Endocrine Pathology

15

INTRODUCTION

I. ENDOCRINE SYSTEM

A. Group of glands that maintain body homeostasis
B. Functions by release of hormones that travel via blood to distant organs
C. "Feedback" mechanisms control hormone release.

ANTERIOR PITUITARY GLAND

I. PITUITARY ADENOMA

A. Benign tumor of anterior pituitary cells
B. May be functional (hormone-producing) or nonfunctional (silent)
    1. Nonfunctional tumors often present with mass effect.
        i. Bitemporal hemianopsia occurs due to compression of the optic chiasm.
        ii. Hypopituitarism occurs due to compression of normal pituitary tissue.
        iii. Headache
    2. Functional tumors present with features based on the type of hormone produced.
C. Prolactinoma presents as galactorrhea and amenorrhea (females) or as decreased libido and headache (males); most common type of pituitary adenoma
    1. Treatment is dopamine agonists (e.g., bromocriptine or cabergoline) to suppress prolactin production (shrinks tumor) or surgery for larger lesions.
D. Growth hormone cell adenoma
    1. Gigantism in children—increased linear bone growth (epiphyses are not fused)
    2. Acromegaly in adults
        i. Enlarged bones of hands, feet, and jaw
        ii. Growth of visceral organs leading to dysfunction (e.g., cardiac failure)
        iii. Enlarged tongue
    3. Secondary diabetes mellitus is often present (GH induces liver gluconeogenesis).
    4. Diagnosed by elevated GH and insulin growth factor-1 (IGF-1) levels along with lack of GH suppression by oral glucose
    5. Treatment is octreotide (somatostatin analog that suppresses GH release), GH receptor antagonists, or surgery.
E. ACTH cell adenomas secrete ACTH leading to Cushing syndrome (see "Adrenal Cortex" below).
F. TSH cell, LH-producing, and FSH-producing adenomas occur, but are rare.

II. HYPOPITUITARISM

A. Insufficient production of hormones by the anterior pituitary gland; symptoms arise when > 75% of the pituitary parenchyma is lost.
B. Causes include
    1. Pituitary adenomas (adults) or craniopharyngioma (children)—due to mass effect or pituitary apoplexy (bleeding into an adenoma)
    2. Sheehan syndrome—pregnancy-related infarction of the pituitary gland
        i. Gland doubles in size during pregnancy, but blood supply does not increase significantly; blood loss during parturition precipitates infarction.

ii. Presents as poor lactation, loss of pubic hair, and fatigue

3. Empty sella syndrome—congenital defect of the sella
   i. Herniation of the arachnoid and CSF into the sella compresses and destroys the pituitary gland.
   ii. Pituitary gland is "absent" (empty sella) on imaging.

POSTERIOR PITUITARY GLAND

I. BASIC PRINCIPLES

A. Antidiuretic hormone (ADH) and oxytocin are made in the hypothalamus and then transported via axons to the posterior pituitary for release.
   1. ADH acts on the distal tubules and collecting ducts of the kidney to promote free water retention.
   2. Oxytocin mediates uterine contraction during labor and release of breast milk (let-down) in lactating mothers.

II. CENTRAL DIABETES INSIPIDUS

A. ADH deficiency
B. Due to hypothalamic or posterior pituitary pathology (e.g., tumor, trauma, infection, or inflammation)
C. Clinical features are based on loss of free water.
   1. Polyuria and polydipsia with risk of life-threatening dehydration
   2. Hypernatremia and high serum osmolality
   3. Low urine osmolality and specific gravity
D. Water deprivation test fails to increase urine osmolality (useful for diagnosis).
E. Treatment is desmopressin (ADH analog).

III. NEPHROGENIC DIABETES INSIPIDUS

A. Impaired renal response to ADH
B. Due to inherited mutations or drugs (e.g., lithium and demeclocycline)
C. Clinical features are similar to central diabetes insipidus, but there is no response to desmopressin.

IV. SYNDROME OF INAPPROPRIATE ADH (SIADH) SECRETION

A. Excessive ADH secretion
B. Most often due to ectopic production (e.g., small cell carcinoma of the lung); other causes include CNS trauma, pulmonary infection, and drugs (e.g., cyclophosphamide).
C. Clinical features are based on retention of free water.
   1. Hyponatremia and low serum osmolality
   2. Mental status changes and seizures—Hyponatremia leads to neuronal swelling and cerebral edema.
D. Treatment is free water restriction or demeclocycline.

THYROID GLAND

I. THYROGLOSSAL DUCT CYST

A. Cystic dilation of thyroglossal duct remnant
   1. Thyroid develops at the base of tongue and then travels along the thyroglossal duct to the anterior neck.
   2. Thyroglossal duct normally involutes; a persistent duct, however, may undergo cystic dilation.
B. Presents as an anterior neck mass

II. **LINGUAL THYROID**
- A. Persistence of thyroid tissue at the base of tongue
- B. Presents as a base of tongue mass

HYPERTHYROIDISM

I. **BASIC PRINCIPLES**
- A. Increased level of circulating thyroid hormone
  1. Increases basal metabolic rate (due to increased synthesis of Na^+-K^+ ATPase)
  2. Increases sympathetic nervous system activity (due to increased expression of β_1-adrenergic receptors)
- B. Clinical features include
  1. Weight loss despite increased appetite
  2. Heat intolerance and sweating
  3. Tachycardia with increased cardiac output
  4. Arrhythmia (e.g., atrial fibrillation), especially in the elderly
  5. Tremor, anxiety, insomnia, and heightened emotions
  6. Staring gaze with lid lag
  7. Diarrhea with malabsorption
  8. Oligomenorrhea
  9. Bone resorption with hypercalcemia (risk for osteoporosis)
  10. Decreased muscle mass with weakness
  11. Hypocholesterolemia
  12. Hyperglycemia (due to gluconeogenesis and glycogenolysis)

