Hyperthyroidism

Hypermetabolic state due to Elevated circulating T3 and T4, the resulting clinical syndrome being known as **thyrotoxicosis**.

Clinical features of thyrotoxicosis: Weight loss, diarrhea, Exophthalmos, pretibial myxedema, tachycardia, palpitations, Warm moist skin, proximal myopathy, Nervousness , tremor, Heat intolerance and excessive sweating.

1°	➢ Hyperfunctioning ("**toxic**") multinodular goiter ➢ Hyperfunctioning ("toxic") thyroid adenoma ➢ Iodine-induced hyperthyroidism
2°	TSH-secreting pituitary adenoma

Diagnosis:
The measurement of serum TSH is the most useful single screening test for hyperthyroidism. **T3, T4 and radioactive iodine uptake** are used as well.

Graves' disease: An **autoimmune disease;** autoantibodies **mimic** the stimulatory action of TSH.
➢ Between the ages of **20 and 40,** Women more than men and the most common cause of Hyperthyroidism
Genetic susceptibility with HLA- DR3

Pathogenesis

- **Thyroid-stimulating immunoglobulin**: ↑ thyroid hormone.
- **Thyroid growth-stimulating immunoglobulin**: leads to proliferation of thyroid follicular epithelium.
- **TSH-binding inhibitor immunoglobulin**: ↓ thyroid hormone.

Infiltrative ophthalmopathy: 1. Infiltration of the retro-orbital space by mononuclear cells (Mostly T cells). **2.** Inflammatory edema. **3.** Accumulation of **glycosaminoglycans**. **4.** ↑ adipocytes

Clinical findings

➢ Thyroid enlargement, pretibial myxedema
➢ Infiltrative ophthalmopathy

Histology

➢ Scalloped colloid appearance
➢ Epithelial cells turn columnar, Lymphocytosis

Hypothyroidism: Insufficient circulating T4 and T3 leads to a **hypometabolic** state

Causes

1°	➢ Hashimoto's thyroiditis ➢ Iodine deficiency ➢ Thyroid dysgenesis ➢ Congenital biosynthetic defect ➢ Post ablative
2°	Caused by deficiency of TSH

Clinical Features

- Cretinism: During infancy, It manifests with: Severe mental retardation, short stature, coarse facial features, a protruding tongue, obesity and umbilical hernia.
- Myxedema: Glycosaminoglycans and hyaluronic acid, in skin, subcutaneous tissue, visceral sites. Non-pitting edema, a broadening and coarsening of facial features, tongue enlargement, deepening voice.
- Hair loss (skull and eyebrows), Oligomenorrhoea, Somnolence, Bradycardia & Slowness in memory

Hashimoto's thyroiditis:	An organ specific autoimmune disease in which the immune system reacts against a variety of thyroid antigens (thyroglobulin and thyroid peroxidase): Most common cause of hypothyroidism. Female predominance of 10:1 to 20:1. Age 45-65.
Clinical Features	Painless enlargement, Goiter, which recedes after time due to atrophy and fibrosis. Hypothyroidism, thyrotoxicosis in the early stages. ↑ risk for the development of B cell non-Hodgkin lymphomas and predisposition to papillary carcinomas.
Grossly	**1.** Diffusely enlarged. **2.** Cut surface is pale, firm, and somewhat nodular **3.** In advanced cases, the gland is **shrunken and fibrotic**
Histologically	• Infiltration of the parenchyma by lymphocytes and plasma cells, well-developed **germinal centers** • ↑ of the number of cells lining the follicles and ↓ in the amount of stored colloid. **Oncocytes or Hürthle cells.**

Subacute Granulomatous Thyroiditis: (de Quervain)

- The thyroid is infiltrated by multinucleated giant cells
- between the ages of **30 and 50,** Self-limited, caused mostly by a viral infection
- Most common cause of painful thyroid gland
- fever, malaise, tenderness on palpation and variable enlargement of the thyroid

Histology

- Disruption of thyroid follicles. Granulomatous reaction with giant cells.
- Polymorphonuclear infiltrate.

