased, and radioiodine scans show a diffuse uptake of iodine.

Diffuse and Multinodular Goiters

- Enlargement of the thyroid, or goiter, is the most common manifestation of thyroid disease.
- Diffuse and multinodular goiters reflect impaired synthesis of thyroid hormone, which is most often caused by dietary iodine deficiency.
- Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH level.

Morphology

- Two phases can be identified in the evolution of diffuse nontoxic goiter: the hyperplastic phase and the phase of colloid involution.
- In the hyperplastic phase, the thyroid gland is diffusely and symmetrically enlarged, although the increase is usually modest, and the gland rarely exceeds 100 to 150 gm.

Clinical Course

- the vast majority of persons with simple goiters are clinically euthyroid.
- Therefore, the clinical manifestations are primarily related to mass effects from the enlarged thyroid gland.
- Although serum T3 and T4 levels are normal, the serum TSH is usually elevated or at the upper range of normal, as is expected in marginally euthyroid individuals.

- With time, recurrent episodes of hyperplasia and involution combine to produce a more irregular enlargement of the thyroid, termed multinodular goiter.
- Multinodular goiters produce the most extreme thyroid enlargements and are more frequently mistaken for neoplastic involvement.

Morphology

- Multinodular goiters are multilobulated, asymmetrically enlarged glands that can reach weights of more than 2000 gm.
- The pattern of enlargement is quite unpredictable and may involve one lobe far more than the other, producing lateral pressure on midline structures, such as the trachea and esophagus. In other instances the goiter grows behind the sternum and clavicles to produce the so-called intrathoracic or plunging goiter.
- On cut section, irregular nodules containing variable amounts of brown, gelatinous colloid are present. Older lesions have areas of hemorrhage, fibrosis, calcification, and cystic change.
- The microscopic appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of follicular hyperplasia.

PARATHYROID GLANDS

The activity of the parathyroid glands is controlled by the level of free calcium in the bloodstream rather than by trophic hormones secreted by the hypothalamus and pituitary.

The metabolic functions of PTH in regulating serum calcium levels:

- It increases the renal tubular reabsorption 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 levels.
- It augments gastrointestinal calcium absorption.

Hyperparathyroidism

- Hyperparathyroidism occurs in two major forms—primary and secondary—and, less commonly, tertiary.
- The first condition represents an autonomous, spontaneous overproduction of PTH;
- the latter two conditions typically occur as secondary phenomena in individuals with chronic renal insufficiency

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is one of the most common endocrine disorders, and it is an important cause of hypercalcemia.

The frequency of the various parathyroid lesions underlying the hyperfunction is :

- Adenoma: 85% to 95%
- Primary hyperplasia (diffuse or nodular): 5% to 10%
- Parathyroid carcinoma: ∼1%

Morphology

- The typical parathyroid adenoma averages 0.5 to 5.0 gm; is a well-circumscribed, soft, tan to reddish-brown nodule; and is invested by a delicate capsule.
- Primary hyperplasia may occur sporadically or as a component of MEN syndrome. Although classically all four glands are involved, there is frequently asymmetry with apparent sparing of one or two glands, making the distinction between hyperplasia and adenoma difficult.
- Microscopically, the most common pattern seen is that of chief cell hyperplasia, which may involve the glands in a diffuse or multinodular pattern. Less commonly, the constituent cells contain abundant water-clear cells (“water-clear cell hyperplasia”).

Clinical Course

- Primary hyperparathyroidism may be:
- (1) asymptomatic and identified after a routine chemistry profile,
- (2) associated with the classic clinical manifestations of primary hyperparathyroidism.

SECONDARY HYPERPARATHYROIDISM

- Renal failure is by far the most common cause of secondary hyperparathyroidism, although several other diseases, including inadequate dietary intake of calcium, steatorrhea, and vitamin D deficiency, may also cause this disorder.
- Chronic renal insufficiency is associated with decreased phosphate excretion, which in turn results in hyperphosphatemia.
- The elevated serum phosphate levels directly depress serum calcium levels and thereby stimulate parathyroid gland activity.
- Loss of renal substance reduces the availability of α-1-hydroxylase necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption of calcium

Morphology

- The parathyroid glands in secondary hyperparathyroidism are hyperplastic.
- Microscopically, the hyperplastic glands contain an increased number of chief cells, or cells with more abundant, clear cytoplasm (so-called water-clear cells) in a diffuse or multinodular distribution.
- Metastatic calcification may be seen in many tissues, including lungs, heart, stomach, and blood vessels.

Clinical Course

- The clinical features of secondary hyperparathyroidism are usually dominated by symptoms of chronic renal failure.
- The vascular calcification associated with secondary hyperparathyroidism may occasionally result in significant ischemic damage to skin and other organs, a process sometimes referred to as calciphylaxis.
- Parathyroidectomy may be necessary to control the hyperparathyroidism.

Hypoparathyroidism

Hypoparathyroidism is **far less common** than is hyperparathyroidism.

- Surgically induced hypoparathyroidism.
- Autoimmune hypoparathyroidism is often associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency; this syndrome is known as autoimmune polyendocrine syndrome type 1 (APS1)
- Autosomal-dominant hypoparathyroidism is caused by gain-of-function mutations in the calcium-sensing receptor (CASR) gene.
- Familial isolated hypoparathyroidism (FIH) is a rare condition with either autosomal dominant or autosomal recessive patterns of inheritance.
- Congenital absence of parathyroid glands can occur in conjunction with other malformations, such as thymic aplasia and cardiovascular defects, or as a component of the 22q11 deletion syndrome.

Hypoparathyroidism

- The hallmark of hypocalcemia is **tetany**, which is characterized by neuromuscular irritability, resulting from decreased serum ionized calcium concentration.
- The classic findings on physical examination are **Chvostek sign** and **Trousseau sign**.
- Mental status changes include emotional instability, anxiety and depression, confusional states, hallucinations, and frank psychosis.
- Intracranial manifestations include calcifications of the basal ganglia, parkinsonian-like movement disorders, and increased intracranial pressure with resultant papilledema.
- Ocular disease takes the form of calcification of the lens and cataract formation.
- Cardiovascular manifestations include a conduction defect that produces a characteristic prolongation of the QT interval in the electrocardiogram.
- Dental abnormalities include dental hypoplasia, failure of eruption, defective enamel and root formation, and abraded carious teeth