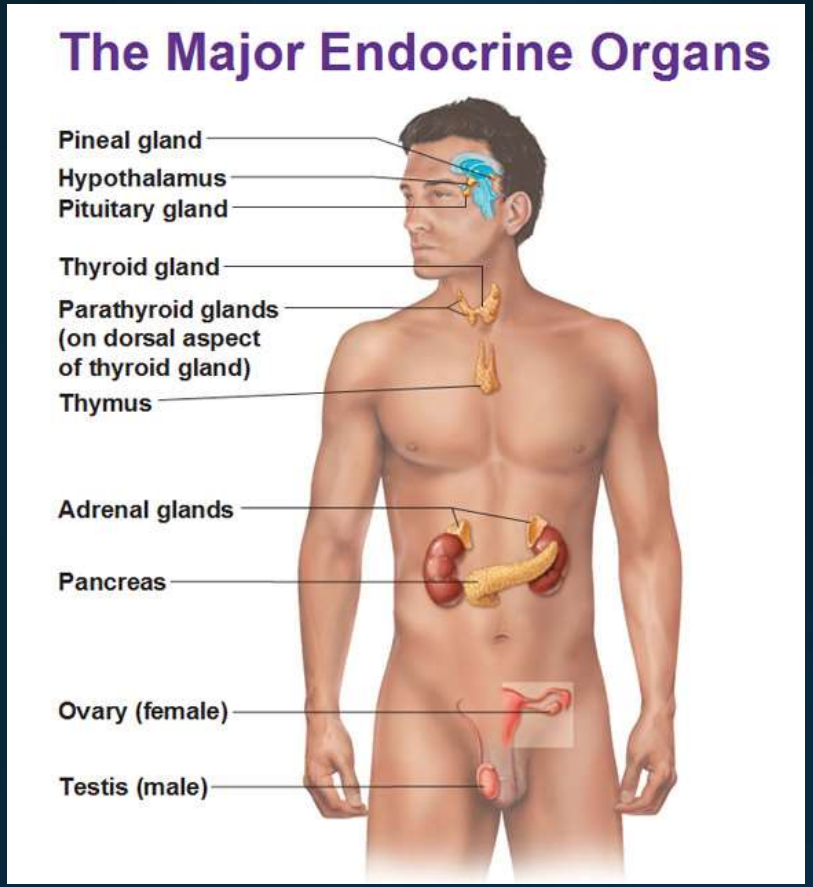
THE ENDOCRINE SYSTEM

ENDOCRINE ORGANS

- Pituitary gland
- Thyroid gland
- Parathyroid glands
- Endocrine pancreas
- Adrenal glands
- Pineal gland



Endocrine Signaling

- Hormones
  - Trigger biochemical signals upon interacting with cell-surface receptors
    - Peptide hormones
    - Small molecules
  - Diffuse across the plasma membrane and interact with intracellular receptors
- Feedback inhibition
- Diseases
  - Under- and over-production of hormones
  - Development of mass lesions

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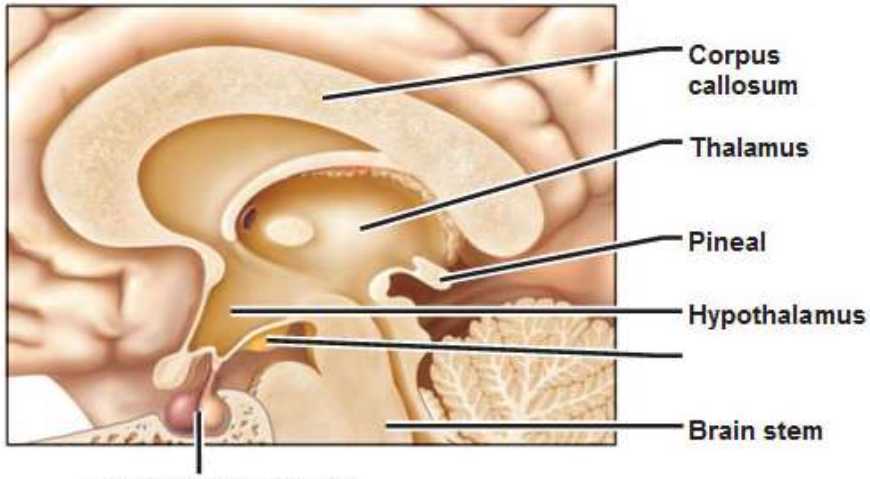
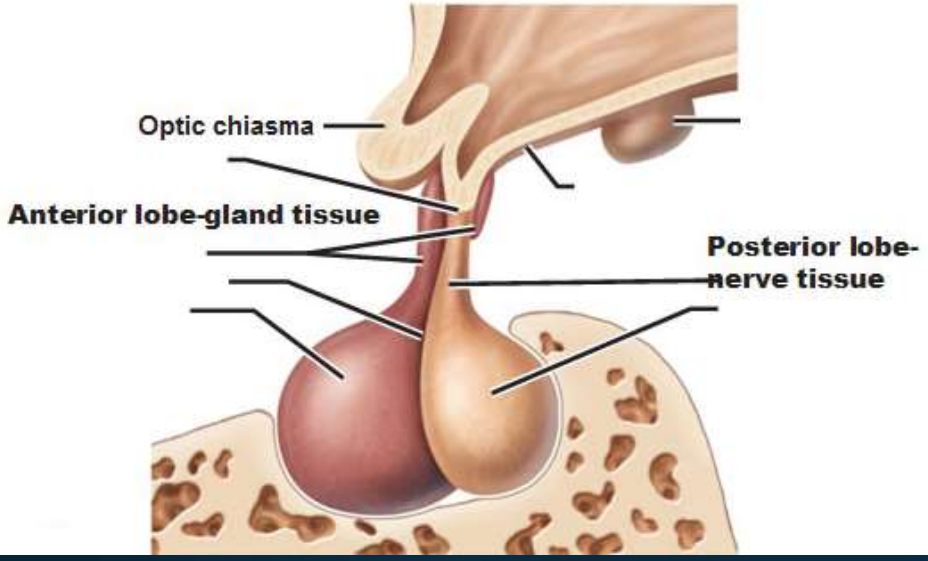
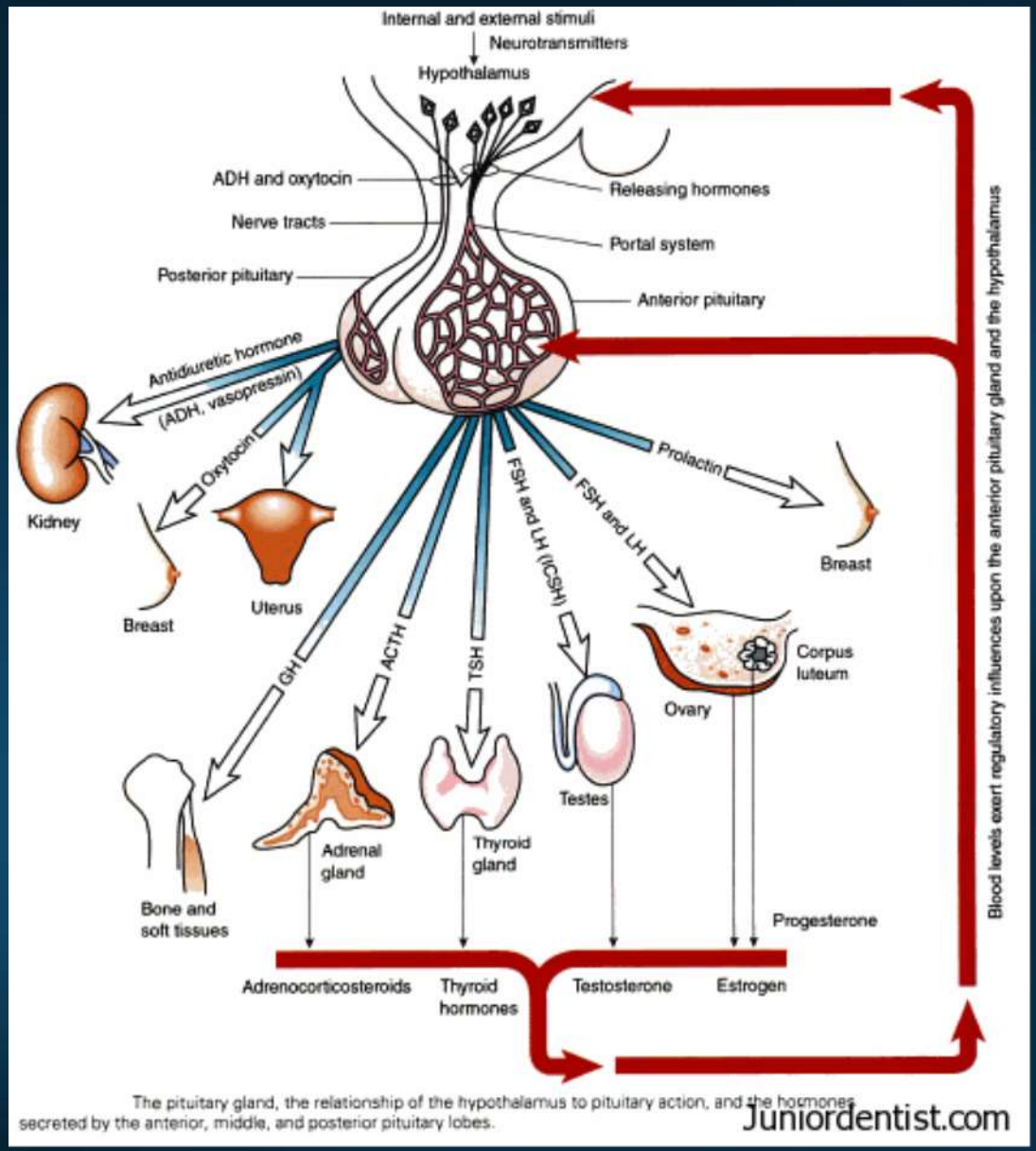
PITUITARY GLAND

- Small, bean-shaped; 1 cm; 0.5 gm
- Morphologic and functional components
  - Anterior lobe (adenohypophysis, 80%)
  - Posterior lobe (neurohypophysis)
- Cells of anterior pituitary
  - Somatotrophs – acidophil; GH
  - Lactotrophs – acidophil; prolactin
  - Corticotrophs – basophil; ACTH, POMC, MSH, endorphins and lipotropin
  - Thyrotrophs – basophil; TSH
  - Gonadotrophs – basophil; FSH and LH

The Pituitary Gland

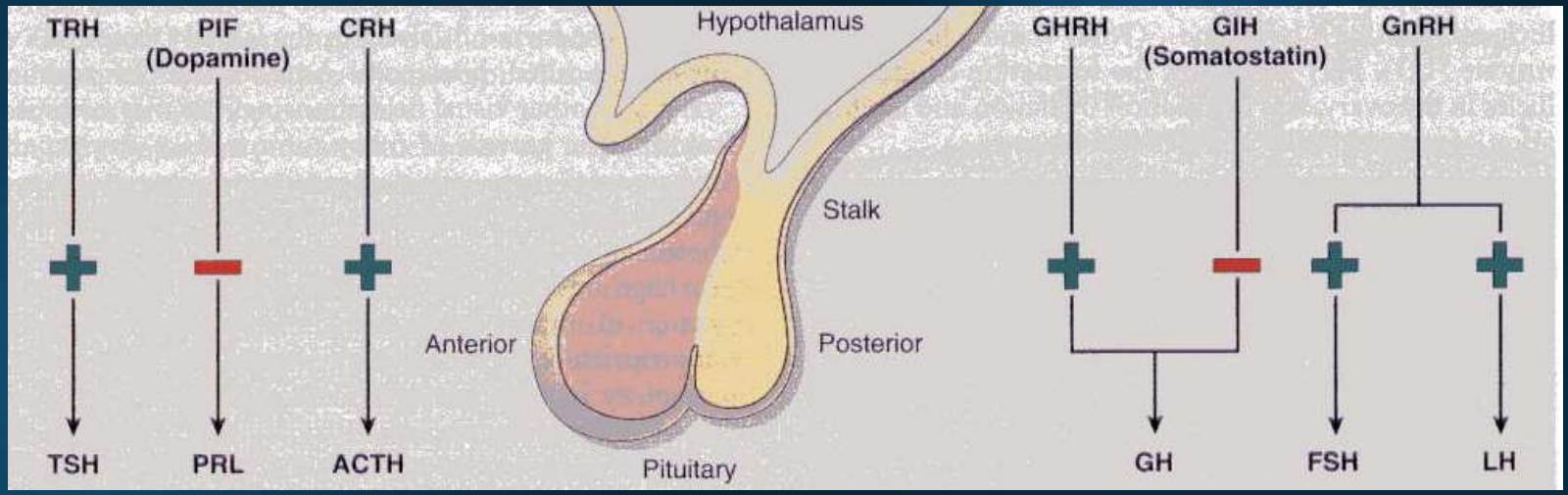






The pituitary gland, the relationship of the hypothalamus to pituitary action, and the hormones secreted by the anterior, middle, and posterior pituitary lobes.

ANTERIOR PITUITARY HORMONES



Pituitary Gland

- Cells of posterior pituitary
  - Modified glial cells (pituicytes) and axonal processes – ADH and oxytocin
- Diseases of posterior pituitary
  - Increased or decreased secretion of ADH

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Pituitary Gland: Clinical Manifestations

- 1. Hyperpituitarism

  Adenoma, hyper-plasia, and carci-noma of anterior pituitary; Secretion of hormones by nonpituitary tumors
- 2. Hypopituitarism

  Deficiency of trophic hormones due to ischemic injury, surgery or radiation and inflammatory reactions

3. Local mass effects – sellar expansion, bone erosion, & disruption of diaphragmatic sella→ visual defect, inc. ICP pituitary apoplexy

Pituitary Adenomas and Hyperpituitarism

- Most common cause of hyperpituitarism: adenomas
- Less common causes:

  1. hyperplasia and carcinomas of anterior pituitary
  2. secretion of hormones by some extrapituitary tumors
  3. hypothalamic disorders

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Classification of Pituitary Adenomas

- Microadenoma – less than 1 cm
- Macroadenoma – more than 1 cm
- Functional – hormone excess & S/Sx
- Silent – hormone production w/o S/Sx
- Hormone-negative – absent hormone
- Usually single cell type with single predominant hormone
- Classified based on hormone/s produced

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Classification of Pituitary Adenomas

Pituitary Cell Type	Hormone	Tumor Type	Associated Syndrome
Corticotroph	ACTH and other POMC-derived peptides	ACTH cell (corticotroph) adenoma	Cushing syndrome Nelson syndrome
Somatotroph	GH	GH cell (somatotroph) adenoma	Gigantism (children) Acromegaly (adults)
Lactotroph	Prolactin	Prolactin cell (lactotroph) adenoma	Galactorrhea and amenorrhea (in females) Sexual dysfunction, infertility
Mammosomatotroph	Prolactin, GH	Mammosomatotroph	Combined features of GH and prolactin excess
Thyrotroph	TSH	TSH cell (thyrotroph) adenoma	Hyperthyroidism
Gonadotroph	FSH, LH	Gonadotroph, "null cell," oncocytic adenomas	Hypogonadism, mass effects, and hypopituitarism

Adapted from Ezzat S, Asa SL: Mechanisms of disease: the pathogenesis of pituitary tumors. Nat Clin Prac Endocrinol Metab 2:200–230, 2006.

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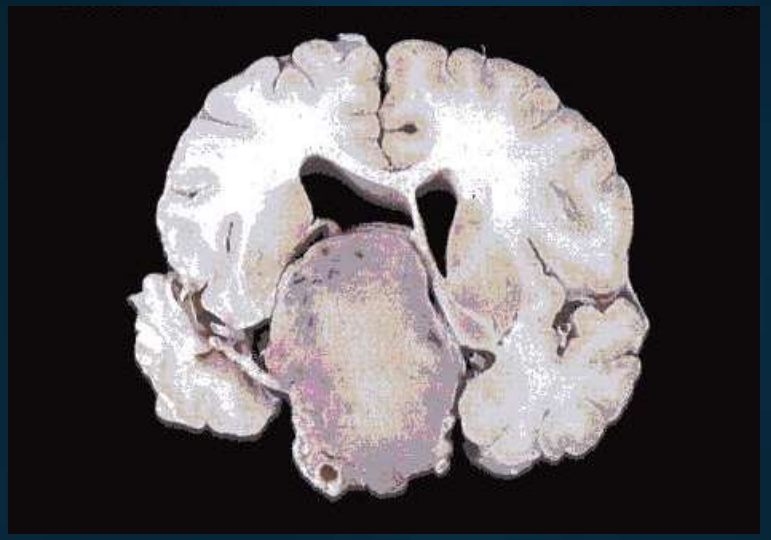
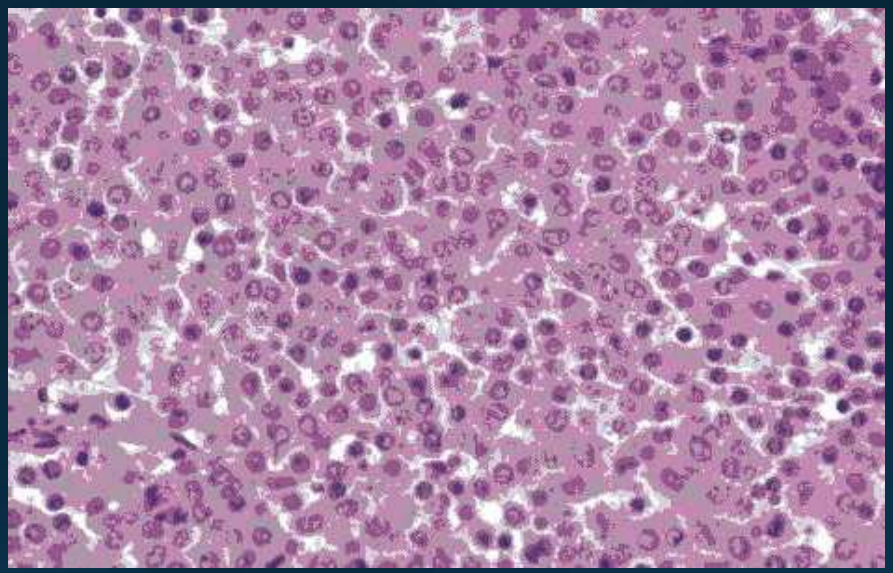
PITUITARY ADENOMA

- Morphology: soft, well-circumcribed; monomorphic, sparse reticulin framework; 30%, invasive adenoma
- Clinical course: endocrine abnormalities and mass effect





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PITUITARY ADENOMAS: PROLACTINOMAS

- Most frequent type, 30% of all clinically recognized pituitary adenomas
- Small to large, expansile tumors
- Weakly acidophilic or chromophobe cells
- Propensity for dystrophic calcification (psammoma bodies to pituitary stone)
- Char. by its efficiency & proportionality

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PROLACTINOMAS

- Prolactinemia → amenorrhea, galactorrhea, loss of libido, & infertility
- Physiologic prolactinemia: pregnancy
- Pathologic prolactinemia: lactotroph hyperplasia; stalk effect; drugs; estrogens; renal failure; hypothyroidism
- Treatment: surgery or bromocriptine

HYPOPITUITARISM

- Decreased secretion of pituitary hormones due to hypothalamus or pituitary diseases
- 75% of parenchyma lost or absent
- Hypopituitarism + posterior pituitary dysfunction (diabetes insipidus) → almost always hypothalamic origin
- Most cases due to destructive processes

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HYPOPITUITARISM: Other Mechanisms

- 1. Tumors and other tumor masses
- 2. Pituitary surgery or radiation
- 3. Pituitary apoplexy
- 3. Ischemic necrosis & Sheehan syndrome
- 4. Rathke cleft cyst
- 5. Empty sella syndrome
- 6. Genetic defects
- 7. Hypothalamic lesions: tumors, inflammatory disorders and infections

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HYPOPITUITARISM: Clinical Manifestations