Riedel's thyroiditis

It's exceptionally **rare**. Characterized by replacement of the thyroid by **fibrous tissue**, often with involvement of adjacent tissues **(retroperitoneum).** The etiology is unknown. Patients present with an enlarged thyroid, which is **hard** and **immobile** on palpation thereby **mimicking carcinoma**. The condition may be associated with **retroperitoneal fibrosis**.

Multinodular Goiter

Enlargement of the thyroid, or goiter, is the most common manifestation of thyroid disease, it has two subtypes:

Endemic	In geographic areas where there is little iodine.
Sporadic	Less common than endemic goiter; occurs in **Females more than males.**

Pathogenesis

- Impairment of thyroid hormone synthesis → a **compensatory** rise in the serum TSH → TSH-induced **hypertrophy and hyperplasia** of thyroid follicular cells → diffuse and symmetric enlargement of the gland.
- With time, Recurrent episodes of hyperplasia → a more **irregular enlargement** of the thyroid termed Multinodular goiter.

Grossly	Microscopically
Asymmetrically enlarged glands. Irregular nodules. **Brown gelatinous** colloid. On Cut surface, it shows: Fibrosis, hemorrhage & cystic change.	Colloid-rich follicles & Flattened follicular epithelium

Solitary Thyroid Nodule

Palpably discrete swelling within an otherwise apparently normal thyroid gland

Incidence	1-10%, single nodules: Female/Male 4:1, ↑ throughout life,
Majority	Localized, non-neoplastic conditions or benign neoplasms such as follicular adenomas.

Diagnosis

- One dominant nodule in a multinodular goiter. - Thyroid cysts. - Thyroid neoplasm.
- Asymmetrical enlargement due to non-neoplastic disease (e.g. Hashimoto's thyroiditis)

Thyroid Neoplasms

Morphologic evaluation of a nodule by **fine needle aspiration**, combined with histologic study of surgically **resected thyroid parenchyma** provide the most definitive information about its nature (whether it's benign or malignant).
The major risk factor predisposing to thyroid cancer is exposure to **ionizing radiation.**

Follicular Adenoma

Benign masses derived from follicular epithelium Careful evaluation of the integrity of the capsule is critical in distinguishing adenomas from follicular carcinomas.

Degree of follicular formation	Pathogenesis	Morphology
○ Macrofollicular adenomas (simple colloid) ○ Fetal or microfollicular, embryonal or trabecular (during embryogenesis)	▪ Somatic mutations in the genes encoding for TSH receptor or, the alpha subunit of Gs ▪ Mutations in RAS or (PIK3CA).	▪ Solitary, typically discrete, spherical nodule compressing adjacent nonneoplastic parenchyma with a **well-defined, intact capsule.** ▪ **(Hürthle cell change).**

	Genetic factors	Morphology	Metastasis	Clinical Features/prognosis
Papillary	**Activation of the MAP kinase pathway:** Rearrangements of the tyrosine kinase receptors **RET** or **NTRK1 or Activating point mutations in BRAF**. ***RET/PTC (fusion)*** translocations	Un-encapsulated, papillary structure, **psammoma bodies, orphan Annie nuclei, grooves nuclei & pseudoinclusions. Can present in several ways but Follicular variant is the most common:** encapsulated and is associated with a lower incidence of lymph node metastases and extrathyroidal extension.	Cervical **lymph node** metastases	3rd or 4th decade. Painless mass in the neck. Excellent prognosis
Follicular	Chromosomes (2;3) translocation results in ***PAX8/PPARG* fusion genes,** Mutations in **PI-3K/AKT signaling pathway:** Gain-of-function point mutations of ***RAS* and *PIK3CA* or** Loss-of-function mutations of ***PTEN***	Solitary, encapsulated, may appear like papillary carcinoma, only lacking its nuclear features. Hürthle cell variants, degenerative changes, such as central fibrosis and foci of calcification may be seen **Widely invasive**: Extensive invasion of adjacent thyroid parenchyma or extrathyroidal tissues. They have a greater proportion of solid or trabecular growth pattern, less follicular differentiation, and ↑ mitotic activity.	**Hematogenous dissemination**	Between 40-60, frequent in areas with iodine deficiency. Prognosis: Poorer than papillary
Medullary	**(MEN-2)** and are associated with RET proto-oncogene **mutation.**	Derived from parafollicular cells (C-cells). **Grossly: Sporadic (70%)** originates in one lobe & **Familial: Bilaterality and multicentric C-cell hyperplasia** **Microscopically: Acellular amyloid deposits & calcitonin** within the cytoplasm of the tumor cells as well as in the stromal amyloid. Most secrete calcitonin	-	**MEN: both have:** Medullary carcinoma of the thyroid & pheochromocytoma. **Type 2A:** Parathyroid adenoma **Type 2B:** Ganglioneuroma **Sporadic clinical features:** mass in the neck, with compression effects
Ana-plastic	De novo or more commonly by dedifferentiation.	**Poorly differentiated highly anaplastic cells**, Very **pleomorphic**	Widely	>65, rapid growth rate, lethal & prognosis is very poor

