CHAPTER SEVEN
PATHOLOGY OF THE ENDOCRINE SYSTEM

THE PITUITARY GLAND

This is a small, bean-shaped structure that lies at the base of the brain within the confines of the sella turcica. It is connected to the hypothalamus by a "stalk," composed of axons extending from the hypothalamus. The pituitary is composed of two morphologically and functionally distinct components: the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis). The adenohypophysis, in H&E stained sections, shows a colorful collection of cells with basophilic, eosinophilic or poorly staining ("chromophobic") cytoplasm. (Fig. 7-1) Immnohistochemistry (and sometimes electron microscopy) is usually employed in typing the hormone(s) present in various pituitary lesions. The release of trophic hormones is under the control of releasing or inhibiting factors produced in the hypothalamus.

Hyperpituitarism

Causes

A. Pituitary; usually anterior lobe
1. Adenoma (the most common cause)
2. Hyperplasia
3. Carcinoma

B. Extra-pituitary causes
1. Hormone producing extra-pituitary tumors (ectopic hormone production)
2. Certain hypothalamic disorders

Pituitary adenomas are classified according to the hormone(s) produced by the neoplastic cells; these are detected by immunohistochemically-stained tissue sections. Pituitary adenomas can be functional (associated with hormone excess with their associated clinical manifestations) or silent. Adenomas are usually composed of a single cell type and produce a single predominant hormone. However, some adenomas can secrete two hormones (e.g. growth hormone and prolactin). Other adenomas are hormone negative. Adenomas are divided on the basis of whether the size is less or exceeds 1 cm. (microadenomas and macroadenomas respectively). Macroadenomas can cause hypopituitarism by compressing the adjacent non-neoplastic parenchyma.

Pathogenesis

Guanine nucleotide-binding protein (G-protein) mutations are the best characterized molecular abnormalities. Such mutations eventuate in a persistent increase in intracellular cAMP, which is a potent mitogenic stimulus promoting cellular proliferation and hormone synthesis and secretion.

Gross features

- Adenomas are usually soft & well-circumscribed
- Larger lesions extend superiorly through the sellar diaphragm compressing the optic chiasm and adjacent structures (Fig. 7-2 A).
- Invasive adenomas refer to nonencapsulated tumors that infiltrate adjacent bone, dura, and even brain.

Microscopic features (Fig. 7-2 B).

- Adenomas are composed of monomorphic, polygonal cells displayed in sheets, cords, or papillae. Their nuclei may be uniform or pleomorphic but the mitotic activity is scanty. The cytoplasm of the constituent cells may be acidophilic, basophilic, or chromophobic.
- The connective tissue is scanty that is why many lesions are soft & even gelatinous in consistency. The functional status of an adenoma cannot be predicted from its histologic appearance.

Pituitary adenomas are responsible for 10% of intracranial neoplasms. High-resolution CT or MRI suggests that 20% of "normal" adult pituitary glands contain an incidental usually silent adenoma measuring 3 mm or more in diameter. The peak incidence of pituitary adenomas is from 30 to 50 years.

Prolactinomas are the most common type of hyperfunctioning pituitary adenoma.

Hyperprolactinemia causes amenorrhea, galactorrhea, loss of libido, and infertility.

Growth Hormone-Producing Adenomas (somatotroph cell adenomas) are the second most common type of functional pituitary adenoma. Because the clinical manifestations of excessive growth hormone may be slight, the tumor may be quite large by the time they come to clinical attention. If such tumors occur before closure of...
epiphyses (prepubertal children), excessive levels of growth hormone result in **gigantism**. If elevated levels persist, or present after closure of the epiphyses, individuals develop **acromegaly**.

**Corticotroph Cell Adenomas** are mostly small (**microadenomas**) at the time of diagnosis. They may be clinically silent or cause hypercortisolism referred to as **Cushing disease** (originally described by Dr. Harvey Cushing). Large, clinically aggressive corticotroph adenomas may develop after surgical removal of the adrenal glands for treatment of Cushing syndrome. This condition, known as **Nelson syndrome**, occurs in most cases because of a loss of the inhibitory effect of adrenal corticosteroids on a preexisting corticotroph microadenoma. Because the adrenals are absent in individuals with Nelson syndrome, hypercortisolism does not develop. Instead, patients present with the mass effects of the pituitary tumor. Because ACTH is synthesized as part of a larger prohormone that includes melanocyte-stimulating hormone (MSH), there may also be **hyperpigmentation**.

**Other Anterior Pituitary Neoplasms**
- Gonadotroph adenomas (luteinizing hormone [LH]-producing and follicle-stimulating hormone [FSH]-producing)
- Thyrotroph (thyroid-stimulating hormone [TSH]-producing) adenomas
- Nonfunctioning pituitary adenomas (**hormone-negative (null cell) adenomas**) Nonfunctioning adenomas constitute approximately 25% of all pituitary tumors; they typically present through their mass effects.

**Pituitary carcinomas** are exceedingly rare. In addition to local extension beyond the sella turcica, these tumors virtually always have distant metastases.

**Hypopituitarism** is caused by
1. **Loss of the anterior pituitary parenchyma**
   a. congenital
   b. acquired
2. **Disorders of the hypothalamus** e.g. tumors; these interfere with the delivery of pituitary hormone-releasing factors from the hypothalamus.

**Most cases of anterior pituitary hypofunction are caused by the following:**
1. Nonfunctioning pituitary adenomas
2. **Ischemic necrosis of the anterior pituitary** is an important cause of pituitary insufficiency. This requires destruction of 75% of the anterior pituitary. Causes include
   a. **Sheehan syndrome**, refers to postpartum necrosis of the anterior pituitary, and is the most cause. During pregnancy the anterior pituitary enlarges considerably because of an increase in the size and number of prolactin-secreting cells. However, this physiologic enlargement of the gland is not accompanied by an increase in blood supply. The enlarged gland is therefore vulnerable to ischemic injury, especially in women who develop significant hemorrhage and hypotension during the peripartum period. The posterior pituitary is usually not affected.
   b. Disseminated intravascular coagulation
   c. Sickle cell anemia
   d. Elevated intracranial pressure
   e. Traumatic injury
   f. Shock states
3. **Iatrogenic** i.e. surgical removal or radiation-induced destruction
4. **Inflammatory lesions** such as sarcoidosis or tuberculosis
5. **Metastatic neoplasms** involving the pituitary.
6. **Mutations affecting the pituitary transcription factor Pit-1**

Children can develop growth failure (**pituitary dwarfism**) as a result of growth hormone deficiency. Gonadotropin or gonadotropin-releasing hormone (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. Prolactin deficiency results in failure of postpartum lactation.

**Posterior Pituitary Syndromes**
The posterior pituitary, or neurohypophysis, is composed of modified glial cells (termed pituicytes) and axonal processes extending from nerve cell bodies in the hypothalamus. The hypothalamic neurons produce two peptides: antidiuretic hormone (ADH) and oxytocin that are stored in axon terminals in the neurohypophysis. The clinically important posterior pituitary syndromes involve ADH production and include

1. Diabetes insipidus and
2. Inappropriate secretion of (high levels of) ADH.

ADH is released into the general circulation in response to increased plasma oncotic pressure & left atrial distention. It acts on the renal collecting tubules to increase the resorption of free water. ADH deficiency causes diabetes insipidus, a condition characterized by polyuria. Diabetes insipidus from ADH deficiency is designated as central, to differentiate it from nephrogenic diabetes insipidus due to renal tubular unresponsiveness to otherwise normal levels of circulating ADH. The clinical manifestations of both diseases are similar and include the excretion of large volumes of dilute urine with low specific gravity. Serum sodium and osmolality are increased as a result of excessive renal loss of free water, resulting in thirst and polydipsia. In the syndrome of inappropriate ADH secretion, ADH excess causes resorption of excessive amounts of free water, with resultant hyponatremia. The most common causes of the syndrome include the secretion of ectopic ADH by malignant neoplasms (particularly small-cell carcinomas of the lung), and local injury to the hypothalamus and/or neurohypophysis. The clinical manifestations are dominated by hyponatremia, cerebral edema, and resultant neurologic dysfunction.