- Depends on specific hormones lacking
- GH deficiency: pituitary dwarfism
- Gonadotropin (GnRH) deficiency: amenorrhea & infertility in women; decreased libido, impotence, and loss of pubic and axillary hair in men
- TSH deficiency: hypothyroidism
- ACTH deficiency: hypoadrenalism
- Prolactin deficiency: failure of lactation
- MSH deficiency: Pallor

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POSTERIOR PITUITARY SYNDROMES

- 1. Diabetes insipidus:
  - Characterized by polyuria
  - Causes: head trauma, tumors and inflammatory lesions & surgery of hypothalamus & pituitary; spontaneously
  - Central, if due to ADH deficiency, or nephrogenic, if due to renal tubular unresponsiveness to ADH
  - S/S: polyuria; low specific gravity; increased serum Na+ & osmolality; thirst & polydipsia

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POSTERIOR PITUITARY SYNDROMES

- 2. Secretion of inappropriately high levels of ADH: ADH excess causes resorption of excessive amounts of free water → hyponatremia
- Causes: ectopic ADH by neoplasms; non-neoplastic diseases of the lung, local injury to hypothalamus or posterior pituitary or both
- S/Sx: hyponatremia, cerebral edema and neurologic dysfunction; total body water increased; blood volume, normal; no peripheral edema

HYPOTHALAMIC SUPRASELLAR TUMORS

- Induce hypo- or hyperfunction of anterior pituitary, diabetes insipidus, or both
- 1. Gliomas - chiasm
- 2. Craniopharyngioma – vestigial remnants of Rathke pouch
- Bimodal: 5 – 15 y/o; 6th decade or >
- Children: endocrine deficiency; adults- visual dysfunction

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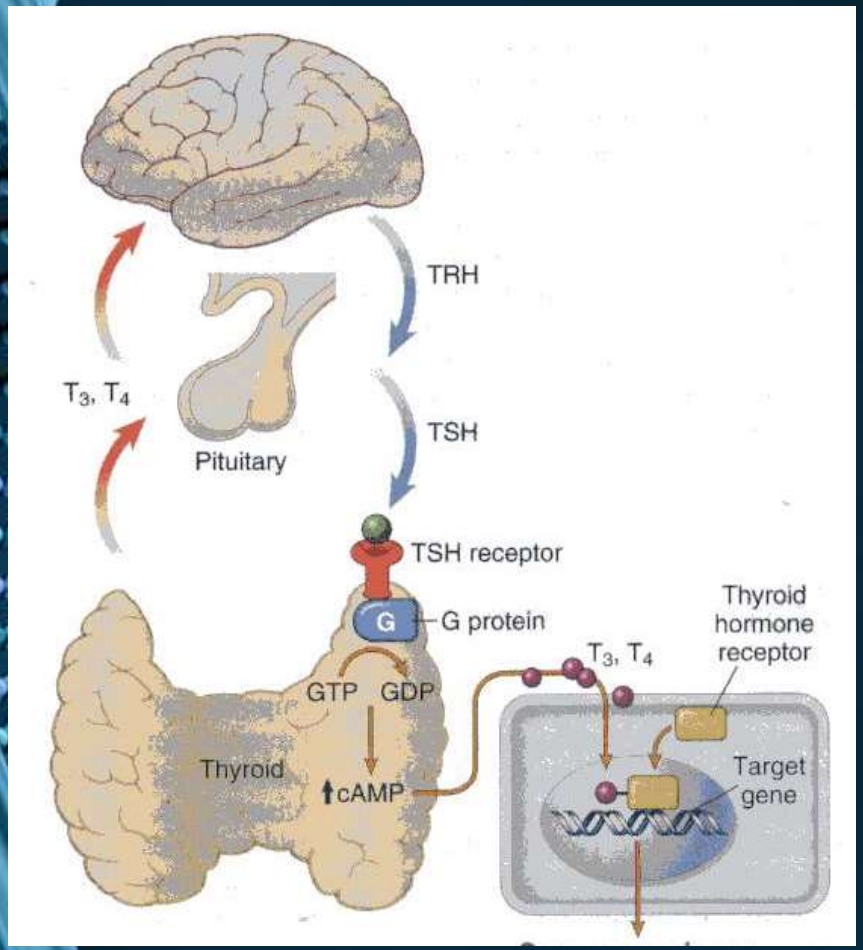
THYROID GLAND



- Bulky lateral lobes, thin isthmus,
- Evagination of pharyngeal epithelium that descends from foramen cecum as part of thyroglossal duct
- Excessive descent→ substernal thyroid
- 15-25 gm; lobules, 20-40 follicles; 50 -500 um; cuboidal-low columnar epithelium; PAS (+) thyroglobulin

THYROID GLAND

- Functions:
  - 1. Up-regulation of carbohydrate and lipid catabolism
  - 2. stimulation of protein synthesis
  - 3. brain development (1 & 2 increases BMR)
- Puberty, pregnancy, & physiologic stress → transient hyperplasia
- Function inhibited by goitrogens, suppress T3 & T4 synthesis→ TSH increases→ hyperplasia e.g., propylthiouracil, & iodide in large doses
- Parafollicular cells or C cells: synthesize and secrete calcitonin

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Thyroid Gland: Pathology

- 1. Conditions associated with hyperthyroidism
- 2. Conditions associated with hypothyroidism
- 3. Mass lesions of the thyroid

HYPERTHYROIDISM

- Thyrotoxicosis: hypermetabolic state due to elevated circulating levels of T_3 & T_4
- Hyperthyroidism: due to hyperfunction of thyroid gland
- Primary hyperthyroidism: arising from intrinsic thyroid abnormality
- Secondary hyperthyroidism: arising from processes outside of thyroid
- Most common causes: diffuse hyperplasia (85%), hyperfunctional multinodular goiter, and hyperfunctional adenoma of thyroid

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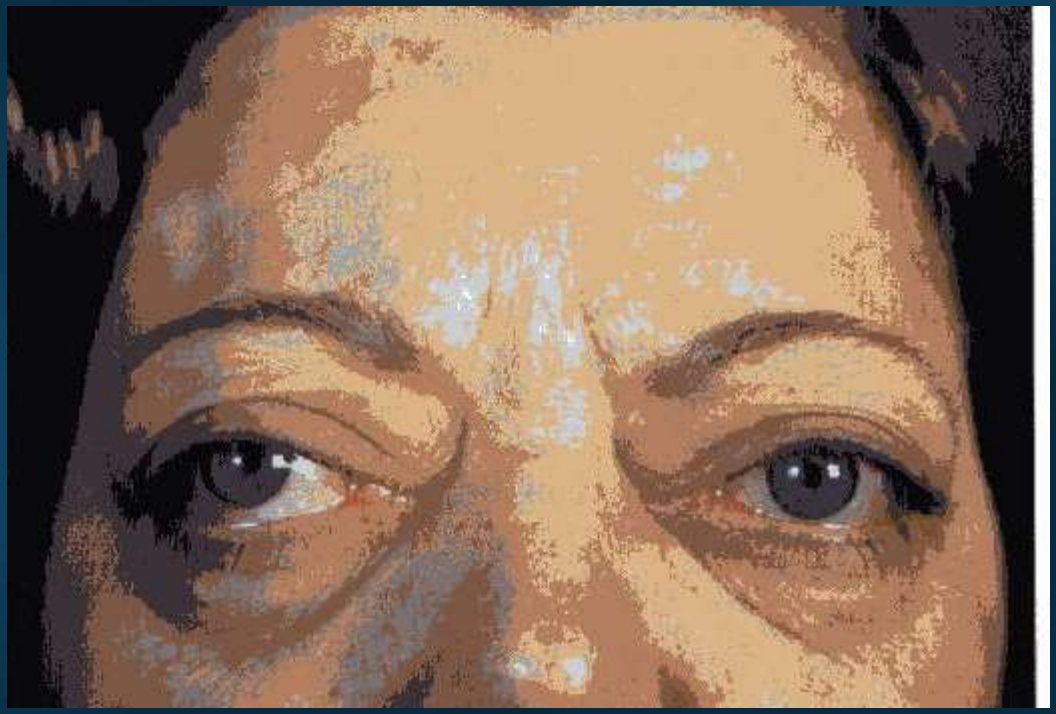
HYPERTHYROIDISM: Clinical Course

- Increased basal metabolic rate
- Soft, warm, flushed skin
- Heat intolerance
- Weight loss despite of increased appetite
- Cardiac manifestations
- Neuromuscular system
- Ocular changes
- Skeletal system
- Thyroid storm: medical emergency
- Apathetic hyperthyroidism

HYPERTHYROIDISM: Clinical Course



HYPERTHYROIDISM: Clinical Course

- Diagnosis: decreased TSH, increased T_4 or occasionally, decreased T_4, increased T_3 (T_3 toxicosis)
- Pituitary-associated (secondary) hyperthyroidism: TSH, normal or raised; do TRH stimulation test→ rise in TSH excludes 2^o hyperthyroidism
- RAIU measurement
- Treatment: multiple medications: B-blocker, thionamide, iodine solution, & agents to inhibit peripheral conversion of T_4 to T_3; radioiodine for 6 -18 weeks for ablation

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Disorders Associated with Thyrotoxicosis

ASSOCIATED WITH HYPERTHYROIDISM

Primary

- Diffuse toxic hyperplasia (Graves disease)
- Hyperfunctioning (“toxic”) multinodular goiter
- Hyperfunctioning (“toxic”) adenoma
- Iodine-induced hyperthyroidism
- Neonatal thyrotoxicosis associated with maternal Graves disease

Secondary

TSH-secreting pituitary adenoma (rare)

NOT ASSOCIATED WITH HYPERTHYROIDISM

- Granulomatous (de Quervain) thyroiditis (painful)
- Subacute lymphocytic thyroiditis (painless)
- Struma ovarii (ovarian teratoma with ectopic thyroid)
- Factitious thyrotoxicosis (exogenous thyroxine intake)

HYPOTHYROIDISM

- Caused by any structural or functional derangement in the production of adequate thyroid hormone
- Primary – intrinsic thyroid abnormality
- Secondary – pituitary disease
- Tertiary – hypothalamic failure
- Thyroprivic: absence or loss of parenchyma
- Goitrous: enlargement due to TSH

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Causes of Hypothyroidism

PRIMARY

Developmental (thyroid dysgenesis: PAX8, FOXE1, TSH receptor mutations)
Thyroid hormone resistance syndrome (THRB mutations)
Postablative Surgery, radioiodine therapy, or external irradiation

Autoimmune hypothyroidism Hashimoto thyroiditis[*]

Iodine deficiency[*]
Drugs (lithium, iodides, p-aminosalicylic acid)[*]
Congenital biosynthetic defect (dyshormonogenetic goiter)[*]

SECONDARY (CENTRAL)

Pituitary failure
Hypothalamic failure (rare)

HYPOTHYROIDISM: Clinical Manifestations

- 1. Cretinism:
  - Hypothyroidism in infancy or early childhood
  - Mentally retarded
  - Sporadic cretinism due enzyme deficiency
  - Impaired development of skeletal system and CNS→ severe MR, short stature, coarse facial features, protruding tongue, & umbilical hernia
  - Maternal thyroid def. before development of fetal thyroid gland →severe MR; after, normal

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HYPOTHYROIDISM: Clinical Manifestations

- 2. Myxedema (Gull disease):
  - Hypothyroidism in older child or adult
  - Slowing of physical and mental activity→ generalized fatigue, apathy, mental sluggishness, slowed speech and intellectual functions, listless, cold-intolerance, overweight
  - Reduced cardiac output→ shortness of breath and decreased exercise capacity

HYPOTHYROIDISM: Clinical Manifestations

- 2. Myxedema (Gull disease):
  - Decreased sympathetic activity→ constipation and decreased sweating
  - Decreased blood flow→ cool, pale skin
  - Histologically, accumulation of matrix substances, glycosaminoglycans and hyaluronic acid→ edema, broadening and coarsening of facial features, tongue enlargement, and deepening of voice

HYPOTHYROIDISM: Clinical Manifestations

DIAGNOSIS:

- serum TSH level
- most sensitive screening test
- increased in primary; not, in hypothalamic & pituitary disease
- T4 decreased in all patients with hypothyroidism of any origin

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THYROIDITIS

- Inflammation of thyroid gland
- Acute illness with severe thyroid pain
  - Infectious thyroiditis
  - Subacute granulomatous thyroiditis
- Little inflammation, thyroid dysfunction
  - Subacute lymphocytic thyroiditis
  - Fibrous (Reidel) thyroiditis
- Common and clinically significant thyroiditis: Hashimoto thyroiditis, subacute granulomatous thyroiditis, and subacute lymphocytic thyroiditis

PALPATION THYROIDITIS

- Caused by vigorous clinical palpation of the thyroid gland→ multifocal follicular disruption associated with chronic inflammation and occasional giant cell formation
- Normal thyroid function
- Usually incidental finding

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GRAVES DISEASE

- Most common cause of endogenous hyperthyroidism
- Triad of clinical findings:
  - 1. hyperthyroidism due to diffuse thyroid enlargement
  - 2. infiltrative ophthalmopathy → exophthalmos
  - 3. localized, infiltrative dermopathy (pretibial myxedema)
- Peak incidence: 20 -40 y/o; women 7X> than men
- Genetic factors: family members; HLA-B8 & -DR3; CTLA-4 gene polymorphism; chromosome 6p and 20q

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GRAVES DISEASE: Pathogenesis

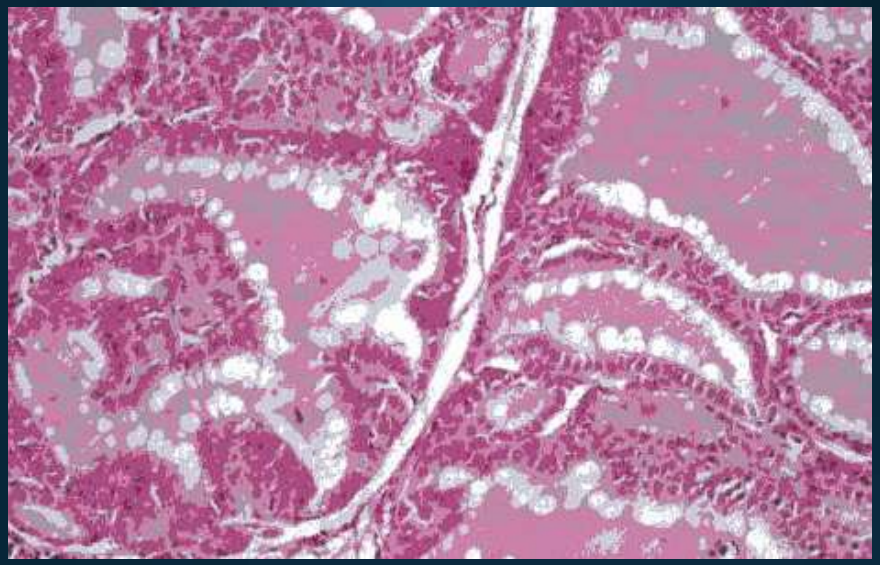
- Antibodies to TSH receptor, thyroid peroxisomes, and thyroglobulin present
- Autoantibodies to TSH receptor central to pathogenesis
- Types of TSH receptor antibodies
  - 1. TSI – relatively specific for Graves disease; IgG Ab, stimulates adenyl cyclase → increased release of thyroid hormones
  - 2. TGI → proliferation of thyroid epithelium
  - 3. TBII – mimic action of TSH→ stimulate thyroid epithelial cell activity (hyperthyroidism) or inhibit thyroid function→ hypothyroidism

GRAVES DISEASE: Pathogenesis

- Trigger for initiation of autoimmune reaction, uncertain; breakdown in helper T-cell tolerance→ production of anti-TSH autoantibodies?
- Mechanism of infiltrative ophthalmopathy:
  - 1. marked infiltration of retro-orbital space by mononuclear cells
  - 2. inflammatory edema & swelling of extraocular muscles
  - 3. accumulation of ECM
  - 4. fatty infiltration

GRAVES DISEASE: Morphology

- Symmetrically enlarged thyroid
- Diffuse hypertrophy and hyperplasia of follicular cells
- Smooth, soft, & meaty; intact capsule
- Too many cells, crowding
- Pale, scalloped colloid
- Lymphoid infiltrates, germinal center common



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GRAVES DISEASE: Clinical Course

- Thyrotoxicosis + clinical triad
- Audible bruit due to increased blood flow
- Wide, staring gaze and lid lag due to sympathetic overactivity
- Laboratory: elevated free T_4 & T_3; depressed TSH levels; RAIU, increased
- Treatment: beta-adrenergic antagonist; thionamides, radiation ablation, & surgery

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DIFFUSE AND MULTINODULAR GOITERS

- Enlargement of thyroid (goiter) is most common manifestation of thyroid disease
- Due to impaired synthesis of hormone caused by dietary iodine deficiency→ compensatory rise in TSH→ hypertrophy and hyperplasia of follicular cells→ goiter → euthyroidism
- Congenital biosynthetic defect or endemic iodine deficiency → goitrous hypothyroidism
- Enlargement proportional to duration of thyroid hormone deficiency

DIFFUSE NONTOXIC (SIMPLE) GOITER

- Diffusely involve entire gland without producing nodularity
- Colloid goiter: endemic or sporadic
- Endemic: soil, water, and food supply contain low levels of iodine; >10% of population with goiter; goitrogens (excessive calcium and vegetables)
- Sporadic: female; puberty or young adult; due to ingestion of substance that interfere with thyroid hormone synthesis or enzymatic defects

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DIFFUSE NONTOXIC (SIMPLE) GOITER

- Morphology: hyperplastic phase or colloid involution phase; abundant colloid flattened, cuboidal epithelium
- Clinical course: euthyroid; mass effects; T3 & T4, normal; TSH increased; cretinism, if due to dyshormonogenetic goiter

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MULTINODULAR GOITER

- Due to recurrent episodes of hyperplasia and involution of simple goiter
- Produce the most extreme thyroid enlargement and frequently mistaken for neoplasm
- Arise due to variations among follicular cells response to external stimuli
- Uneven follicular hyperplasia, generation of new follicles, and uneven accumulation of colloid→ tensions & stresses→ hemorrhage, scarring, calcifications→ stromal enclosure→ nodules

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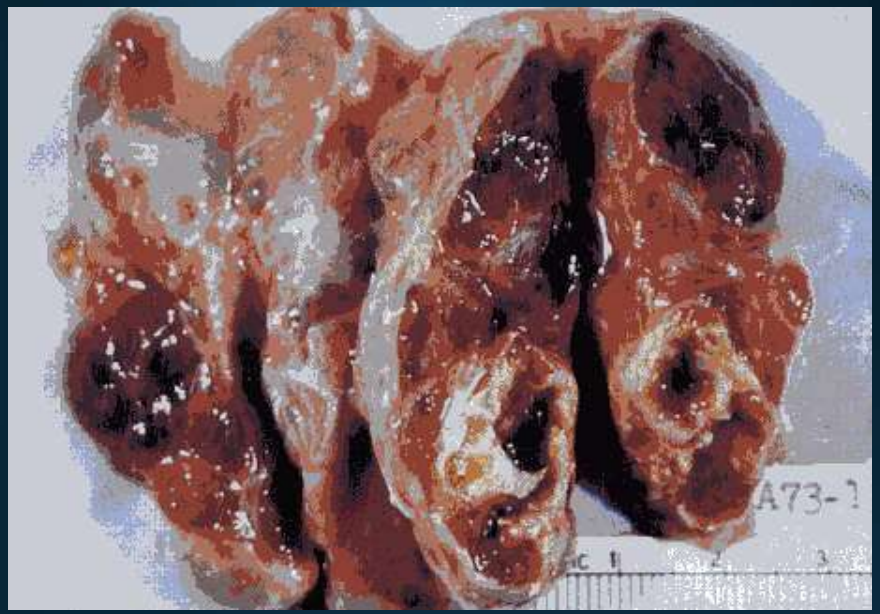
MULTINODULAR GOITER

Morphology

- Multilobulated, asymmetrically enlarged glands
- Intrathoracic or plunging goiter
- Irregular nodules, variable amount of colloid
- Hemorrhage, fibrosis, calcification, cyst
- Colloid-rich follicles, flattened, inactive epithelium, areas of hypertrophy, hyperplasia



