CHAPTER 11

Endocrine

THYROID

What two arteries supply the thyroid gland?	1. Superior thyroid artery 2. Inferior thyroid artery
Where does each originate?	Superior thyroid artery arises from external carotid artery/inferior thyroid artery arises from thyrocervical trunk of subclavian artery. Note: In <5% of patients there is the thyroidea ima artery, which arises from the aorta or innominate artery (replaces absent inferior thyroid artery).
What two nerves innervate the thyroid gland?	1. Superior laryngeal nerve 2. Inferior (recurrent) laryngeal nerve
What does the recurrent laryngeal nerve (RLN) course around on the:	
Right?	Subclavian artery
Left?	Arch of the aorta adjacent to ligamentum arteriosum (See Fig. 11-1)
Where are the two most common places the RLN is injured during surgery?	1. Penetration into cricothyroid membrane 2. Crossing the inferior thyroid artery
Which is the only laryngeal muscle not innervated by the RLN?	Cricothyroid, which is innervated by the external branch of the superior laryngeal nerve
What is the main function of this muscle?	Adduction (tension) of vocal cords (however, does not affect cord position in injury to the RLN)
Unilateral injury to the RLN leads to what two symptoms?	Weak voice and ineffective cough (↑ aspiration risk)

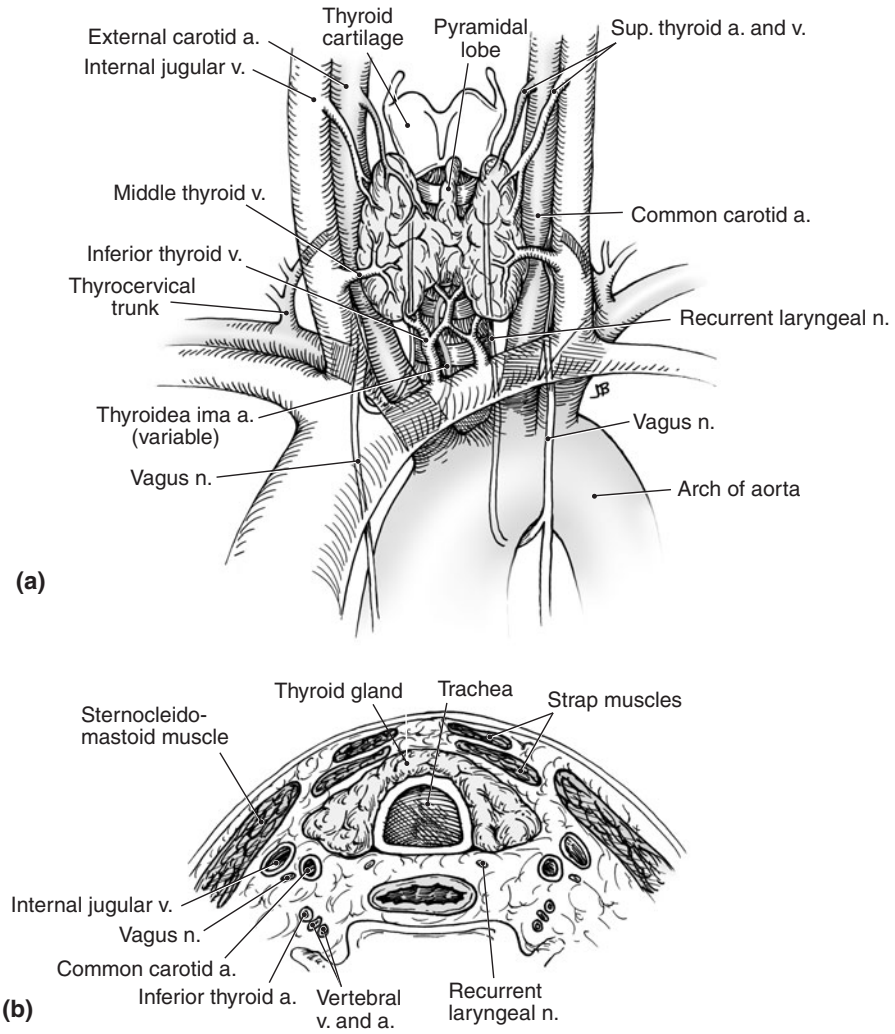

Figure 11-1 Anatomy of thyroid and surrounding neck structures. [*Reproduced, with permission, from Brunicardi CF et al (eds): Schwartz's Principles of Surgery, 8th ed. New York: McGraw-Hill, 2005:1399.*]

Bilateral injury may cause what?	Airway obstruction requiring emergency tracheostomy (though this is usually temporary because vocal cord paralysis is usually transient)
What is the function of follicular cells?	Produce, store, release T_3 (triiodothyronine) and T_4 (thyroxine)
Parafollicular cells (C cells)?	Secrete calcitonin

What are the four steps in thyroid hormone production?

1. Iodide trapping: Iodine, converted to iodide in enterocytes is taken up by thyroid with an adenosine triphosphate (ATP)-dependent mechanism.
2. Organification: Iodide is converted back to iodine and conjugated to tyrosine residues on thyroglobulin. Catalyzed by thyroid peroxidase.
3. Coupling: of monoiodotyrosines and diiodotyrosines to form T_3 and T_4.
4. Release: with stimulation by thyroid-stimulating hormone (TSH), lysosomal degradation of thyroglobulin results in release of T_3 and T_4.