II. **GRAVES DISEASE**
- A. Autoantibody (IgG) that stimulates TSH receptor (type II hypersensitivity)
- B. Leads to increased synthesis and release of thyroid hormone
  1. Most common cause of hyperthyroidism
  2. Classically occurs in women of childbearing age (20–40 years)
- C. Clinical features include
  1. Hyperthyroidism
  2. Diffuse goiter—Constant TSH stimulation leads to thyroid hyperplasia and hypertrophy (Fig. 15.1A).
  3. Exophthalmos and pretibial myxedema
     - i. Fibroblasts behind the orbit and overlying the shin express the TSH receptor.
     - ii. TSH activation results in glycosaminoglycan (chondroitin sulfate and hyaluronic acid) buildup, inflammation, fibrosis, and edema leading to exophthalmos and pretibial myxedema.

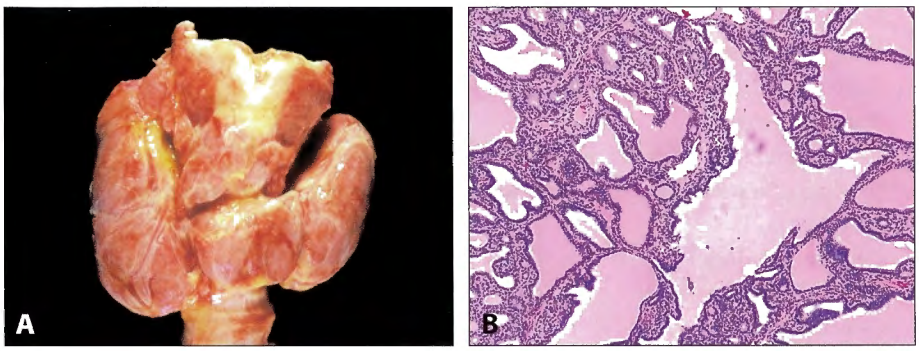


Fig. 15.1 Graves disease. **A**, Diffuse goiter. **B**, Microscopic appearance. (A, Courtesy of Ed Uthman, MD)

D. Irregular follicles with scalloped colloid and chronic inflammation are seen on histology (Fig. 15.1B).
E. Laboratory findings include
   1. ↑ total and free T_4; ↓ TSH (free T_3 downregulates TRH receptors in the anterior pituitary to decrease TSH release)
   2. Hypocholesterolemia
   3. Increased serum glucose
F. Treatment involves β-blockers, thioamide, and radioiodine ablation.
G. Thyroid storm is a potentially fatal complication.
   1. Due to elevated catecholamines and massive hormone excess, usually in response to stress (e.g., surgery or childbirth)
   2. Presents as arrhythmia, hyperthermia, and vomiting with hypovolemic shock
   3. Treatment is propylthiouracil (PTU), β-blockers, and steroids.
      i. PTU inhibits peroxidase-mediated oxidation, organification, and coupling steps of thyroid hormone synthesis, as well as peripheral conversion of T_4 to T_3.

III. MULTINODULAR GOITER

A. Enlarged thyroid gland with multiple nodules (Fig. 15.2)
B. Due to relative iodine deficiency
C. Usually nontoxic (euthyroid)
D. Rarely, regions become TSH-independent leading to T_4 release and hyperthyroidism ('toxic goiter').

HYPOTHYROIDISM

I. CRETINISM

A. Hypothyroidism in neonates and infants
B. Characterized by mental retardation, short stature with skeletal abnormalities, coarse facial features, enlarged tongue, and umbilical hernia
   1. Thyroid hormone is required for normal brain and skeletal development.
C. Causes include maternal hypothyroidism during early pregnancy, thyroid agenesis, dyshormonogenetic goiter, and iodine deficiency.
   1. Dyshormonogenetic goiter is due to a congenital defect in thyroid hormone production; most commonly involves thyroid peroxidase

II. MYXEDEMA

A. Hypothyroidism in older children or adults
B. Clinical features are based on decreased basal metabolic rate and decreased sympathetic nervous system activity.
   1. Myxedema—accumulation of glycosaminoglycans in the skin and soft tissue; results in a deepening of voice and large tongue
   2. Weight gain despite normal appetite
   3. Slowing of mental activity
   4. Muscle weakness
   5. Cold intolerance with decreased sweating
   6. Bradycardia with decreased cardiac output, leading to shortness of breath and fatigue
   7. Oligomenorrhea
   8. Hypercholesterolemia
   9. Constipation
C. Most common causes are iodine deficiency and Hashimoto thyroiditis; other causes include drugs (e.g., lithium) and surgical removal or radioablation of the thyroid.

THYROIDITIS

I. HASHIMOTO THYROIDITIS

A. Autoimmune destruction of the thyroid gland; associated with HLA-DR5
   1. Most common cause of hypothyroidism in regions where iodine levels are adequate

B. Clinical features
   1. Initially may present as hyperthyroidism (due to follicle damage)
   2. Progresses to hypothyroidism; ↓ T_4 and ↑ TSH
   3. Antithyroglobulin and antithyroid peroxidase antibodies are often present (sign of thyroid damage).

C. Chronic inflammation with germinal centers and Hurthle cells (eosinophilic metaplasia of cells that line follicles) is seen on histology (Fig. 15.3).