THE THYROID GLAND

The thyroid gland develops embryologically from the developing pharyngeal epithelium that descends from the foramen cecum at the base of the tongue to its normal position in the anterior neck. This pattern of descent explains the occasional presence of ectopic thyroid tissue, most commonly located at the base of the tongue (lingual thyroid) or at other sites abnormally high in the neck.

Hyperthyroidism (Thyrotoxicosis) is “a hypermetabolic state caused by elevated circulating levels of free T₃ and T₄”. This may primary (Graves disease) or rarely, secondary (due to pituitary or hypothalamic diseases). The diagnosis is based on clinical features and laboratory data. The measurement of serum TSH concentration provides the most useful single screening test for hyperthyroidism, because TSH levels are decreased in primary cases, even when the disease is still be subclinical. In secondary cases TSH levels are either normal or raised. A low TSH value is usually associated with increased levels of free T₄. Occasionally, hyperthyroidism results from increased levels of T₃ (T₃ toxicosis).

Hypothyroidism is caused by decreased production of adequate levels of thyroid hormones. It is sometimes divided into primary and secondary categories, depending on whether the condition arises from diseases affecting the thyroid or hypothalamic/pituitary disease. The clinical manifestations of hypothyroidism include cretinism and myxedema. Cretinism refers to hypothyroidism developing in infancy or early childhood that is associated with impaired development of the skeletal and central nervous systems; these lead to short stature & severe mental retardation. Hypothyroidism that develops in older children and adults, results in myxedema, which manifests as mental sluggishness, coarsening of facial features, enlargement of the tongue, and deepening of the voice. The latter three are due to accumulation of mucopolysaccharides in the skin, subcutaneous tissue, tongue and larynx. Pericardial effusions are common and in later stages the heart is enlarged, and heart failure may occur. Laboratory evaluation has a vital role in the diagnosis of suspected hypothyroidism because of the nonspecific nature of symptoms. Measurement of the serum TSH is the most sensitive screening test for this disorder. The serum TSH is increased in primary hypothyroidism. The TSH concentration is not increased in hypothyroidism caused by hypothalamic or pituitary disease. Serum T₄ is decreased in individuals with hypothyroidism of any origin.
THYROIDITIS

The more common and clinically significant thyroidites are:
1. Hashimoto thyroiditis
2. Subacute granulomatous thyroiditis
3. Subacute lymphocytic thyroiditis

Hashimoto thyroiditis (Chronic Lymphocytic Thyroiditis) is the most common cause of hypothyroidism. It results from gradual autoimmune destruction of the thyroid gland. There is striking female predominance (10:1 to 20:1), and is most prevalent around a mean age of 50 years.

Pathogenesis
- The dominant feature is progressive destruction of thyroid follicular epithelial cells with gradual replacement by mononuclear cell infiltration and fibrosis.
- Sensitization of CD4+ T-helper cells to thyroid antigens seems to be the initiating event.
- The reaction of CD4+ T cells with thyroid antigens produces interferon γ which promote inflammation and activate macrophages. Injury to the thyroid results from the toxic products of these inflammatory cells.
- CD8+ cytotoxic T cells also contribute to epithelial cells killing as are natural killer cells.
- There is a significant genetic component to disease pathogenesis. This is supported by
  1. The increased frequency of the disease in first-degree relatives,
  2. Unaffected family members often have circulating thyroid autoantibodies.

Gross features (Fig. 7-3 A)
- The thyroid shows moderate, diffuse, and symmetric enlargement.
- The cut surface is pale, gray-tan, firm, nodular and somewhat friable.
- Eventually there is thyroid atrophy

Microscopic features (Fig. 7-3 B)
- There is widespread, diffuse infiltration of the parenchyma by small lymphocytes, plasma cells. The lymphocytes are also form follicles some with well-developed germinal centers.
- The thyroid follicles are atrophic and lined by epithelial cells having abundant eosinophilic, granular cytoplasm (Hürthle cells). This is a metaplastic response to the ongoing injury; ultrastructurally the Hürthle cells are stuffed by numerous mitochondria.
- Interstitial connective tissue is increased and may be abundant.

Hashimoto thyroiditis presents as painless symmetrical goiter with clinical features of hypothyroidism. This is associated with progressive fall of serum T4 and T3 levels & elevated serum TSH levels. Patients often have other autoimmune diseases and are at increased risk for the development of B-cell non-Hodgkin lymphomas.

Subacute Granulomatous (de Quervain) Thyroiditis is much less common than Hashimoto disease. Patients often have an upper respiratory infection just before the onset of thyroiditis. Thus, a viral infection is probably the cause. Microscopically, there is disruption of thyroid follicles, with extravasation of colloid. The extravasated colloid provokes a granulomatous reaction, with giant cells. The condition is self-limited.

Subacute lymphocytic thyroiditis may follow pregnancy (postpartum thyroiditis) but mostly affects middle-aged women. It is most likely autoimmune in etiology, because circulating antithyroid antibodies are found in the majority of patients. In a minority there is progression to hypothyroidism. Microscopically, there is a lymphocytic infiltration and hyperplastic germinal center within the thyroid parenchyma. There is no significant destruction of the thyroid follicles (cf. Hashimoto thyroiditis).

Riedel thyroiditis is a rare disorder of unknown etiology, characterized by extensive fibrosis involving the thyroid and the surrounding neck structures. The presence of a hard and fixed thyroid mass may be confused clinically with thyroid cancer. It may be associated with idiopathic fibrosis in other sites, such as the retroperitoneum. The presence of circulating antithyroid antibodies in most patients suggests an autoimmune etiology.

Palpation thyroiditis is caused by vigorous clinical palpation of the thyroid gland that results in disruption of thyroid follicles at multiple sites associated with chronic inflammatory cells. It is usually an incidental finding in thyroids resected for other reasons.
GRAVES DISEASE

Robert Graves in 1835 was the first to report the association of enlargement of the thyroid gland with long continued palpitations in females. Graves disease is the most common cause of hyperthyroidism and characterized by the triad of
1. Thyrotoxicosis, caused by a diffusely enlarged, hyperfunctioning thyroid
2. Exophthalmos, a form of infiltrative ophthalmopathy (40% of patients)
3. Pretibial myxedema (minority of cases)
The peak incidence is between 20 and 40 years, with women predominating (7:1).

Pathogenesis

Graves disease is an autoimmune disorder in which autoantibodies to the TSH receptors are central to disease pathogenesis; the most important of these is thyroid-stimulating immunoglobulin (TSI). The latter is an IgG antibody that binds to the TSH receptors of follicular cells with resultant increased release of thyroid hormones. This antibody is present in most patients and is relatively specific for Graves disease. The initiation of the autoimmune reaction in Graves disease seems to be a breakdown in helper T-cell tolerance, resulting in the production of anti-TSH autoantibodies. Genetic susceptibility to the disease is evidenced by an increased in the incidence of the disease among family members of affected patients.

Autoimmune disorders of the thyroid thus span a spectrum in which Graves disease lies at one extreme and Hashimoto disease occupies the other end. Sometimes hyperthyroidism may supervene on preexisting Hashimoto thyroiditis (hashitoxicosis), while at other times individuals with Graves disease may spontaneously develop thyroid hypofunction. In both disorders the frequency of other autoimmune diseases, such as SLE, pernicious anemia, & type 1 diabetes, is increased.