What is the hormonal control of thyroid hormone release?

TRH is released from the hypothalamus, which stimulates the release of TSH in the anterior pituitary through the portal circulation. T_3 is primarily responsible for negative feedback at the hypothalamus and pituitary levels (See Fig. 11-2).

What is the physiologic role of T_3 and T_4?

↑ metabolic rate (pulse, CO, catecholamines, blood glucose). Excess causes nervousness, irritability, heart arrhythmias

What class of medications may be used to temporarily relieve the symptoms caused by T_3 and T_4?

Beta blockers (inhibit peripheral conversion of T_4 to T_3)

What is the difference between the terms hyperthyroidism and thyrotoxicosis?

- Thyrotoxicosis is a hypermetabolic state resulting from an increase in the levels of circulating thyroid hormone. Can result from increased synthesis (hyperthyroidism), inflammation, and destruction of the thyroid gland releasing existing thyroid hormone, or exogenous thyroid hormone.
- Hyperthyroidism is a type of thyrotoxicosis that results in the increased biosynthesis and secretion of thyroid hormones T_3 and T_4.

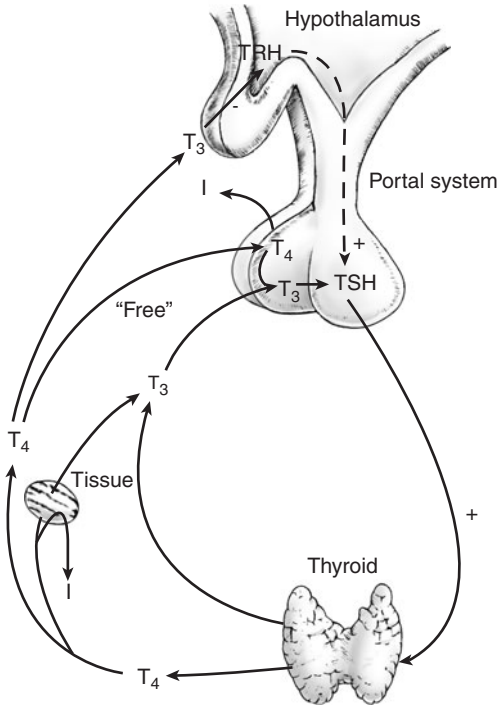

Figure 11-2 Hypothalamic-pituitary-thyroid axis.

Determine whether the following are associated with hypo- or hyperthyroidism:

Weight loss	Hyperthyroidism (associated with normal appetite)
Myxedema coma	Hypothyroidism
Pretibial myxedema	Hyperthyroidism
Facial/periorbital myxedema	Hypothyroidism
Menorrhagia	Hypothyroidism
Amenorrhea	Hyperthyroidism
Carpal tunnel	Hypothyroidism
Arrhythmia	Hyperthyroidism
Bradycardia	Hypothyroidism

What is the percentage of T_3 and T_4 released by the thyroid in euthyroid states?

~ 20% T_3 and 80% T_4.

How is the ratio of T_3 to T_4 affected in hyperthyroid states?

↑↑↑ T_3 and ↑/normal T_4, results in an ↑ T_3:T_4 output from the thyroid.

What is a better indicator of thyroid function free T_4 or total T_4?

Free T_4, because it is not affected by thyroid binding globulin, which is increased in pregnancy, estrogen, and progesterone and decreased in protein losing disorders, such as nephrotic syndrome and liver disease.

What is the most sensitive test for hypo- or hyperthyroidism?

Thyroid stimulating hormone (TSH). Low in primary hyperthyroid disorders, High in primary hypothyroid.

What is the physiologic role of calcitonin?

Inhibit osteoclast activity, though no effect on skeletal system following total thyroidectomy

Where is the embryologic origin of the thyroid gland?

Foramen cecum. C cells derived from neural crest cells, which is part of amine precursor uptake and decarboxylation (APUD) system.

A 10-year-old boy is seen for an asymptomatic, well-defined, midline neck mass that moves upward with protrusion of the tongue. What is the likely diagnosis?

Thyroglossal duct cyst (TDC), which is always connected to the base of the tongue. 80% found juxtaposed to the hyoid bone (cysts may become infected).

How is this treated?

Sistrunk operation—cystectomy in continuity with the mid-portion hyoid bone and a small section of muscle around the foramen cecum

Note: Avoid I & D—makes future complete excision more difficult.

What must be ruled out before excision for a TDC?

Ectopic thyroid. Palpate for normal thyroid placement (use computed tomography [CT] or ultrasound [US] if gland is not palpated).

Pediatric patient with difficulty swallowing, visible mass midline at the back of the tongue with no palpable thyroid gland.

Disease?

Lingual thyroid: failure of descent of the primordial thyroid tissue.

