Pathology of the Endocrine System

Endocrine system
1. Endocrine organs
2. Endocrine components in mixed organs
3. Diffuse endocrine system – “paracrine”

Endocrine-related Problems
- Overproduction of a hormone
- Underproduction of a hormone
- Nonfunctional receptors that cause target cells to become insensitive to hormones

Hypothalamus and Pituitary gland
Hypothalamus – Pituitary gland

Pituitary gland

Pituitary Hormones

Anterior pituitary

Hormones produced and released:

- Thyrotropin
- Adrenocorticotropin
- Luteinizing hormone
- Follicle-stimulating hormone

Posterior pituitary

Hormones released:

- Oxytocin
- Vasopressin

Growth hormone
- Prolactin
- Melanocyte-stimulating hormone
- Endorphins
- Enkephalins
Clinical Manifestations of Pituitary Disease

- Hyperpituitarism
- Hypopituitarism
- Local mass effects
- Diseases of the posterior pituitary: Increased or decreased ADH

Hyperpituitarism

- Increased secretion of one or more of pituitary hormones
  - Pituitary adenoma
  - Pituitary hyperplasia
  - Pituitary carcinoma
  - Secretion of hormones by nonpituitary tumors
  - Hypothalamic disorder

Hypopituitarism

- Deficient secretion of one or more of pituitary hormones
  - Pituitary tumor compressing normal tissue
  - Sheehan Syndrome: ischemic injury from PPH
  - Pituitary apoplexy: hemorrhage or infarct in normal tissue or inactive adenoma
  - Trauma, surgery or radiation
  - Infiltrative disease including infection, inflammation, and some tumors
  - Genetic abnormalities of pituitary development
  - Empty sella syndrome

Local mass effects

- Headaches: Increase intracranial pressure – stretching of dura
- Visual field defect: Nasal retinal fiber compression
- Cranial nerve palsies (III, IV, V, and VI): Lateral extension of the tumor
The most common and important diseases of the pituitary gland - Pituitary adenoma

**Functioning adenoma**
- Overproduction of hormones: common GH and Prolactin and few ACTH

**Non-functioning adenoma**
- Mass effect: Bitemporal hemianopia and hypopituitarism

**Incidence:** about 10% of intracranial neoplasms (discovered incidentally in up to 25% of routine autopsies)
- Usually found in adults, with a peak incidence from the thirties to the fifties
- Most pituitary adenomas occur as isolated lesions. In about 3% of cases associated with multiple endocrine neoplasia (MEN) type I

**Bitemporal Hemianopsia**
Prolactinoma from Lactotroph

The most frequent type of hyperfunctioning pituitary adenoma - Galactorrhea, amenorrhea, infertility

Growth Hormone from Somatotroph

- The second most common type of functioning pituitary adenoma
- Gigantism in children before closure of epiphyses - a generalized increase in body size with disproportionately long arms and legs
- Acromegaly in adult or after closure of epiphyses - Enlargement of the jaw, hands, feet, and visceral organs (thyroid, heart, liver, and adrenals)
Corticotroph cell adenoma

- Hypercortisolism by pituitary adenoma
- Hyperpigmentation
- Cushing disease

Hypopituitarism

- 70-90% (≥75%) parenchymal loss
- Congenital (rare): Mutation Pit-1
- Acquired
  - Tumor or Other mass lesion: Non-functioning adenoma, metastatic tumor, cyst etc.
  - Ablation by surgery or radiation
  - Ischemic necrosis and Sheehan syndrome
  - Empty sella syndrome: Primary & Secondary
  - Pituitary apoplexy
  - Inflammatory lesion

The clinical manifestations

- Depend on the specific hormone lacking
  - Growth hormone deficiency in children develop growth failure (pituitary dwarfism)
  - Gonadotropin (GnRH) deficiency leads to amenorrhea and infertility in women and decreased libido, impotence, and loss of pubic and axillary hair in men.
  - TSH and ACTH deficiencies result in symptoms of hypothyroidism and hypoadrenalism, respectively
  - Prolactin deficiency results in failure of postpartum lactation