D. Increased risk for B-cell (marginal zone) lymphoma; presents as an enlarging thyroid gland late in disease course

II. SUBACUTE GRANULOMATOUS (DE QUERVAIN) THYROIDITIS

A. Granulomatous thyroiditis that follows a viral infection

B. Presents as a tender thyroid with transient hyperthyroidism

C. Self-limited; rarely (15% of cases) may progress to hypothyroidism

III. RIEDEL FIBROSING THYROIDITIS

A. Chronic inflammation with extensive fibrosis of the thyroid gland

B. Presents as hypothyroidism with a 'hard as wood,' nontender thyroid gland

C. Fibrosis may extend to involve local structures (e.g., airway).
   1. Clinically mimics anaplastic carcinoma, but patients are younger (40s), and malignant cells are absent

THYROID NEOPLASIA

I. BASIC PRINCIPLES

A. Usually presents as a distinct, solitary nodule
   1. Thyroid nodules are more likely to be benign than malignant.

B. ^{131}I radioactive uptake studies are useful to further characterize nodules.
   1. Increased uptake ('hot' nodule) is seen in Graves disease or nodular goiter.
   2. Decreased uptake ('cold' nodule) is seen in adenoma and carcinoma; often warrants biopsy

C. Biopsy is performed by fine needle aspiration (FNA).

II. FOLLICULAR ADENOMA

A. Benign proliferation of follicles surrounded by a fibrous capsule (Fig. 15.4)

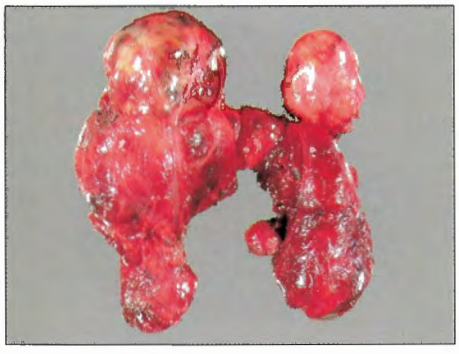


Fig. 15.2 Multinodular goiter. (Courtesy of Jamie Steinmetz, MD)

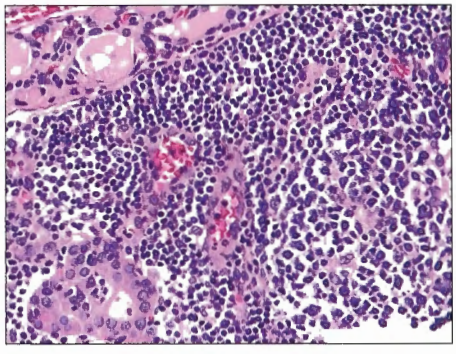


Fig. 15.3 Hashimoto thyroiditis.

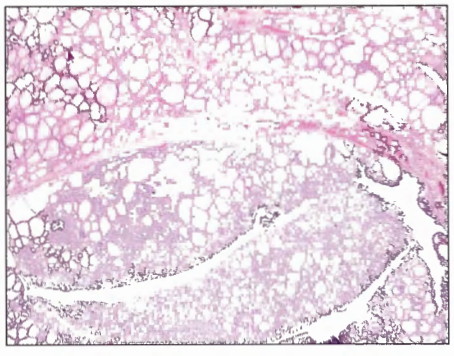


Fig. 15.4 Follicular adenoma.

B. Usually nonfunctional; less commonly, may secrete thyroid hormone

III. PAPILLARY CARCINOMA

A. Most common type of thyroid carcinoma (80% of cases)
B. Exposure to ionizing radiation in childhood is a major risk factor.
C. Comprised of papillae lined by cells with clear, 'Orphan Annie eye' nuclei and nuclear grooves (Fig. 15.5A); papillae are often associated with psammoma bodies (Fig. 15.5B).
D. Often spreads to cervical (neck) lymph nodes, but prognosis is excellent (10-year survival > 95%)

IV. FOLLICULAR CARCINOMA

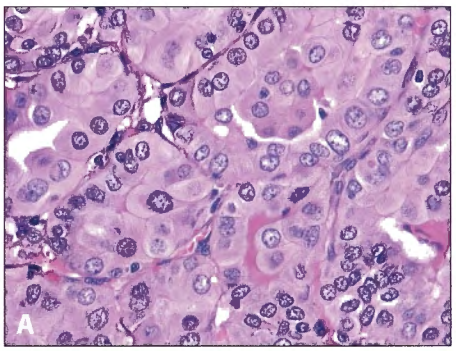
A. Malignant proliferation of follicles surrounded by a fibrous capsule with invasion through the capsule (Fig. 15.6)
   1. Invasion through the capsule helps distinguish follicular carcinoma from follicular adenoma.
   2. Entire capsule must be examined microscopically.
   3. FNA only examines cells and not the capsule; hence, a distinction between follicular adenoma and follicular carcinoma cannot be made by FNA.
B. Metastasis generally occurs hematogenously.

V. MEDULLARY CARCINOMA

A. Malignant proliferation of parafollicular C cells; comprises 5% of thyroid carcinomas
   1. C cells are neuroendocrine cells that secrete calcitonin.
   2. Calcitonin lowers serum calcium by increasing renal calcium excretion but is inactive at normal physiologic levels.
   3. High levels of calcitonin produced by tumor may lead to hypocalcemia.
   4. Calcitonin often deposits within the tumor as amyloid.
B. Biopsy reveals sheets of malignant cells in an amyloid stroma (Fig. 15.7).
C. Familial cases are often due to multiple endocrine neoplasia (MEN) 2A and 2B, which are associated with mutations in the *RET* oncogene.
   1. MEN 2 results in medullary carcinoma, pheochromocytoma, and parathyroid adenomas (2A) or ganglioneuromas of the oral mucosa (2B).
   2. Detection of the *RET* mutation warrants prophylactic thyroidectomy.

VI. ANAPLASTIC CARCINOMA

A. Undifferentiated malignant tumor of the thyroid (Fig. 15.8); usually seen in elderly
B. Often invades local structures, leading to dysphagia or respiratory compromise
C. Poor prognosis



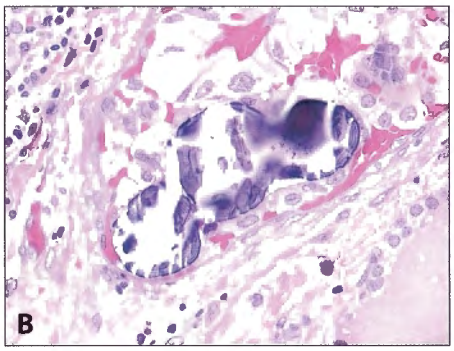


Fig. 15.5 Papillary carcinoma. **A**, Nuclear features. **B**, Psammoma bodies.