Treatment?	Exogenous thyroid: supplementation to decrease TSH and size of ectopic thyroid tissue. Radioactive iodine ablation second line. Surgery usually not necessary. Treatment needed if choking, dysphagia, airway obstruction, hemorrhage.
The pyramidal lobe is a remnant of what structure?	Distal thyroglossal duct, present in 50% of individuals, becomes palpable from disorders resulting in thyroid hypertrophy.
What is a goiter?	Enlargement of thyroid (regardless of functional status): can be diffuse, uninodular, or multinodular. Thyroid masses will move as patient swallows and may produce dysphagia or dyspnea, especially when arms are lifted above the head, if large or retrosternal.
How are small, euthyroid goiters treated?	Observation
Large, euthyroid goiters?	Exogenous thyroid to suppress TSH to decrease or stabilize size
What are five indications for surgical resection of goiters?	1. Obstructive symptoms 2. Continued growth with exogenous T_4 therapy 3. Suspected/proven malignancy 4. Substernal extension of goiter 5. Cosmetically unacceptable
What are four common causes of thyrotoxicosis?	1. Graves' disease (most common cause in United States, ~70%) 2. Solitary toxic nodule 3. Toxic multinodular goiter 4. de Quervain's thyroiditis (transient) Note: Less common causes include factitious thyrotoxicosis and struma ovarii.
Which one has a low radioactive iodine uptake (RAIU)?	de Quervain's thyroiditis: due to release of stored hormone from injury to the thyroid gland, not increased hormone production. Note: This test is not helpful in distinguishing causes of hypothyroidism.

What are the two radioisotopes used for thyroid imaging?	1. Radioiodine (I-131 or I-123) 2. Technetium-99m pertechnetate (^{99m}Tc)
Cold nodules on RAIU will appear as what (hot or cold) using ^{99m}Tc?	Cold
Hot nodules using ^{99m}Tc will appear as hot or cold on RAIU scan?	Hot or cold: ^{99m}Tc is trapped by the thyroid but not organified. Thus, a cold/nonfunctioning nodule that is very vascular may appear "hot" with ^{99m}Tc but "cold" with RAIU.
A patient with hyperthyroidism has increased, homogeneous uptake of radioactive iodine with diffuse goiter. What is the likely diagnosis?	Graves' disease
What will the RAIU scan demonstrate in a patient with a toxic (hot) nodule(s)?	Increased uptake in the nodule(s) with decreased uptake in the remaining gland (due to suppression of TSH)
Is malignancy more common in a "hot" or "cold" lesion?	Cold, 15–20% carry malignancy; hot, <5% carry malignancies
Are thyroid nodules more common in males or females?	Females
Is cancer more common in a thyroid nodule found in a male or female?	Male
Match the following with the appropriate diagnosis of Graves', Hashimoto's, and/or de Quervain's diseases:	
Antibodies against the thyrotropin receptor	Graves' disease
Subacute thyroiditis	de Quervain's thyroiditis (multinucleated giant cell infiltrate)
Chronic thyroiditis	Hashimoto's thyroiditis (lymphocytic infiltrate)—also Riedel's (fibrous) thyroiditis
Antibodies to thyroid peroxidase and/or thyroglobulin	Hashimoto's thyroiditis
Diffuse, nonpitting edema and thickening of the skin on lower legs	Graves' disease (pretibial myxedema)
Often follows flu-like illness (coxsackievirus, mumps)	de Quervain's thyroiditis
Nontender, diffuse enlargement of thyroid gland	Hashimoto's thyroiditis, Graves' disease

Exophthalmos	Graves' disease (proptosis usually referred to nonendocrinological cause of eye protrusion)
Most common cause of hyperthyroidism	Graves' disease
Thyrotoxicosis with a reduced RAIU	de Quervain's thyroiditis—early stages; from release of preformed thyroglobulin (struma ovarii (rare) can also present similarly)
↑ Risk of thyroid lymphoma	Hashimoto's thyroiditis (biopsy needed to distinguish from lymphoma)
Tender thyroid gland	de Quervain's thyroiditis (enlargement may be asymmetrical)

GRAVES' DISEASE

What are two medical treatments for Graves' disease?	1. Antithyroid medications—propylthiouracil (PTU), methimazole 2. Radioactive iodine ablation, which does not injure parathyroids or ↑ cancer risk
What is the preferred surgical treatment?	Subtotal thyroidectomy (must balance risk of recurrence with euthyroidism). Can be done in two ways—bilateral subtotal thyroidectomy or doing total lobectomy on one side and subtotal thyroidectomy on the other (Hartley-Dunhill procedure). Advantage of Hartley-Dunhill procedure is the ability to reenter only one side of the neck if reoperation is needed.
Medical therapy fails to improve what comorbid condition of Graves' disease?	Ophthalmopathy, which may cause blindness from compression of optic nerve or limited eye mobility from inferior or medial recti muscle involvement. Thyroidectomy may stabilize or improve ophthalmopathy, possibly by removing antigen stimulation.
What is the mechanism of action of PTU?	Inhibition of thyroperoxidase and peripheral conversion of T_4 to T_3. May be used to treat thyroid storm.

What are the six surgical indications for subtotal thyroidectomy?

1. Young patient (↑ cancer risk, best chance at being euthyroid)
2. Pregnant or breast feeding patients (antithyroid medications cross placenta ➔ fetal goiter)
3. Goiters causing compressive symptoms
4. Allergic/adverse reaction to antithyroid medications
5. Confirmed or suspected cancer
6. Severe ophthalmopathy—progresses in 33% of patients after RAI vs 16% after surgery

What is the most common side effect of radioactive iodine ablation or surgery?