Sheehan syndrome

- Postpartum necrosis of anterior pituitary
- Pregnancy
  - Hypertrophy/Hyperplasia of Lactotroph
  - Not increase blood supply
  - Blood loss during delivery
- Agalactia, amenorrhea, hypothyroidism, adrenocortical insufficiency
Posterior Pituitary Syndromes

Clinically significant:
- Diabetes insipidus
- SIADH

Diabetes insipidus

- ADH deficiency → Excessive urination (polyuria) owing to an inability of the kidney to resorb water properly from the urine
- Etiology: a variety of processes, including
  - Head trauma
  - Tumors
  - Inflammatory disorders of the hypothalamus and pituitary
  - Effect from Brain surgery

Diabetes insipidus

- The clinical manifestations of DI
  - Excretion of large volumes of dilute urine with an inappropriately low specific gravity.
  - Serum sodium and osmolality are increased owing to excessive renal loss of free water, resulting in thirst and polydipsia.
  - Life-threatening dehydration: Patients who can not drink adequate water to compensate for urinary losses

Syndrome of inappropriate ADH secretion: SIADH

- Water retention, hyponatremia, hypotonicity
- Excess ADH:
  - Paraneoplastic secretion: Small cell lung CA
  - Tumor trauma inflammation
    - Pulmonary lesion
    - Brain lesion
  - Drugs
Thyroid gland: consists of two bulky lateral lobes connected by a relatively thin isthmus, usually located below and anterior to the larynx +/- presence of a pyramidal lobe.

Thyroid follicular cells – forming follicles: converting thyroglobulin into thyroxine (T4) and triiodothyronine (T3) and releasing into the systemic circulation.

Parafollicular cell (C-cell) – minor population arranging in small clusters in the interstitium: producing calcitonin.

Ectopic thyroid gland:

most commonly located at the base of the tongue (lingual thyroid) or at other sites abnormally high in the neck.
Thyroglossal Duct Cyst

- Remnant of thyroglossal duct
- Midline of neck
- Move related to tongue movement

Cystic lesion is lined by squamous or respiratory epithelium and presence of thyroid follicles at the cystic wall

What is “Goiter”?

- Goiter – enlargement of thyroid gland (not specific term, not specific etiology and associated with decreased or increased hormone output)
  - Toxic goiter: thyroid enlargement associated with increased thyroid hormone output
  - Non-toxic goiter: thyroid enlargement with normal hormonal level

Thyroid enlargement: diffuse or nodular

- Irregular multinodular enlargement of the entire thyroid: Multinodular goiter in elderly
- Focal nodular enlargement within the thyroid: Thyroid tumor
- Symmetrical slightly nodular firm enlargement of the whole thyroid: Hashimoto’s thyroiditis
- Symmetrical enlargement of the thyroid: Graves’ disease or in puberty/pregnancy
### Thyrotoxicosis vs Hyperthyroidism

- Thyrotoxicosis - hypermetabolic state caused by elevated circulating levels of free T3 and T4
- Hyperthyroidism - hyperfunction of the thyroid gland
- Most of thyrotoxicosis caused by hyperthyroidism
- Hyperthyroidism: Primary or Secondary

### Disorders Associated with Thyrotoxicosis

#### Primary hyperthyroidism
- Diffuse toxic hyperplasia (Graves disease)
- Hyperfunctioning ("toxic") multinodular goiter
- Hyperfunctioning ("toxic") adenoma
- Hyperfunctioning thyroid carcinoma
- Iodine-induced hyperthyroidism
- Neonatal thyrotoxicosis associated with maternal Graves disease

#### Secondary hyperthyroidism

### Disorders Associated with Thyrotoxicosis

- TSH-secreting pituitary adenoma (rare)
- Not Associated with Hyperthyroidism
- Subacute granulomatous thyroiditis (painful)
- Subacute lymphocytic thyroiditis (painless)
- Struma ovarii (ovarian teratoma with ectopic thyroid)
- Factitious thyrotoxicosis (exogenous thyroxine intake)