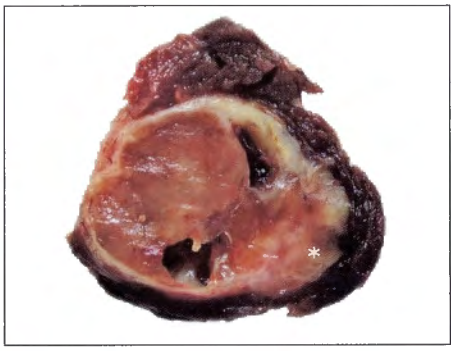


Fig. 15.6 Follicular carcinoma. (Courtesy of Bulent Celasun, MD)

PARATHYROID GLANDS

I. BASIC PRINCIPLES

A. Chief cells regulate serum free (ionized) calcium via parathyroid hormone (PTH) secretion, which
   1. Increases bone osteoclast activity, releasing calcium and phosphate
   2. Increases small bowel absorption of calcium and phosphate (indirectly by activating vitamin D)
   3. Increases renal calcium reabsorption (distal tubule) and decreases phosphate reabsorption (proximal tubule)

B. Increased serum ionized calcium levels provide negative feedback to decrease PTH secretion.

II. PRIMARY HYPERPARATHYROIDISM

A. Excess PTH due to a disorder of the parathyroid gland itself

B. Most common cause is parathyroid adenoma (>80% of cases); sporadic parathyroid hyperplasia and parathyroid carcinoma are less common causes.

C. Parathyroid adenoma is a benign neoplasm, usually involving one gland.
   1. Most often results in asymptomatic hypercalcemia; however, may present with consequences of increased PTH and hypercalcemia such as
      i. Nephrolithiasis (calcium oxalate stones)
      ii. Nephrocalcinosis—metastatic calcification of renal tubules (Fig. 15.9), potentially leading to renal insufficiency and polyuria
      iii. CNS disturbances (e.g., depression and seizures)
      iv. Constipation, peptic ulcer disease, and acute pancreatitis
      v. Osteitis fibrosa cystica—resorption of bone leading to fibrosis and cystic spaces (Fig. 15.10)
   2. Laboratory findings include ↑ serum PTH, ↑ serum calcium, ↓ serum phosphate, ↑ urinary cAMP, and ↑ serum alkaline phosphatase.
   3. Treatment involves surgical removal of the affected gland.

III. SECONDARY HYPERPARATHYROIDISM

A. Excess production of PTH due to a disease process extrinsic to the parathyroid gland

B. Most common cause is chronic renal failure.
   1. Renal insufficiency leads to decreased phosphate excretion.
   2. ↑ serum phosphate binds free calcium.
   3. ↓ free calcium stimulates all four parathyroid glands.
   4. ↑ PTH leads to bone resorption (contributing to renal osteodystrophy).
   5. Lab findings include ↑ PTH, ↓ serum calcium, ↑ serum phosphate, and ↑ alkaline phosphatase.

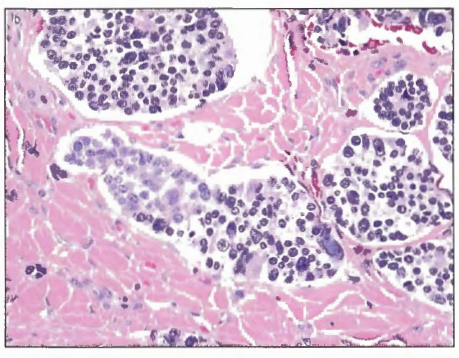


Fig. 15.7 Medullary carcinoma.

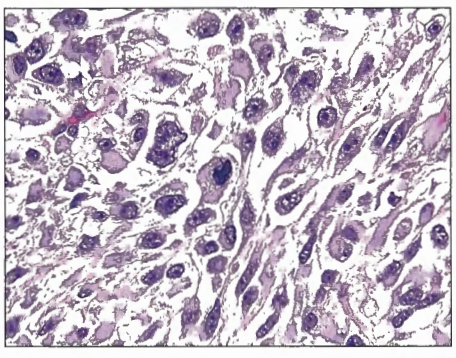


Fig. 15.8 Anaplastic carcinoma.

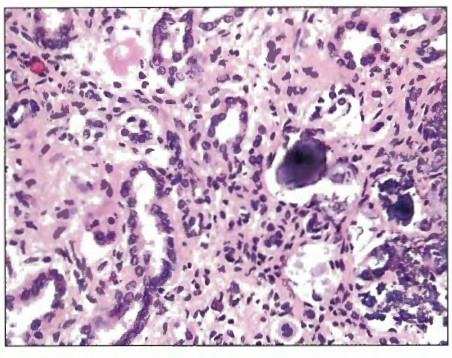


Fig. 15.9 Nephrocalcinosis.

IV. HYPOPARATHYROIDISM

A. Low PTH
B. Causes include autoimmune damage to the parathyroids, surgical excision, and DiGeorge syndrome
C. Presents with symptoms related to low serum calcium
   1. Numbness and tingling (particularly circumoral)
   2. Muscle spasms (tetany)—may be elicited with filling of a blood pressure cuff (Trousseau sign) or tapping on the facial nerve (Chvostek sign)
D. Labs reveal ↓ PTH levels and ↓ serum calcium.
E. Pseudohypoparathyroidism is due to end-organ resistance to PTH.
   1. Labs reveal hypocalcemia with ↑ PTH levels.
   2. Autosomal dominant form is associated with short stature and short 4th and 5th digits.