Hypothyroidism

Why is it necessary to achieve a euthyroid state before radioactive iodine ablation therapy?

Discontinuing antithyroid drugs in a euthyroid patient allows for maximal uptake of radioactive iodine.

Before surgery?

Minimize the risk of thyroid storm intra- and postop (also ↓ size and vascularity of gland)

What are the other preop medications that should be given?

Propranolol is best for presurgical thyroid therapy if patient is pregnant. Lugol's solution (iodine) for 10 days preoperatively to decrease vascularity and inhibit release of thyroid hormone.

Following surgery a woman with poorly controlled Graves' disease develops fever (103°F), diaphoresis, tachycardia (140 bpm) with periods of atrial fibrillation, and nausea/vomiting. She complains of heat intolerance and becomes agitated with tremors. What is the likely diagnosis?

Thyroid storm. This is an emergency diagnosed on clinical grounds—can lead to high-output cardiac failure and shock.

What are common causes?

Any stressor: infection, surgery, trauma, unstable medical condition (DKA, CVA). In only 1–2% of patients with hyperthyroidism will develop, usually in patients with poorly treated Graves' or toxic multinodular goiter.

What is another common cause for these symptoms?

Delirium tremen, also consider septic shock, neuroleptic malignant syndrome, diabetes mellitus (DM), pheochromocytoma.

What are the four steps for treating this condition?

1. PTU: blocks the production and conversion of T_4 to T_3.
2. Lugol's solution or potassium iodide: inhibits the release of T_4 and T_3.
3. Dexamethasone: stress response causes cortisol deficiency (also blocks conversion of T_4 to T_3.
4. Propranolol/esmolol: inhibits response to catecholamines and blocks conversion of T_4 to T_3—Use caution as may worsen high-output congestive heart failure (CHF).

Note: Mortality—90% if untreated; 20% if treated.

What is the preferred treatment for toxic multinodular goiter?

Surgical resection. Lobectomy with subtotal thyroidectomy on the other side (ie, Hartley-Dunhill) after hyperthyroidism has been controlled. No need to preserve gland since chronic thyroid medication is needed to prevent recurrence.

Why is RAIU not preferred for treating toxic multinodular goiter disease?

- Poor/uneven uptake requires large doses.
- Greater likelihood of recurrent hyperthyroidism.
- RAI—Induced thyroiditis may cause swelling leading to airway compromise.

Determine whether the following refer to primary or secondary hypothyroidism.

↓TSH/↓T_4 and T_3

Secondary hypothyroidism (pituitary failure)—does not respond to thyrotropin-releasing hormone (TRH)

↑TSH/↓T_4 and T_3

Primary hypothyroidism

A 6-year-old boy presents with a fever and swollen, tender thyroid with erythema of the overlying skin. The boy recently had an earache which went untreated. What is the likely diagnosis?

Acute, suppurative thyroiditis. This is rare, but usually occurs following upper respiratory infection or otitis media (OM) and is associated with developmental abnormalities (ie, thyroglossal duct or brachial cleft cysts).

Note: May also develop in the immunocompromised.

How is this treated?

Antibiotics and surgery if abscess develops or to correct anatomic abnormality

What is Riedel's thyroiditis?

A very rare condition where dense fibrotic tissue replaces thyroid parenchyma and extends to involve adjacent tissues (trachea, esophagus, parathyroid glands, RLN)

What are the characteristic exam findings of the thyroid?

Hard, stony or woody, fixed, painless goiter

What are the typical thyroid function lab values?

Euthyroid, but may be hypothyroid if there is extensive fibrosis

How is this treated?

Corticosteroids eorticosteroids and surgery, which relieves compression on trachea and establishes diagnosis

A 60-year-old male is referred for evaluation for a solitary thyroid nodule. There is no history of radiation exposure or family history of cancer. Exam reveals a small, nontender, hard mass without any associated lymphadenopathy. What is the next step in establishing a diagnosis?

Fine needle aspiration (FNA)

The test is reported as nondiagnostic. What should be done next?

Repeat the FNA, as this is the most important test in evaluating a mass. Thyroid cancer is more common in women; however, a thyroid mass has a greater likelihood to be cancerous in men.

Testing shows the mass to be a benign colloid nodule. What is the next step in management?

T_4 therapy and monitor suppression with TSH levels:

- If mass is unchanged in size, repeat FNA
- If mass shrinks, continue T_4
- If mass enlarges, thyroidectomy

Note: Thyroidectomy is accepted if there is a family or radiation exposure history.

A suspicious follicular lesion that is "hot" on RAIU can be treated with RAI or thyroidectomy.

What are two indications for surgical resection of a cystic thyroid mass?