### Clinical manifestations of thyrotoxicosis

- Excess thyroid hormone and overactivity of sympathetic nervous system
  - Increase in the basal metabolic rate: soft and warm and flushed skin, heat intolerance with increased sweating and weight loss (despite increased appetite)
  - Cardiac manifestations are among the earliest and most consistent features of hyperthyroidism: Tachycardia, palpitations, and cardiomegaly
- Overactivity of the sympathetic nervous system produces tremor, hyperactivity, emotional lability, anxiety, inability to concentrate, and insomnia and Proximal muscle weakness (thyroid myopathy)
- Ocular changes: wide, staring gaze and lid lag and thyroid ophthalmopathy associated with proptosis in Graves disease
- Sympathetic hyperstimulation of the gut results in hypermotility, malabsorption, and diarrhea
- Osteoporosis: Thyroid hormone stimulates bone resorption

- Thyroid storm: abrupt onset of severe hyperthyroidism.
- Apathetic hyperthyroidism refers to thyrotoxicosis occurring in the elderly
- Diagnosis of hyperthyroidism: Clinical and lab such as TSH, T3 and T4
  - Primary hyperthyroidism: decrease TSH, Increase T3 and T4

**Hypothyroidism**

- Disease effect structure or function derangement that interferes with the production of adequate levels of thyroid hormone.
- Divided into: primary and secondary categories, depending on intrinsic abnormality in the thyroid or occurs as a result of pituitary disease; rarely, hypothalamic failure is a cause of tertiary hypothyroidism

**Cause of Hypothyroidism**

- Primary
  - Developmental (thyroid dysgenesis: PAX-8, TTF-2, TSH-receptor mutations)
  - Thyroid hormone resistance syndrome (TRβmutations)
  - Surgery, radiiodine therapy, or external radiation
  - Autoimmune hypothyroidism: Hashimoto thyroiditis*
  - Iodine deficiency*
  - Drugs (lithium, iodides, p-aminosalicylic acid)*
  - Congenital biosynthetic defect (dyshormonogenetic goiter)*
- Secondary: Pituitary failure
- Tertiary: Hypothalamic failure (rare)
Clinical manifestations of hypothyroidism

- **Cretinism in infant or early childhood**
  - 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

- **Myxedema in old child or adult**
  - Slowing of physical and mental activity: initial symptoms including generalized fatigue, apathy, and mental sluggishness, slow speech and intellectual functions, cold-intolerant, frequently overweight, shortness of breath, decreased exercise capacity, constipation, decreased sweating and cool skin.

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**Thyroiditis**

- Inflammation of the thyroid gland: characterized by some form of thyroid inflammation.

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**Infectious thyroiditis**

- May be acute or chronic
- Acute infections: hematogenous spread or direct seeding of the gland from adjacent to organ eg Pyriform sinus
- Mycobacterial, fungal, and *Pneumocystis* infections - chronic infection in immunocompromised host
- May cause sudden onset of neck pain and tenderness in the area of the gland and is accompanied by fever, chills, and other signs of infection.
- Self-limited or can be controlled with appropriate therapy
**Hashimoto thyroiditis**

- the most common cause of hypothyroidism in areas of sufficient iodine
- characterized by gradual thyroid failure because of autoimmune destruction of the thyroid gland
- most prevalent between 45 and 65 years of age with a female predominance of 10:1 to 20:1
- an autoimmune disease in which the immune system reacts against a variety of thyroid antigens: the most common autoantibody → anti-microsomal antibody and antibody against thyroglobulin

- In the usual clinical course, hypothyroidism develops gradually
- In some case, early stage present with thyrotoxicosis "Hashitoxicosis"
- decreased radioactive iodine uptake
- develop: Other autoimmune diseases, B-cell Lymphoma

**Subacute (granulomatous) thyroiditis**

- Granulomatous or De Quervain thyroiditis
- Most common 30 - 50 and women> men (3:1 to 5:1).
- Related to Viral infection: Coxackie, Mumps, Influenza, Echovirures, Adenoviruses – postviral inflammation
- Transient hyperthyroidism, pain, fever, malaise, fatigue, enlarged thyroid and tender – always complete recovery
- Low radioactive iodine uptake