MULTINODULAR GOITER: Clinical Course

- Mass effects → cosmetic effects
- May cause airway obstruction, dysphagia, and compression of large vessels in neck and upper thorax
- Euthyroid; minority, hyperthyroidism (toxic multinodular goiter) without exophthalmos and dermopathy (Plummer syndrome)
- Hypothyroidism in specific clinical settings
- RAIU, uneven
- Mask or mimic neoplastic diseases of thyroid

NEOPLASMS OF THE THYROID

- Solitary nodules: more likely neoplastic than are multiple nodules
- Nodules in younger patients: >neoplastic
- Nodules in males: >neoplastic
- Radiation to head & neck : >malignant
- Hot nodules: >benign
- Solitary nodules: 1 – 10%; 4x>women; benign, 10:1
- Carcinomas: 1% of solitary nodules; indolent, 90% survival at 20 years

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THYROID ADENOMA

- Discrete, solitary masses derived from follicular epithelium, follicular adenomas
- Classified based on degree of follicle formation and colloid content
  - Simple colloid adenoma (macrofollicular)
  - Fetal (microfollicular) adenoma
  - Embryonal (trabecular) adenoma
- Rare forerunner of cancer
- Vast majority, nonfunctional; small proportion, produce hormone
- Functional (toxic) adenomas, thyroid autonomy

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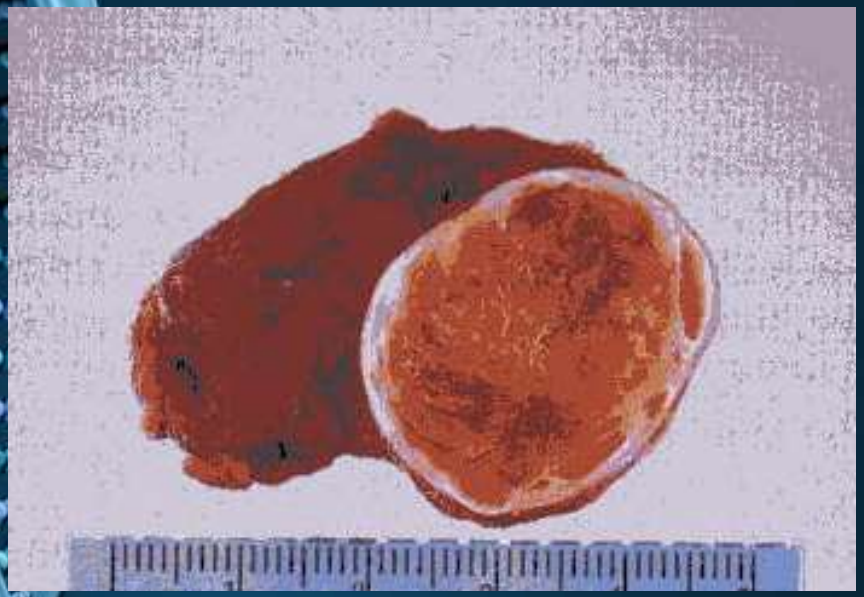
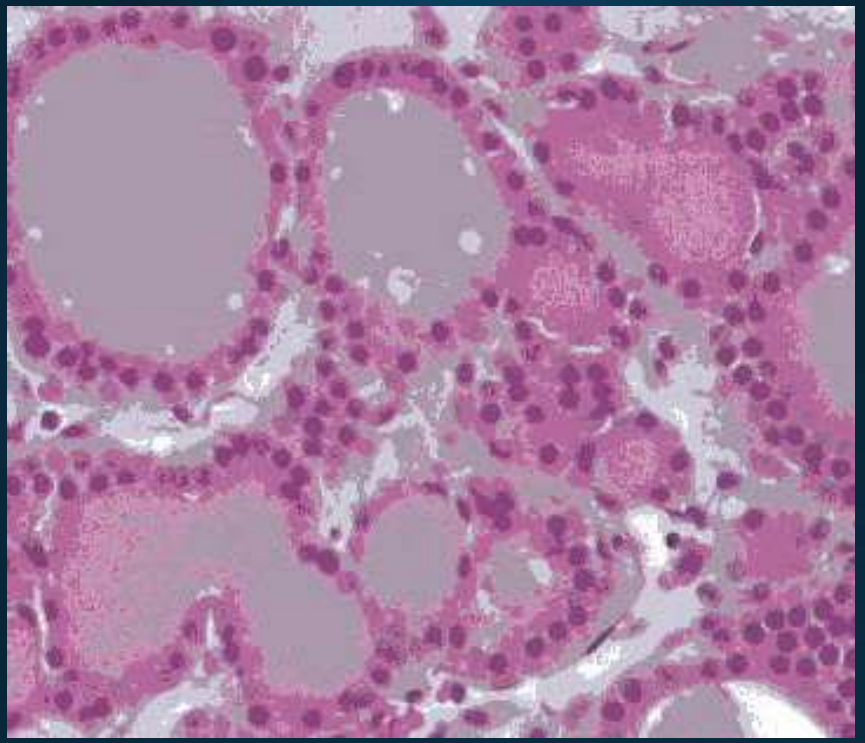
THYROID ADENOMA: Pathogenesis

- Important role: TSH receptor signaling pathway
- Activating (gain of function) somatic mutations in TSH receptor or alpha-subunit of Gs → chronic overproduction of cAMP → generate cells that acquire growth advantage → Clonal expansion of autonomous follicular cells → thyrotoxicosis (functional adenoma)

THYROID ADENOMA:Morphology





THYROID ADENOMA: Clinical Course

- Unilateral painless mass; large, dysphagia
- Radionuclide scanning, usually cold nodule; 10% cold nodules, malignant; rare in hot nodules
- Minority of cases, hyperthyroidism, occ'ly dependent on TSH→ regress on administration of thyroid hormone
- USG & FNAB; need to evaluate capsule & exclude CA → histopath of resected specimen is definitive

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OTHER BENIGN TUMORS

- Cysts- cystic degeneration of follicular adenoma and multinodular goiter
- Dermoid cyst
- Lipoma
- Hemangiomas
- Teratomas

CARCINOMAS

- 1.5% of all cancers
- Mostly adults, papillary Ca may be in childhood
- Female, early and middle-adult years
- Mostly well-differentiated
- Major subtypes:
  - Papillary carcinoma (75 – 85%)
  - Follicular carcinoma (10 – 20%)
  - Medullary carcinoma (5%)
  - Anaplastic carcinoma (<5%)

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CARCINOMAS: Pathogenesis

- Genetic factors:
  - Important in both familial and nonfamilial (sporadic) thyroid carcinoma
  - Familial CA usually medullary; papillary & follicular, rare

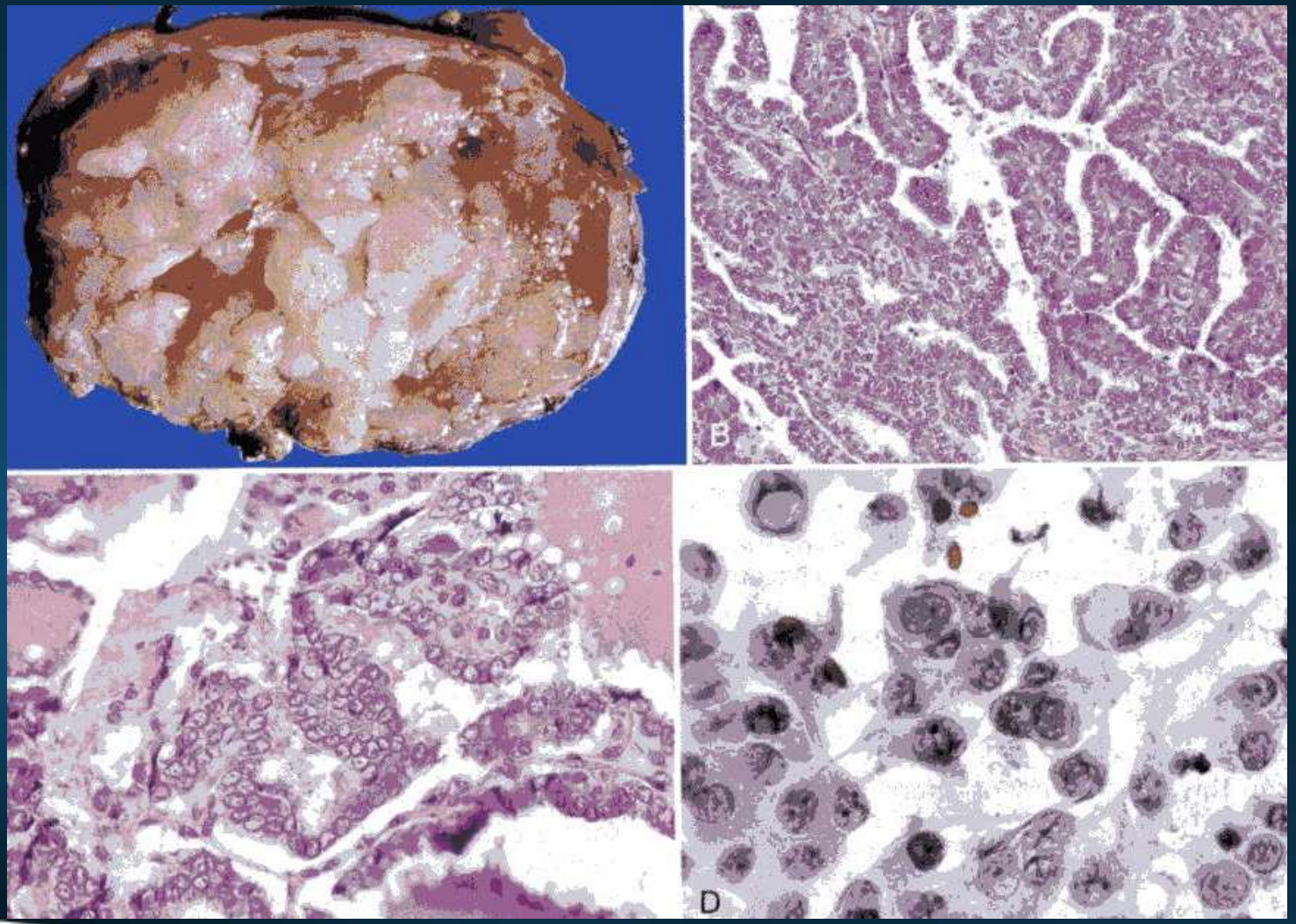
CARCINOMAS: Pathogenesis (Genetic Factors)

Follicular CA	Papillary CA	Medullary CA	Anaplastic CA
50%, mutation in RAS oncogene; 1/3, PAX8-PPARgam-ma1 fusion	- Rearrange-ments of RET or NTRK1 - Activating mutation in BRAF oncogene -10 -20%, RAS mutation -Ret/PTC fusion	familial; MEN-2; 95%, germ-line RET proto-oncogene mutations	Arise de novo or by dedif-ferentiation of a well-diff papillary or follicular CA - p53 point mutation

CARCINOMAS: Pathogenesis (Environmental Factors)

- Major risk factor: ionizing radiation particularly during the first two decades
- Long-standing multinodular goiter→ follicular carcinomas
- Hashimoto thyroiditis→ most thyroid lymphomas

PAPILLARY CARCINOMA: Morphology



PAPILLARY CARCINOMA

- Morphology:
  - Encapsulated variant - diffuse sclerosing
  - Follicular variant - hyalinizing trabecular
  - Tall cell variant

PAPILLARY CARCINOMA: Clinical Course

- Asymptomatic thyroid nodules, mass in cervical lymph node
- Hoarseness, dysphagia, cough, or dyspnea, advance disease; lung metastasis
- Diagnosis: Radionuclide scanning (cold), FNAB
- Excellent prognosis; >95%, 5-year survival; 5-20%, recurrence; 10 -20%, distant metastasis
- Prognosis depends on age (>40 y/o, less favorable), extrathyroidal extension, & stage

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FOLLICULAR CARCINOMA

- 2nd most common form of thyroid cancer
- Accounts for 10-20%
- Women, older age group, peak 40s & 50s
- Increased in areas of iodine deficiency
- High frequency of RAS mutations in both follicular adenoma & carcinoma, related?

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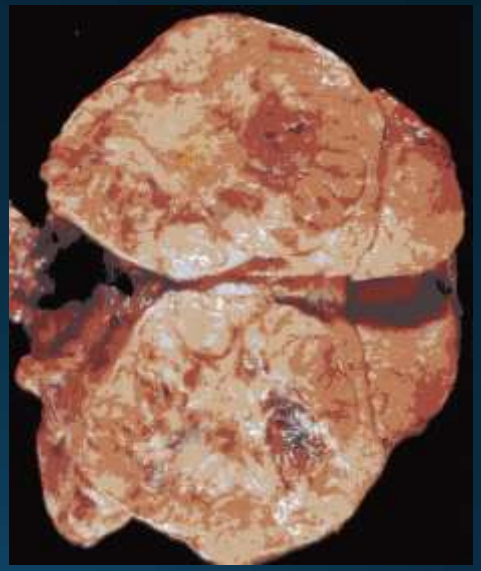
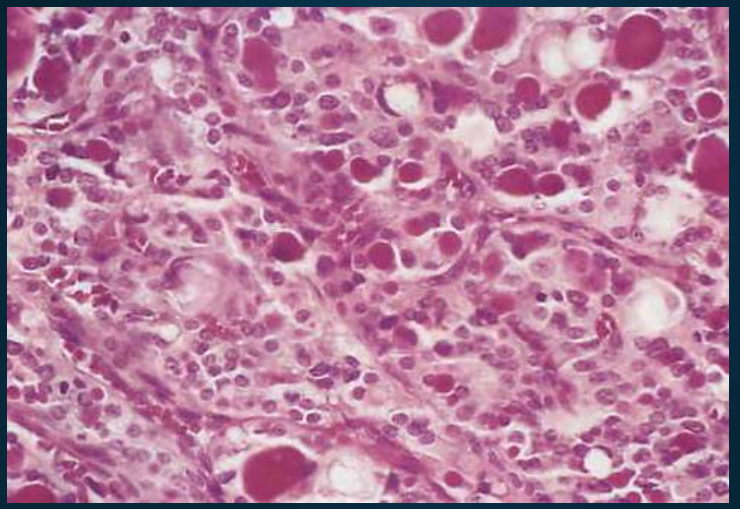
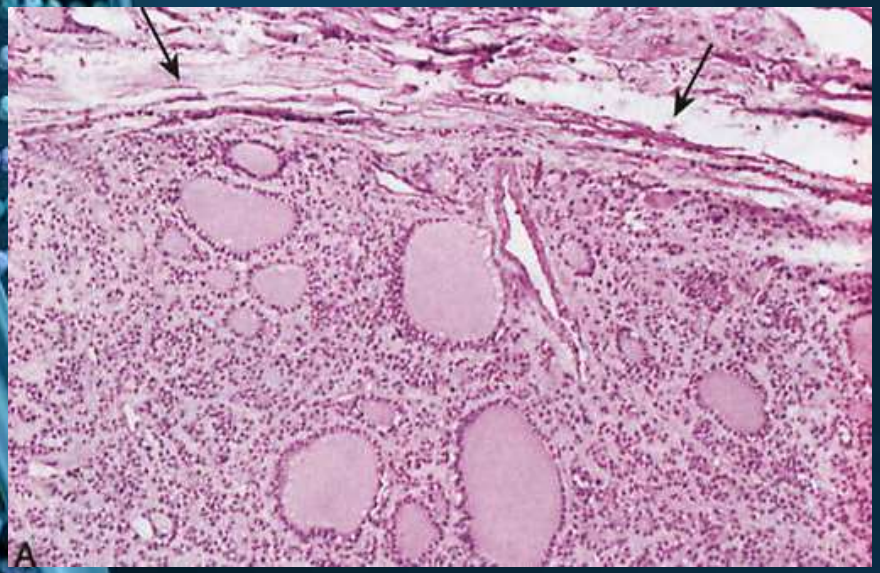
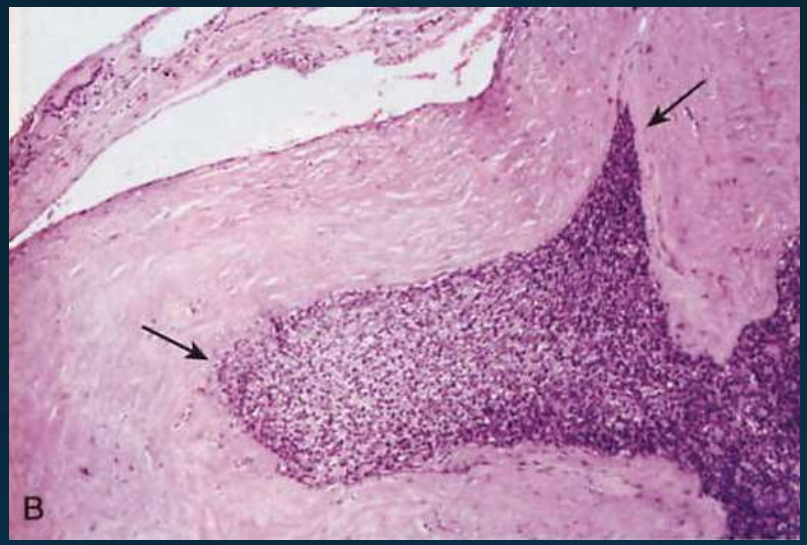
FOLLICULAR CARCINOMA: Morphology









FOLLICULAR CARCINOMA: Morphology

- Minimally invasive follicular carcinoma
  - Requires extensive histologic sampling of the tumor-capsule-thyroid interface to exclude capsular and/or vascular invasion of capsular or vessels beyond the capsule
- Widely invasive follicular carcinoma
  - Extensive invasion of adjacent thyroid parenchyma or extrathyroidal tissues
  - More solid or trabecular growth pattern, increased mitosis

FOLLICULAR CARCINOMA: Clinical Course

- Slowly enlarging painless nodules
- Cold nodules on scintigrams
- Better differentiated lesions→ warm nodules→ hyperthyroidism
- Vascular invasion > lymphatics (bones, lungs, liver)
- Prognosis depends on extent of invasion and stage
- Minimally invasive, >90% 10-year survival
- Treatment: total thyroidectomy + RAI + thyroid hormone

MK

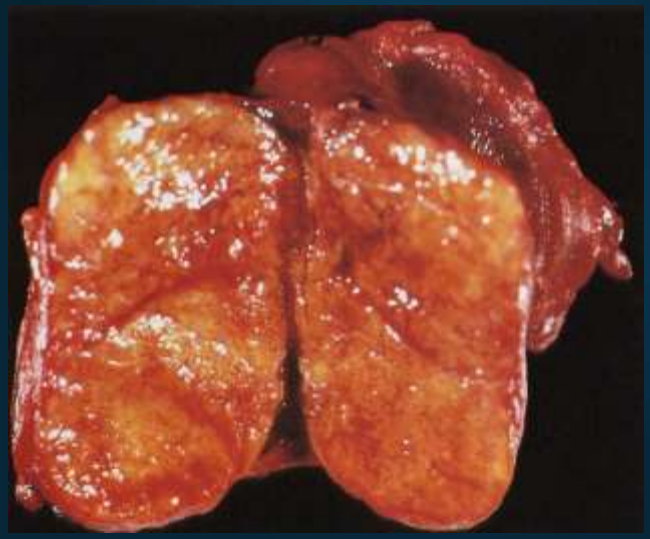
MEDULLARY CARCINOMA

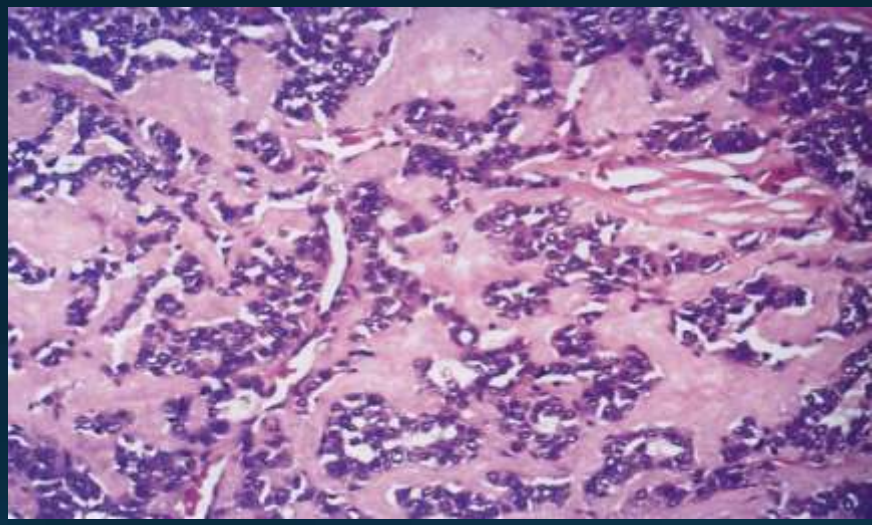
- Neuroendocrine tumor derived from parafollicular cells or C cells
- Secrete calcitonin, measured for diagnosis and post-operative follow-up; other PP hormones
- 80%, sporadic; 20%, MEN syndrome 2A or 2B or as familial medullary thyroid CA
- Mutation of RET protooncogene
- MEN-2, younger patients, childhood
- sporadic, adults, 40s & 50s