1. Recurrent after three attempts at drainage
2. Residual mass following aspiration

Thyroid cancer incidence increases linearly with low dose radiation (<2000cGy). Why does the incidence of thyroid cancer decrease with doses >-2000cGy?	Higher doses cause destruction of the gland, while lower doses allow mutations to accumulate within the DNA.
Determine the type of thyroid cancer (papillary, follicular and/or medullary) associated with the following:	
The most common thyroid cancer in the United States	**P**apillary carcinoma—**P**opular in the United States (80%)
The most common thyroid cancer following radiation exposure	Papillary carcinoma
The most common thyroid cancer in iodine deficiencies	Follicular carcinoma
Multiple endocrine neoplasia (MEN) 2A or 2B	**M**edullary carcinoma—associated with **M**en
Lymphatic spread	Papillary and medullary carcinoma—**LMNOP** = **L**ymphatic (spread is) **M**edullary **N**eoplasm **o**r **P**apillary
Multicentric	Papillary and medullary carcinoma
Unifocal	**F**ollicular carcinoma = **F**ocal
Hematogenous spread	Follicular carcinoma (medullary anaplastic carcinomas also commonly spread via bloodstream)
Distant metastases to lung and bone	Papillary and follicular carcinoma
What are the three types of thyroid carcinoma arising from follicular cells?	Papillary, follicular (also Hürthle cell tumor, a subtype of follicular carcinoma), anaplastic
C cells (1 type)?	Medullary
What protein is measured to monitor patients who underwent thyroidectomy for thyroid cancer?	Thyroglobulin Note: If extremely elevated prior to surgery this suggests metastatic thyroid cancer, otherwise not a reliable test to determine benign vs malignant lesions.
What is the only reliable tumor marker for thyroid carcinoma?	Calcitonin, for medullary carcinoma. Serum thyroglobulin may be elevated in benign causes and is not always elevated in malignant causes.

What is the recommended treatment for medullary thyroid cancer (MTC)?

Total thyroidectomy due to the aggressiveness and multicentricity of MTC

A patient is found to have MTC on FNA. What are two associated conditions that must be evaluated before surgery?

Pheochromocytoma and hyperparathyroidism

What lab tests are used to evaluate fort hese conditions?

24-hour urinary levels of VMA, metanephrine, catecholamine for pheochromocytoma

Serum calcium for hyperparathyroidism

What genetic test should be performed on all patients with MTC?

RET oncogene mutations. MEN syndromes are inherited in autosomal dominant pattern. If children acquire mutation, it is recommended they too undergo total thyroidectomy.

Why must a pheochromocytoma be excluded before total thyroidectomy of an MTC?

To avoid a hypertensive crisis. Always treat the pheochromocytoma first.

What is the most sensitive tumor marker to evaluate for recurrent/persistent MTC?

Calcitonin

What is the best tumor marker for predicting prognosis?

Carcinoembryonic antigen (CEA)

A 30-year-old female presents for evaluation of a firm, slowly enlarging, nontender mass that moves with swallowing. Palpation of the lateral neck reveals a solitary, firm mass. FNA reveals thyroid carcinoma. What is the likely tumor type?

Papillary carcinoma. Remember papillary carcinoma tends to spread via lymphatics. Lateral neck mass likely cervical lymph node metastasis, so called "lateral aberrant thyroid." FNA may be performed on lymph node or thyroid mass.

If no other abnormal findings are discovered, what is the prognosis?

Excellent (>90% 10-year survival)

Does lymph node involvement worsen prognosis of papillary thyroid carcinoma?

No. ~50% present with positive lymph nodes and does *not* affect prognosis. Prognosis is more adversely affected by advanced age, poorly encapsulated, and extrathyroidal invasion.

A patient with papillary carcinoma undergoes total thyroidectomy. After surgery the thyroglobulin begins to increase. What is the likely explanation?

Recurrent or persistent disease

What is/are the next step(s) in diagnosis and treatment?

RAIU, which allows detection and treatment of persistent or metastatic disease. Only helpful if patient underwent total thyroidectomy, as residual thyroid will preferably uptake RAI.

Note: Total thyroidectomy is advised for papillary carcinoma due to multicentricity (↓ recurrence) of the tumor as well as increasing the sensitivity of thyroglobulin and RAIU for detecting/treating the carcinoma.

A 30-year-old female presents for evaluation of a firm, nontender, fixed thyroid mass that moves during swallowing. FNA reveals a follicular type lesion. What is the next step in diagnosis and treatment?

Thyroid lobectomy. >80% will be benign. FNA cannot distinguish benign follicular adenomas from follicular carcinomas.

Intraop frozen section reveals capsular and vascular invasion. What is the next step in treatment?

Total thyroidectomy to treat follicular carcinoma, which also allows for RAIU detection/ treatment of metastatic disease. Mean survival rate is 60% at 10 years, but depends on age, grade of tumor, and metastases.

A patient is evaluated for a rapidly enlarging neck mass, dysphagia, and cough. Biopsies reveal anaplastic carcinoma. What is the prognosis?

Poor, with 5-year-survival rate <10%. Most die within a few months of diagnosis.

What is the role of surgery for this cancer?

To protect the airway. Conservative resection is recommended to reduce postop morbidities. Prophylactic tracheostomy may be required. Chemoradiation has limited efficacy.

PARATHYROID

What is the origin of:

Superior parathyroid glands?

Fourth pharyngeal pouch, also the C cells of the thyroid

Inferior parathyroid glands?

Third pharyngeal pouch, also the thymus

Where are the most common abnormal parathyroid locations for:

Superior parathyroid glands?
Intrathyroidal or posterior mediastinum

Inferior parathyroid glands?
Superior mediastinum (often associated with thymus gland)

Note: Inferior parathyroid glands more often associated with ectopic locations that range from the base of the skull to the thymus gland.