Adrenocortical Hyperfunction

three distinctive hyperadrenal clinical syndromes, each caused by abnormal production of one or more of the hormones produced by the three layers of the cortex.	(1) ***Cushing syndrome***, characterized by an excess of **cortisol**. (2) ***Hyperaldosteronism.*** (3) *Adrenogenital* or *virilizing syndromes* caused by an excess of androgens.

Hypercortisolism "Cushing Syndrome":	Caused by any condition that produces an elevation in glucocorticoid levels	
It could be:		
1-Exogenous	Most common cause of Cushing syndrome is the *administration of exogenous glucocorticoids* ("iatrogenic" Cushing syndrome)	
2-Endogenous	**ACTH-dependent**	**ACTH-independent (adrenal Cushing syndrome)**
	Cushing disease (ACTH-producing microadenoma; rarely CRH-dependent pituitary hyperplasia) (associated with bilateral nodular cortical hyperplasia). **Ectopic corticotropin syndrome** (ACTH-secreting pulmonary small-cell carcinoma, bronchial carcinoid tumor)	Adrenal adenoma (**unilateral adrenocortical neoplasm**) → contralateral adrenal atrophy. Adrenal carcinoma (unilateral adrenocortical neoplasm) → **contralateral adrenal atrophy**
Morphology	**In pituitary**	**In adrenal glands**
	The most common alteration is termed Crooke hyaline change	**Depends on the cause of hypercortisolism; it could be:** **1-** Bilateral Cortical atrophy: results from exogenous glucocorticoids. **2-** Diffuse hyperplasia: individuals with ACTH dependent Cushing syndrome **3-** Adenoma or carcinoma. **4-** Macronodular or micronodular hyperplasia.
CF	Obesity or weight gain, Rounded face "Moon-like", Easy bruising, Thin skin, Hypertension & Abdominal striae	
Diagnosis	**1. Serum ACTH:**	**2. High dose dexamethasone suppression test:**
	- Low → Primary cause (adrenal problem). - High → Pituitary adenomas and ectopic ACTH. (Secondary cause)	- Suppression of ACTH→ pituitary adenomas. - Fail of suppression of ACTH→ ectopic ACTH.

Hyperaldosteronism:	Hyperaldosteronism may be **primary** or **secondary** to an extraadrenal cause.	
1°	Primary, autonomous overproduction of aldosterone, with **suppression of the renin-angiotensin** system & ↓ plasma renin activity	
Causes	• Bilateral idiopathic hyperaldosteronism • Adrenocortical neoplasm (Conn syndrome) • familial hyperaldosteronism (rare)	
2°	This condition is characterized by **increased levels of plasma renin**	**Might present in association with:** ↓ renal perfusion, pregnancy, Arterial hypovolemia and edema
CF	**Hypertension: 1° hyperaldosteronism → most common** cause of **2° hypertension & Hypokalemia.**	
Morpho-logy	• Aldosterone-producing adenomas are almost always **solitary** • Composed of **lipid-laden** cortical cells more closely resembling **fasciculata cells**	• Adrenal cortexes are not atrophic • **Spironolactone bodies.**

Adrenocortical Hypofunction

May be caused by either 1° adrenal disease or decreased stimulation of the adrenals resulting from a deficiency of ACTH (2°hypoadrenalism).