Gross features (Fig. 7-4 A)
- The thyroid gland is diffusely but moderately enlarged
- It is usually smooth, soft, and hyperemic

Microscopic features (Fig. 7-4 B).
- The follicular epithelial cells are tall, columnar, and more crowded than usual. This crowding often results in the formation of small pseudopapillae, which project into the follicular lumen
- The colloid within the follicle lumens is pale, with scalloped margins.
- Lymphoid infiltrates and mature plasma cells are present throughout the interstitium; germinal centers are common.

Clinical features: there are features of thyrotoxicosis, as well as signs that are associated exclusively with Graves disease
1. Diffuse, smooth & symmetric enlargement of the thyroid, ophthalmopathy (Fig. 7-5)
2. Abnormal protrusion of the eyeball (exophthalmos).
3. Scaly thickening and induration of the skin (pretibial myxedema), most common in the skin overlying the shins. Laboratory findings in Graves disease include elevated serum free T4 and T3 and depressed serum TSH.

Diffuse and Multinodular Goiters

These reflect impaired synthesis of thyroid hormones, most often caused by dietary iodine deficiency. Impairment of thyroid hormone synthesis leads to a compensatory rise in the serum TSH, which, in turn, causes compensatory hypertrophy and hyperplasia of thyroid follicular cells and, ultimately, gross enlargement of the thyroid gland. These changes are able to overcome the hormone deficiency resulting in euthyroid metabolic state. If the underlying disorder is sufficiently severe (e.g., a congenital biosynthetic defect), the compensatory responses may be inadequate to overcome the impairment in hormone synthesis, resulting in goitrous hypothyroidism. The degree of thyroid enlargement is proportional to the level and duration of thyroid hormone deficiency.

Endemic goiter occurs in geographic areas (typically mountainous) where the soil, water, and food supply contain little iodine. The term endemic is used when goiters are present in more than 10% of the population in a given region. With increasing availability of dietary iodine supplementation, the frequency and severity of endemic goiter have declined significantly. Sporadic goiter is less common than endemic goiter. The condition is more common in females than in males, with a peak incidence in puberty or young adult life, when there is an increased physiologic demand for T4. Sporadic goiter may be caused by
1. Ingestion of substances that interfere with thyroid hormone synthesis, such as excessive intake of calcium, cabbage, cauliflower, etc.
2. Hereditary enzymatic defects interfering with thyroid hormone synthesis (*dyshormonogenetic goiter*).

In most cases, however, the cause of sporadic goiter is not apparent.

**Pathological features (Fig. 7-6)**

- Initially there is diffuse, symmetric enlargement of the gland (*diffuse goiter*). The follicles are lined by crowded columnar cells, which may pile up and form pseudopapillae similar to those seen in Graves disease.
- If dietary iodine subsequently increases, or if the demands for thyroid hormone decrease, the stimulated follicular epithelium involutes to form an enlarged, colloid-rich gland (*simple colloid goiter*). The cut surface of the thyroid in such cases is usually brown, glassy, and translucent. *Microscopically*, the follicular epithelium may be hyperplastic in the early stages of disease or flattened and cuboidal during periods of involution. Colloid is abundant.
- Recurrent episodes of hyperplasia and involution combine to produce a more irregular enlargement of the thyroid (*multinodular goiter*). They may be nontoxic or may induce thyrotoxicosis (*toxic multinodular goiter*). Grossly, Multinodular goiters are multilobulated, asymmetrically enlarged glands, which may reach massive size. On the cut surface, irregular nodules containing variable amounts of brown, gelatinous colloid are present. *Regressive changes* are quite common, particularly in older lesions, and include areas of fibrosis, hemorrhage, calcification, and cystic change. *Microscopically*, there are colloid-rich follicles lined by flattened, inactive epithelium and areas of follicular epithelial hypertrophy and hyperplasia, accompanied by the regressive changes mentioned above.

**The dominant clinical features**: in addition to the obvious disfigurement induced by a large neck mass, goiters may also cause airway obstruction, dysphagia, and compression of large vessels in the neck and upper thorax. A hyperfunctioning ("toxic") nodule may develop within a long-standing goiter, resulting in hyperthyroidism. This condition is not accompanied by the infiltrative ophthalmopathy and dermopathy. Less commonly, there may be hypothyroidism.

**NEOPLASMS OF THE THYROID**

Fortunately, the overwhelming majority of solitary thyroid nodules are benign lesions.

**Causes of a solitary thyroid nodule** include

1. Non-neoplastic conditions
   a. a dominant nodule of otherwise multinodular goiter
   b. simple cysts
   c. foci of thyroiditis
2. Neoplastic conditions
   a. Follicular adenomas
   b. Carcinomas

*It is the microscopic evaluation of a given thyroid nodule, done by fine-needle aspiration biopsy and/or histologic study of surgically resected thyroid tissue, that provides the most definitive information about its nature.*

**ADENOMAS** are derived from follicular epithelium. As in the case of all thyroid neoplasms, *follicular adenomas* are usually solitary. Clinically and morphologically, they may be difficult to distinguish, from hyperplastic nodules & from the less common follicular carcinomas. Although the vast majority of adenomas are nonfunctional, a small proportion are "toxic adenomas" and causes clinically apparent thyrotoxicosis.

**Pathogenesis**

*Somatic mutations* most often in the TSH receptor itself, cause *chronic overproduction of cAMP*, generating cells that acquire proliferative advantage. This results in clonal expansion of epithelial cells that leads to the formation of follicular adenoma. About 20% of follicular adenomas have *point mutations in the RAS* family of oncogenes, which have been also identified in 50% of follicular carcinomas. This raises the possibility that some adenomas may progress to carcinomas.

**Gross features (Fig. 7-7 A)**
The adenoma is solitary, spherical mass that compresses adjacent thyroid tissue. It is well demarcated from the adjacent parenchyma by a well-defined capsule.

**Microscopic features (Fig. 7-7 B)**

- The uniform neoplastic cells are arranged in uniform follicles that contain colloid.
- The follicular growth pattern within the adenoma is usually quite distinct from the adjacent non-neoplastic thyroid.
- The tumor is surrounded by a fibrous capsule.
- The above two features help distinguish an adenoma from a nodule of a multinodular goiter, in which nodular and uninvolved parenchyma demonstrate comparable growth patterns.
- Occasionally, the neoplastic cells acquire brightly eosinophilic granular cytoplasm (Hürthle cell adenoma) (Fig. 7-8), which does not differ clinically and in behavior from those of a conventional adenoma.
- The hallmark of all follicular adenomas is the presence of an intact well-formed capsule encircling the tumor. **Careful evaluation of the integrity of the capsule is critical in the distinction of follicular adenomas from follicular carcinomas**, which demonstrate capsular and/or vascular invasion. Because of the need for evaluating capsular integrity, **the definitive diagnosis of thyroid adenoma involves exclusion of follicular carcinoma, & this can only be made after careful histologic examination of the resected specimen**. Suspected adenomas of the thyroid are therefore removed surgically to exclude malignancy.

**THYROID CARCINOMAS**

Most cases of thyroid carcinoma occur in adults, although papillary carcinomas, may present in childhood. A female predominance has been noted in the early and middle adult years; this is probably related to the expression of estrogen receptors on neoplastic thyroid epithelium. In contrast, cases presenting in childhood and late adult life are distributed equally among males and females. The major subtypes of thyroid carcinoma and their relative frequencies are as follows:

- Papillary carcinoma 80%
- Follicular carcinoma 15%
- Medullary carcinoma 4%
- Anaplastic carcinomas 1%

Most thyroid carcinomas are derived from the follicular epithelium, except for medullary carcinomas, which is derived from the parafollicular C cells.

**Pathogenesis**

Both genetic and environmental factors are implicated in the pathogenesis of thyroid cancers.

1. **Genetic influences** are implicated in both familial and sporadic forms of thyroid cancer.