MK

MEDULLARY CARCINOMA: Morphology

- Sporadic: Solitary
- Familial: bilateral and multicentric; foci of C-cell hyperplasia
- Firm, pale gray to tan, infiltrative
- Nests, trabeculae, or follicles of polygonal to spindle-shaped cells
- Acellular amyloid deposits in the stroma





MEDULLARY CARCINOMA: Clinical Course

- Neck mass +/- dysphagia or hoarseness
- Sometimes, paraneoplastic syndrome due to PP hormones
- Hypocalcemia not a prominent feature
- Screening of relatives for elevated calcitonin & *RET* mutations→ early detection → prophylactic thyroidectomy
- C-cell hyperplasia & micromedullary CA (<1cm): asymptomatic carriers

MK

ANAPLASTIC CARCINOMA

- undifferentiated tumors of thyroid follicular epithelium
- Aggressive tumors with almost 100% MR
- Mean age: 65 y/o
- 50%, history of multinodular goiter
- 20%, history of differentiated carcinoma
- 20- 30%, with concurrent differentiated cancer, frequently papillary CA

MK

ANAPLASTIC CARCINOMA

- Histologic patterns:
  - 1. large, pleomorphic giant cells
  - 2. spindle cells with sarcomatous appearance
  - 3. mixed spindle and giant cells
  - 4. small cells
- Clinical course: rapidly enlarging, bulky neck mass; mostly spread beyond capsule and metastasize to lungs on presentation; compression and invasion symptoms
- Almost uniformly fatal, death in <1 year of dx

CONGENITAL ANOMALIES: Thyroglossal Duct or Cyst

- Most common clinically significant congenital anomaly
- Vestigial remnant of tubular development of thyroid→ persistent sinus tract→ part obliterated→ cysts→ accumulation of mucinous secretions→ spherical mass or swellings
- Midline of neck, anterior to trachea
- Lined by SSE or thyroidal acinar epithelium + intense lymphocytic infiltrates→ infection→ abscess, rarely, give rise to cancers

PARATHYROID GLANDS

- Abnormalities of both hyperfunction and hypofunction
- Come to attention because of excessive secretion of PTH than mass effects
- Hyperparathyroidism
  - Primary – autonomous, spontaneous overproduction of PTH
  - Secondary) in patients with chronic renal
  - Tertiary) insufficiency

MK

PARATHYROID GLANDS: Primary Hyperparathyroidism

- One of most common endocrine disorders
- Important cause of hypercalcemia
- Causes:
  - 1. Adenoma – 75 – 80%
  - 2. Primary hyperplasia – 10 – 15%
  - 3. Parathyroid carcinoma - <5%
- Adults; women>men (3:1); 50s or later

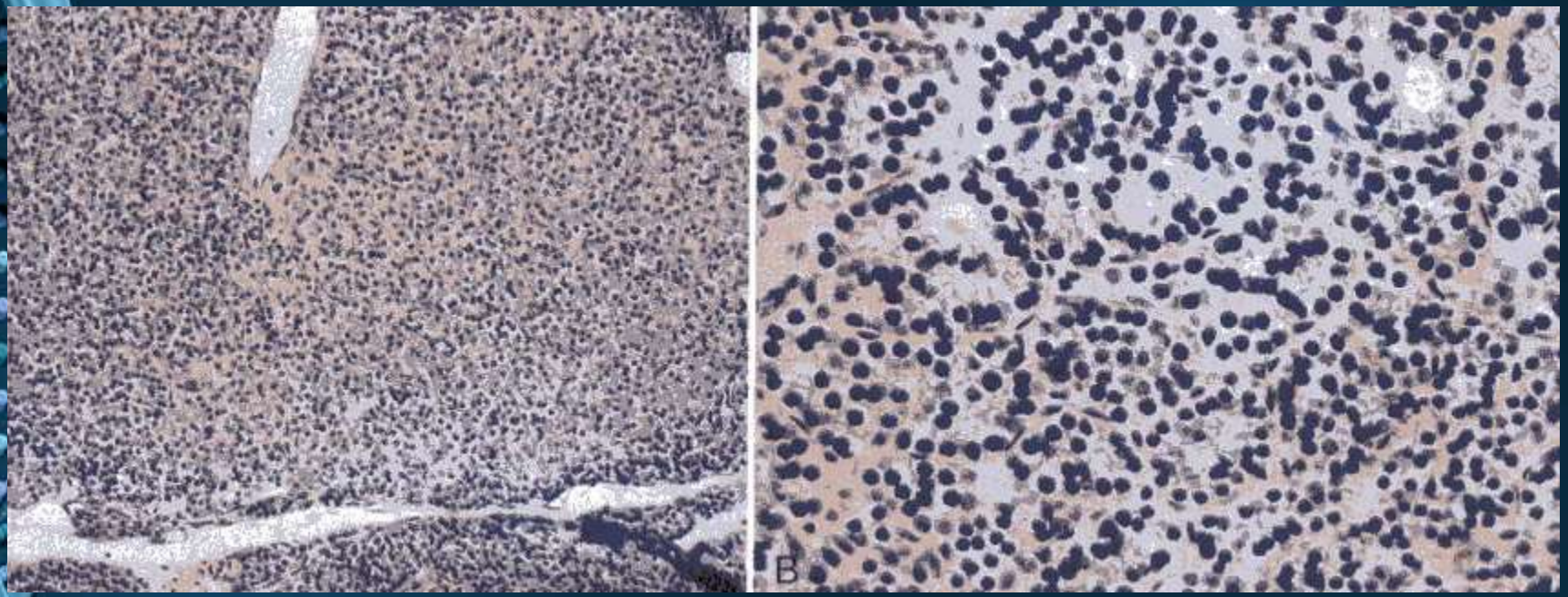
PARATHYROID GLANDS: Primary Hyperparathyroidism

- Genetic syndromes associated with familial primary hyperparathyroidism
  - 1. Multiple Endocrine Neoplasia-1 (MEN-1) due to inactivation of MEN1 gene; a tumor suppressor gene
  - 2. MEN-2: caused by activating mutations in RET
  - 3. Familial hypocalciuric hypercalcemia (FHH): mutations in parathyroid calcium-sensing receptor gene (CASR), AD
- Sporadic parathyroid adenoma are monoclonal
  - Molecular defects: PRAD1(encodes cyclin) & MEN1 gene

PARATHYROID GLANDS: Primary Hyperparathyroidism

- Morphology: with skeletal & renal changes
  - Adenoma: solitary, 0.5 – 5 gm, well-circumscribed, soft, tan to reddish-brown nodule, delicate capsule; histologically composed of uniform, polygonal chief cells with central nuclei
  - Hyperplasia: involves all four glands with asymmetry, <1 gm total wt,; chief cell or water-clear cell hyperplasia
  - Carcinoma: invasion & metastasis, criteria

PARATHYROID ADENOMA



Primary Hyperparathyroidism: Clinical Course

- Asymptomatic hyperparathyroidism
  - Detected after a routine chemistry profile
  - Most commonly, increase in ionized calcium
  - Serum PTH inappropriately elevated→ hypophosphatemia & increased urinary calcium & phosphate
- Symptomatic primary hyperparathyroidism
  - Reflect combined effects of increased PTH and hypercalcemia
  - Painful bones, renal stones, abdominal groans, and psychic moans

PARATHYROID GLANDS

TABLE 24–5 Causes of Hypercalcemia

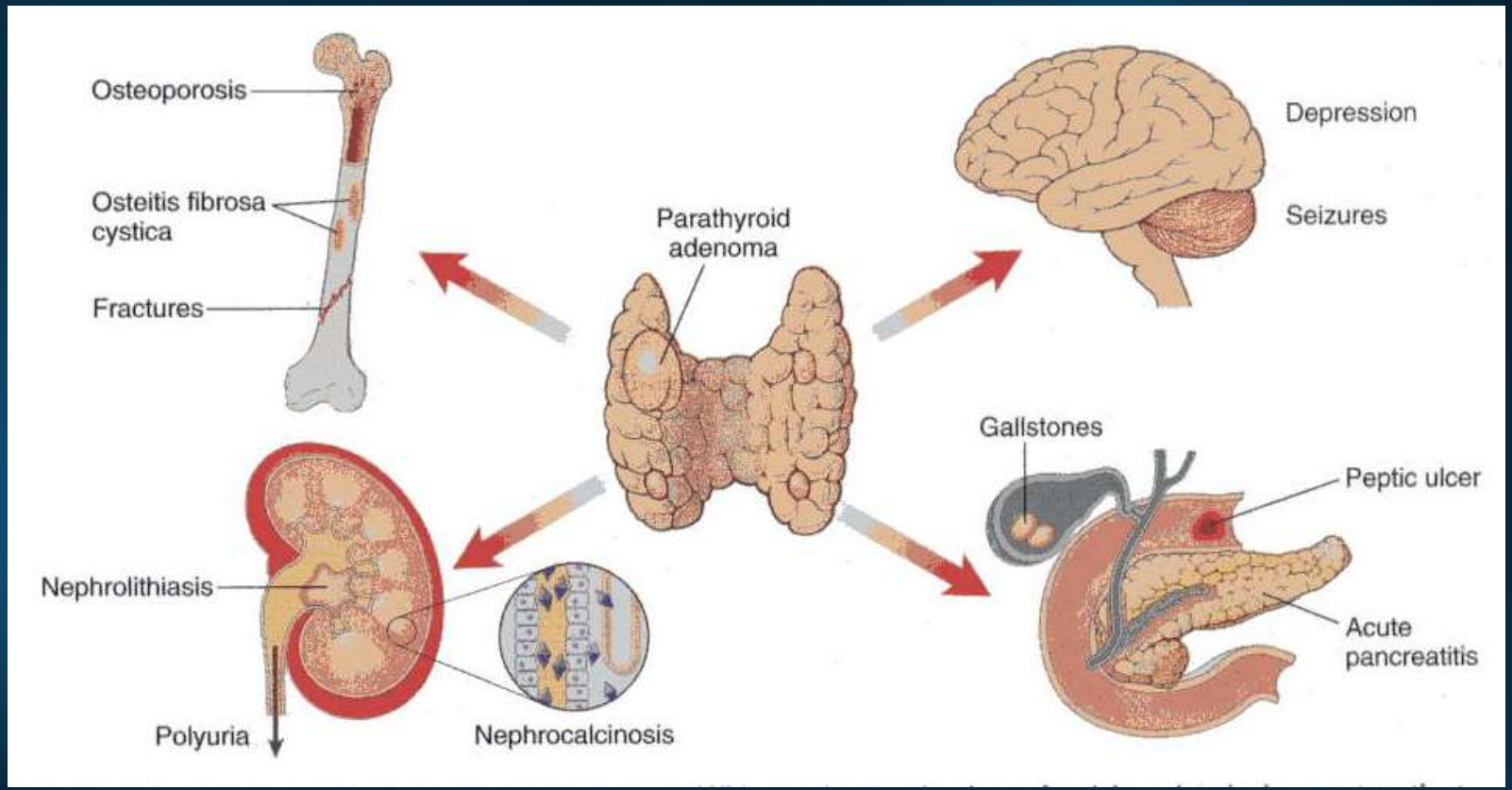
Raised PTH	Decreased PTH
Hyperparathyroidism Primary (adenoma > hyperplasia)* Secondary† Tertiary†	Hypercalcemia of malignancy Osteolytic metastases (RANKL-mediated) PTH-rP–mediated Vitamin D toxicity
Familial hypocalciuric hypercalcemia	Immobilization Thiazide diuretics Granulomatous disease (sarcoidosis)

*Primary hyperparathyroidism is the most common cause of hypercalcemia overall. Malignancy is the most common cause of *symptomatic* hypercalcemia. Primary hyperparathyroidism and malignancy account for nearly 90% of cases of hypercalcemia.

†Secondary and tertiary hyperparathyroidism are most commonly associated with progressive renal failure.

PTH-rP, Parathyroid hormone–related protein. RANKL, Receptor activator of nuclear factor κB ligand.

CARDINAL FEATURES OF HYPERPARATHYROIDISM



Secondary Hyperparathyroidism

- Caused by any condition with low serum calcium→ compensatory overactivity of parathyroid glands
- Most commonly due to renal failure
- Other causes: inadequate intake of Ca++ steatorrhea, & vit. D deficiency
- Mechanism complex, not fully understood
- Decreased phosphate excretion → hyperphosphatemia → depress serum Calcium level → stimulate parathyroid activity
- Loss of renal substance→ dec. alpha-1-hydroxylase→ dec. synthesis of vit. D → dec. intestinal absorption of calcium

Secondary Hyperparathyroidism

- Morphology: hyperplastic parathyroid; chief cells or water-clear cells; diffuse or multinodular
- Bone changes & metastatic calcification
- Clinical Course: dominated by chronic renal failure; less severe hyperparathyroidism
- Calciphylaxis
- Parathyroid activity may become autonomous and excessive→ tertiary hyperparathyroidism
- Treatment: Parathyroidectomy

HYPOPARATHYROIDISM

- Less common
- Due to deficient PTH
- Causes:
  - Surgically-induced
  - Congenital absence of all glands
  - Familial hypoparathyroidism- associated with chronic mucocutaneous candidiasis & primary adrenal insuff (APS1); mutant AIRE gene
  - Idiopathic hypoparathyroidism- autoimmune

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HYPOPARATHYROIDISM: Clinical Course

- Related to severity & chronicity of hypocalcemia
- Hallmark: tetany, characterized by neuromuscular irritability, e.g., Chvostek sign & Trousseau sign
- Changes in mental status, emotional instability, anxiety, & depression
- Intracranial manifestations, calcifications
- Ocular disease
- CV manifestations and dental abnormalities

PSEUDOHYPOPARATHYROIDISM

- Due to end organ resistance to actions of PTH
- Serum PTH, normal or elevated
- Types:
  - 1. Pseudohypoparathyroidism type 1A: asst'd with multihormone (PTH, TSH, & LH/FSH) resistance and Albright hereditary osteodystrophy (AHO); maternal allele
  - 2. Pseudpseudohypoparathyroidism: paternal allele; AHO w/o multihormone resistance

MK

THE ENDOCRINE PANCREAS

- 1 million islets of Langerhans
- Measures 100 to 200 um
- Weigh 1 – 1.5 gm in aggregate
- Four major cell types
  - Beta cells: 68%; insulin; induce hypoglycemia
  - Alpha cells: 20%;glucagon; induce hyperglycemia
  - Delta cells: 10%; somatostatin; suppresses both insulin and glucagon secretion
  - PP cells: 2%; pancreatic polypeptide; stimulate secretion of gastric and intestinal enzymes and inhibit intestinal motility

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THE ENDOCRINE PANCREAS

- Two minor cell types
  - DI cells: vasoactive intestinal peptide (VIP); induces glycogenosis and hyperglycemia
  - enterochromaffin cells: serotonin
- Two main disorders of islet cells
  - Diabetes mellitus
  - Pancreatic endocrine tumors

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DIABETES MELLITUS

- A group of metabolic disorders characterized by hyperglycemia
- Due to defects in insulin secretion, insulin action, or both
- Chronic hyperglycemia and metabolic dysregulation → multiple organ damage
- Leading cause of end-stage renal disease, adult-onset blindness, and nontraumatic lower extremity amputations in the U.S.

GTK

DIABETES MELLITUS: Diagnosis

- Normal value: 70 -120 mg/dL
- Dx established by any one of 3 criteria
  - 1. a random glucose >200 mg/dL, with classical signs and symptoms
  - 2. a fasting glucose >126 mg/dL on more than one occasion
  - 3. an abnormal OGTT in which the glucose is >200 mg/dL 2 hours after a standard carbohydrate load
- Euglycemic: FBS = <110 mg/dL or <140 mg/dL following OGTT

MK

DIABETES MELLITUS: Diagnosis

- Impaired glucose tolerance (IGT): FBS = >110 mg/dL but <126 or OGTT values >140 but <200 mg
- individuals with IGT progress to overt diabetes mellitus at a rate of 5 – 10%/year plus risk for CV disease

MK

TABLE 24–6 Classification of Diabetes Mellitus

1. **Type 1 diabetes** (β-cell destruction, leads to absolute insulin deficiency)
   - Immune-mediated
   - Idiopathic
2. **Type 2 diabetes** (insulin resistance with relative insulin deficiency)
3. **Genetic defects of β-cell function**
   - Maturity-onset diabetes of the young (MODY), caused by mutations in:
     - Hepatocyte nuclear factor 4α [HNF-4α] (MODY1)
     - Glucokinase (MODY2)
     - Hepatocyte nuclear factor 1α [HNF-1α] (MODY3)
     - Insulin promoter factor [IPF-1] (MODY4)
     - Hepatocyte nuclear factor 1β [HNF-1β] (MODY5)
     - Neurogenic differentiation factor 1 [Neuro D1] (MODY6)
   - Mitochondrial DNA mutations
4. **Genetic defects in insulin processing or insulin action**
   - Defects in proinsulin conversion
   - Insulin gene mutations
   - Insulin receptor mutations
5. **Exocrine pancreatic defects**
   - Chronic pancreatitis
   - Pancreatectomy
   - Neoplasia
   - Cystic fibrosis
   - Hemachromatosis
   - Fibrocalculous pancreatopathy
6. **Endocrinopathies**
   - Acromegaly
   - Cushing syndrome
   - Hyperthyroidism
   - Pheochromocytoma
   - Glucagonoma
7. **Infections**
   - Cytomegalovirus
   - Coxsackie virus B
8. **Drugs**
   - Glucocorticoids
   - Thyroid hormone
   - α-interferon
   - Protease inhibitors
   - β-adrenergic agonists
   - Thiazides
   - Nicotinic acid
   - Phenytoin
9. **Genetic syndromes associated with diabetes**
   - Down syndrome
   - Klinefelter syndrome
   - Turner syndrome
10. **Gestational diabetes mellitus**

NTK

NORMAL INSULIN PHYSIOLOGY

- Normal glucose homeostasis regulated by:
  - 1. glucose production in the liver
  - 2. glucose uptake and utilization by peripheral tissues chiefly skeletal muscles
  - 3. actions of insulin and counter-regulatory hormones, e.g., glucagon, on glucose
- Insulin and glucagon have opposing regulatory effects on glucose homeostasis
- During fasting states, low insulin and high glucagon levels facilitate gluconeogenesis and glycogenolysis while decreasing glycogen synthesis→ prevents hypoglycemia

MK

Regulation of Insulin Release

- Insulin and C-peptide are secreted in equimolar quantities after physiologic stimulation
- C-peptide levels used to measure endogenous insulin secretion
- Glucose most important stimulus for insulin synthesis and release
- Intestinal hormones, leucine, & arginine stimulate insulin release but not synthesis
- GLUT-2: insulin-independent, glucose-transport protein that facilitates glucose uptake in B-cells during hyperglycemia