What is the location of recurrent laryngeal nerve to the:

Superior parathyroid gland?
Ventral

Inferior thyroid gland?
Dorsal

What is the main blood supply of the parathyroid glands?
Inferior thyroid artery. The parathyroids are drained by the ipsilateral superior, middle, and inferior veins.

What are the two most common cells in the parathyroid glands?
1. Chief cells—secrete PTH
2. Oxyphil cells—unknown function

What is the function of PTH?
- ↑ Serum Ca
- ↓ Serum phosphate

What are the mechanisms by which PTH ↑ serum Ca and ↓ serum phosphate in:

Bone?
(+) Osteoclasts = ↑ Ca and phosphate

Kidney?
- ↑ Ca reabsorption distal collecting tubule
- ↓ phosphate reabsorption proximal collection tubule
- (+) 1α—hydroxylase

Gut?
↑ Ca reabsorption

- 25-hydroxy vitamin D produced by liver ➔ 1,25-dihydroxy vitamin D produced by kidney ➔ ↑ Ca reabsorption in duodenum (passively in jejunum)

What are the two most common causes of hypercalcemia?

1. Primary hyperparathyroidism
2. Malignancy (lytic lesions or ectopic PTH production)

Note: Immunoassays are able to distinguish PTH from the parathyroid vs tumor. Alkaline phosphatase may be elevated in both conditions.

What are other causes of hypercalcemia?

Remember the mnemonic for hypercalcemia:

CHIMPANZEES

Calcium supplementation

Hyperparathyroidism

Iatrogenic (thiazides)/**I**mmobility

Milk alkali syndrome/**M**yeloma

Paget's disease

Addison's disease/**A**cromegaly

Neoplasm

Zollinger-Ellison syndrome/MEN

Excess vitamin A

Excess vitamin D

Sarcoidosis/granulomatous disease

What are the three most common causes of primary hyperparathyroidism?

1. Solitary adenoma ~80%
2. Hyperplasia ~15%
3. Parathyroid carcinoma ~2%

Intraoperatively a patient is found to have two grossly enlarged parathyroid glands. What is the likely cause for this?

With two or more abnormal glands it is assumed to be due to hyperplasia (as opposed to multiple adenomas) until proven otherwise. Hyperplasia may be asymmetrical.

How is this diagnosed?

Biopsy of other glands and all will show hypercellularity

How is this treated?

Two methods:

- Removal of three complete glands and one partial gland
- Removal of all four glands with autotransplantation

Determine whether the following refer to primary, secondary, or tertiary hyperparathyroidism:

↓Ca, ↑↑PTH

Secondary hyperparathyroidism

↑Ca, ↑↑↑PTH	Primary hyperparathyroidism (also with pseudohyperparathyroidism and ectopic PTH production)
↑Ca, ↑PTH, and calcinosis	Tertiary hyperparathyroidism
Four gland hyperplasia	Primary (hyperplasia), secondary, and tertiary hyperparathyroidism
Often found in patients with chronic renal disease	Secondary hyperparathyroidism

Note: Ca refers to ionized calcium.

What are the surgical indications for parathyroidectomy?

1. All symptomatic patients
2. Asymptomatic patients with:
   - Ca >11 mg/dL
   - <50 years of age
   - Osteopenia (<2 standard deviations from age, race, and gender)
   - Calciuria (>400 mg/d)
   - ↓ Cr clearance

What are the common symptoms of hypercalcemia?

Kidney stones, painful bones, abdominal groans, psychic moans, fatigue overtones

1. Kidney:
   - Nephrolithiasis or nephrocalcinosis (calcium phosphate or oxalate stones)—never both
2. Bones:
   - Osteopenia/osteoporosis
   - Osteitis fibrosa cystica/brown tumors
3. Abdominal:
   - PUD (PTH ↑ gastrin secretion)
   - Cholelithiasis (calcium bilirubinate stones)
   - Pancreatitis
4. Neuropsychiatric:
   - Basically any symptom: depression, fatigue, anxiety, psychosis, obtundation, coma
5. Musculoskeletal:
   - Muscle aches, arthralgias, proximal weakness (likely due to neuropathy), pseudogout (calcium pyrophosphate crystals)

Note: Also ↑ risk of HTN and CHF.

What is osteitis fibrosa cystica?

Extensive bone resorption with marrow fibrosis and cysts. Part of a continuum of bony changes associated with hyperparathyroidism: Demineralization ➔ osteitis fibrosa (↑ osteoclast activity leads to bone resorption and peritrabecular fibrosis) ➔ osteitis fibrosa cystica

What is a brown tumor (also known as osteoclastoma)?

Seen in osteitis fibrosa cystica represents localized replacement of bone with vascularized fibrous tissue which may undergo necrosis and cyst formation (high hemosiderin content produces brown color)

Surgery improves all symptoms of hyperparathyroidism except which one?

Anxiety

What does a neck mass palpated in a patient with hyperparathyroidism likely suggest?

Thyroid pathology—physical exam usually not helpful for evaluating parathyroid pathologies

What is the embryologic origin of the adrenal cortex?