   **Papillary thyroid carcinomas**: two major types of genetic alterations are involved in the pathogenesis of papillary thyroid carcinomas.
   - Chromosomal rearrangements involving the tyrosine kinase receptor gene RET. Such rearrangements result in the formation of fusion genes, known as ret/PTC (receptor of tyrosine kinase/papillary thyroid carcinoma),
   - Point mutations in the BRAF oncogene

   Both these genetic changes independently activate the carcinogenic **MAP kinase signaling pathway**.

   **Follicular thyroid carcinomas**: approximately 50% of such tumors harbor mutations in the RAS family of oncogenes.

   **Medullary carcinomas**: familial medullary thyroid carcinomas occur in MEN 2, and are associated with germ-line RET proto-oncogene mutations. RET mutations are also seen in nonfamilial (sporadic) medullary thyroid cancers.

   **Anaplastic carcinomas**: inactivating point mutations in the p53 tumor suppressor gene are common in anaplastic tumors.

2. **Environmental factors**
   - Exposure to ionizing radiation, particularly during the first 2 decades of life, is one of the most important predisposing factor for the development of thyroid cancer. The incidence of carcinoma of the thyroid is substantially higher among atomic bomb survivors in Japan and in those exposed to ionizing radiation after the
Chernobyl nuclear plant disaster. The overwhelming majority of cancers arising in this setting are papillary thyroid cancers, and most have RET gene rearrangements.

b. Long-standing multinodular goiter has been suggested as a predisposing factor since areas with iodine deficiency-related endemic goiter have a higher prevalence of follicular carcinomas.

**Papillary Carcinoma**

This is the most common thyroid malignancy & although it can present in any age group, the mean age at the time of initial diagnosis is 40 years.

**Gross features**

- The size of the primary tumor ranges from microscopic to huge. A very high proportion of thyroid cancers measuring < 1 cm in diameter are of papillary type.
- The tumor may be solitary or multifocal
- It is either well circumscribed encapsulated or ill-defined with infiltrative margins.
- Most cases are solid, whitish, firm, and clearly invasive; sometimes papillary formations are evident. (Fig. 7-9 A).

**Microscopic features** (Fig. 7-9 B)

- The diagnosis of papillary carcinoma is based on nuclear features even in the absence of a papillary architecture. The nuclei of papillary carcinoma cells contain very finely dispersed chromatin, which imparts an optically clear appearance referred to as "ground-glass" nuclei. In addition, invaginations of the cytoplasm may give the appearance of intranuclear pseudo-inclusions. Nuclear clefting is another feature of papillary carcinoma cells.
- A papillary architecture is present in many cases, although some tumors are composed predominantly or exclusively of follicles; these follicular variants still behave biologically as papillary carcinomas if they have the nuclear features described above.
- Concentrally calcified structures termed psammoma bodies are often present within the tumor.

Papillary carcinomas present most often as a painless mass in the neck, either within the thyroid or as metastasis in a cervical lymph node. Metastases to adjacent cervical lymph nodes occur in 50% of cases. The presence cervical nodal metastases does not seem to influence the generally good prognosis of these cancers. In a minority of patients, hematogenous metastases are present, most commonly to the lung. Papillary carcinomas are indolent lesions, with 10-year survival rates in excess of 95%.

**Follicular Carcinoma**

This is the second most common form of thyroid cancer. It shares with papillary carcinoma the same predilection for females, but it occurs, on the average, in patients who are a decade older. The incidence of follicular carcinoma is increased in areas of dietary iodine deficiency. The high frequency of RAS mutations in follicular adenomas and carcinomas suggests that they may be related tumors.

**Pathological features** (Fig. 7-10)

- Most follicular carcinomas are composed of fairly uniform cells forming small follicles, reminiscent of normal thyroid.
- Similar to follicular adenomas, Hürthle cell variants of follicular carcinomas may be seen.
- Follicular carcinomas may be frankly infiltrative or minimally invasive. The latter are sharply demarcated lesions that may be impossible to distinguish from follicular adenomas on gross examination. This distinction requires extensive histological sampling of the tumor-capsule-thyroid interface, to exclude of confirm the presence of capsular and/or vascular invasion.
- Follicular lesions in which the nuclear features are typical of papillary carcinomas should be regarded as papillary cancers.

Follicular carcinomas present most frequently as solitary "cold" thyroid nodules. These neoplasms tend to metastasize through the bloodstream to the lungs, bone, and liver. Regional nodal metastases are uncommon, in contrast to papillary carcinomas.
Medullary Carcinoma
This is a neuroendocrine neoplasm derived from the parafollicular cells C cells. Like normal C cells, medullary carcinomas secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up of patients. In some cases, the tumor cells secrete other polypeptide hormones. Medullary carcinomas are either sporadic (80% of cases) or familial (FMTC; 20%). The latter occur either in the setting of MEN syndromes or without an associated MEN syndrome. Sporadic & FMTC with out MEN occur in adults, with a peak incidence around the age of 60 years. Cases associated with MEN, in contrast, occur in younger patients and may even arise in children.

Gross features (Fig. 7-11)
- The tumor may arise as a solitary multiple nodules involving both lobes of the thyroid. Multicentricity is particularly common in familial cases.
- The tumor is unencapsulated, solid, and yellowish tan in color
- Larger lesions often contain areas of necrosis and hemorrhage and may extend through outside the thyroid.

Microscopic features (Fig. 7-11)
- These tumors are composed of polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles.
- Amyloid deposits, derived from altered calcitonin molecules, are present in the adjacent stroma in many cases and are a distinctive feature of these tumors.
- Calcitonin is readily demonstrable both within the cytoplasm of the tumor cells and in the stromal amyloid by immunohistochemical methods.
- Electron microscopy reveals variable numbers of intracytoplasmic membrane-bound electron-dense granules.
- One of the peculiar features of familial medullary carcinomas is the presence of multicentric C-cell hyperplasia in the surrounding thyroid parenchyma. Foci of C-cell hyperplasia are believed to represent the precursor lesions of medullary carcinomas.

Sporadic cases of medullary carcinoma present most often as a mass in the neck, sometimes associated with compression effects such as dysphagia or hoarseness. Notably, hypocalcemia is not a feature, despite the presence of raised calcitonin levels. Screening of relatives for elevated calcitonin levels or RET mutations permits early detection of tumors in familial cases. Specific RET mutations have been found to correlate with an aggressive behavior in medullary carcinomas.

Anaplastic (undifferentiated) Carcinoma (Fig. 7-12)
Anaplastic carcinomas of the thyroid are among the most aggressive, uniformly fatal human neoplasms. The mean age of occurrence is 65 years. It is speculated that anaplastic carcinoma develops by "dedifferentiation" from more differentiated tumors (e.g. papillary carcinoma) as a result of genetic changes, including loss of function of the p53 tumor suppressor gene.
The cancer presents as a bulky mass that grows rapidly beyond the thyroid capsule into adjacent neck structures. Microscopically, the tumors are composed of highly anaplastic large cells either pleomorphic giant cells &/or spindle cells (sarcomatoid).

PARATHYROID GLANDS
Hyperparathyroidism
This is either primary or secondary, and, less commonly, tertiary. The primary form represents an autonomous overproduction of PTH, while the latter two conditions occur as secondary phenomena in individuals with chronic renal failure.
Primary hyperparathyroidism is an important cause of hypercalcemia. It is caused by parathyroid
1. Adenoma (80%)
2. Primary hyperplasia (15%)
3. Parathyroid carcinoma (5%).
Pathologic features
The changes seen in primary hyperparathyroidism include those
1. In the parathyroid glands
2. In other organs affected by elevated levels of calcium.

