PULSE NOTES

A High-Yield USMLE Step 1 Companion

Expanded explanations of First Aid topics, UWorld-derived insights, and enhanced illustrations across major organ systems.

UP
USMLE PULSE

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DEDICATION

This work is dedicated to my family.

Remember

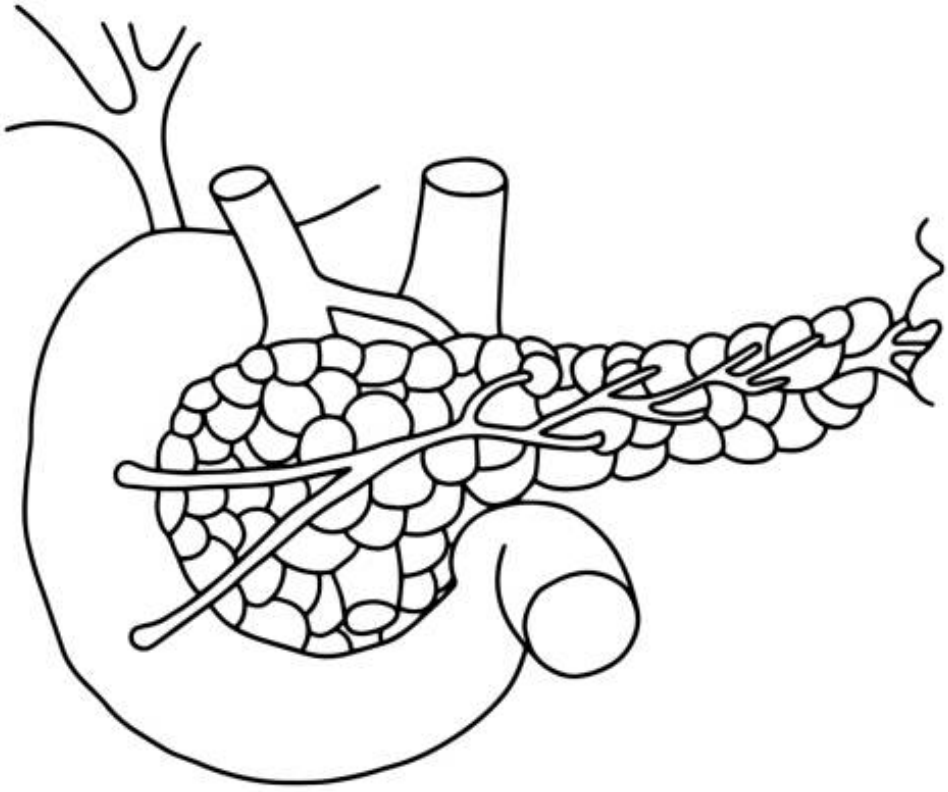
Every challenge is an opportunity to grow stronger.

Index

How to Use The Notes Effectively ?

Join Telegram for the E-version and new updates for the notes

Endocrine



USMLE PULSE

Index

1)Hypothalamus

1. Kallmann syndrome

A. What is the pathophysiology of Kallmann syndrome results? (High Yield)

Failure of GnRH-secreting neurons to migrate from their origin in the olfactory placode to their normal anatomic location in the hypothalamus due to a mutation in the **KAL-1 gene or the fibroblast growth factor receptor-1 gene**.

Key Word in case = hypogonadism and anosmia

When is puberty considered delayed? (High Yield)

Absence or incomplete development of secondary sexual characteristics by age 14 in boys and by age 12 in girls.

N.B.

- **Testicular enlargement** is the first sign of puberty in boy
- breast enlargement is the first sign in girls.

2)Pituitary

1.Prolactin

1)What are the clinical features of Prolactinoma? (High Yield)

1. **General:**
    - Headache
    - Visual field defects
    - Suppression of other pituitary hormones
2. **Premenopausal women:**
    - Oligomenorrhea/amenorrhea
    - Infertility
    - Galactorrhea
    - Hot flashes
    - Decreased bone density
3. **Postmenopausal women:**
    - Mass-effect symptoms
4. **Men**:
    - infertility, decreased libido, impotence, gynecomastia

2. What is the DD of Secondary hypogonadism with a pituitary mass? (High Yield)

- High prolactin levels from a prolactin-secreting adenoma (prolactinoma) can suppress secretion of GnRH, leading to decreased LH secretion and lower testosterone production
- Non–prolactin-secreting tumors can disrupt the inhibitory dopaminergic regulation of prolactin secretion, leading to hyperprolactinemia and (usually mild) hypogonadism
- Direct compression of gonadotrope cells with loss of LH secretion (independent of prolactin effect), with a normal prolactin level

Other high yield ideas regarding prolactin (High Yield)

1-Drugs causing hyperprolactinemia:

- Antipsychotics
- Metoclopramide
- Methyldopa
- Verapamil

2- Drugs used to treat hyperprolactinemia and prolactinoma:
dopamine agonists (eg, bromocriptine, cabergoline)

3-If sever the pituitary stalk prolactin will increase due to the decreased dopamine inhibitory effect

4- **TRH can have stimulatory effects on prolactin:** Lactotroph cells express TRH receptors which stimulates synthesis and release of prolactin. The elevated TRH levels in the pituitary in patients with primary hypothyroidism can therefore increase prolactin secretion and lead to hyperprolactinemia.