**SUBACUTE LYMPHOCYTIC (PAINLESS) THYROIDITIS**

- Painless thyroiditis or silent thyroiditis
- Uncommon cause of hyperthyroidism
- most in middle-aged adults and women > men, especially during the postpartum period (postpartum thyroiditis)
- Unknown Pathogenesis
<table>
<thead>
<tr>
<th>Riedel thyroiditis</th>
<th>Graves disease</th>
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<tbody>
<tr>
<td>• a rare disorder of unknown etiology</td>
<td>• characterized by &quot;violent and long continued palpitations in females&quot; associated with enlargement of the thyroid gland.</td>
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<tr>
<td>• characterized by extensive fibrosis involving the thyroid and contiguous</td>
<td>• most common cause of endogenous hyperthyroidism</td>
</tr>
<tr>
<td>neck structures</td>
<td>• Triad of clinical findings:</td>
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<tr>
<td>• associated with idiopathic fibrosis in other sites in the body, such as the</td>
<td>- Hyperthyroidism owing to hyperfunctional,</td>
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<tr>
<td>retroperitoneum</td>
<td>diffuse enlargement of the thyroid</td>
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<td>• most patients present with circulating antithyroid antibodies - suggests an</td>
<td>- Infiltrative ophthalmopathy with resultant exophthalmos</td>
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<tr>
<td>autoimmune etiology</td>
<td>- Localized, infiltrative dermopathy, sometimes called pretibial myxedema,</td>
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<td></td>
<td>which is present in a minority of patients</td>
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<tr>
<td>• Peak incidence between the ages of 20 and 40, women &gt; men = 7 time</td>
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<tr>
<td>• Autoantibodies to the TSH receptor are central to disease pathogenesis</td>
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<tr>
<td>- Thyroid-stimulating immunoglobulin (TSI): specific for Graves disease - a</td>
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<td>long-acting thyroid stimulator (LATS)</td>
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<tr>
<td>- Thyroid growth-stimulating immunoglobulins (TGI): increase proliferation of</td>
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<td>thyroid follicular epithelium</td>
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<tr>
<td>- TSH-binding inhibitor immunoglobulins (TBII) : stimulating or inhibiting</td>
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</tbody>
</table>
• Symmetrically enlarged thyroid gland with meaty brown cut surfaces (not > 80 gm.)
• Diffuse hypertrophy and hyperplasia of thyroid follicular epithelial cells with papillae, decrease and pale colloid with scalloping and lymphoid infiltrate

• Elevated free T4 and T3 levels and depressed TSH levels
• Radioactive iodine uptake is increased, and radioiodine scans show a diffuse uptake of iodine.

**Diffuse and Multinodular Goiter**

- Enlargement of the thyroid, or goiter, is the most common manifestation of thyroid disease.
- Diffuse and multinodular goiters reflect impaired synthesis of thyroid hormone, most often caused by dietary iodine deficiency.
- The degree of thyroid enlargement is proportional to the level and duration of thyroid hormone deficiency.

- Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH level, which, in turn, causes hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland. The compensatory increase in functional mass of the gland is able to overcome the hormone deficiency, ensuring an euthyroid metabolic state in the vast majority of individuals.
**Diffuse nontoxic (simple) goiter**

- diffusely involves the entire gland without producing nodularity
- Called as colloid goiter - the enlarged follicles are filled with colloid
- occurs in both an endemic and a sporadic distribution

**Endemic goiter**

- Occurs in geographic areas where the soil, water, and food supply contain only low levels of iodine
- Particularly common in mountainous areas
- The lack of iodine leads to decreased synthesis of thyroid hormone and a compensatory increase in TSH, leading to follicular cell hypertrophy and hyperplasia and goitrous enlargement

**Sporadic goiter**

- Occurs less frequently than does endemic goiter
- Striking female preponderance and a peak incidence at puberty or in young adult life
- Can be caused by a number of conditions:
  - ingestion of substances that interfere with thyroid hormone synthesis.
  - result from hereditary enzymatic defects that interfere with thyroid hormone synthesis, all transmitted as autosomal-recessive conditions (dyshormonogenetic goiter; see above).
  - cause of sporadic goiter is not apparent in most cases
• Substances that interfere with thyroid hormone synthesis at some level, such as excessive calcium and vegetables belonging to the *Brassica* and *Cruciferae* families (e.g., cabbage, cauliflower, Brussels sprouts, turnips, and cassava)

**diffuse nontoxic goiter:**

**Hyperplastic phase**
- Diffusely and symmetrically enlarged thyroid glands, rarely exceeds 100 to 150 gm.
- The follicles are lined by crowded columnar cells, which may pile up and form projections similar to those seen in Graves disease. The accumulation is not uniform throughout the gland, and some follicles are hugely distended, whereas others remain small.