ENDOCRINE PANCREAS

I. BASIC PRINCIPLES

A. Composed of clusters of cells termed islets of Langerhans (Fig. 15.11)
B. A single islet consists of multiple cell types, each producing one type of hormone.
C. Insulin is secreted by beta cells, which lie in the center of the islets.
   1. Major anabolic hormone; upregulates insulin-dependent glucose transporter protein (GLUT4) on skeletal muscle and adipose tissue (glucose uptake by GLUT4 decreases serum glucose)
   2. Increased glucose uptake by tissues leads to increased glycogen synthesis, protein synthesis, and lipogenesis.
D. Glucagon is secreted by alpha cells; it opposes insulin in order to increase blood glucose levels (e.g., in states of fasting) via glycogenolysis and lipolysis.

II. TYPE 1 DIABETES MELLITUS

A. Insulin deficiency leading to a metabolic disorder characterized by hyperglycemia
B. Due to autoimmune destruction of beta cells by T lymphocytes
   1. Characterized by inflammation of islets
   2. Associated with HLA-DR3 and HLA-DR4
   3. Autoantibodies against insulin are often present (sign of damage) and may be seen years before clinical disease develops.
C. Manifests in childhood with clinical features of insulin deficiency
   1. High serum glucose—Lack of insulin leads to decreased glucose uptake by fat and skeletal muscle.

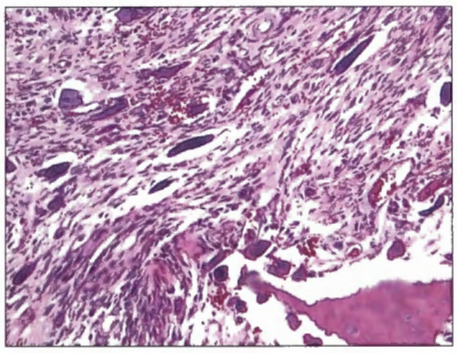


Fig. 15.10 Osteitis fibrosa cystica.

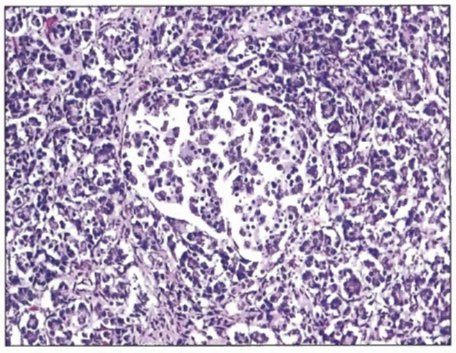


Fig. 15.11 Islets of Langerhans.

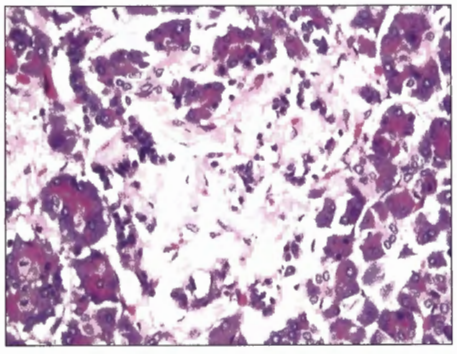


Fig. 15.12 Amyloid in islets, type II DM.

2. Weight loss, low muscle mass, and polyphagia—Unopposed glucagon leads to gluconeogenesis, glycogenolysis and lipolysis, which further exacerbates hyperglycemia.
3. Polyuria, polydipsia, and glycosuria—Hyperglycemia exceeds renal ability to resorb glucose; excess filtered glucose leads to osmotic diuresis.
4. Treatment involves lifelong insulin.

D. Risk for diabetic ketoacidosis
1. Characterized by excessive serum ketones
2. Often arises with stress (e.g., infection); epinephrine stimulates glucagon secretion increasing lipolysis (along with gluconeogenesis and glycogenolysis).
   i. Increased lipolysis leads to increased free fatty acids (FFAs).
   ii. Liver converts FFAs to ketone bodies (β-hydroxybutyric acid and acetoacetic acid).
3. Results in hyperglycemia (> 300 mg/dL), anion gap metabolic acidosis, and hyperkalemia
4. Presents with Kussmaul respirations, dehydration, nausea, vomiting, mental status changes, and fruity smelling breath (due to acetone)
5. Treatment is fluids (corrects dehydration from polyuria), insulin, and replacement of electrolytes (e.g., potassium).

III. TYPE 2 DIABETES MELLITUS

A. End-organ insulin resistance leading to a metabolic disorder characterized by hyperglycemia
1. Most common type of diabetes (90% of cases); affects 5–10% of the US population
2. Incidence is rising.

B. Arises in middle-aged, obese adults
1. Obesity leads to decreased numbers of insulin receptors.
2. Strong genetic predisposition exists.

C. Insulin levels are increased early in disease, but later, insulin deficiency develops due to beta cell exhaustion; histology reveals amyloid deposition in the islets (Fig. 15.12).

D. Clinical features include polyuria, polydipsia, and hyperglycemia, but disease is often clinically silent.

E. Diagnosis is made by measuring glucose levels (normal is 70–120 mg/dL).
1. Random glucose > 200 mg/dL
2. Fasting glucose > 126 mg/dL
3. Glucose tolerance test with a serum glucose level > 200 mg/dL two hours after glucose loading

F. Treatment involves weight loss (diet and exercise) initially; may require drug therapy to counter insulin resistance (e.g., sulfonylureas or metformin) or exogenous insulin after exhaustion of beta cells

G. Risk for hyperosmolar non-ketotic coma
1. High glucose (> 500 mg/dL) leads to life-threatening diuresis with hypotension and coma.
2. Ketones are absent due to small amounts of circulating insulin.