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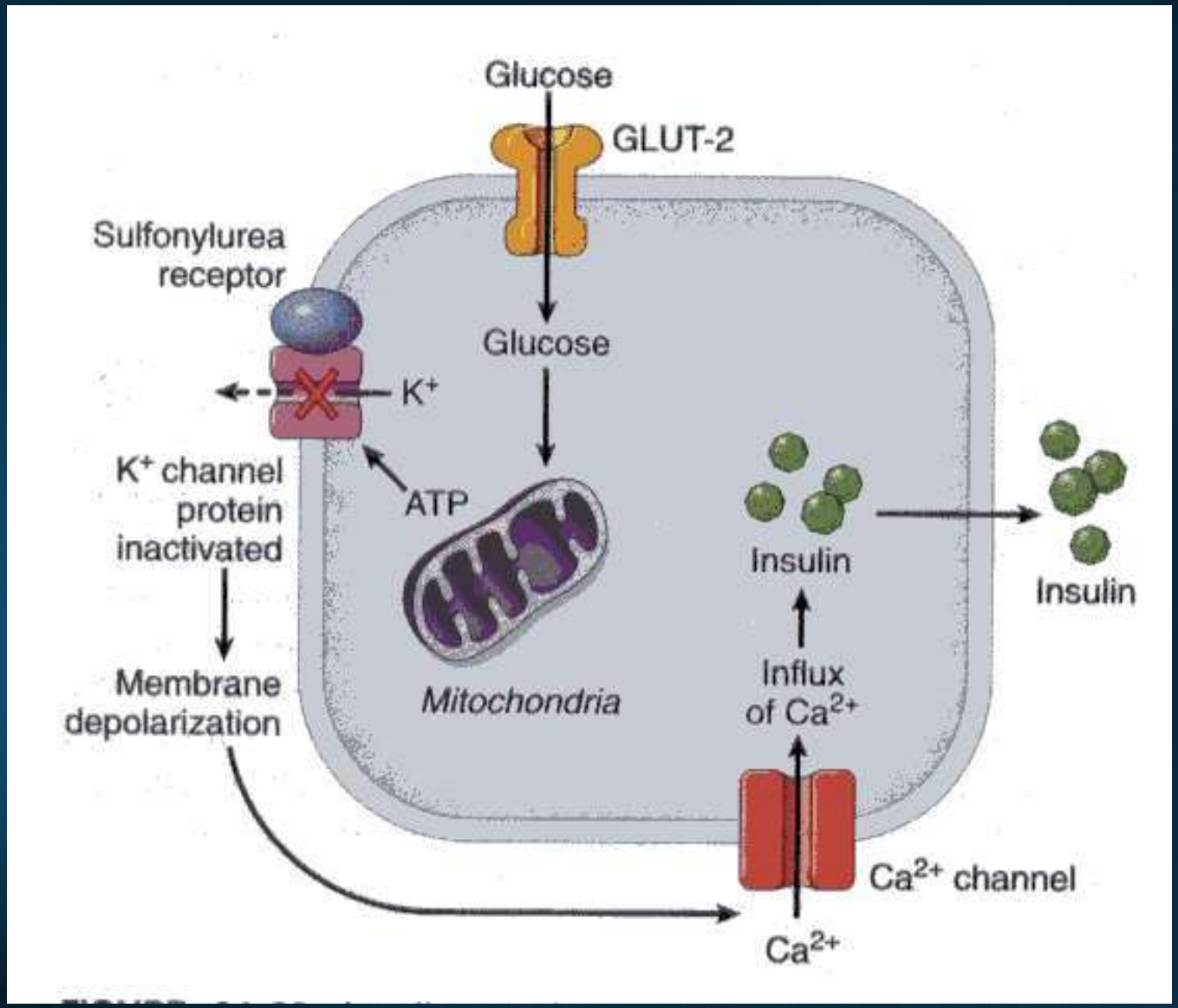
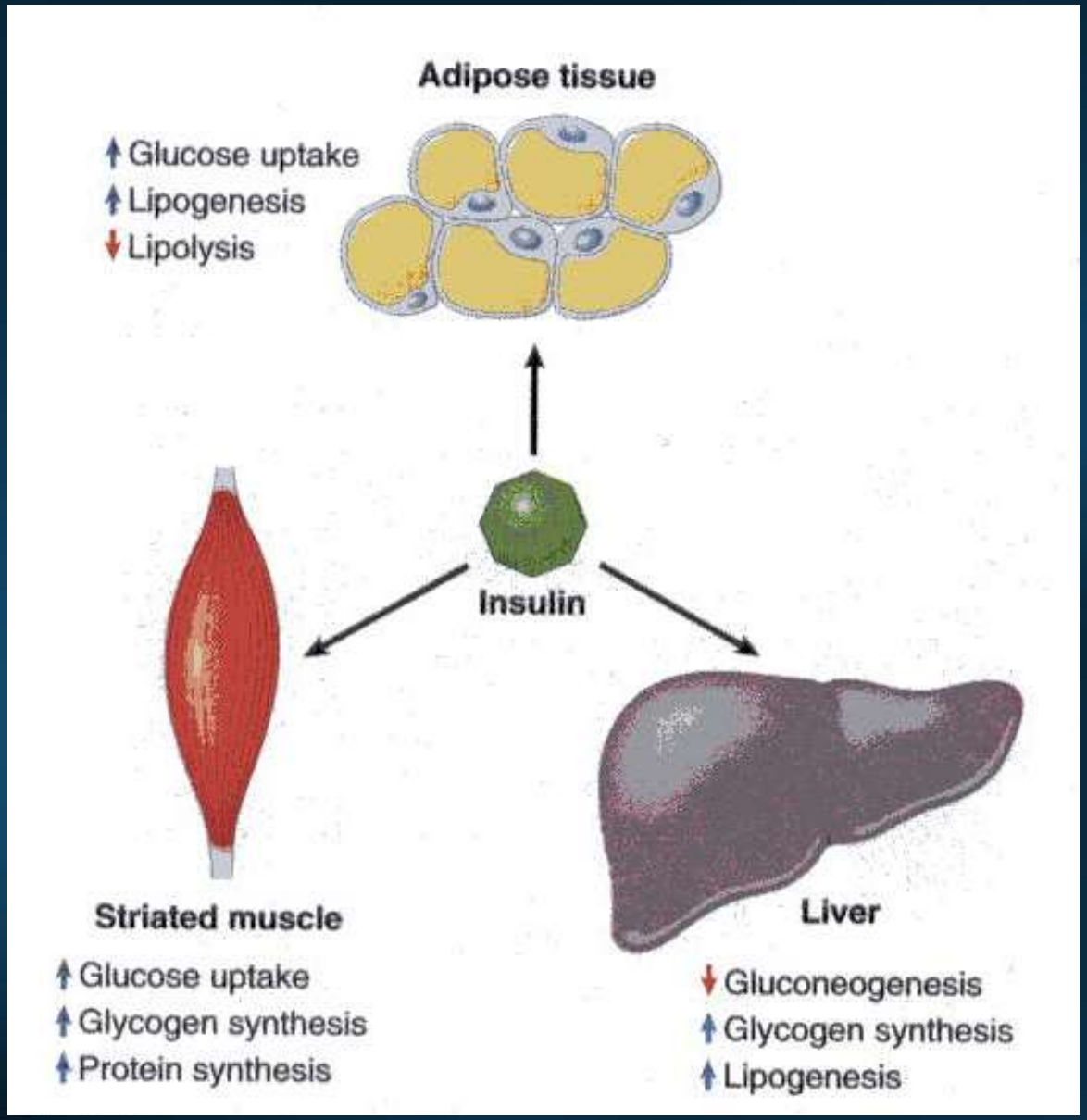
Regulation of Insulin Release



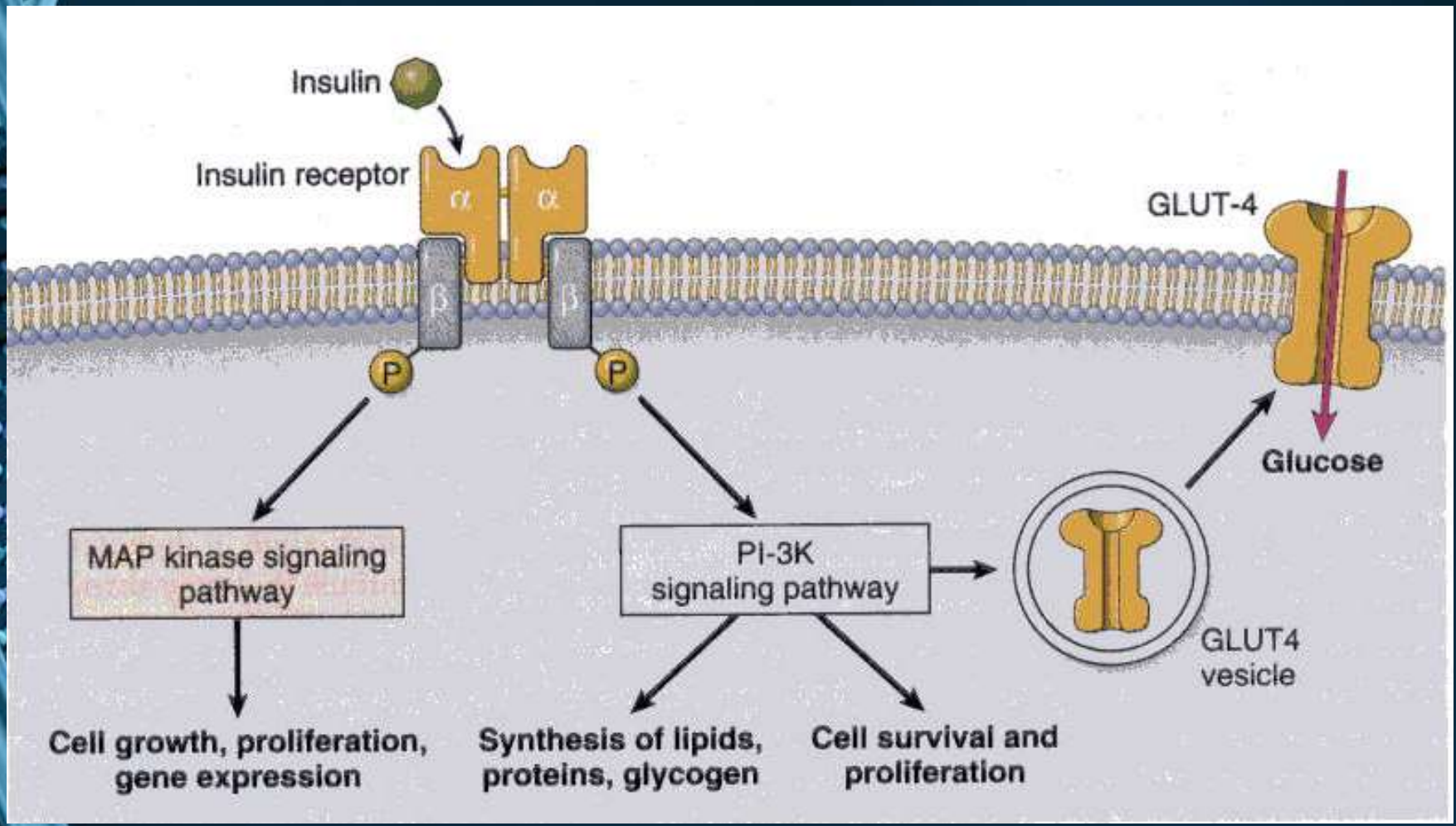
Metabolic Actions of Insulin



Metabolic Actions of Insulin

- Most potent anabolic hormone with multiple synthetic and growth promoting effects
- Principal metabolic function: increase rate of glucose transport into striated muscles, fat cells, and liver
- Glucose uptake in other peripheral tissues, especially the brain, is insulin-independent
- Anabolic effects due increased synthesis and decreased degradation of glycogen, lipids, and proteins

Insulin Action on Target Cell



Pathogenesis of Type 1 Diabetes Mellitus

- Results from severe lack of insulin caused by an immunologically-mediated destruction of B-cells
- Commonly develops in childhood, manifest at puberty, and progresses with age
- An autoimmune disease where genetic susceptibility and environmental factors play important roles
- Idiopathic type 1 DM: rare, evidence for autoimmunity not definitive

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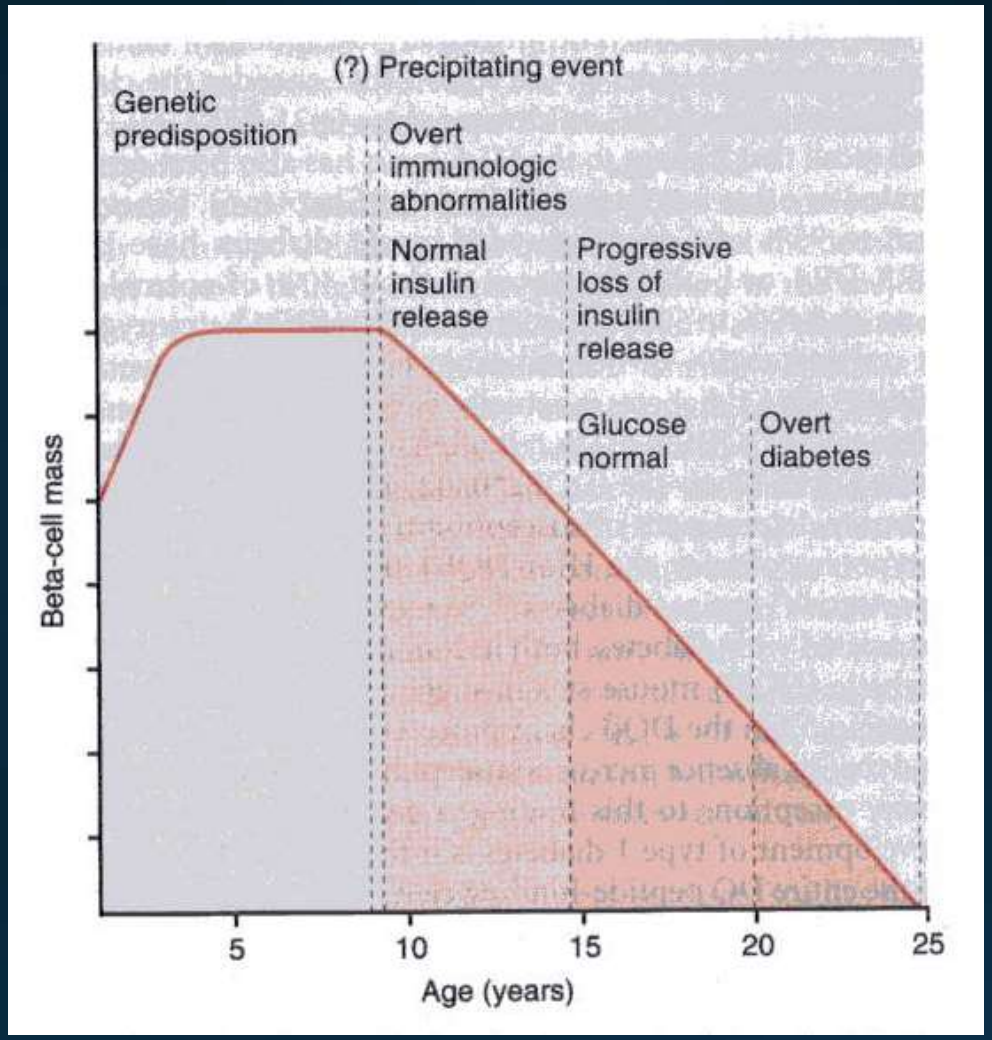
Mechanisms of B-cell Destruction

- T-lymphocytes reacting against B-cell antigens: CD4+ T cells & CD8+ cytotoxic T lymphocytes → insulitis
- Locally produced cytokines damage B-cells: IFN-gamma by T-cells; TNF & IL-1 by macrophage→ apoptosis
- Autoantibodies against islet cells and insulin in 70-80%
- Hyperglycemia and ketosis occur after more than 90% B-cells destroyed



Pathogenesis of Type 1 Diabetes Mellitus

- Genetic susceptibility:
  - Mapped to at least 20 loci
  - Most important is class II MHC, HLA-DR3, DR4 or both in 90 -95% in chromosome 6p21
  - Non-MHC genes: insulin & CTLA-4
- Environmental factors:
  - Infections, e.g., viruses, coxsackievirus B, mumps, CMV, rubella, & IM→ tissue damage & inflammation or produce proteins that mimic self-antigen

Pathogenesis of Type 2 Diabetes Mellitus

- Genetic factors even more important than in type 1 diabetes
- 50 – 90% concordance in identical twins
- Metabolic defects:
  - Insulin resistance to the effects of insulin on glucose uptake, metabolism, or storage
  - B-cell dysfunction, manifest as both qualitative and quantitative defects, e.g., inadequate insulin secretion & decreased B-cell mass, islet degeneration, & amyloid deposition