**diffuse nontoxic goiter:**

**Colloid phase**
- If dietary iodine subsequently increases or if the demand for thyroid hormone decreases, the stimulated follicular epithelium involutes to form an enlarged, colloid-rich gland (colloid goiter).
- Cut surface of the thyroid is usually brown, somewhat glassy, and translucent
- Histologically, the follicular epithelium is flattened and cuboidal, and colloid is abundant during periods of involution.

• The vast majority of patients with simple goiters are clinically euthyroid.
• Clinical manifestations are primarily related to mass effects from the enlarged thyroid gland
• Serum T3 and T4 levels are normal, the serum TSH is usually elevated or at the upper range of normal
Multinodular goiter

- Recurrent episodes of hyperplasia and involution combine to produce a more irregular enlargement of the thyroid - the most extreme thyroid enlargements.
- All long-standing simple goiters convert into multinodular goiters.
- May be nontoxic or may induce thyrotoxicosis (toxic multinodular goiter).
- Can occur in both sporadic and endemic forms of simple goiter.
- Same female-to-male distribution.

Gross: Multilobulated, asymmetrically enlarged glands, can achieve a weight of more than 2000 gm.

Cut surfaces: irregular nodules containing variable amounts of brown, gelatinous colloid with areas of hemorrhage, fibrosis, calcification, and cystic change.

The microscopic appearance includes colloid-rich follicles lined by flattened, inactive epithelium and areas of follicular epithelial hypertrophy and hyperplasia, accompanied by the degenerative changes.
Uneven radioactive iodine uptake in multinodular goiter

Solitary thyroid nodule

- a palpably discrete swelling within an otherwise apparently normal thyroid gland
- Increase incidence in Endemic area
- The incidence of thyroid nodules increases throughout life
- about four times more common in women than in men

Majority of solitary thyroid nodules -> non-neoplastic conditions (e.g., nodular hyperplasia, simple cysts, or foci of thyroiditis) or benign neoplasms

Most malignant epithelial tumor of thyroid gland present as a solitary thyroid nodule

Neoplastic nodule: solitary nodules > multiple nodules

Neoplastic nodule: in younger patients > in older patients.

Neoplastic nodule: males > females

A history of radiation treatment to the head and neck region asso. with an increased incidence of thyroid malignancy
Nodules that take up radioactive iodine in imaging studies (hot nodules) are more likely to be benign than malignant.

Fine-needle aspiration biopsy and histologic study of surgically resected thyroid parenchyma, that provides the most definitive information about its nature.

**Thyroid gland neoplasm**
- Neoplasm of Parafollicular C cell
- Neoplasm of thyroid follicular cell

**Benign**
- Follicular adenoma

**Malignant**
- Follicular carcinoma
- Papillary carcinoma
- Anaplastic carcinoma

Benign neoplasms outnumber thyroid carcinomas by a ratio of nearly 10:1.

**Follicular Adenoma**
- typically discrete, solitary mass
- derived from follicular epithelium
- difficult to distinguish from dominant nodules of follicular hyperplasia or from the less common follicular carcinomas
- the vast majority of adenomas - nonfunctional, a small proportion produce thyroid hormones and cause clinically apparent thyrotoxicosis ("toxic adenomas")
• a well-defined, intact capsule
• average about 3 cm in diameter, but some are smaller and others are much larger (up to 10 cm in diameter)
• The color ranges from gray-white to red-brown, depending on the cellularity of the adenoma and its colloid content

**Malignancy of thyroid gland**

• relatively uncommon
• The major subtypes of thyroid carcinoma
  - Papillary carcinoma (75% to 85% of cases)
  - Follicular carcinoma (10% to 20% of cases)
  - Medullary carcinoma (5% of cases)
  - Anaplastic carcinoma (<5% of cases)
• Papillary carcinoma found in children (F=M)
• Other present in the early and middle adult years (F>M)