Primary Acute Adrenocortical Insufficiency (adrenal crisis)	Primary Chronic Adrenocortical Insufficiency: Addison Disease	Secondary Adrenocortical Insufficiency
- Persons with **chronic** adrenocortical insufficiency may develop **an acute crisis** after any Stress. - Happens if steroid treatment is withdrawn too rapidly.	- **Autoimmune adrenalitis** - **Infections**, particularly tuberculosis, **AIDS.** - **Metastatic Neoplasms :** carcinomas of the **lung and breast** are the source of majority of metastases in the adrenals.	- Any disorder of the **hypothalamus and pituitary** that **reduces the output of ACTH** leads to a syndrome of hypoadrenalism. - The hyperpigmentation of primary Addison disease is lacking & Low serum ACTH.

CF	GIT disturbance, Hyperpigmentation in patients with **primary** adrenal disease, Hyperkalemia, hyponatremia, volume depletion, and hypotension, **Secondary hypoadrenalism,** Hypoglycemia, hypotension and dehydration
Pheochromocytoma	A **functioning tumor** derived from the chromaffin cells of the adrenal medulla, and is classified as **a paraganglioma.**
CF	- **Overproduction** of catecholamines produces isolated paroxysmal episodes of **hypertension**, associated with headaches, sweating, palpitations, pallor, anxiety & nausea. - **Pain** in the abdomen or chest, nausea, and vomiting - **↑ risk** of myocardial ischemia, heart failure, renal injury, and stroke (cerebrovascular accident).

Diabetes

Diagnosis

1- A random glucose concentration > 200 mg/dL, with classical signs and symptoms.
2- A fasting glucose concentration ≥ 126 mg/dL on more than one occasion.
3- An abnormal (OGTT), in which the glucose concentration > 200 mg/dL 2 hrs after a standard carbohydrate load.

Definition:
A condition characterized by an **absolute or relative deficiency of insulin** and/or **insulin resistance**, inducing **hyperglycemia**.

MODY: A rare case of DM, autosomal dominant. Due to a **genetic defect in β cell function** and is rather common in Gulf and Arabian countries.

Type	1	2
Definition	**An autoimmune disease in which islet destruction (β-cell) is caused primarily by immune effector cells reacting against endogenous beta cell antigens.**	Interrelationship between insulin **resistance** in its target tissues and **β-cell dysfunction**
Management	**Insulin absolutely required**.	Lifestyle modification; diet, exercise, oral drugs, often insulin supplement needed.
Development	In childhood, manifests at puberty, and progresses with age.	Adults with an increased prevalence in **obese persons** and in the elderly (>65).
Onset	**Abrupt**, resulting from a chronic autoimmune attack on beta cells that usually starts many years before the disease becomes evident.	
Characteristics	- Few if any functional B cells in the islets of Langerhans. - Extremely limited or nonexistent insulin secretion.	- Insulin resistance. - Beta cell dysfunction.
Pathogenesis	**Genetic Factors: HLA-DR3 or HLA-DR4,** *CTLA4* **and** *PTPN22.* **Environmental event/factors:** Viruses, chemicals. **Autoimmunity:** islet cell antibodies against components of the B cells	**Genetic Factors:** "diabetogenic" genes. **B-Cell Function:** exhibit impaired B-cell insulin release in response to glucose stimulation.
Morphology	**Lymphocytic infiltrate** in the islets (**insulitis**), **macrophages** and neutrophils. **No** deposition of amyloid or fibrosis in islets	No reduction in the number of **B- cells.** Leukocytic infiltration of the islets, Fibrous tissue & **Islet amyloid** is often present particularly in patients over 60 years of age (long-standing).
Pathology	▪ The exocrine pancreas in chronic T1DM often exhibits **diffuse interlobular** and **interacinar fibrosis**, accompanied by **atrophy** of the acinar cells.	
Clinical features	↑ gluconeogenesis **Classic triad 3P: Polyuria, Polydipsia & Polyphagia.** ▪ **Weight loss and weakness**. **Severe insulin deficiency** → diabetic **kectoacidosis** → **ketone bodies** o **ketonuria & ketonemia.** o **Superimposed dehydration → metabolic ketoacidosis.** o Infection ↑ insulin requirements → **diabetic ketoacidosis.**	▪ Polyuria and polydipsia, patients often are older than 40 years & obese. ▪ The metabolic derangements are much less severe. Patients in the decompensated state develop **hyperosmolar nonketotic coma**. ▪ No ketoacidosis.