IV. LONG-TERM CONSEQUENCES OF DIABETES

A. Nonenzymatic glycosylation (NEG) of vascular basement membranes
1. NEG of large- and medium-sized vessels leads to atherosclerosis and its resultant complications.
   i. Cardiovascular disease is the leading cause of death among diabetics.
   ii. Peripheral vascular disease in diabetics is the leading cause of nontraumatic amputations.

2. NEG of small vessels (arterioles) leads to hyaline arteriolosclerosis (Fig. 15.13A).
   i. Involvement of renal arterioles leads to glomerulosclerosis, resulting in small, scarred kidneys with a granular surface (Fig. 15.13B).
   ii. Preferential involvement of efferent arterioles leads to glomerular hyperfiltration injury with microalbuminuria that eventually progresses to nephrotic syndrome; characterized by Kimmelstiel-Wilson nodules in glomeruli
3. NEG of hemoglobin produces glycated hemoglobin (HbA_{1C}), a marker of glycemic control.

B. Osmotic damage
1. Glucose freely enters into Schwann cells (which myelinate peripheral nerves), pericytes of retinal blood vessels, and the lens.
2. Aldose reductase converts glucose to sorbitol, resulting in osmotic damage.
3. Leads to peripheral neuropathy, impotence, blindness, and cataracts; diabetes is the leading cause of blindness in the developed world.

V. PANCREATIC ENDOCRINE NEOPLASMS

A. Tumors of islet cells; account for < 5% of pancreatic neoplasms.
1. Often a component of MEN 1 along with parathyroid hyperplasia and pituitary adenomas

B. Insulinomas present as episodic hypoglycemia with mental status changes that are relieved by administration of glucose.
1. Diagnosed by ↓ serum glucose levels (usually < 50 mg/dL), ↑ insulin, and ↑ C-peptide

C. Gastrinomas present as treatment-resistant peptic ulcers (Zollinger-Ellison syndrome); ulcers may be multiple and can extend into the jejunum.

D. Somatostatinomas present as achlorhydria (due to inhibition of gastrin) and cholelithiasis with steatorrhea (due to inhibition of cholecystokinin).

E. VIPomas secrete excessive vasoactive intestinal peptide leading to watery diarrhea, hypokalemia, and achlorhydria.

ADRENAL CORTEX

I. BASIC PRINCIPLES

A. Composed of three layers; each secretes predominantly one class of hormones.
1. Glomerulosa produces mineralocorticoids (e.g., aldosterone).
2. Fasciculata produces glucocorticoids (e.g., cortisol).
3. Reticularis produces weak androgens (e.g., DHEA).

B. Cortical hormones are derived from cholesterol.

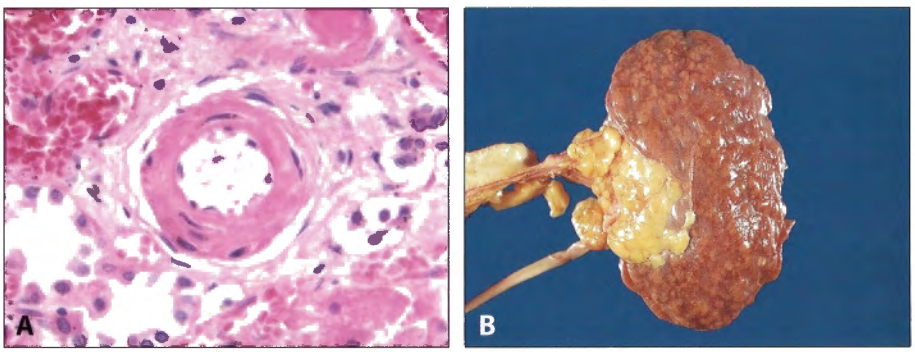


Fig. 15.13 Complications of diabetes. **A**, Hyaline arteriolosclerosis. **B**, Glomerulosclerosis.

1. Sequential enzymatic modification produces mineralocorticoids, glucocorticoids, and androgens (Fig. 15.14).
2. Each layer secretes distinct hormones based on enzymes present in that layer.

II. HYPERALDOSTERONISM

A. Excess aldosterone

B. Classically presents as HTN, hypokalemia, and metabolic alkalosis
   1. Aldosterone increases absorption of sodium and secretion of potassium and hydrogen ions in the distal tubule and collecting duct.
   2. Increased sodium expands plasma volume leading to HTN.

C. Primary hyperaldosteronism is most commonly due to bilateral adrenal hyperplasia (60%, Fig. 15.15) or adrenal adenoma (40%, Conn syndrome, Fig. 15.16); adrenal carcinoma is rare.
   1. CT is useful to determine pathology
   2. Treatment for bilateral adrenal hyperplasia is mineralocorticoid receptor antagonist (e.g., spironolactone or eplerenone); adenoma and carcinoma are surgically resected.

D. Secondary hyperaldosteronism arises with activation of the renin-angiotensin system (e.g., renovascular hypertension or CHF).