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**Follicular Carcinoma**

• the second most common form of thyroid cancer
• present in women, and at an older age than do papillary carcinomas, with a peak incidence in the forties and fifties.
• increased incidence in areas of dietary iodine deficiency
• present as slowly enlarging painless nodules
• Most frequently be cold nodule
• single nodules that may be well circumscribed or widely infiltrative
Papillary Thyroid Carcinoma

- the most common form of thyroid cancer
- occur at any age but most often in the twenties to forties
- account for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation
- present as asymptomatic thyroid nodules, but the first manifestation may be a mass in a cervical lymph node – lymphatic metastasis
- Diagnostic test: radionuclide scanning and fine-needle aspiration
- Most are cold nodule

Papillary Thyroid Carcinoma

- Genetic factors: Mutation of RET(10q11.2)
- Papillary thyroid cancers have an excellent prognosis, with a 10-year survival rate in excess of 95%
- solitary or multifocal lesions: Some, well-circumscribed and even encapsulated; others may infiltrate the adjacent parenchyma with ill-defined margins.

On the cut surface, they may appear granular and may sometimes contain grossly discernible papillary foci.

Branching papillae having a fibrovascular stalk covered by a single to multiple layers of cuboidal epithelial cells.
Nuclear features: an optically clear or empty appearance with intranuclear inclusion or groove

Concentrically calcified structures termed psammoma bodies

Parathyroid gland

• derived from the developing pharyngeal pouches that also give rise to the thymus.

• The four glands normally lie in close proximity to the upper and lower poles of each thyroid
Chief and Oxyphilic cells

- Chief cells vary from light - dark pink to clear cytoplasm with central, round, uniform nuclei.
- Oxyphilic cells slightly larger than the chief cells, with acidophilic cytoplasm.

The activity of the parathyroid glands

- PTH controlled by the level of free (ionized) calcium in the bloodstream
- Normally, decreased levels of free calcium stimulate the synthesis and secretion of PTH.

The metabolic functions of PTH

- Activates osteoclasts - mobilizing calcium from bone.
- Increases the renal tubular reabsorption of calcium - conserving free calcium.
- Increases the conversion of vitamin D to its active dihydroxy form in the kidneys.
- Increases urinary phosphate excretion - lowering serum phosphate levels.
- Increase gastrointestinal calcium absorption.

Hypercalcemia

- May be caused by elevated levels of PTH
- However, malignancy is the most common cause of clinically apparent hypercalcemia, while primary hyperparathyroidism is a more common cause of asymptomatic elevated blood calcium.
Cause of Hypercalcemia

- Complication of malignancy: lung, breast, head and neck, renal cancer
- Osteolytic metastasis
- PTH-related protein (PTHrP): SCCA
- Hematologic malignancy: multiple myeloma

Pathology of Parathyroid

- Problems caused by Over and Under-production of PTH
- Hyperparathyroidism occurs in two major forms-primary and secondary-and, less commonly, tertiary.
- Primary hyperPTH: an autonomous, spontaneous overproduction of PTH
- Secondary and Tertiary hyperPTH: typically occur as secondary phenomena in patients with chronic renal insufficiency.

Hyperparathyroidism

Primary hyperparathyroidism

- is one of the most common endocrine disorders- an important cause of Hypercalcemia
- The frequency of the various parathyroid lesions:
  - Adenoma: 75% to 80%
  - Primary hyperplasia (diffuse or nodular): 10% to 15%
  - Parathyroid carcinoma: less than 5%
Primary hyperparathyroidism

• usually a disease of adults, most > 50 yrs
• more common in women than in men by a ratio of nearly 3:1
• More than 95% of cases, the disorder is caused by sporadic parathyroid adenomas or sporadic hyperplasia
• Small fractions associated with MEN1 and MEN 2 A

Parathyroid adenomas

• almost always solitary and, similar to the normal parathyroid glands, may lie in close proximity to the thyroid gland or in an ectopic site (e.g., the mediastinum).
• 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.

• Adenoma is composed predominantly of fairly uniform, polygonal chief cells with small, centrally placed nuclei with a fibrous capsule and scant adipose tissue
**Primary hyperplasia**

- May occur sporadically or as a component of MEN syndrome.
- Classically all four glands are involved, frequently asymmetry with apparent sparing of one or two glands, making the distinction between hyperplasia and adenoma difficult.
- The most common pattern seen is that of chief cell hyperplasia, which may involve the glands in a diffuse or multinodular pattern.