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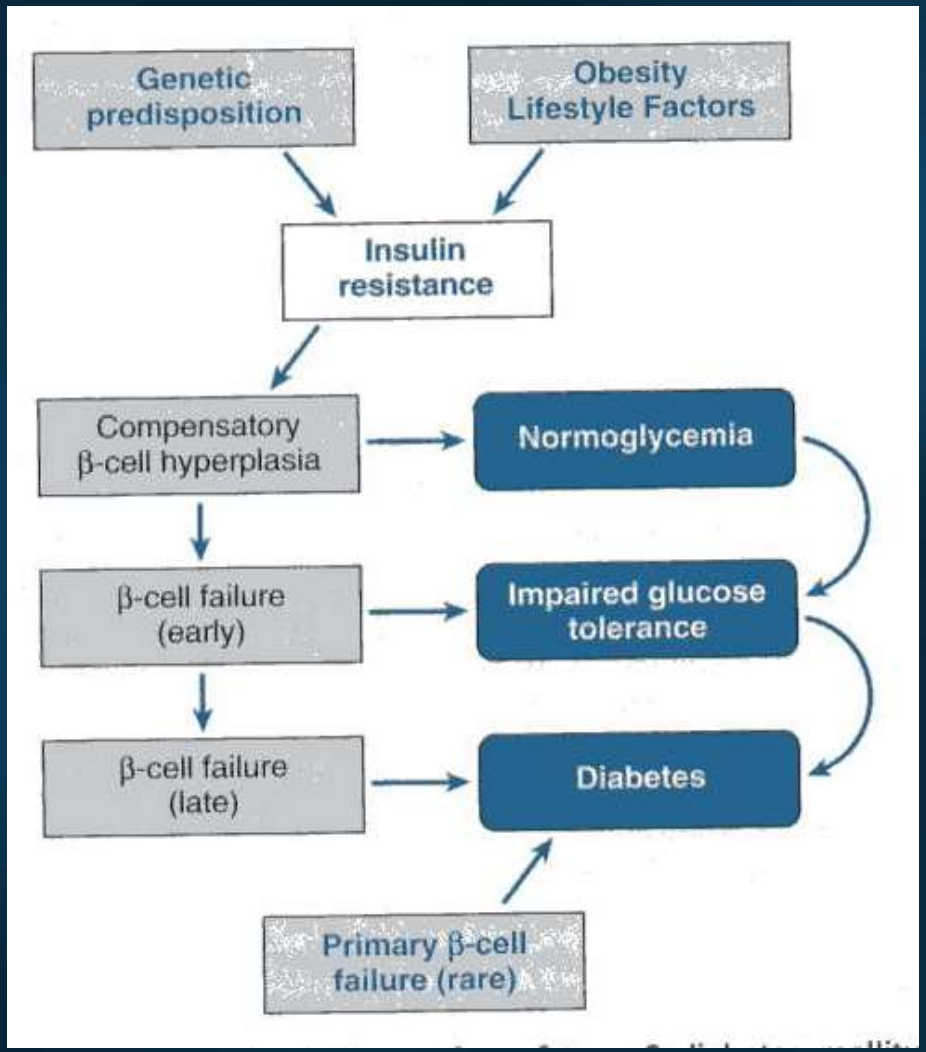
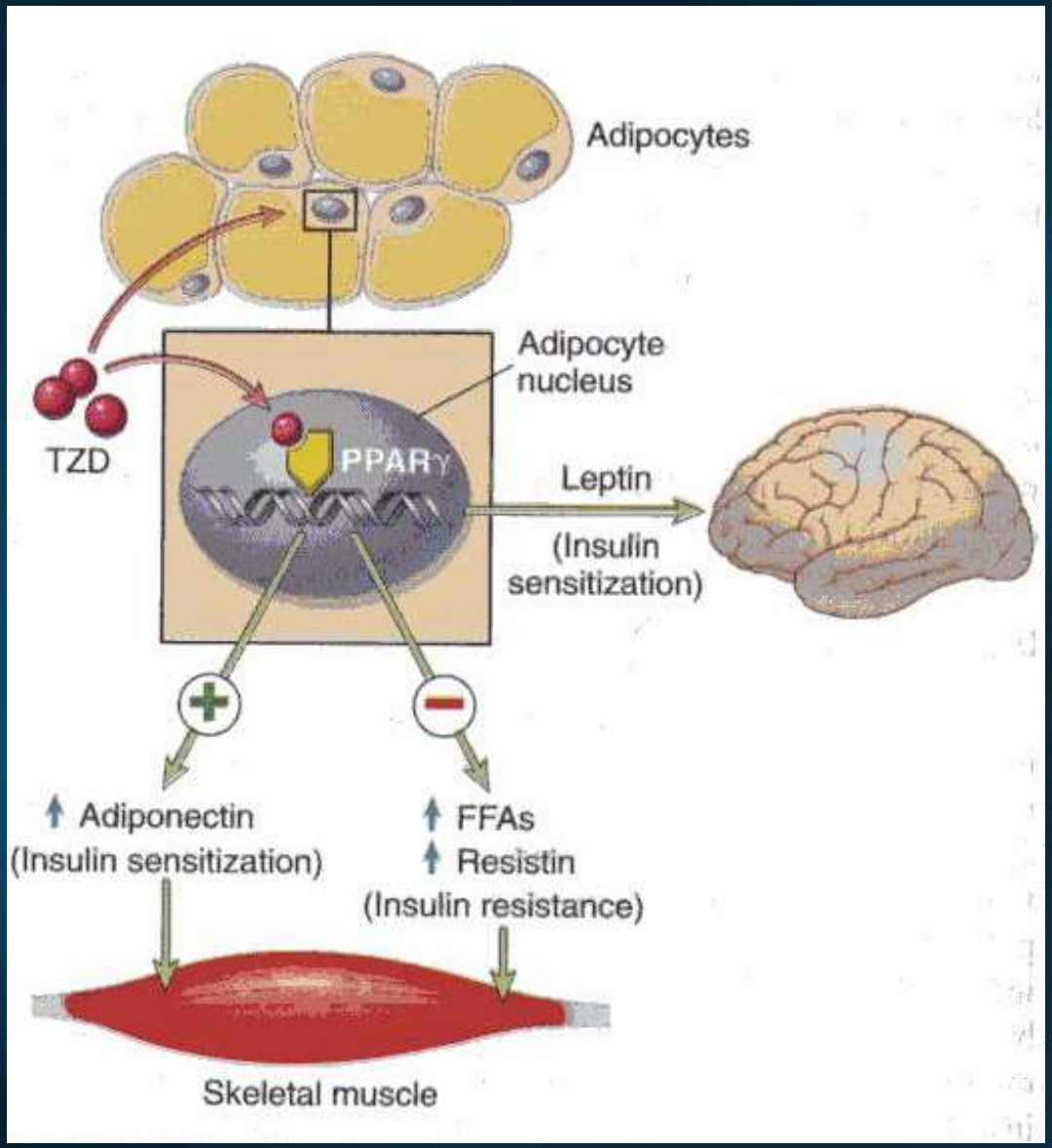
Pathogenesis & Metabolic Staging in Type 2 Diabetes Mellitus



Obesity and Insulin Resistance



Monogenic Forms of Diabetes

- Result from either a primary defect in B-cell function or defect in insulin/insulin receptor signaling
- MODY: 2 – 5%; primary defect in B-cell function w/o B-cell loss
- MODY1, 3, & 5: severe B-cell insulin secretory defects→ diabetic complications
- MODY2: mild chronic hyperglycemia; gestational diabetes
- Vast majority do not develop type 2 DM

Pathogenesis of Long Term Complications of Diabetes

- Complications:
  - 1. macrovascular–accelerated atherosclerosis
  - 2. microvascular – diabetic retinopathy, nephropathy, and neuropathy
- Mechanisms:
  - 1. formation of AGEs
  - 2. activation of Protein Kinase C
  - 3. Intracellular hyperglycemia with disturbances in polyol pathways

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Morphology of Diabetes

- Pancreas:
  - Type 1: reduced number & size of islets, insulitis, beta-cell degranulation
  - Type 2: subtle reduction of islet cell mass, amyloid replacement
- Diabetic macrovascular disease:
- Microangiopathy
- Diabetic nephropathy
- Diabetic ocular complications
- Diabetic neuropathy

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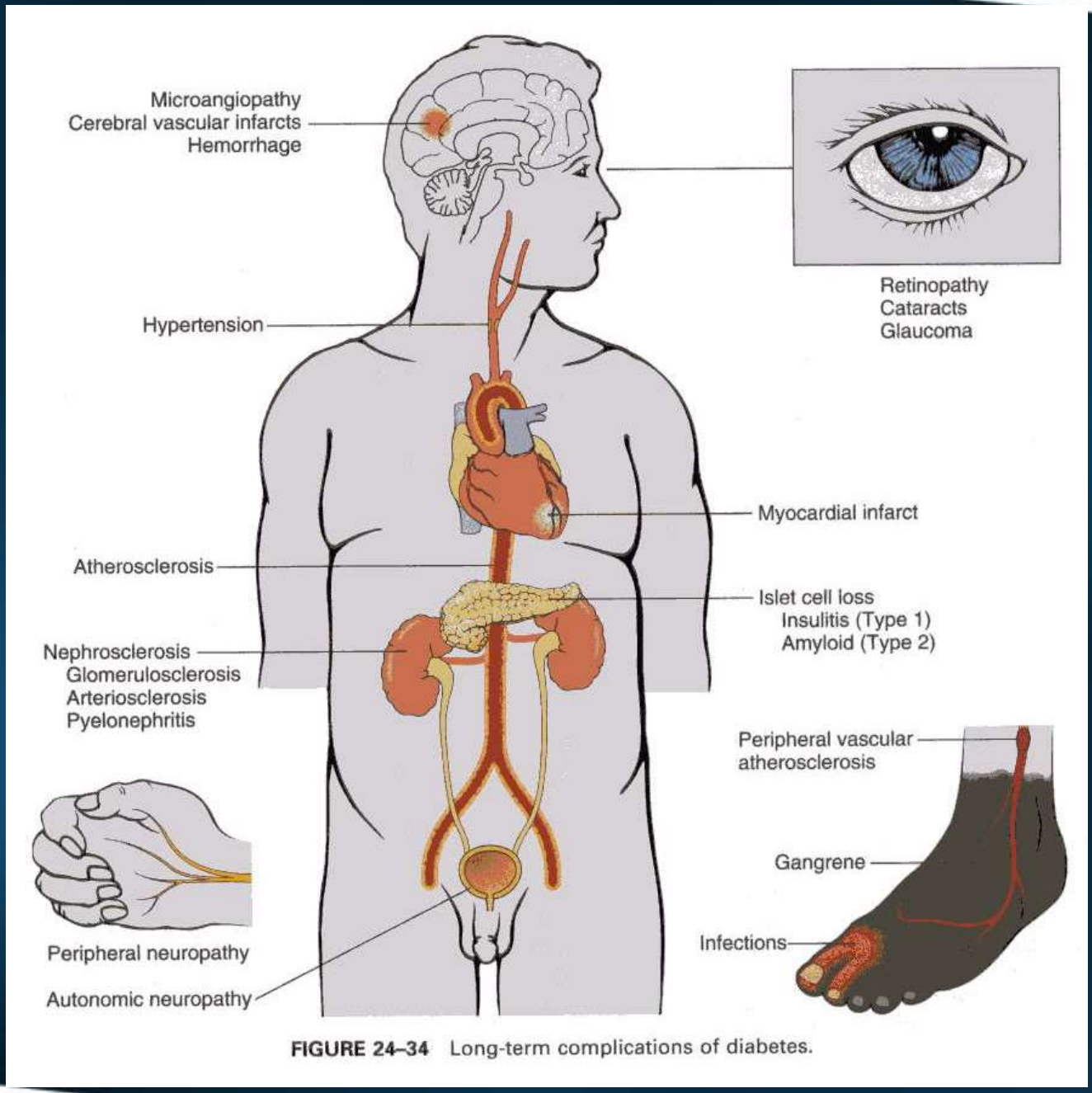
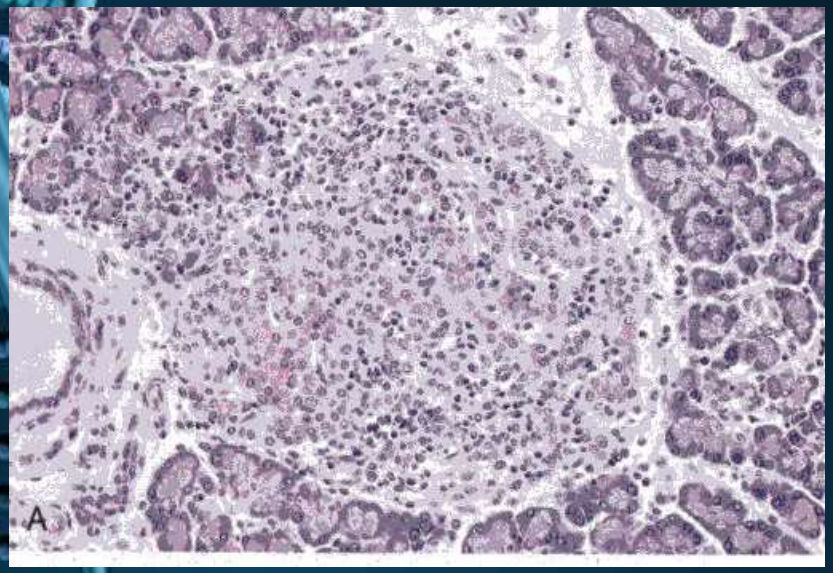
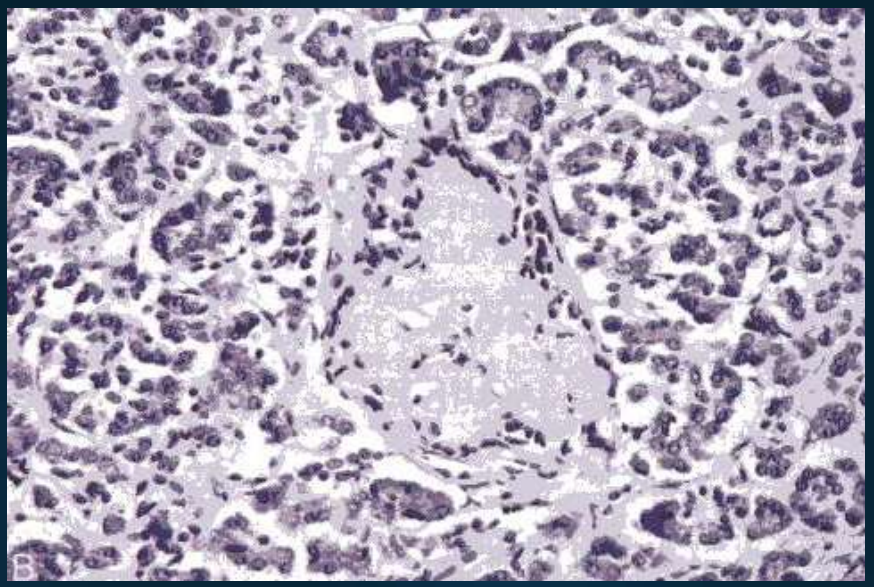
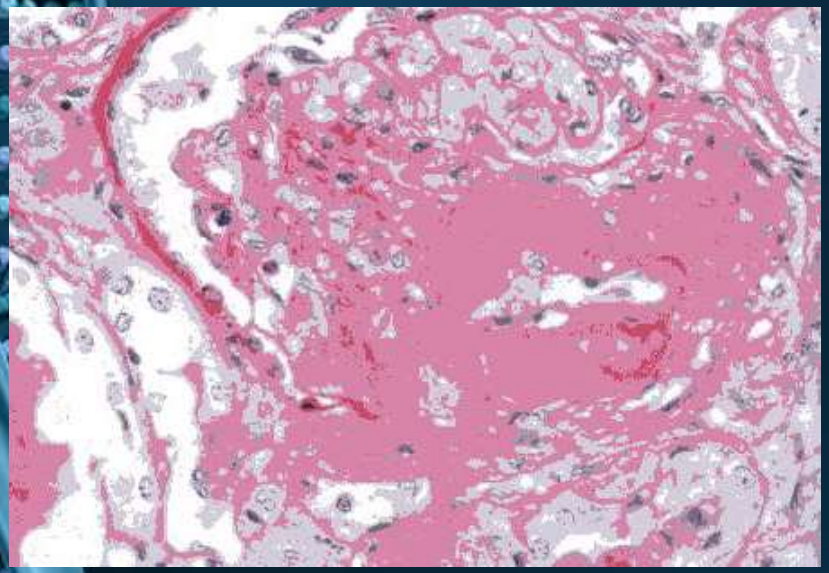


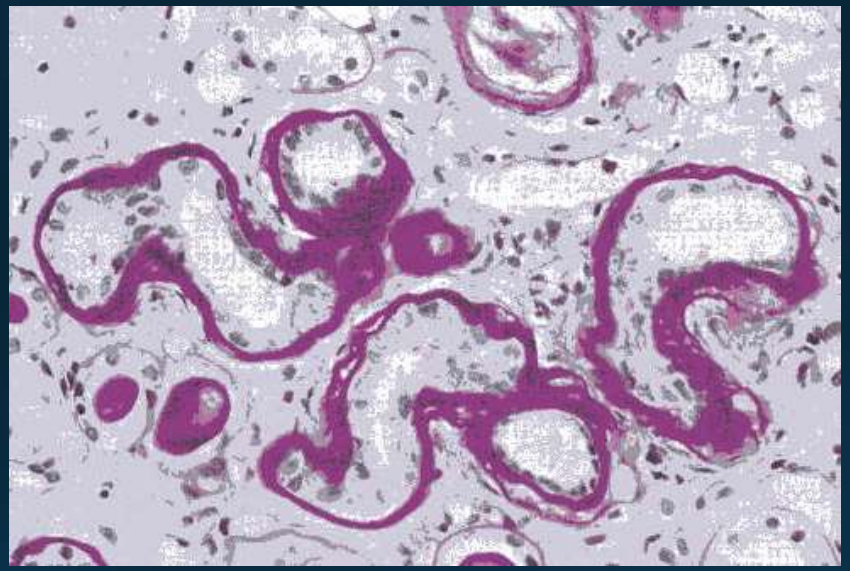
FIGURE 24–34 Long-term complications of diabetes.

Diabetes Mellitus: Morphology









Type I DM: Metabolic Derangements & Clinical Features

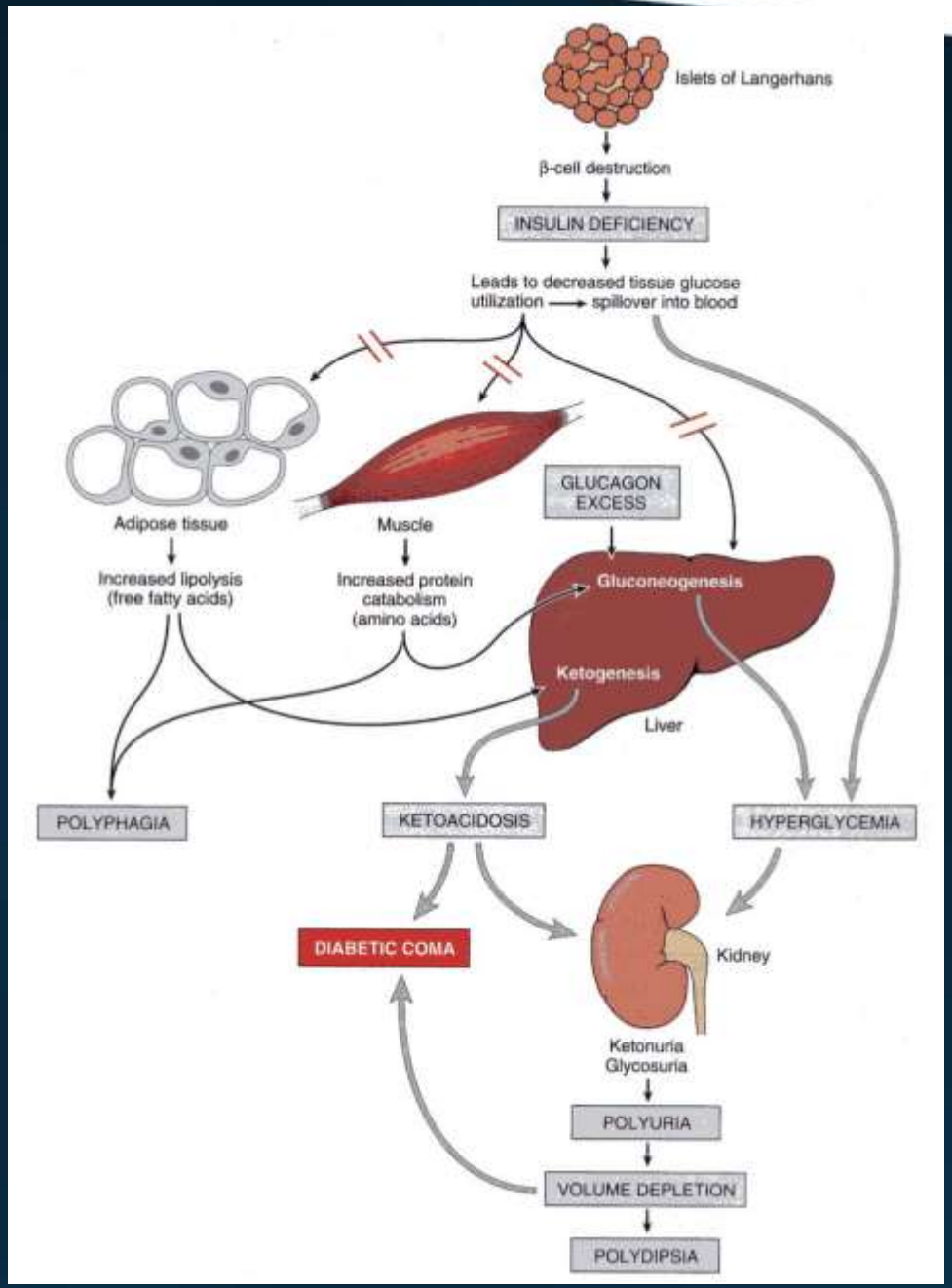


TABLE 24–8 Type 1 Versus Type 2 Diabetes Mellitus (DM)

	Type 1 DM	Type 2 DM
Clinical	Onset: <20 years Normal weight Markedly decreased blood insulin Anti-islet cell antibodies Ketoacidosis common	Onset: >30 years Obese Increased blood insulin (early);normal to moderate decreased insulin (late) No anti-islet cell antibodies Ketoacidosis rare; nonketotic hyperosmolar coma
Genetics	30–70% concordance in twins Linkage to MHC Class II HLA genes	50–90% concordance in twins No HLA linkage Linkage to candidate diabetogenic genes (PPARγ, calpain 10)
Pathogenesis	Autoimmune destruction of β-cells mediated by T cells and humoral mediators (TNF, IL-1, NO) Absolute insulin deficiency	Insulin resistance in skeletal muscle, adipose tissue and liver β-cell dysfunction and relative insulin deficiency
Islet cells	Insulitis early Marked atrophy and fibrosis β-cell depletion	No insulitis Focal atrophy and amyloid deposition Mild β-cell depletion

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Diabetes Mellitus: Treatment

- Primary prevention of type 2 diabetes: lifestyle and dietary alterations
- Secondary prevention of diabetic complications: strict glycemic control
- Islet cell transplantation: cure for type 1 diabetes

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PANCREATIC ENDOCRINE NEOPLASMS