Mesoderm

Adrenal medulla?

Ectoderm (neural crest)

What are the three layers of the adrenal cortex, and which hormone(s) does each produce?

1. Zona glomerulosa: mineralcorticoid (aldosterone)
2. Zona fasciculata: glucocorticoids (cortisone and hydrocortisone)
3. Zona reticularis: estrogen, androgen, progesterone (precursor to estrogen/androgen)

What hormone(s) is/are produced by the adrenal medulla?

Catecholamines (epinephrine and norepinephrine)

What are four major stimulators of aldosterone release?

1. Hyponatremia
2. Sympathetic stimulation
3. ↓ Renal blood flow
4. Hyperkalemia

Describe the pathway of stimulation.

Juxtaglomerular cells release renin ➔ angiotensin I release ➔ pulmonary ACE ➔ angiotensin II ➔ aldosterone release

Where is the most common location for ectopic adrenocortical tissue?

Arises from mesoderm near the gonads; therefore, most common location is the testes, ovaries, and spermatic cord.

What is the organ of Zuckerkandl?

During development neural crest cells migrate to para-aortic, paravertebral, and developing adrenal cortex. These ectopic locations usually regress. The largest region of ectopic medullary tissue is at the aortic bifurcation, near the inferior mesenteric artery, and is referred to as the organ of Zuckerkandl.

What is its significance?

Most common location for ectopic pheochromocytomas—may account for up to 10% of cases.

Where does the venous blood from the left adrenal gland drain?

Left renal vein

Right adrenal gland?

Inferior vena cava

Note: Arterial blood arises from the phrenic artery, aorta, and renal artery.

A 35-year-old female presents with refractory moderate-severe hypertension, hypokalemia, and metabolic alkalosis. What is the likely diagnosis?

Conn's syndrome (primary hyperaldosteronism)

What is the most common cause?

Solitary adenoma ~70% (idiopathic bilateral hypertrophy ~30%).

How is the diagnosis confirmed?

Diagnosis requires imaging with CT unless patient is pregnant or cannot tolerate IV contrast. Plasma aldosterone:renin >25:1 suggests diagnosis.

A patient is noted to have bilateral enlargement of adrenal glands on CT scan. What is the next step in diagnosis?

Scintigraphy (NP-59, a cholesterol derivative). An adenoma will appear as a "unilateral hot nodule" with contralateral suppression, or less commonly, selective catheterization of adrenal vein to measures aldosterone : cortisol ratio.

How is this treated?

If unilateral, then adrenalectomy (correct potassium and hypertension first), if bilateral, then medical management with potassium sparing diuretic (spironolactone)

How can one distinguish between primary and secondary hyperaldosteronism?

Measure plasma renin. Low plasma renin suggests primary hyperaldosteronism.

What are common causes of secondary hyperaldosteronism?	Conditions that cause ↓ CO or intravascular volume—CHF, cirrhosis, nephrotic syndrome
What is the most common cause of:	
Nonfunctioning adrenocortical adenoma seen on CT?	Benign adenoma
Functional adrenocortical adenoma seen on CT?	Primary hyperaldosteronism (80%), Cushing's syndrome (10%)
What physical finding is seen in primary but not secondary adrenocortical insufficiency?	Hyperpigmentation (though not a universal sign) due to corticotropin and melanocyte-stimulating hormone being produced by the same progenitor hormone
What segment(s) of the adrenal gland are destroyed in Addison's disease?	The entire adrenal cortex, which produces mineralocorticoids and glucocorticoids. Symptoms arise when >90% of both cortices are destroyed.
A patient with Addison's disease is recovering from surgery when you are called by the nurse stating the patient has a temperature of 103°F with confusion, nausea, vomiting, and orthostatic hypotension. What is the likely diagnosis?	Acute adrenal crisis (though sepsis should also be in the differential)
How is this treated?	Administration of hydrocortisone
How could this have been prevented?	By increasing the steroid dose before times of stress
What are the causes of Addison's disease?	There are many causes—use "vitamin E" mnemonic for developing differentials. **V** vascular: hemorrhage, embolus (heparin-induced thrombocytopenia [HIT]) **I**nfectious: human immunodeficiency virus (HIV), tuberculosis (TB), histoplasmosis, fungal, pseudomonas, meningococcus, or any infection that causes stress response **T**rauma: abdominal/surgical, or stress response **A**utoimmune: associated with other autoimmune disorders: sarcoid, Graves', DM I, pernicious anemia, etc **M**etabolic: amyloidosis, hemochromatosis