**Parathyroid carcinomas**

- Difficult to distinguish from adenomas
- Diagnosis of carcinoma based on cytologic detail is unreliable, and invasion of surrounding tissues and metastasis are the only reliable criteria of malignancy.

**Symptomatic Primary Hyperparathyroidism**

"painful bones, renal stones, abdominal groans, and psychic moans"

- Bone disease: secondary to fractures of bones weakened by osteoporosis or osteitis fibrosa cystica
- Nephrolithiasis (renal stones)
- Gastrointestinal disturbances include constipation, nausea, peptic ulcers, pancreatitis, and gallstones.
- Central nervous system alterations include depression, lethargy, and eventually seizures.
- Neuromuscular abnormalities include complaints of weakness and fatigue.
- Cardiac manifestations include aortic or mitral valve calcifications (or both).
### Secondary hyperparathyroidism
- is caused by any condition associated with a chronic depression in the serum calcium level because low serum calcium leads to compensatory overactivity of the parathyroid glands
- Renal failure is by far the most common cause of secondary hyperparathyroidism,
- Other diseases, including inadequate dietary intake of calcium, steatorrhea, and vitamin D deficiency, may also cause this disorder.

### Hypoparathyroidism
- is far less common than is hyperPTH
- Possible causes of deficient PTH secretion resulting in hypoparathyroidism:
  - Surgically induced hypoparathyroidism
  - Congenital absence of all glands, as in certain developmental abnormalities, such as thymic aplasia and cardiac defects (22q11.2 syndrome)

### Hypoparathyroidism
- Familial hypoparathyroidism associated with chronic mucocutaneous candidiasis and primary adrenal insufficiency; this syndrome is known as autoimmune polyendocrine syndrome type 1 (APS1) - mutations autoimmune regulator (AIRE)
- Idiopathic hypoparathyroidism most likely represents an autoimmune disease with isolated atrophy of the glands: 60% autoantibodies directed against the calcium-sensing receptor (CASR) in the parathyroid gland

### Clinical manifestations of Hypoparathyroidism
- The hallmark is tetany- neuromuscular irritability, resulting from decreased serum ionized calcium concentration.
- range from circumoral numbness or paresthesias (tingling) of the distal extremities and carpopedal spasm, to life-threatening laryngospasm and generalized seizures.
- Physical Ex: Chvostek sign and Trousseau sign.
Clinical manifestations of Hypoparathyroidism

- Mental status changes
- Intracranial manifestations
- Ocular disease; cataract formation
- Cardiovascular manifestations; conduction defect
- Dental abnormalities; dental hypoplasia, failure of eruption, defective enamel and root formation, and abraded carious teeth.

Pseudohypoparathyroidism

- End-organ resistance to the actions of PTH.
- Serum PTH levels are normal or elevated.

Endocrine pancreas

Diabetes mellitus

- Group of metabolic disorders sharing the common underlying feature of hyperglycemia
- Defects of insulin secretion or insulin action or both
### Diagnosis - DM

- Random glucose concentration greater than 200 mg/dL with classical signs and symptoms (polyuria, polydipsia and polyphagia)
- Fasting glucose concentration greater than 126 mg/dL
- Abnormal oral glucose tolerance test (OGTT), in which glucose concentration > 200 mg/dL 2 hours after standard carbohydrate load

### Types of DM

- **Type 1 Diabetes**
  - Autoimmune diseases
  - Pancreatic β-cell destruction
  - Absolute deficiency of insulin
  - 5-10% of all cases
  - Most common subtype diagnosed in patient younger than 20 years
- **Type 2 diabetes**
  - Insulin resistance: decreased response of peripheral tissue to insulin

### Clinical features

- Hyperglycemia
  - glycosuria
  - polyuria
- Renal water loss with hyperosmolarity
  - deplete intracellular water
  - trigger thirst center in the brain
  - polydipsia
- Deficiency of insulin
  - catabolism of protein and fat
  - polyphagia