- Islet cell tumors
- Rare, 2% of all pancreatic neoplasms
- Single or multiple; benign or malignant
- Propensity to elaborate hormones, some nonfunctional
- Features suggestive of CA: infiltration beyond capsule, high mitotic index, tumor necrosis, & cellular atypia
- Unequivocal criteria for malignancy: Metastasis, vascular invasion, and gross invasion of adjacent viscera

PANCREATIC ENDOCRINE NEOPLASMS

- Hyperinsulinism: Insulinoma
  - Triad; hypoglycemia, <50mg/dL, CNS manifestations, precipitated by fasting or exercise, relieved by feeding or IV glucose
- Hypergastrinemia (Zollinger-Ellison syndrome): Gastrinomas→ severe PU in 90-95% of patients; >50% locally invasive or have metastasized on diagnosis; 25%, MEN-1; >50%, diarrhea
- Multiple endocrine neoplasia
- Others: glucagonomas, somatostatinomas, VIPomas (WDHA), Pancreatic carcinoid tumors

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ADRENAL GLANDS

- 4 gm
- Cortex
  - Zona glomerulosa: mineralocorticoid; aldosterone
  - Zona fasciculata: glucocorticoids; cortisol
  - Zona reticularis: sex steroids; androgen and estrogen
- Medulla: catecholamines; epinephrine

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ADRENAL PATHOLOGY

- Hyperadrenal clinical syndromes
  - Cushing syndrome
  - Hyperaldosteronism
  - Adrenogenital or virilizing syndromes
- Adrenal insufficiency
  - Primary acute adrenocortical insufficiency
  - Primary chronic adrenocortical insufficiency (Addison disease)
  - Secondary adrenocortical insufficiency

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Cushing Syndrome (Hypercortisolism)

- Possible sources of excess cortisol
  - Administration of exogenous glucocorticoids
  - Primary hypothalamic-pituitary diseases associated with hypersecretion of ACTH
  - Hypersecretion of cortisol by an adrenal adenoma, carcinoma, or nodular hyperplasia
  - Secretion of ectopic ACTH by a nonendocrine neoplasm

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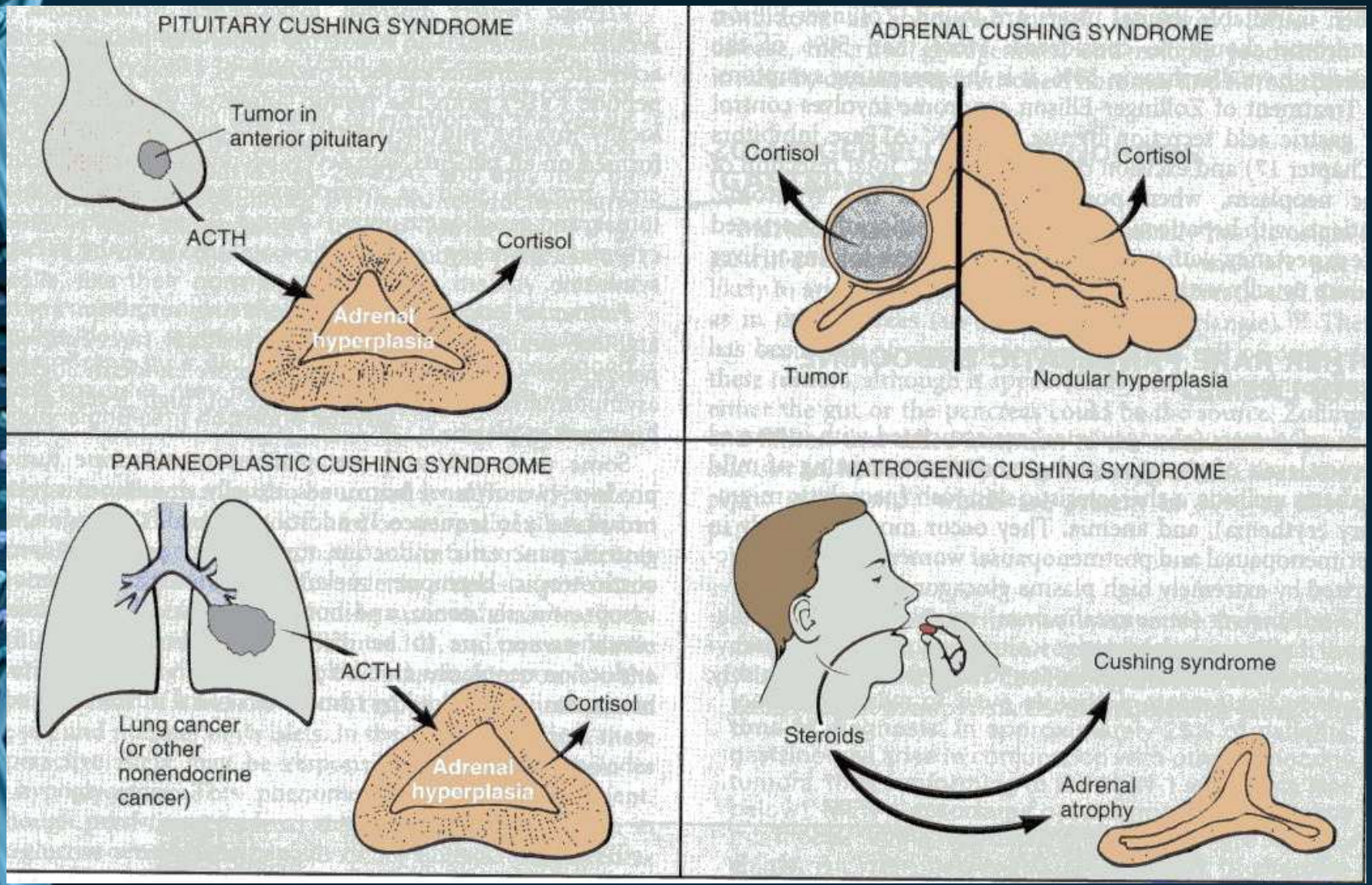
CUSHING SYNDROME



Cushing Syndrome: Morphology

- Pituitary: Crooke hyaline change
- Adrenals: depends on cause
  - Cortical atrophy in exogenous glucocorticoids
  - Diffuse hyperplasia) endogenous glucocorti-
  - Nodular hyperplasia) coids; atrophy of adja-
  - Adenoma, rarely carcinoma) cent adrenal

  Cortex and that of contralateral adrenal gland

TABLE 24–9 Major Features of Cushing Syndrome with Approximate Frequency

Clinical Features	Percentages
Central obesity (about trunk and upper back)	85–90%
Moon facies	85%
Weakness and fatigability	85%
Hirsutism	75%
Hypertension	75%
Plethora	75%
Glucose intolerance/diabetes	75/20%
Osteoporosis	75%
Neuropsychiatric abnormalities	75–80%
Menstrual abnormalities	70%
Skin striae (sides of lower abdomen)	50%

CUSHING SYNDROME: DIAGNOSIS

- 1. increased 24-Hour urine free cortisol
- 2. loss of normal diurnal pattern of cortisol secretion
- 3. serum ACTH level and measurement of urinary steroid excretion after low and high dose dexamethasone administration
  - Pituitary Cushing syndrome
  - Ectopic ACTH
  - Cushing syndrome due to Adrenal tumor

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Hyperaldosteronism

- Chronic excess of aldosterone→ Na+ retention and K+ excretion→ hypertension and hypokalemia
- Primary hyperaldosteronism: autonomous over-production of aldosterone→ suppression of renin-angiotensin system→ decreased plasma renin activity
  - Adrenocotical neoplasm: 80% adenoma (Conn syndrome)
  - Primary adrenocortical hyperplasia
  - Glucocorticocid-remediable hyperaldosteronism

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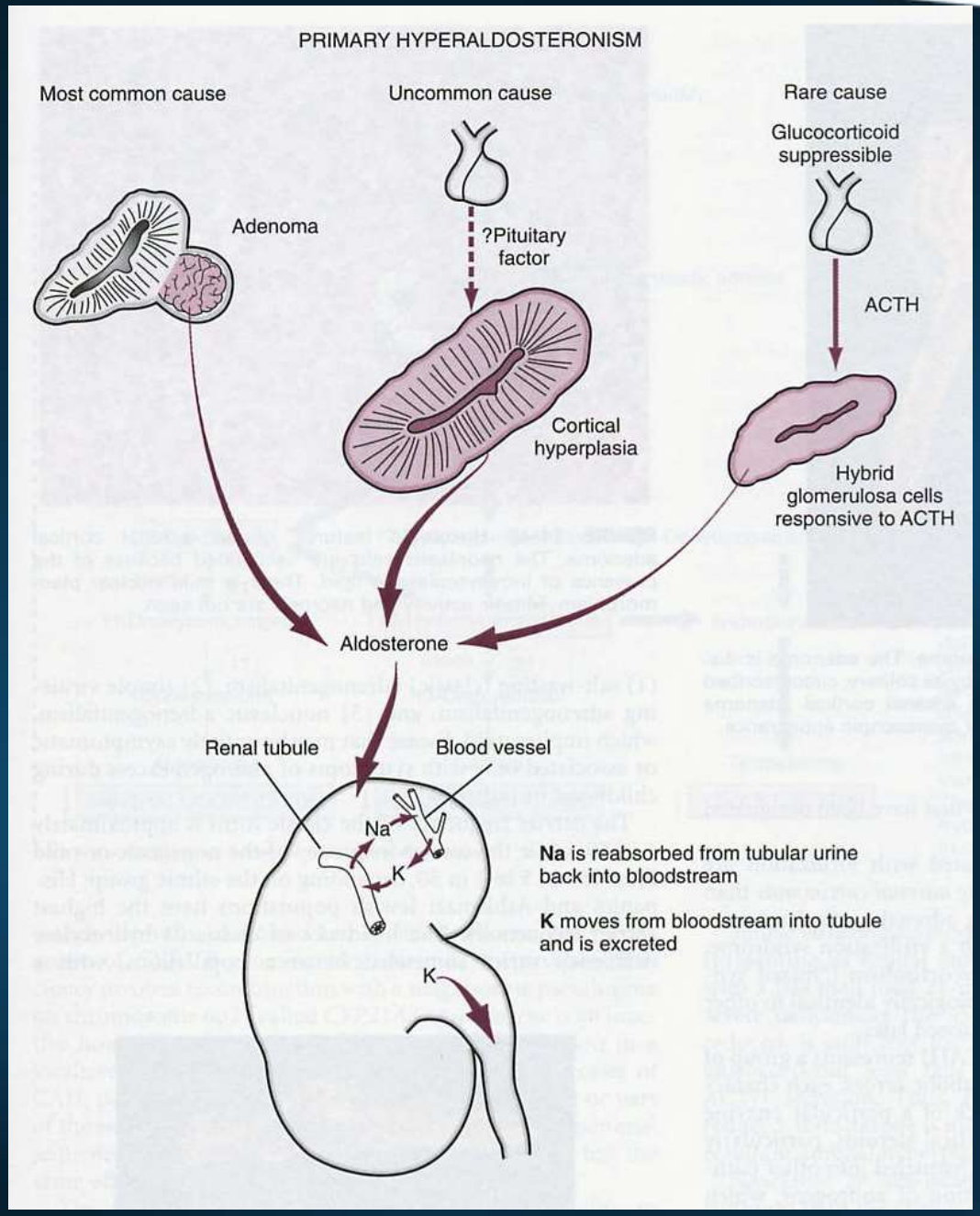
PRIMARY HYPERALDOSTERONISM
Most common cause
Uncommon cause
Rare cause
Glucocorticoid suppressible
Adenoma
?Pituitary factor
ACTH
Cortical hyperplasia
Hybrid glomerulosa cells responsive to ACTH
Aldosterone
Renal tubule
Blood vessel
Na
K
K
Na is reabsorbed from tubular urine back into bloodstream
K moves from bloodstream into tubule and is excreted

Hyperaldosteronism

- Secondary hyperaldosteronism: aldosterone release occurs in response to activation of the renin-angiotensin system
  - Decreased renal perfusion (arteriolar nephrosclerosis, renal artery stenosis)
  - Arterial hypovolemia and edema (CHF, cirrhosis, nephrotic syndrome)
  - Pregnancy (estrogen-induced increases in plasma renin substrate)

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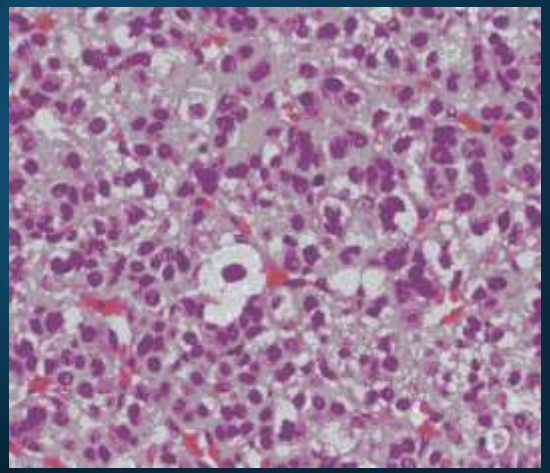

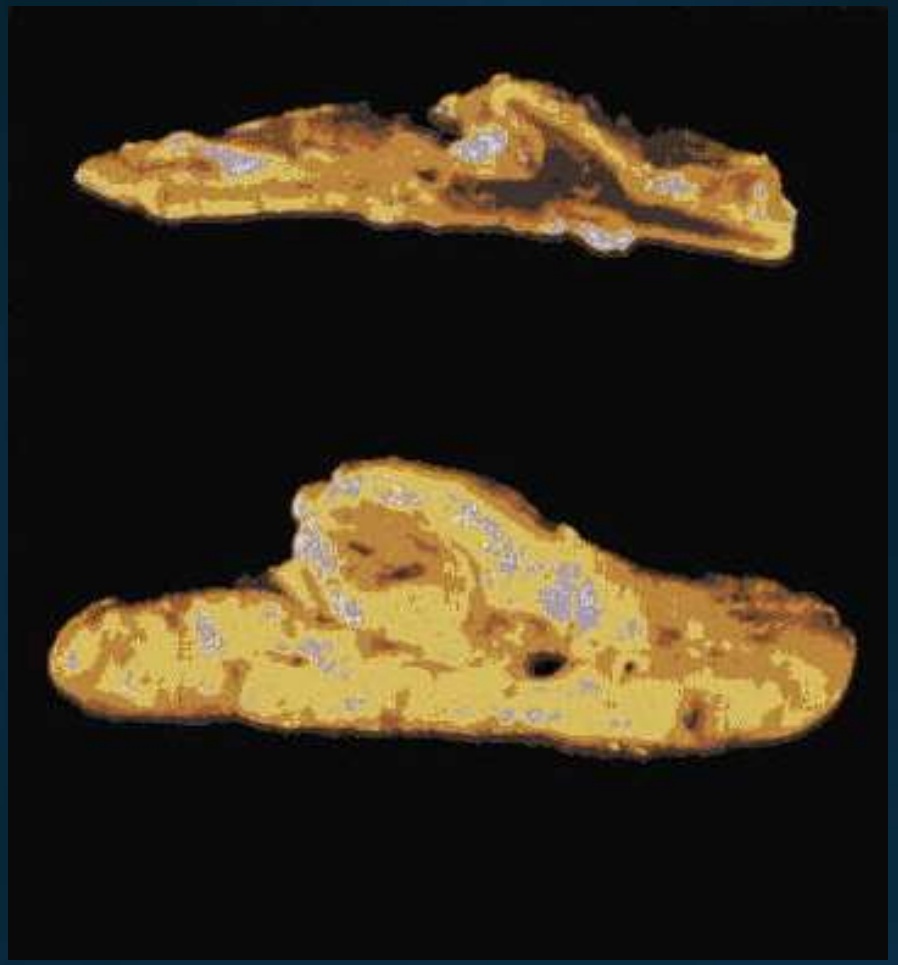

Primary Hyperaldosteronism: Clinical Course

- Hypertension
- Hypokalemia→ neuromuscular manifestations, weakness, paresthesias, visual disturbance, occasionally, tetany
- Diagnosis: elevated levels of aldosterone and depressed levels of renin
- Treatment: adenoma – excision; 1^{o} adrenal hyperplasia – aldosterone antagonist (spironolactone); 2^{o} – treat the cause

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Adrenal Insufficiency

- Primary hypoadrenalism: due to primary adrenal disease→ acute or chronic
  - Primary acute adrenocortical insufficiency (adrenal crisis): stress, massive adrenal hge
- Secondary hypoadrenalism: decreased stimulation of adrenals due to deficiency of ACTH

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TABLE 24–10 Adrenocortical Insufficiency

Primary Insufficiency

Loss of cortex
- Congential adrenal *hypo*plasia
  - X-linked adrenal hypoplasia (*DAX-1* gene on Xp21)
  - "Miniature" type adrenal hypoplasia (unknown cause)
- Adrenoleukodystrophy (*ALD* gene on Xq28)
- Autoimmune adrenal insufficiency
  - Autoimmune polyendocrinopathy syndrome type 1 (*AIRE-1* gene on 21q22)
  - Autoimmune polyendocrinopathy syndrome type 2 (polygenic
  - Isolated autoimmune adrenalitis (polygenic)
- Infection
  - Acquired immune deficiency syndrome
  - Tuberculosis
  - Fungi
  - Acute hemorrhagic necrosis (*Waterhouse-Friderichsen syndrome)*
- Amyloidosis, sarcoidosis, hemochromatosis
- Metastatic carcinoma

Metabolic failure in hormone production
- Congenital adrenal *hyper*plasia (cortisol and aldosterone deficiency with virlization)
- Drug- and steroid-induced inhibition of adrenocorticotropic hormone or cortical cell function

Secondary Insufficiency

Hypothalamic pituitary disease
- Neoplasm, inflammation (sarcoidosis, tuberculosis, pyogens, fungi)

Hypothalamic pituitary suppression
- Long-term steroid administration
- Steroid-producing neoplasms

Waterhouse-Friderichsen Syndrome: Characteristics

- Overwhelming bacterial infection
- Rapidly progressive hypotension leading to shock
- DIC with widespread purpura
- Rapidly developing adrenocortical insufficiency associated with massive bilateral adrenal hemorrhage
  - Due to direct bacterial seeding of small vessels, DIC, endotoxin-induced vasculitis or some form of hypersensitivity vasculitis

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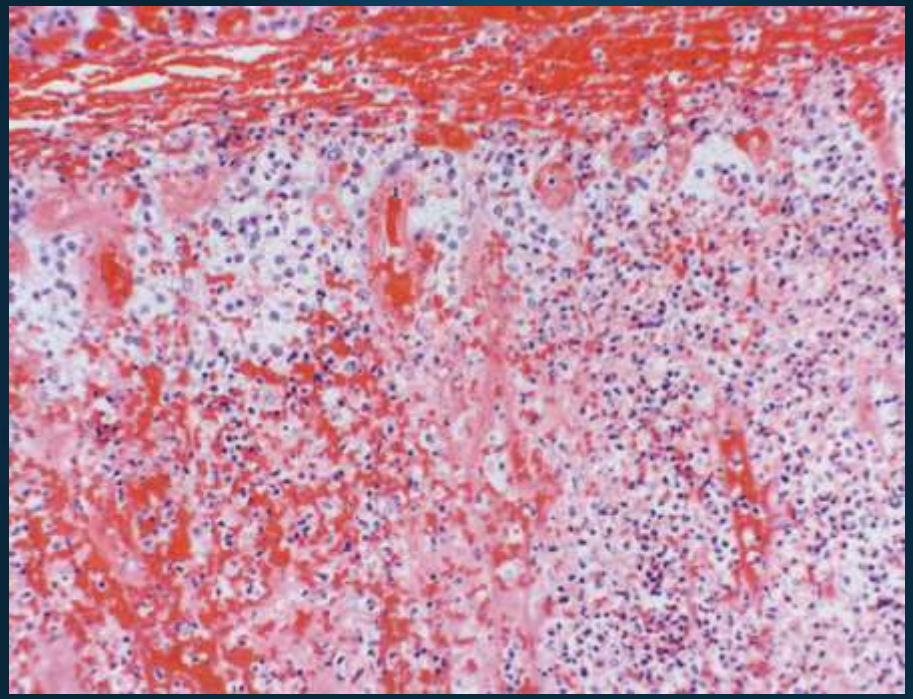
Waterhouse-Friderichsen Syndrome