Diabetes Complications

Diabetic Macrovascular Disease

Hyaline arteriosclerosis: Hyaline thickening of the wall of arterioles & narrowing of the lumen. (in the kidneys and eyes).
Arteriosclerosis: severe & accelerated

Diabetic Microvascular Disease

- Responsible for many of the complications of diabetes, including renal failure, Blindness & neuropathy.
- Effects on tissue perfusion and wound healing are profound.
- ↓ blood flow to the heart.

Diabetic microangiopathy: diffuse thickening of the capillary vascular basement membranes

Diabetic nephropathy

The earliest manifestation is the appearance of small amounts of albumin in the urine (greater than 30 but less than 300 mg/day—i.e., microalbuminuria)
The glomeruli exhibit a unique lesion termed **Kimmelstiel-Wilson disease or nodular glomerulosclerosis.**

Vascular changes: renal atherosclerosis and hyaline arteriosclerosis (afferent & efferent)
Parenchymal changes: pyelonephritis with ↑ propensity to develop necrotizing papillitis.
Glomerular changes:

Diffuse mesangial sclerosis

- A diffuse ↑ in mesangial matrix along with mesangial cell proliferation & Basement membrane thickening.
- Glomerulosclerosis marked → patients manifest the nephrotic syndrome. May be seen with old age and hypertension.

Nodular glomerulosclerosis

- Ball-like deposits of a laminated matrix situated in the periphery of the glomerulus.
- Nodules are PAS-positive & usually contain trapped mesangial cells.

Diabetic retinopathy

Diabetics have ↑ propensity for glaucoma & cataract formation, both of which contribute to visual impairment.

Non-proliferative changes	Proliferative changes
Microangiopathy **in the retinal blood vessels,** micro aneurysms & Venous dilatation. Retinal hemorrhages (blots), edema **&** Exudates (cotton wool spots)	**Neovascularization and fibrosis,** → **retinal detachment** & **blindness.**

Diabetic neuropathy

The **most common** and distressing complication

- **Microvasculopathy** contributes.
- Affects Sensory and Autonomic Innervations, peripheral sensory impairment, and autonomic nerve dysfunction.

Polyneuropathy:
Symmetric peripheral neuropathy (most frequent), affecting both motor and sensory nerves ("glove & stocking" pattern). Pain and abnormal sensations in the extremities. Can lead to **foot ulcers**.
Autonomic neuropathy:
Cause impotence with bladder and bowel dysfunction.
Diabetic mononeuropathy, which may manifest as sudden footdrop or wristdrop or isolated cranial nerve palsies.

Infections

↑ tendency to develop infections. Bacterial & Fungal Infections occur in poorly controlled diabetic hyperglycemia.

- Renal papillary necrosis may be a devastating complication of bladder infection.
- ↑ susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis.
- In a person with diabetic neuropathy, a trivial infection in a toe → (**gangrene**, bacteremia, pneumonia)
- **Mucormycosis:** A dangerous infectious complication of poorly controlled diabetes is often fatal fungal infection tends to originate in the nasopharynx or paranasal sinuses and spreads rapidly to the orbit and brain.

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Good Luck.