Parathyroid changes: these take one of three possibilities

A. Adenoma this is a solitary, well-circumscribed, soft, brownish to yellow, encapsulated nodule. By definition, parathyroid adenomas are almost invariably confined to single glands (Fig. 7-13), and the remaining glands are either of normal in size or shrunken due to feedback inhibition by elevated serum calcium. Microscopically, parathyroid adenomas are composed predominantly of chief cells (Fig. 7-13 A). A rim of compressed, non-neoplastic parathyroid tissue is often visible at the edge of the adenoma.

B. Hyperplasia, which affects typically all the glands. Microscopically, the most common pattern seen is that of chief-cell hyperplasia. Less commonly, the constituent cells contain abundant clear cytoplasm due to accumulation of glycogen, a condition designated as water-clear cell hyperplasia.

C. Carcinoma, which is usually a hard tumor. Intra-operatively, a hard and adherent parathyroid is often a hint to the possibility of carcinoma rather than adenoma. Like adenoma, they typically a single-gland lesion and chief cells tend to predominate in most cases. The only two valid criteria for malignancy are (1) invasion of surrounding tissues and (2) metastatic dissemination.

Changes in other organs; these are found in the skeleton and kidneys.

1. Skeletal changes include prominence of osteoclasts that erode bone matrix, particularly in the metaphyses of long tubular bones. Bone resorption is accompanied by increased osteoblastic activity and the formation of new bone trabeculae. In severe cases the cortex is grossly thinned and the marrow contains increased amounts of fibrous tissue accompanied by foci of hemorrhage and cyst formation (ostitis fibrosa cystica). Aggregates of osteoclasts, reactive giant cells, and hemorrhagic debris occasionally form masses that may be mistaken for neoplasms (brown tumors of hyperparathyroidism). (Fig. 7-14)

2. Nephrolithiasis & nephrocalcinosis: PTH-induced hypercalcemia favors the formation of urinary tract stones (nephrolithiasis) as well as calcification of the renal interstitium and tubules (nephrocalcinosis).

3. Metastatic calcification secondary to hypercalcemia may also be seen in the stomach, lungs, myocardium, and blood vessels.

Primary hyperparathyroidism is usually a disease of adults and is more common in women than in men by a ratio of nearly 3:1. The most common lab. feature is an increase in serum ionized calcium. Malignancy is the most common cause of clinically apparent hypercalcemia in adults and primary hyperparathyroidism is the most common cause of clinically silent hypercalcemia. In persons with hypercalcemia caused by parathyroid hyperfunction, serum PTH is inappropriately elevated, whereas serum PTH is low to undetectable in hypercalcemia caused by nonparathyroid diseases, including malignancy.

Secondary hyperparathyroidism is caused by any condition associated with chronic hypocalcemia, which leads to compensatory overactivity of the parathyroids. Renal failure is by far the most common cause. The parathyroid glands are hyperplastic. Bone changes and metastatic calcification are similar to those seen in primary hyperparathyroidism.

The clinical manifestations of secondary hyperparathyroidism are usually dominated by those related to chronic renal failure and elevated serum levels of PTH. In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia, a process sometimes termed Tertiary hyperparathyroidism.

HYPOPARATHYROIDISM

The major causes of hypoparathyroidism include

1. Iatrogenic i.e. unintentional removal of parathyroids during thyroidectomy.
2. Congenital absence of the parathyroid glands
3. Autoimmune hypoparathyroidism: a hereditary deficiency syndrome arising from autoantibodies to multiple endocrine organs (parathyroid, thyroid, adrenals, and pancreas).

The major clinical manifestations of hypoparathyroidism are referable to hypocalcemia and include increased neuromuscular irritability, cardiac arrhythmias, and, on occasion, seizures.
ENDOCRINE PANCREAS

DIABETES MELLITUS

This is “a group of metabolic disorders sharing the common underlying characteristic of hyperglycemia.”

Diabetes is an important disease because
1. It is common (affects 7% of the population).
2. It increases the risk of atherosclerotic coronary artery and cerebrovascular diseases.
3. It is a leading cause of
   a. Chronic renal failure
   b. Adult-onset blindness
   c. Nontraumatic lower extremity amputations (due to gangrene)

Classification
Diabetes is divided into two broad classes:
1. Type 1 diabetes (10%): characterized by an absolute deficiency of insulin secretion caused by pancreatic β-cell destruction, usually as a result of an autoimmune attack.
2. Type 2 diabetes (80%): caused by a combination of peripheral resistance to insulin action and an inadequate secretion of insulin from the pancreatic β cells in response to elevated blood glucose levels.

The long-term complications in kidneys, eyes, nerves, and blood vessels are the same in both types.

Pathogenesis

Type 1 diabetes is an autoimmune disease and as in all such diseases, genetic susceptibility and environmental influences play important roles in the pathogenesis. The islet destruction is caused primarily by T lymphocytes reacting against immunologic epitopes on the insulin hormone located within β-cell; this results in a reduction of β-cell mass. The reactive T cells include CD4+ T cells of the Th1 subset, which cause tissue injury by activating macrophages, and CD8+ cytotoxic T lymphocytes; these directly kill β cells and also secrete cytokines that activate further macrophages. The islets show cellular necrosis and lymphocytic infiltration (insulitis). Autoantibodies against a variety of β-cell antigens, including insulin are also detected in the blood and may also contribute to islet damage.

Type 2 Diabetes Mellitus: the pathogenesis remains unsettled. Environmental influences, such as inactive lifestyle and dietary habits that eventuates in obesity, clearly have a role. Nevertheless, genetic factors are even more important than in type 1 diabetes. Among first-degree relatives with type 2 diabetes the risk of developing the disease is 20% to 40%, as compared with 5% in the general population.

The two metabolic defects that characterize type 2 diabetes are 1. A decreased ability of peripheral tissues to respond to insulin (insulin resistance) and 2. β-cell dysfunction manifested as inadequate insulin secretion in the face of hyperglycemia. In most cases, insulin resistance is the primary event and is followed by increasing degrees of β-cell dysfunction.

Morphology of Diabetes and Its Late Complications

The important morphologic changes are related to the many late systemic complications of diabetes and thus are likely to be found in arteries (macrovascular disease), basement membranes of small vessels (microangiopathy), kidneys (diabetic nephropathy), retina (retinopathy), and nerves (neuropathy). These changes are seen in both type 1 and type 2 diabetes.

The changes are divided into pancreatic & extrapancreatic

A. Pancreatic changes are inconstant and are more commonly associated with type 1 than with type 2 diabetes. One or more of the following alterations may be present.

1. Reduction in the number and size of islets
2. Leukocytic infiltration of the islets (insulitis) principally by T lymphocytes.
3. Amyloid replacement of islets; which is seen in advanced stages. (Fig. 7-15)

B. Extrapancreatic changes

1. Diabetic macrovascular disease is reflected as accelerated atherosclerosis affecting the aorta and other large and medium-sized arteries including the coronaries. Myocardial infarction is the most common cause of death in diabetics. Gangrene of the lower limbs due to advanced vascular disease, is about 100 times more common in diabetics than in the general population.
2. **Hyaline arteriolosclerosis** is the vascular lesion associated with hypertension. It is both more prevalent and more severe in diabetics than in nondiabetics, but it is not specific for diabetes and may be seen in elderly nondiabetics without hypertension. (Fig. 7-16)

3. **Diabetic microangiopathy** is one of the most consistent morphologic features of diabetes, which reflected morphologically as diffuse thickening of basement membranes. The thickening is most evident in the capillaries of the retina, renal glomeruli, and peripheral nerves. The thickened capillary basement membranes are associated with leakiness to plasma proteins. The microangiopathy underlies the development of diabetic nephropathy, retinopathy, and some forms of neuropathy.

4. **Diabetic Nephropathy:** renal failure is second only to myocardial infarction as a cause of death from diabetes. Three lesions encountered are:
   1. Glomerular lesions
   2. Renal vascular lesions, principally arteriolosclerosis; and
   3. Pyelonephritis, including necrotizing papillitis.