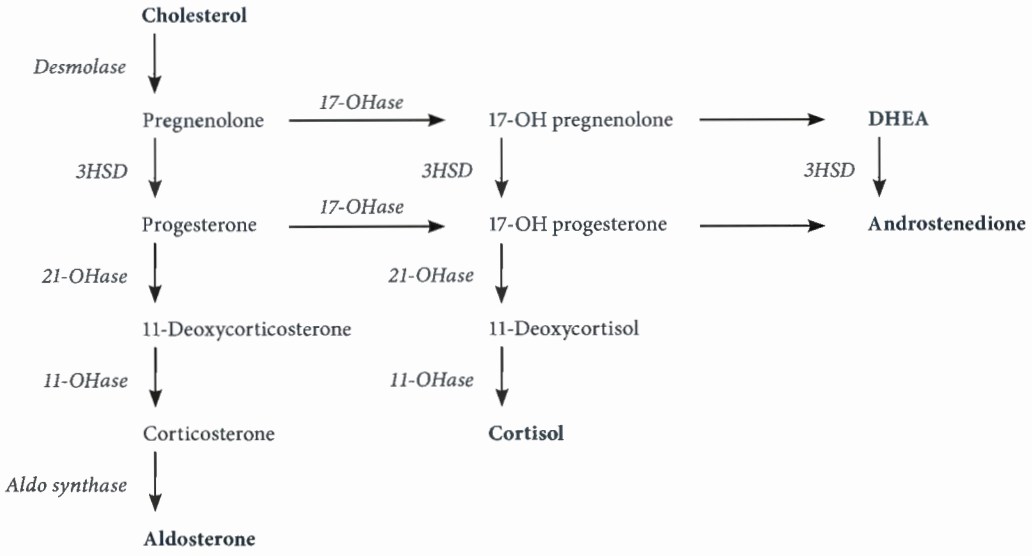


Fig. 15.14 Steroidogenesis, adrenal cortex.

Fig. 15.15 Adrenal hyperplasia.

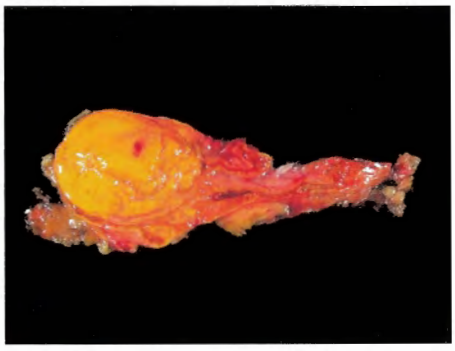


Fig. 15.16 Adrenal adenoma.

E. Primary and secondary hyperaldosteronism are distinguished by plasma renin and edema
   1. Primary is characterized by low renin and no edema (aldosterone escape).
   2. Secondary is characterized by high renin; edema is often present.

F. Glucocorticoid-remediable aldosteronism (GRA) leads to familial hyperaldosteronism
   1. Aberrant expression of aldosterone synthase in the fasciculata due to genetic mutation; autosomal dominant
   2. Classically presents as child with HTN and hypokalemia; aldosterone is high and renin is low.
   3. Responds to dexamethasone; confirmed with genetic testing

G. Liddle syndrome mimics hyperaldosteronism.
   1. Decreased degradation of sodium channels in collecting tubules due to genetic mutation; autosomal dominant
   2. Presents as child with HTN, hypokalemia, and metabolic alkalosis, but with low aldosterone and low renin
   3. Diagnosed by genetic testing
   4. Treatment is potassium-sparing diuretics (e.g., amiloride or triamterene), which block tubular sodium channels; spironolactone is not effective.

H. Syndrome of apparent mineralocorticoid excess (SAME) also mimics hyperaldosteronism.
   1. 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) deficiency allows cortisol to activate renal aldosterone receptors; autosomal recessive
   2. Presents as child with HTN, hypokalemia, and metabolic alkalosis, but with low aldosterone and low renin
   3. Diagnosed by low urinary free cortisone and genetic testing
   4. May also arise with licorice (glycyrrhetinic acid), which blocks 11β-HSD2

III. HYPERCORTISOLISM (CUSHING SYNDROME)

A. Excess cortisol

B. Clinical features include
   1. Muscle weakness with thin extremities—Cortisol breaks down muscle to produce amino acids for gluconeogenesis.
   2. Moon facies, buffalo hump, and truncal obesity—High insulin (due to high glucose) increases storage of fat centrally.
   3. Abdominal striae—Impaired collagen synthesis results in thinning of skin
   4. HTN often with hypokalemia and metabolic alkalosis
      i. High cortisol increases sensitivity of peripheral vessels to catecholamines.
      ii. At very high levels, cortisol cross-reacts with mineralocorticoid receptors (aldosterone is not increased).
   5. Osteoporosis
   6. Immune suppression

C. Diagnosis is based on 24-hour urine cortisol level (increased), late night salivary cortisol level (increased), and low-dose dexamethasone suppression test.
   1. Low-dose dexamethasone suppresses cortisol in normal individuals but fails to suppress cortisol in all causes of Cushing syndrome.

D. Plasma ACTH distinguishes ACTH-dependent causes of Cushing syndrome from ACTH-independent causes (table 15.1).
   1. If ACTH-independent, next step is CT to look for an adrenal lesion.
   2. If ACTH-dependent, next step is high-dose dexamethasone test.

E. High-dose dexamethasone suppresses ACTH production by a pituitary adenoma (serum cortisol is lowered) but does not suppress ectopic ACTH production (serum cortisol remains high).

Table 15.1 Cushing Syndrome

CAUSE	ACTH	HIGH-DOSE DEXAMETHASONE	IMAGING	TREATMENT
Exogenous glucocorticoids (most common iatrogenic cause)	Low	N/A	N/A	Tapering of steroids, if possible
ACTH-secreting pituitary adenoma (70%, Cushing disease)	High (↑); androgen excess may be present.	Suppression	Pituitary adenoma	Transsphenoidal resection of pituitary adenoma; bilateral adrenalectomy in refractory cases can lead to enlargement of pituitary adenoma, resulting in hyperpigmentation, headaches, and bitemporal hemianopsia (Nelson syndrome)
Ectopic ACTH secretion (15%)	High (↑↑); androgen excess and hyperpigmentation may be present.	No suppression	Ectopic source of ACTH (e.g., small cell carcinoma or carcinoid)	Resection of ectopic source
Primary adrenal adenoma (10%), hyperplasia, or carcinoma	Low	N/A	Adenoma/ carcinoma with contralateral atrophy or bilateral *nodular* hyperplasia	Resection of adenoma/carcinoma or bilateral resection of hyperplasia with hormone replacement

F. Treatment generally involves surgical resection
   1. Ketoconazole or metyrapone useful if surgery is not an option

IV. CONGENITAL ADRENAL HYPERPLASIA

A. Due to enzymatic defects in cortisol production; autosomal recessive
   1. High ACTH (decreased negative feedback) leads to bilateral adrenal hyperplasia.
   2. Mineralocorticoids and androgens may be increased or decreased depending on the enzyme defect.

