1 **THE ENDOCRINE SYSTEM**

2 **ENDOCRINE ORGANS**

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

3 **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

4 **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

5

6

7 **ANTERIOR PITUITARY HORMONES**

8 **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

9 **Pituitary Gland: Clinical Manifestations**

1 • 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
-

10 **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

11 **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
-

12

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

14 **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

15 **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
-

16 **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

17 **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
-

18 **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

19 **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

20 **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
-

21 **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
-

22 **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

23 **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

24 **Thyroid Gland: Pathology**

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

25 **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

26 **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

27 **HYPERTHYROIDISM: Clinical Course**

28 **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

29

30 **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

31

32 **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

33 **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

34 **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

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35 **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

•

36 **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

-

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37 **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

38 **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

39 **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

40 **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

41 **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
-

42 **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

43 **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
-

44 **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

45 **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

46 **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
-

47 **MULTINODULAR GOITER**
- 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

48 **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
-

49 **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

50 **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
-
-
-

51 **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)

52 **THYROID ADENOMA:Morphology**

53 **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
-

54 **OTHER BENIGN TUMORS**

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

55 **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%)
-

56 **CARCINOMAS: Pathogenesis**

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

57 **CARCINOMAS:**
Pathogenesis (Genetic Factors)

58 **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

59 **PAPILLARY CARCINOMA: Morphology**

60 **PAPILLARY CARCINOMA**

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

61 **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
-

62 **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?

63 **FOLLICULAR CARCINOMA: Morphology**

64 **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

65 **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

66 **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

67 **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
-

68 **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

69 **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

70 **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

71 **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
-
-

72 **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

73 **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
  -

74 **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
-

75 **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

76 **PARATHYROID ADENOMA**

77 **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

78 **PARATHYROID GLANDS**

79 **CARDINAL FEATURES OF HYPERPARATHYROIDISM**

80 **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
-

81 **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

82 **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

83 **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

84 **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

85 **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

86 **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

87 **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.

88 **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
-

89 **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

90

91 **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

92 **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

93 **Regulation of Insulin Release**

94 **Metabolic Actions of Insulin**

95 **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

96 **Insulin Action on Target Cell**

97 **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

98 **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

99 **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

100 **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

101 **Pathogenesis & Metabolic Staging in Type 2 Diabetes Mellitus**

102 **Obesity and Insulin Resistance**

103 **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

104 **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

105 **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

106

107 **Diabetes Mellitus: Morphology**

108 **Type I DM: Metabolic Derangements & Clinical Features**

109

110 **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

111 **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

112 **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
-

113 **ADRENAL GLANDS**

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

114 **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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115 **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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116 **CUSHING SYNDROME**

117 **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

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119 **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

120 **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

121

122 **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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123

124 **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° adrenal hyperplasia – aldosterone antagonist (spironolactone); 2° – treat the cause

125 **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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127 **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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128 **Waterhouse-Friderichsen Syndrome**

129 **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

130 **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

131 **Adrenal Carcinoma**

132 **Paraganglion System**

133 **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
  -

134

135 **Pheochromocytoma: Morphology**

136 **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

137 **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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139 **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

140 **PINEOCYTOMA**

141 **END END END END END**