   **Glomerular lesions:** these include
   a. diffuse glomerular capillary basement membrane thickening
   b. diffuse glomerular sclerosis: diffuse increase in mesangial matrix; always associated with the above.
   c. nodular glomerulosclerosis (Kimmelstiel-Wilson lesion) refers to a rounded deposit of a laminated matrix situated in the periphery of the glomerulus (Fig. 7-17). These nodules are PAS positive. Nodular glomerulosclerosis is encountered in up to 30% of long-term diabetics and is a major cause of morbidity and mortality. The change is pathognomonic of diabetes. Both forms of glomerulosclerosis (diffuse and nodular) induce sufficient ischemia to cause scarring of the kidneys, manifested by a finely granular cortical surface (Fig. 7-18).

   **Pyelonephritis:** both acute and chronic pyelonephritis are more common & more severe in diabetics than in the general population. One special pattern of acute pyelonephritis, necrotizing papillitis (or papillary necrosis), is also much more prevalent in diabetics.

   **Ocular Complications of Diabetes:** Visual impairment up to total blindness may occur in long-standing diabetes. The ocular involvement may take the form of
   a. retinopathy
   b. cataract formation
   c. glaucoma

   **Retinopathy** is the most common of the above three. It consists of a group of changes that together are considered diagnostic of the disease. The lesion in the retina takes two forms:
   1. Nonproliferative (background) retinopathy
   2. Proliferative retinopathy.

   **Nonproliferative retinopathy** includes retinal hemorrhages, exudates, microaneurysms, and most importantly, thickening of the retinal capillaries (micro-angiopathy). Underlying all of these changes is thickening of the retinal capillaries (microangiopathy), which leads to focal weakening of capillary structure.

   **Proliferative retinopathy** is a process of neovascularization and fibrosis. This lesion leads to serious consequences, including blindness, especially if it involves the macula. Vitreous hemorrhages can result from rupture of newly formed capillaries; the resultant organization of the hemorrhage can pull the retina off its foundation leading to retinal detachment. (Fig. 7-19)

   **Diabetic Neuropathy:** the most frequent is a peripheral, symmetric neuropathy of the lower extremities that affects mainly the sensory function. Other forms produce disturbances in bowel and bladder function, sexual impotence, and diabetic mononeuropathy. The latter may manifest as sudden footdrop, wristdrop, or isolated cranial nerve palsies. One of the causes of the neurologic changes is again microangiopathy. The loss of pain sensation in the lower limbs can result in the development of ulcers that heal poorly and are a major cause of morbidity.

   In both forms of long-standing diabetes, cardiovascular events such as myocardial infarction, renal vascular insufficiency, and cerebrovascular accidents are the most common causes of mortality. Diabetic nephropathy is a leading cause of end-stage renal disease. By 20 years after diagnosis, more than 75% of type 1 diabetics and about 20% of type 2 diabetics with overt renal disease will develop end-stage renal disease, requiring dialysis or renal transplantation.
Diabetics are plagued by an enhanced susceptibility to infections of the skin, as well as to tuberculosis, pneumonia, and pyelonephritis. Such infections cause the deaths of about 5% of diabetics.

**PANCREATIC ENDOCRINE NEOPLASMS (islet cell tumors)**
These are most common in adults, may be single or multiple, and benign or malignant. The latter metastasize to lymph nodes and liver. They tend to be functional. Like other endocrine neoplasms, it is difficult to predict their behavior purely on their light microscopic criteria. In general, tumors less than 2 cm in size tend to behave in an indolent manner. The vast majority of insulinomas (the most common subtype) are benign, while the vast majority of other pancreatic endocrine neoplasms tend to be malignant.

**Insulinomas (β-cell tumors)** are the most common of pancreatic endocrine neoplasms; they are generally benign but may produce sufficient insulin to induce hypoglycemia.

**Gross features**
- These are mostly solitary lesions, & usually small (<2 cm in diameter),
- They tend to be encapsulated, pale to red-brown nodules located anywhere in the pancreas. Microscopically, they look like giant islets, with preservation of the regular cords of monotonous cells.
- By immunocytochemistry, insulin can be localized in the tumor cells (Fig. 7-20).
- Under the electron microscope, neoplastic β cells, like their normal counterparts, display distinctive round granules.

The critical laboratory findings in insulinomas are high circulating levels of insulin and a high insulin-to-glucose ratio.

**Gastrinomas** are associated with hypersecretion of gastrin. These tumors may be pancreatic, duodenal or peripancreatic ("gastrinoma triangle"). Zollinger and Ellison were the first to report the association of pancreatic islet cell lesions with hypersecretion of gastric acid and severe peptic ulceration (Zollinger-Ellison syndrome). Over half of gastrinomas are locally invasive or have already metastasized at the time of diagnosis. In 25% of the cases, gastrinomas form a member of MEN-1 syndrome. In Zollinger-Ellison syndrome, hypergastrinemia stimulates extreme gastric acid secretion, which in turn leads to multiple duodenal and gastric ulcers. In addition, ulcers may also occur in the jejunum.

**Other rare pancreatic endocrine neoplasms**
- **α-Cell tumors (glucagonomas)** characterized by extremely high plasma glucagon levels.
- **δ-Cell tumors (somatostatinomas)** characterized by high plasma somatostatin.
- **VIPoma** characterized by production of vasoactive intestinal peptide (VIP).

**THE ADRENAL GLANDS**

**ADRENAL CORTEX**
The adrenal cortex synthesizes three different types of steroids:
1. **Glucocorticoids** (principally cortisol), which are synthesized primarily in the zona fasciculata
2. **Mineralocorticoids**, the most important being aldosterone, which is generated in the zona glomerulosa; and
3. **Sex steroids** (estrogens and androgens), which are produced largely in the zona reticularis.

**Adrenocortical Hyperfunction (Hyperadrenalism)**
Under this heading come three distinctive clinical syndromes:
1. **Hypercortisolism (Cushing syndrome)**
2. **Hyperaldosteronism**
3. **Adrenogenital syndrome** (virilizing)

**Hypercortisolism (Cushing Syndrome)** is caused by any condition that produces an elevation in glucocorticoid levels. The causes of this syndrome are
- **Exogenous** through administration of exogenous glucocorticoids; the most common cause.
- **Endogenous**
  1. Hypothalamic-pituitary diseases causing hypersecretion of ACTH (Cushing disease)
  2. Adrenocortical hyperplasia or neoplasia
  3. Ectopic ACTH secretion by nonendocrine neoplasms (paraneoplastic)
Hypothalamic-pituitary disease associated with oversecretion of ACTH accounts for more than 50% of the endogenous hypercortisolism. The disorder affects mainly women, and it occurs most frequently during the 20s and 30s. ACTH-producing microadenoma (rarely macroadenoma) is responsible for the vast majority of such cases. Alternatively, the anterior pituitary shows areas of corticotroph cell hyperplasia. The latter may be primary, or arise secondarily from excessive stimulation of ACTH release by the hypothalamus. The adrenal glands in patients with Cushing disease show bilateral nodular cortical hyperplasia secondary to overstimulation by elevated levels of ACTH. The cortical hyperplasia, in turn, is responsible for the hypercortisolism.

Primary adrenal neoplasms, such as adrenal adenoma and carcinoma, and rarely by primary bilateral adrenal cortical hyperplasia, are responsible for up to 20% of cases of endogenous Cushing syndrome. This group is designated as ACTH-independent Cushing syndrome (or adrenal Cushing syndrome) because the adrenals function autonomously.

Secretion of ectopic ACTH by nonendocrine tumors is commonly due to a small-cell carcinoma of the lung.