B. 21-hydroxylase deficiency is the most common cause (90% of cases).
   1. Aldosterone and cortisol are decreased; steroidogenesis is shunted towards androgens.
   2. Classic form presents in neonates as hyponatremia and hyperkalemia with life-threatening hypotension (salt-wasting type); females have clitoral enlargement (genital ambiguity).
   3. Nonclassic form presents later in life with androgen excess leading to precocious puberty (males) or hirsutism with menstrual irregularities (females).

C. 11-hydroxylase deficiency also leads to androgen excess, but weak mineralocorticoids (DOC) are increased.
   1. Deoxycorticosterone (DOC) leads to HTN (sodium retention) with mild hypokalemia; renin and aldosterone are low.
   2. Clitoral enlargement is seen in females

D. 17-hydroxylase deficiency leads to decreased cortisol and androgens.
   1. Weak mineralocorticoids (DOC) are increased leading to HTN with mild hypokalemia; renin and aldosterone are low.
   2. Decreased androgens lead to primary amenorrhea and lack of pubic hair (females) or ambiguous genitalia with undescended testes (males).

E. Newborn screening for CAH via serum 17-hydroxyprogesterone is routine

1. Increased in 21- and 11-hydroxylase deficiency
2. Decreased in 17-hydroxylase deficiency

F. Treatment for CAH is glucocorticoids; mineralocorticoids (21-hydroxylase deficiency) or sex steroids (17-hydroxylase deficiency) given as necessary.

V. ADRENAL INSUFFICIENCY

A. Deficiency of adrenal hormones

B. Acute insufficiency presents as weakness and shock. Causes include

1. Abrupt withdrawal of glucocorticoids
2. Treatment of Cushing syndrome
3. Waterhouse-Friderichsen syndrome—hemorrhagic necrosis of the adrenal glands (Fig. 15.17), classically due to sepsis and DIC in young children with *Neisseria meningitidis* infection

C. Chronic insufficiency (Addison disease) presents with vague, progressive symptoms such as hypotension, weakness, fatigue, nausea, vomiting, and weight loss.

D. Addison disease most often arises with progressive adrenal damage.

1. Common causes include autoimmune destruction (most common cause in the West), TB (most common cause in the developing world), and metastatic carcinoma (e.g., from lung).
2. Autoimmune adrenalitis can be a component of autoimmune polyendocrine syndromes

E. Addison disease may also arise with pituitary (secondary) or hypothalamic (tertiary) disease.

1. Hyperpigmentation (high ACTH) and hyperkalemia (low aldosterone) suggest primary adrenal insufficiency; secondary/tertiary insufficiency has no hyperpigmentation (low ACTH) and normal potassium (normal aldosterone).
2. Lack of ACTH response with metyrapone stimulation test supports a secondary or tertiary cause.
3. ACTH response with CRH stimulation test suggests hypothalamic (tertiary) disease.

F. Treatment is glucocorticoids and mineralocorticoids.

ADRENAL MEDULLA

I. BASIC PRINCIPLES

A. Composed of neural crest-derived chromaffin cells

B. Main physiologic source of catecholamines (epinephrine and norepinephrine)

II. PHEOCHROMOCYTOMA

A. Tumor of chromaffin cells (Fig. 15.18)

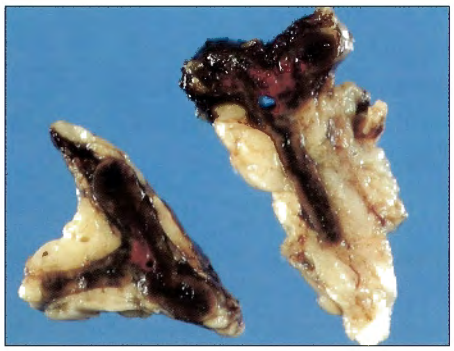


Fig. 15.17 Waterhouse-Friderichsen syndrome. (Courtesy of humpath.com)

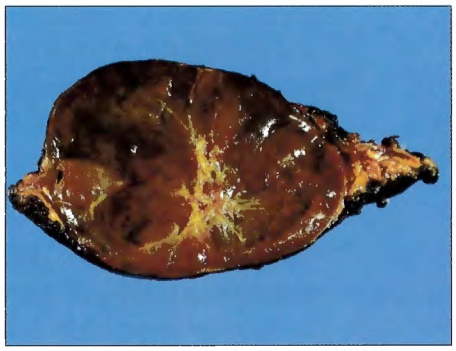


Fig. 15.18 Pheochromocytoma. (Courtesy of humpath.com)

B. Clinical features are due to episodic release of catecholamines.
   1. Episodic HTN, headaches, palpitations, tachycardia, and sweating
C. Diagnosed by increased metanephrines and catecholamines in serum and urine
D. Treatment is adrenalectomy.
   1. Catecholamines may leak into the bloodstream upon manipulation of the tumor.
   2. Phenoxybenzamine (irreversible α-blocker) *followed by* β-blocker is administered preoperatively to prevent a hypertensive crisis.
E. Often follows the 'rule of 10s:' 10% bilateral, 10% familial, 10% malignant, and 10% located outside of the adrenal medulla (e.g., organ of Zuckerkandl at the inferior mesenteric artery root or bladder wall)
   1. Malignancy is defined by metastatic spread; patients require long-term follow-up
F. Associated with MEN 2A and 2B (*RET*), von Hippel-Lindau disease, and neurofibromatosis type 1