	Idiopathic/**i**atrogenic: surgery, abdominal radiation, medications (failure to adjust for drugs that ↑ P450 metabolism), **long term use of corticosteroids** (most common) **N**eoplastic: lymphomas, metastatic disease **E**ndocrine: removal of functional adrenal adenoma (causes transient adrenal insufficiency from chronic inhibition)
A 35-year-old female presents with fatigue, weight gain, with increased "fullness" in the face and back, hypertension, easy bruising, menstrual irregularities, acne, polyuria, and polydipsia. Physical exam reveals striae on the abdomen and thighs that are bright red. What is the likely diagnosis?	Cushing's syndrome—Whenever symptoms span multiple systems, think of endocrine causes first, especially thyroid. Also common are metabolic or infectious causes.
What is the most common cause?	Exogenous glucocorticoids
What is the most common endogenous cause?	Cushing's disease ~70%
What is Cushing's disease?	Cushing's syndrome due to adrenocorticotropic hormone (ACTH) producing adenoma of the pituitary gland associated with headaches and visual changes
A former smoker presents with easy bruising, ↓ libido, and emotional liability. What two lab tests are commonly done to diagnose Cushing's syndrome?	1. 24-hour urine cortisol level as a screening test (3–4× higher in pseudo-Cushing's syndrome). >4× normal is highly suggestive of Cushing's syndrome 2. Dexamethasone suppression (cortisol) test
The patient is found to have elevated urinary cortisol levels. A dexamethasone suppression test shows: **No suppression at low doses** **No suppression at high doses** **What is the likely cause of Cushing's syndrome in this patient?**	A normal individual will have suppression of cortisol secretion at low doses. Suppression at low doses rules out normal individuals with high cortisol. In Cushing's syndrome, cortisol secretion will be reduced by >50% with **high dose** dexamethasone. Patients whose cortisol cannot be suppressed is suggestive of ectopic production of ACTH (usually very high concentrations and associated with hyperpigmentation) or adrenal adenoma.

Where is the most common location of ectopic ACTH production?	Small cell lung cancer (~50%, also by pancreatic, thymoma, or carcinoid tumors). Most of these patients do not appear as cushingoid, but appear as cachectic.
What is the treatment of choice for Cushing's disease?	Transsphenoidal microadenomectomy, which is successful in 80%
A patient has recurrence after initial treatment, what is the next step in treatment?	Repeat excision has ~50% cure rate, therefore pituitary irradiation is recommended. Usually with stereotactic radiosurgery/gamma knife to reduce panhypopituitarism or visual defects.
The patient again fails treatment, what is the next step in managing this patient?	Medical therapy (ie, ketoconazole) or bilateral adrenalectomy. ~90% have uni-/bilateral pathologic changes in adrenal glands (adenomas, hyperplasia).
A patient is found to have a unilateral adrenal adenoma causing Cushing's syndrome. What is the treatment of choice?	Unilateral adrenalectomy (bilateral adrenalectomy if bilateral cortical hyperplasia is present)
What needs to be given perioperatively and postoperatively?	Cortisone, due to suppression of the contralateral adrenal gland from the hyperfunctioning adenoma to prevent an addisonian crisis. Steroids are needed for life in bilateral adrenalectomy.
What is the most common hormone produced by an adrenal cortical carcinoma (ACC)?	Cortisol (30%). ~50% are functional and more common among women. Others secrete androgens, estrogens, aldosterone, or a mix of hormones.
What are the most common signs/ symptoms of:	
Functional ACC?	Rapidly progressive Cushing's syndrome or virilizing features
Nonfunctional ACC?	Abdominal mass and pain

A man presents with Cushing's syndrome. CT of the abdomen reveals a 4-cm mass on the adrenal gland. What is the likely diagnosis?

Though ACC tumors are extremely rare, a male with Cushing's syndrome and an adrenal mass is suspected of ACC until proven otherwise.

What is the best way to distinguish benign vs malignant ACC?

With radiographic studies. Most important factor is size: 6 cm has >90% chance of malignancy. It is difficult to distinguish adenomas from carcinomas with histologic examination.

What is the treatment for ACC?

Surgical excision or debulking and chemotherapy, as they are relatively resistant to radiation. This is reserved for unresectable recurrences or bony metastases, which have a poor prognosis with 25% 5-year survival, 40% if localized disease.

A patient presents complaining of paroxysmal headaches associated with palpitations, flushing, shortness of breath, and diaphoresis. On physical exam the patient is noted to be hypertensive. What is the suspected diagnosis?

Pheochromocytoma, with the classic triad: headache, palpitations, diaphoresis. Hypertension may be sustained or paroxysmal.

What lab test(s) are used to establish the diagnosis?

Urinary catecholamines and the metabolites (metanephrine, normetanephrine, and vanillylmandelic acid)—Assure patient is not taking medicines that ↑/↓ catecholamines (tricyclic antidepressants [TCA], benzodiazepines, alcohol, labetalol, clonidine, iodinated contrast, etc).

A patient suspected of having a pheochromocytoma is found to have elevated levels of norepinephrine. What is the significance of this finding?

Elevated norepinephrine suggests extra-adrenal site of tumor, most likely via the organ of Zuckerkandl. These sites lack phenylethanolamine-*N*-methyltransferase and cannot convert norepinephrine to epinephrine, which is predominately secreted by adrenal pheochromocytomas.

What is the preferred screening imaging modality for evaluating pheochromocytomas?

Noncontrast CT. Iodinated contrast can precipitate a hypertensive crisis. T2 magnetic resonance imaging (MRI) with or without gadolinium is most specific/sensitive.

What is an MIBG scan?

Radioactive iodine labeled metaiodobenzylguanidine (MIBG) nuclear scan that is taken up by chromaffin tissue directly in proportion to catecholamine synthesis/secretion. Normal adrenal medullary tissue does not take up MIBG, this is helpful in locating extra-adrenal sites.