Pathological features

- The main lesions of Cushing syndrome are found in the pituitary and adrenal glands.
- The most common change in the pituitary, results from high levels of endogenous or exogenous glucocorticoids, is termed Crooke hyaline change. In this condition, the normal granular, basophilic cytoplasm of the ACTH-producing cells in the anterior pituitary is replaced by homogeneous, lightly basophilic material. This is due to accumulation of intermediate keratin filaments in the cytoplasm.
- There is one of four changes in the adrenal glands, which depends on the cause.
  1. Cortical atrophy
  2. Diffuse hyperplasia
  3. Nodular hyperplasia
  4. Adenoma, rarely a carcinoma

- In patients in whom the syndrome results from exogenous glucocorticoids, suppression of endogenous ACTH results in bilateral cortical atrophy, due to a lack of stimulation of the cortex by ACTH. In cases of endogenous hypercortisolism, in contrast, the adrenals either are hyperplastic or contain a cortical neoplasm. In Diffuse hyperplasia the adrenal cortex is diffusely thickened and yellow, as a result of an increase in the size and number of lipid-rich cells in the zonae fasciculata and reticularis. Alternatively, there is nodular hyperplasia (Fig. 7-21), which takes the form of bilateral, up to 2.0-cm, yellow nodules scattered throughout the cortex. This macronodularity appears to be an extension of the diffuse hyperplasia, because the cortex between the nodules exactly resembles that found in the diffuse form of this condition.

- Primary adrenocortical neoplasms causing Cushing syndrome may be benign or malignant. The adrenocortical adenomas are yellow tumors surrounded by capsules, and most weigh <30 gm (Fig. 7-22). Microscopically, they are composed of cells that are similar to those encountered in the normal zona fasciculata. The carcinomas associated with Cushing syndrome are unencapsulated masses frequently >300 gm in weight, having all of the anaplastic characteristics of cancer. With both functioning benign and malignant tumors, the adjacent adrenal cortex and that of the contralateral adrenal gland are atrophic because of suppression of endogenous ACTH by high cortisol levels.

ADRENAL INSUFFICIENCY

Adrenocortical hypofunction is either primary (adrenocrtical) or secondary (ACTH deficiency). Primary insufficiency is divided into acute & chronic.

Acute Adrenocortical Insufficiency occurs most commonly in the following clinical settings

- massive adrenal hemorrhage including Waterhouse-Friderichsen syndrome
- Sudden withdrawal of long-term corticosteroid therapy
- Stress in those with chronic adrenal insufficiency

Massive adrenal hemorrhage may destroy the adrenal cortex sufficiently to cause acute adrenocortical insufficiency. This condition may occur

1. in patients maintained on anticoagulant therapy
2. in postoperative patients who develop DIC
3. during pregnancy
4. in patients suffering from overwhelming sepsis (Waterhouse-Friedrichsen syndrome) (Fig. 7-23).

**Waterhouse-Friedrichsen syndrome** is a catastrophic syndrome classically associated with Neisseria meningitidis septicemia but can also be caused by other organisms, including Pseudomonas species, pneumococci & Haemophilus influenzae. The pathogenesis of the syndrome remains unclear, but probably involves endotoxin-induced vascular injury with associated DIC.

**Chronic adrenocortical insufficiency** (Addison disease) results from progressive destruction of the adrenal cortex. More than 90% of all cases are attributable to one of four disorders:
1. autoimmune adrenalitis (the most common cause; 70% of cases)
2. tuberculosis & fungal infections
3. AIDS
4. Metastatic cancers

In such primary diseases, there is hyperpigmentation of the skin & oral mucosa due to high levels of MSH (associated with high levels of ACTH). (Fig. 7-24)

**Autoimmune adrenalitis** is due to autoimmune destruction of steroid-producing cells. It is either isolated or associated other autoimmune diseases, such as Hashimoto disease, pernicious anemia, etc.

**Infections, particularly tuberculous and fungal**

*Tuberculous adrenalitis*, which once was responsible for as many as 90% of cases of Addison disease, has become less common with the advent of antituberculous therapy. When present, tuberculous adrenalitis is usually associated with active infection elsewhere, particularly the lungs and genitourinary tract. Among fungi, disseminated infections caused by *Histoplasma capsulatum* is the main cause.

**AIDS** patients are at risk for developing adrenal insufficiency from several infectious (cytomegalovirus, *Mycobacterium avium-intracellulare*) and noninfectious (Kaposi sarcoma) complications.

**Metastatic neoplasms**: the adrenals are a fairly common site for metastases in persons with disseminated carcinomas. Although adrenal function is preserved in most such patients, the metastatic growths sometimes destroy sufficient adrenal cortex to produce a degree of adrenal insufficiency. *Carcinomas of the lung and breast* are the major primary sources. (Fig. 7-25)

**Secondary Adrenocortical Insufficiency**

Any disorder of the hypothalamus and pituitary, such as metastatic cancer, infection, infarction, or irradiation, that reduces the output of ACTH leads to a syndrome of hypoadrenalism having many similarities to Addison disease. In such secondary disease, the hyperpigmentation of primary Addison disease is lacking because melanotropic hormone levels are low. ACTH deficiency may occur alone, but in some instances, it is only one part of panhypopituitarism, associated with multiple tropic hormone deficiencies. Secondary adrenocortical insufficiency is characterized by low serum ACTH and a prompt rise in plasma cortisol levels in response to ACTH administration.

**Pathological features of adrenocortical deficiency**

- The appearance of the adrenal glands varies with the cause of the insufficiency.
- In secondary hypoadrenalism the adrenals are reduced to small, uniform, thin rim of atrophic yellow cortex that surrounds a central, intact medulla. Histologically, there is atrophy of cortical cells with loss of cytoplasmic lipid, particularly in the zonae fasciculata and reticularis.
- In primary autoimmune adrenalitis there is also atrophy of the cortex associated with a variable lymphoid infiltrate that may extend into the subjacent medulla. The medulla is otherwise normal.
- In *tuberculosis* or *fungal diseases* there is granulomatous inflammatory reaction. Demonstration of the responsible organism may require the use of special stains.
- With *metastatic carcinoma*, the adrenals are enlarged and their normal architecture is obscured by the infiltrating neoplasm.

At least 90% of the gland cortices have to be destroyed for the condition to be clinically apparent.
ADRENOCORTICAL TUMORS
Functional adenomas are commonly associated with hyperaldosteronism and with Cushing syndrome, whereas a virilizing neoplasm is more likely to be a carcinoma. Determination of of the functional status of a tumor is based on clinical evaluation and measurement of the hormone or its metabolites. In other words, functional and nonfunctional adrenocortical neoplasms cannot be distinguished on the basis of morphologic features.

Pathological features
Adrenocortical adenomas (Fig. 7-26)
Most cortical adenomas do not cause hyperfunction and are usually encountered as incidental findings at the time of autopsy or during abdominal imaging for an unrelated cause.
- They are generally small, 1 to 2 cm in diameter.
- On cut surface, adenomas are usually yellow to yellow-brown due to presence of lipid within the neoplastic cells
- Microscopically, adenomas are composed of cells similar to those populating the normal adrenal cortex. The nuclei tend to be small, although some degree of pleomorphism may be encountered even in benign lesions ("endocrine atypia"). The cytoplasm ranges from eosinophilic to vacuolated, depending on their lipid content.

Adrenocortical carcinomas
These are rare and may occur at any age, including in childhood.
- Carcinomas are generally large, invasive lesions.
- The cut surface is typically variegated and poorly demarcated with areas of necrosis, hemorrhage, and cystic change (Fig. 7-27).
- Microscopically, they are composed of well-differentiated cells resembling those of cortical adenomas or bizarre, pleomorphic cells, which may be difficult to distinguish from those of an undifferentiated carcinoma metastatic to the adrenal.
Adrenal cancers have a strong tendency to invade the adrenal vein, vena cava, and lymphatics. Metastases to regional and periaortic nodes are common, as are distant hematogenous spread to the lungs and other viscera. The median survival is about 2 years.