Primary Chronic Adrenocortical Insufficiency (Addison disease)

- Uncommon disorder due to progressive destruction of the adrenal cortex
- Clinical manifestations appear when 90% of adrenal cortex is destroyed
- More than 90% caused by: autoimmune adrenalitis, TB, AIDS, & metastatic cancers
- S/Sx: progressive weakness, easy fatigability, git disturbance, hyperpigmentation, K+ & Na+ loss
- Treatment: corticosteroid therapy

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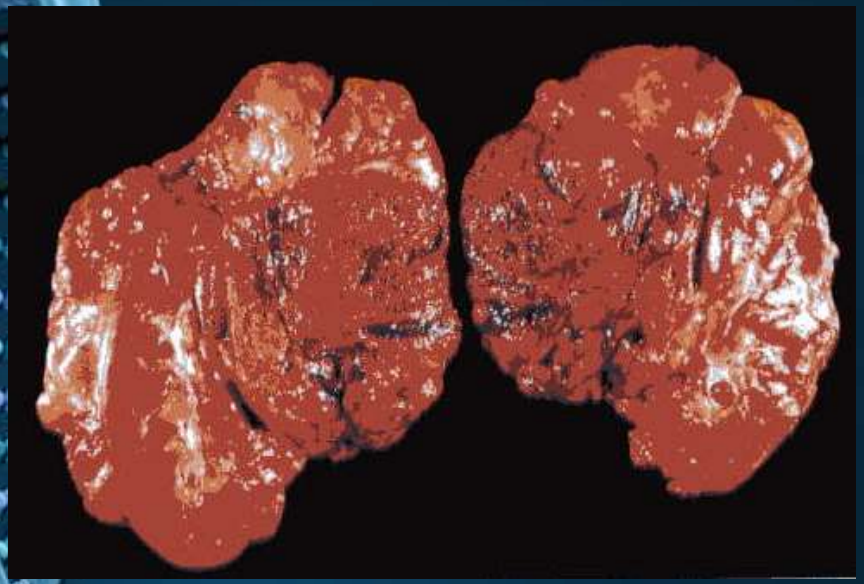
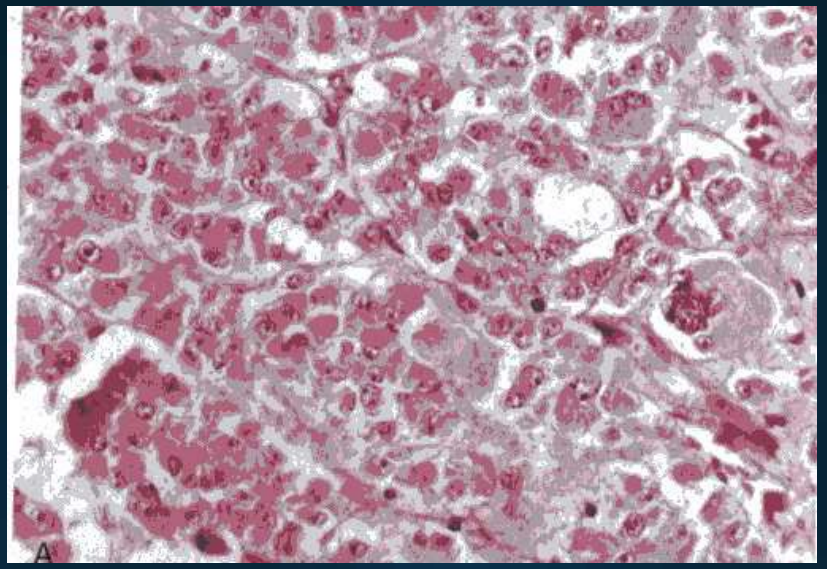
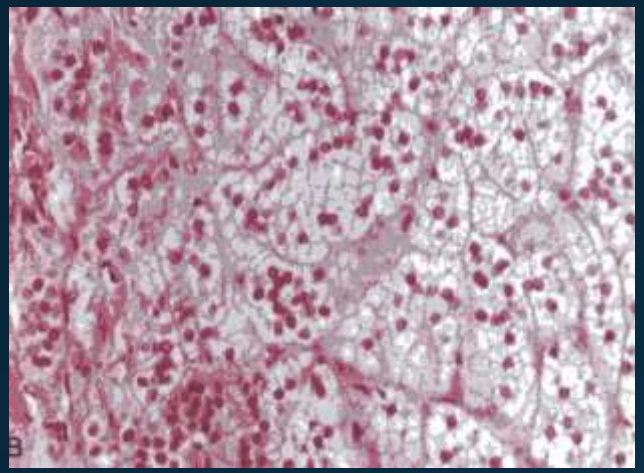
ADRENOCORTICAL NEOPLASMS

- Functional and nonfunctional adrenocortical neoplasms cannot be distinguished on the basis of morphologic features
- Based on clinical evaluation and measurement of hormone or its metabolites
- Functional adenomas→ hyperaldosteronism and Cushing syndrome
- virilizing neoplasm→ carcinoma

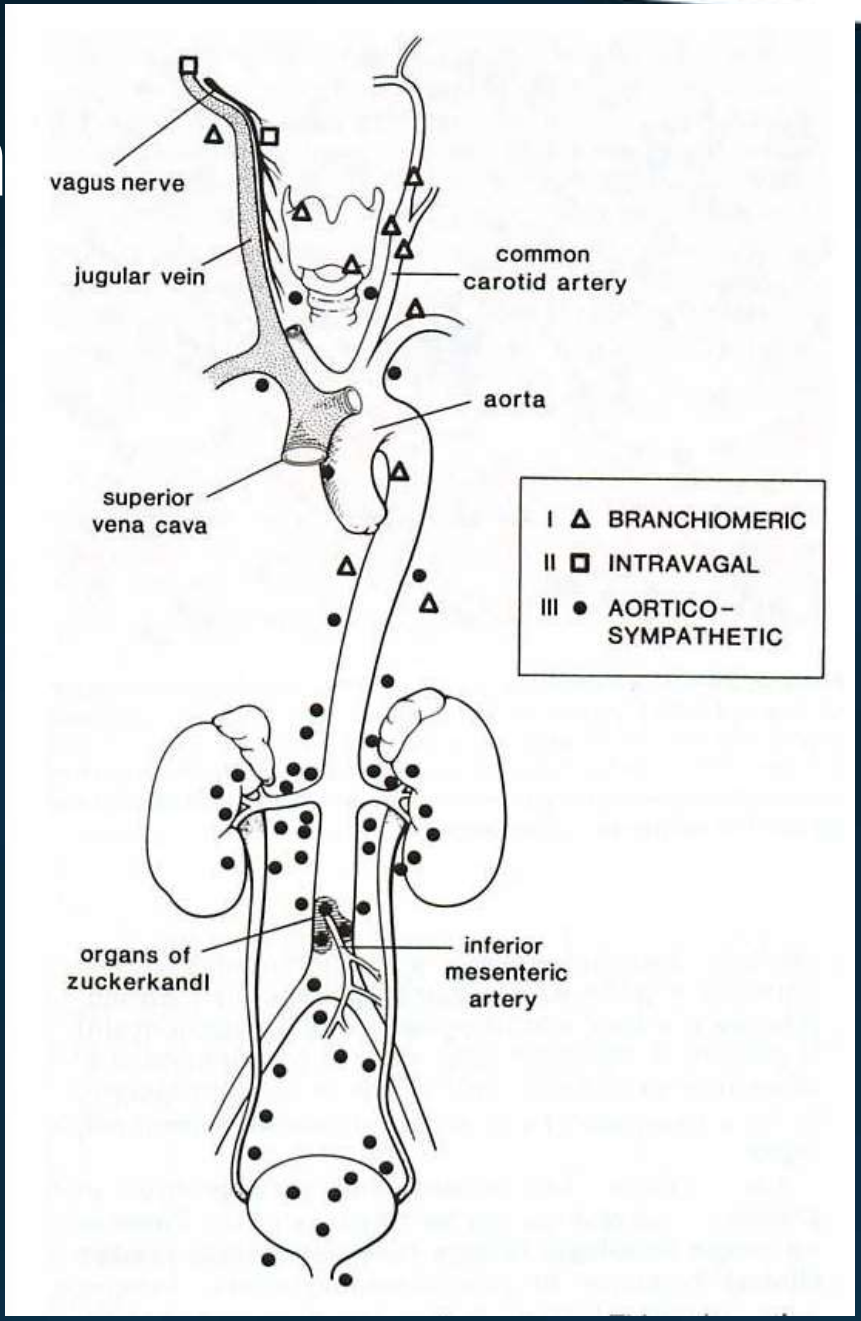
Adrenal Carcinoma







Paraganglion System



PHEOCHROMOCYTOMA

- Composed of chromaffin cells which synthesize and release catecholamines and sometime peptide hormones
- Give rise to surgically correctible forms of hypertension
- “rule of 10”
  - 10% associated with familial syndromes, extra-adrenal, bilateral, malignant, arise in childhood
  - Malignant only if with metastasis

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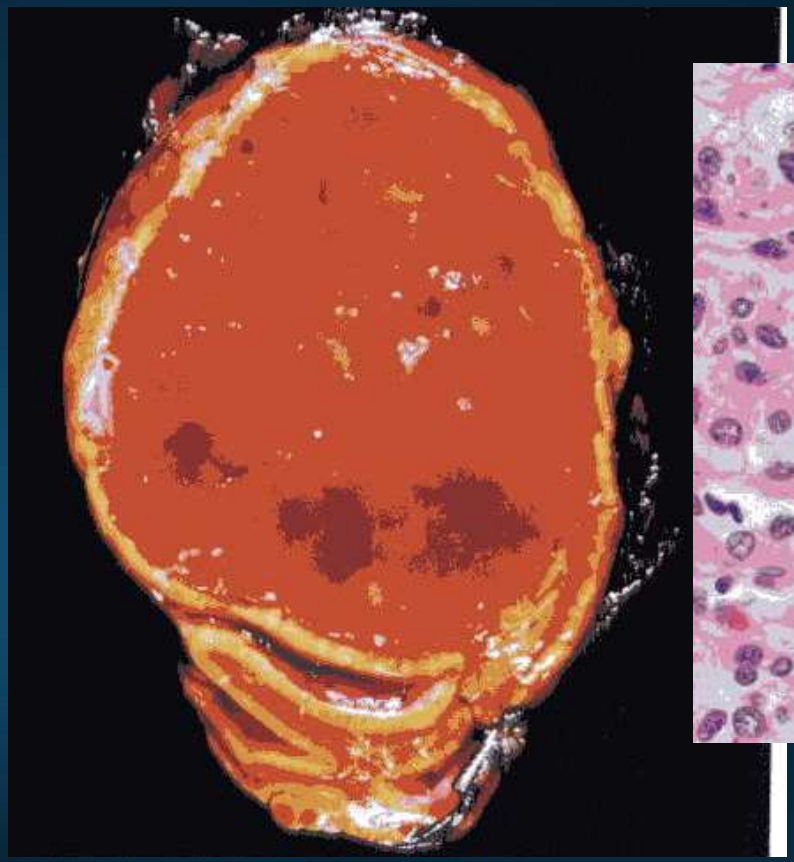
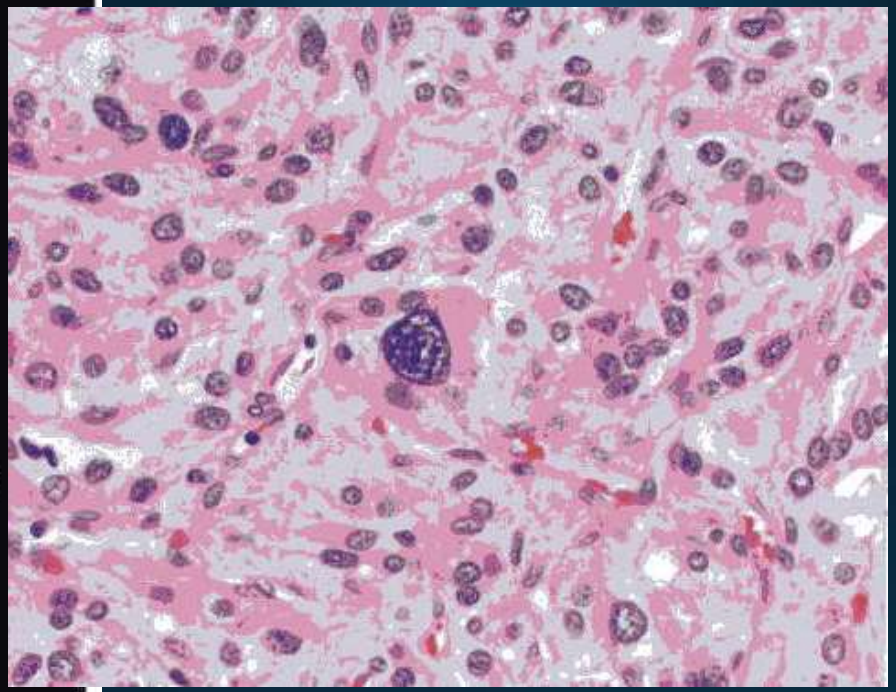
TABLE 24–11 Familial Syndromes Associated with Pheochromocytoma

Syndrome	Components
MEN, type 2A	Medullary thyroid carcinomas and C-cell hyperplasia Pheochromocytomas and adrenal medullary hyperplasia Parathyroid hyperplasia
MEN, type 2B	Medullary thyroid carcinomas and C-cell hyperplasia Pheochromocytomas and adrenal medullary hyperplasia Mucosal neuromas Marfanoid features
von Hippel-Lindau	Renal, hepatic, pancreatic, and epididymal cysts Renal cell carcinomas Pheochromocytomas Angiomatosis Cerebellar hemangioblastomas
von Recklinghausen	Neurofibromatosis Café au lait skin spots Schwannomas, meningiomas, gliomas Pheochromocytomas
Sturge-Weber	Cavernous hemangiomas of fifth cranial nerve distribution Pheochromocytomas

Pheochromocytoma: Morphology





Pheochromocytoma: Clinical Course

- Hypertension, tachycardia, palpitations, headache, sweating, tremor, and sense of apprehension
- Catecholamine cardiomyopathy: CHF, MI, ventricular fibrillation, pulmonary edema, Cerebrovascular accidents
- Diagnosis: urinary excretion of catecholamines & metabolites (VMA and metanephrines)
- Treatment: surgical excision (benign), anti-hypertensives

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MULTIPLE ENDOCRINE TUMOR

- MEN, Type 1: Wermer syndrome; 3Ps (parathyroid, pancreas, & pituitary glands)
- MEN, type 2A: Sipple syndrome; pheochromocytoma, medullary carcinoma, and parathyroid hyperplasia
- MEN, type 2B: MEN-2A + neuromas or ganglioneuromas and marfanoid habitus
- Familial medullary thyroid cancer: variant of MEN-2A, no other clinical manifestations; genetic testing done among kindred; RET mutation→ prophylactic thyroidectomy

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TABLE 24–12 Multiple Endocrine Neoplasia (MEN) Syndromes

	MEN-1	MEN-2A	MEN-2B
Pituitary	Adenomas		
Parathyroid	Hyperplasia +++ Adenomas +	Hyperplasia +	
Pancreatic islets	Hyperplasia ++ Adenomas ++ Carcinomas +++		
Adrenal	Cortical hyperplasia	Pheochromocytoma ++	Pheochromocytoma +++
Thyroid		C-cell hyperplasia +++ Medullary carcinoma +++	C-cell hyperplasia +++ Medullary carcinoma +++
Extraendocrine changes			Mucocutaneous ganglioneuromas Marfanoid habitus
Mutant gene locus	*MEN1*	*RET*	*RET*

Relative frequency: +, uncommon; +++, common.

PINEAL GLAND

- Minute, pinecone-shaped, 100 – 180 mg lying between the superior colliculi at the base of the brain
- Composed of loose, neuroglial stroma enclosing nests of pineocytes (cells with photosensory and neuroendocrine function); 3rd eye
- Pinealomas: pineoblastomas (primitive embryonal tumor) and pineocytomas (pineocytomatous pseudorosettes)
- S/Sx: pressure effects
- Treatment: excision difficult

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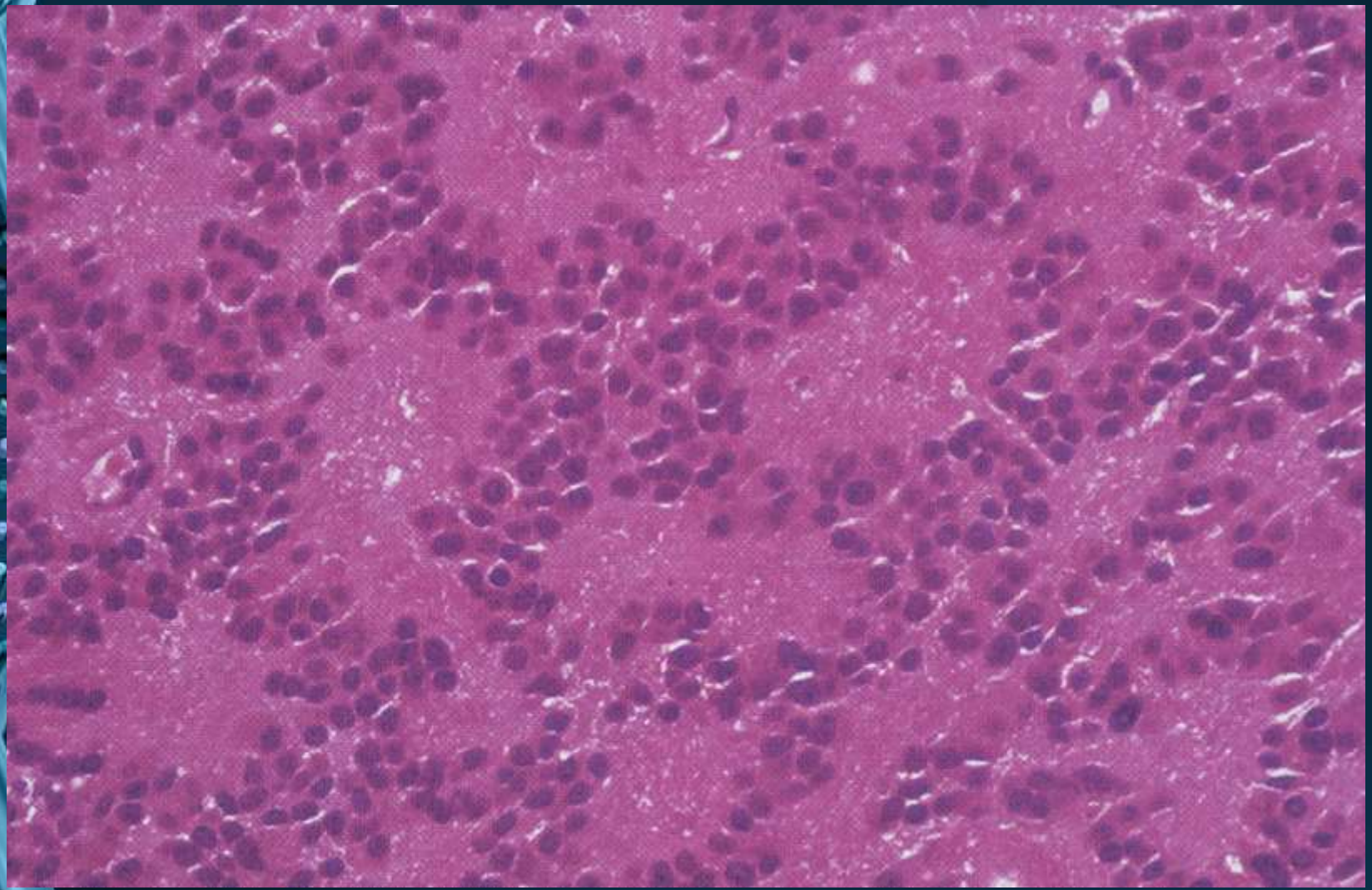
PINEOCYTOMA



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