### Complications

- **Macrovascular disease**
  - Large- and medium-sized muscular arteries
  - Accelerated atherosclerosis
  - Lower extremity gangrene
  - Myocardial infarction
  - Stroke
• Microvascular disease
  - Capillary dysfunction in target organs
  - Diabetic retinopathy
  - Diabetic nephropathy
  - Diabetic neuropathy

Adrenocortical hyperfunction

• Cushing syndrome
  - Hypercortisolism
  - Elevated glucocorticoid level
    1. Exogenous cause
       (iatrogenic cushing syndrome)
    2. Endogenous cause
       • ACTH-dependent : Cushing disease (Pituitary adenoma)
       • ACTH-independent : Adrenal neoplasm and adrenal hyperplasia
Adrenal hyperplasia
Benign neoplasm of adrenal cortex
“Cortical adenoma”
Malignant neoplasm of adrenal cortex
“Cortical carcinoma”
### Clinical features

- Hypertension
- Weight gain
- Truncal obesity, moon facies, buffalo hump
- Decreased muscle mass and, proximal limb weakness
- Secondary diabetes
  - Glucocorticoid: induce gluconeogenesis, inhibit glucose uptake by cells

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### Clinical features

- Thin skin, fragile and easily bruised
- Poor wound healing
- Bone resorption: osteoporosis
- Increased risk of infections
- Mental disturbance
- Hirsutism and menstrual abnormalities

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![Diagram of clinical features](image-url)
Primary hyperaldosteronism

- Chronic excess of aldosterone secretion
- Primary hyperaldosteronism
  - Autonomous overproduction of aldosterone
  - Decreased plasma renin activity
- Hypertension: most common manifestation
Clinical features

- Hypertension
- Most common of secondary hypertension
- Cardiovascular compromised: stroke, MI
- Hypokalemia

Clinical features

- Androgen excess
  - Female: masculinization, clitoral hypertrophy, pseudohermaphrodite, oligomenorrhea, hirsutism, acne in postpubertal woman
  - Male: enlargement of external genitalia, precocious puberty, oligospermia
  - CAH should be suspected in any neonate with ambiguous genitalia
- Deficiency of glucocorticoids and mineralocorticoids

Adrenogenital syndrome

- Disorder of sexual differentiation
- Adrenal causes of androgen excess
- Congenital adrenal hyperplasia
  - Autosomal recessive
  - Deficiency of enzyme involved in the biosynthesis of cortical steroids
  - Increased production of androgen
Adrenocortical insufficiency

- **Primary hypoadrenalism**
  - Primary acute: adrenal crisis
  - Crisis: chronic adrenocortical insufficiency precipitated by any form of stress
  - Maintained external corticosteroid with rapid withdrawal of steroids
  - Massive adrenal hemorrhage: Waterhouse-Friderichsen syndrome

Primary chronic adrenocortical insufficiency (Addison disease)

- 90% of cases
  - Autoimmune adrenalitis (60-70% of cases)
  - Tuberculosis and fungi
  - AIDS
  - Metastatic cancers
### Clinical features

- **Insidious onset**
- **Decreased glucocorticoids and mineralocorticoids level**
- **Progressive weakness and easy fatigability**
- **Gastrointestinal disturbances**
  - Anorexia, nausea, vomiting, weight loss and diarrhea
- **Hyperpigmentation**: sun-exposed areas and pressure points
  - Elevated level of pro-opiomelanocortin (POMC) — precursor of ACTH and MSH
- **Potassium retention, sodium loss**
- **Volume depletion with hypotension**
- **Hypoglycemia**
- **Adrenal crisis**

### Secondary adrenocortical insufficiency

- Disorder of hypothalamus or pituitary gland, metastatic cancer, infection, infarction, irradiation

**Clinical features;**

- Lacking of hyperpigmentation
- Decreased cortisol and androgen
- Normal or near-normal aldosterone level

### Adrenal medulla

**Pheochromocytoma**

- Hypertension: 90% of cases
- Paroxysmal episodes: two third of cases
- Paroxysm may be precipitated by emotional stress, exercise, change in posture and palpation in the region of tumor
- Congestive heart failure, pulmonary edema, myocardial infarction, ventricular fibrillation or cardiovascular accident