ADRENAL MEDULLA
The adrenal medulla is populated by cells derived from the neural crest (chromaffin cells) and their supporting (sustentacular) cells. The chromaffin cells are so named because they stain brown-black after exposure to potassium dichromate. They secrete catecholamines in response to signals from preganglionic nerve fibers in the sympathetic nervous system. Similar collections of cells are distributed throughout the body in the extra-adrenal paraganglion system. Tumors are the most important diseases of the adrenal medulla.

Pheochromocytoma
Pheochromocytomas are neoplasms composed of chromaffin cells, which as their normal counterparts synthesize and release catecholamines. The "rule of 10s" is conviently applied to this tumor: 10% of pheochromocytomas
1. Arise in association with one of several familial syndromes such as MEN syndromes, type 1 neurofibromatosis, von Hippel-Lindau disease, and Sturge-Weber syndrome.
2. Are extra-adrenal, occurring in sites such as the organ of Zuckerkandl and the carotid body, where they are usually called paragangliomas rather than pheochromocytomas.
3. Are bilateral; but in association with familial syndromes, this figure may rise to 50%.
4. Are malignant; frank malignancy, however, is more common in extra-adrenal tumors.

Gross features
- The size of these tumors is quite variable ranging from small to huge masses.
- Sectioning shows yellow-tan, well-defined tumor that compress the adjacent adrenal. Large lesions display areas of hemorrhage, necrosis, and cystic degeneration.
Incubation of the fresh tissue with potassium dichromate solutions converts the tumor a dark brown color. (Fig. 7-28)

**Microscopic features**
- These tumors are composed of polygonal to spindle-shaped *chromaffin cells* and their supporting *sustentacular cells*, arranged in well-defined small nests (Zellballen)," rimmed by a rich vascular network (Fig. 7-28).
- The cytoplasm is often finely granular (catecholamine-containing granules)
- The nuclei are often quite pleomorphic.
- Both capsular and vascular invasion may be encountered in benign lesions, and the presence of mitotic figures per se does not imply malignancy. Therefore, the definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases. These may involve regional lymph nodes as well as more distant sites, including liver, lung, and bone.
- Electron microscopy reveals variable numbers of membrane-bound, electron-dense granules, representing catecholamines.

The clinical course of pheochromocytoma is dominated by *hypertension that may be episodic*, which is associated with tachycardia, palpitations, headache, sweating and tremor. Sudden cardiac death may occur, probably secondary to catecholamine-induced myocardial irritability and ventricular arrhythmias. The laboratory diagnosis of pheochromocytoma is based on demonstration of increased urinary excretion of free catecholamines and their metabolites, such as vanillylmandelic acid (VMA)& metanephrines.

**Neuroblastoma and Related Neoplasms**

*Neuroblastoma* is the second most common solid malignancy of childhood after brain tumors, accounting for up to 10% of all pediatric neoplasms. They are most common during the first 5 years of life. Neuroblastomas may occur anywhere along the sympathetic nervous system and occasionally within the brain. Most neuroblastomas are sporadic. *Spontaneous regression and spontaneous- or therapy-induced maturation are their unique features.*

**Gross features**
- The adrenal medulla is the commonest site of neuroblastomas. The remainder occur along the sympathetic chain, mostly in the paravertebral region of the abdomen and posterior mediastinum.
- They range in size from minute nodules to large masses weighing more than 1 kg.
- Some tumors are delineated by a fibrous pseudo-capsule, but others invade surrounding structures, including the kidneys, renal vein, vena cava, and the aorta.
- Sectioning shows soft, gray-tan, *brain-like tissue*. Areas of necrosis, cystic softening, and hemorrhage may be present in large tumors. (Fig. 7-29)

**Microscopic features**
- Neuroblastomas are composed of small, primitive-appearing neuroblasts with dark nuclei & scant cytoplasm, growing in solid sheets.
- The background consists of light pinkish fibrillary material corresponding to neuritic processes of the primitive cells.
- Typically, *rosettes* can be found in which the tumor cells are concentrically arranged about a central space filled with the fibrillar neurites.
- Supporting features include include immunohistochemical detection of *neuron-specific enolase* and ultrastructural demonstration of small, membrane-bound, cytoplasmic catecholamine-containing secretory granules.
- Some neoplasms show signs of *maturation*, either spontaneous or therapy-induced. Larger *ganglion-like cells* having more abundant cytoplasm with large vesicular nuclei and prominent nucleoli may be found in tumors admixed with primitive neuroblasts (*ganglioneuroblastoma*). Further maturation leads to tumors containing many mature ganglion-like cells in the absence of residual neuroblasts (*ganglioneuroma*). Many factors influence prognosis, but the most important are the stage of the tumor and the age of the patient. Children below 1 year of age have a much more favorable outlook than do older children at a comparable stage of disease. Mircoscopic features are also an independent prognostic factor; evidence of gangliocytic differentiation is indicative of a "favorable" histology. *Amplification of the MYCN oncogene* in neuroblastomas
is a molecular event that has profound impact on prognosis. The greater the number of copies, the worse is the prognosis. MYCN amplification is currently the most important genetic abnormality used in risk stratification of neuroblastic tumors. About 90% of neuroblastomas produce catecholamines (as pheochromocytomas), which are an important diagnostic feature (i.e., elevated blood levels of catecholamines and elevated urine levels of catecholamine metabolites such as vanillylmandelic acid [VMA] and homovanillic acid [HVA]).

**Multiple Endocrine Neoplasia Syndromes (MEN)**
The MEN syndromes are a group of inherited diseases resulting in proliferative lesions (hyperplasias, adenomas, and carcinomas) of multiple endocrine organs. Even in one organ, the tumors are often multifocal. These tumors are usually more aggressive and recur in a higher proportion of cases than similar but sporadic endocrine tumors.

**Multiple Endocrine Neoplasia Type 1 (MEN1)** is inherited in an autosomal dominant pattern. The gene (MEN1) is a tumor suppressor gene; thus, inactivation of both alleles of the gene is believed to be the basis of tumorigenesis. Organs commonly involved include the parathyroid, pancreas, and pituitary (the 3 Ps). Parathyroid hyperplasia is the most consistent feature of MEN-1 but endocrine tumors of the pancreas are the leading cause of death because such tumors are usually aggressive and present with metastatic disease. Zollinger-Ellison syndrome, associated with gastrinomas, and hypoglycemia, related to insulinomas, are common endocrine manifestations. Prolactin-secreting macroadenoma is the most frequent pituitary tumor in MEN-1 patients.

**Multiple Endocrine Neoplasia Type 2 (MEN2)**
MEN type 2 is actually two distinct groups of disorders that are unified by the occurrence of activating mutations of the RET protooncogene. Both are inherited in an autosomal dominant pattern.

**MEN 2A**
Organs commonly involved include:
*Medullary carcinoma* of the thyroid develops in virtually all cases, and the tumors usually occur in the first 2 decades of life. The tumors are commonly multifocal, and foci of C-cell hyperplasia can be found in the adjacent thyroid. *Adrenal pheochromocytomas* develop in 50% of patients; fortunately, no more than 10% are malignant. *Parathyroid gland hyperplasia* with primary hyperparathyroidism occurs in a third of patients.

**Multiple Endocrine Neoplasia, Type 2B**
Organs commonly involved include the thyroid and adrenal medulla. The spectrum of thyroid and adrenal medullary disease is similar to that in MEN-2A. *However, unlike MEN-2A, patients with MEN-2B:*
1. Do not develop primary hyperparathyroidism
2. Develop extraendocrine manifestations: ganglioneuromas of mucosal sites (gastrointestinal tract, lips, tongue) and marfanoid habitus