5-Shehan syndrome (Bridge to reproductive)

3. ADH

1) Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

A. Why does Subarachnoid hemorrhage (SAH) cause SIADH?

1. Hypothalamic damage trigger excessive secretion of ADH
2. Decreased extracellular fluid volume causes a secondary increase in ADH and worsening hyponatremia:

    - Cerebral salt wasting (caused by increased secretion of brain natriuretic peptide, which leads to urinary sodium losses)
    - Secondary adrenal insufficiency (eg, decreased cortisol production due to pituitary injury).

B. what is the mechanism of action of Vaptans? (High Yield)

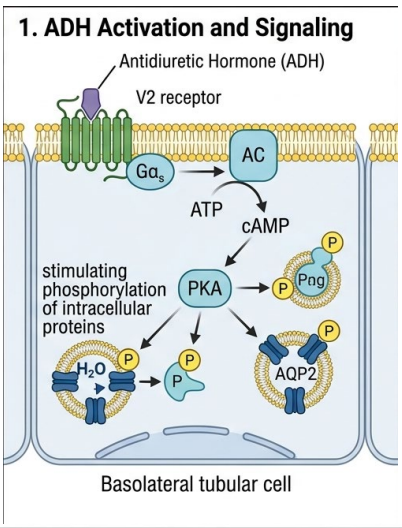
They increase free water excretion by blocking the antidiuretic action of ADH in the kidney and have no direct effect on sodium or potassium excretion:

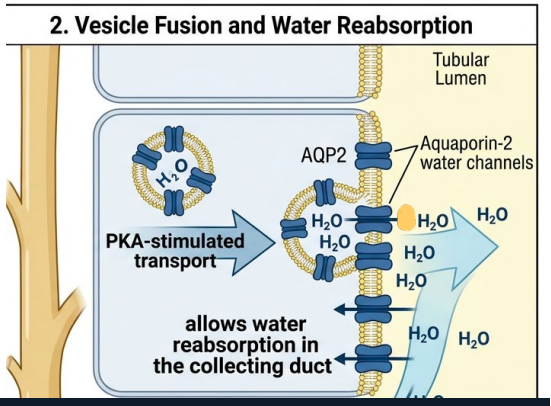
-
- Increased plasma osmolality with increased serum sodium levels
- Increased urine output with lower urine osmolality

C. What is the mechanism of action of ADH? (High Yield)

The collecting duct is impermeable to water in the absence of vasopressin:

1. ADH activates G protein-coupled V2 receptors on the basolateral tubular cell membrane, stimulating phosphorylation of intracellular proteins.
2. Fusion of vesicles containing aquaporin 2 to the luminal membrane, where aquaporin serves as a water channel and allows water reabsorption in the collecting duct.





N.B. ADH work mainly on **medullary CT but to some extent on cortical.** (High Yield)

(High Yield)

- **SIADH can be associated with small cell lung carcinoma as a paraneoplastic syndrome**
- **Central DI or SIADH (2 nearly opposite ideas) can occur secondary to head trauma or meningitis.**
- **Patients with SIADH have a clinically normal extracellular fluid volume and low plasma osmolality (euvolemic hyponatremia) therefore features of volume overload are not seen.**

2) Primary polydipsia and DI

A. Why do we use thiazides in NDI? (High Yield)

Thiazides reduce renal water losses in NDI by inducing a mild volume depletion that increases sodium and water reabsorption in the proximal tubule. This decreases the total amount of water delivered to the collecting ducts, allowing for better retention of supplemental water.

B. A Psychiatric patient can have: (High Yield)

- **Primary polydipsia** due to increased water intake
- **Nephrogenic diabetes insipidus** due to drugs such as lithium (reduces the ability of the kidneys to concentrate urine primarily by antagonizing the action of vasopressin in the collecting tubules and ducts.)

N.B. Nephrogenic diabetes insipidus caused by lithium usually resolves following discontinuation of the drug. However, impairment can be permanent following years of chronic use.

C. What are the most common causes of NDI?

- In adults is commonly due to medications (eg, lithium)
- In children it is typically due to congenital mutations involving the vasopressin (V2) receptor or aquaporin 2 channel.

E. What is Water deprivation test?

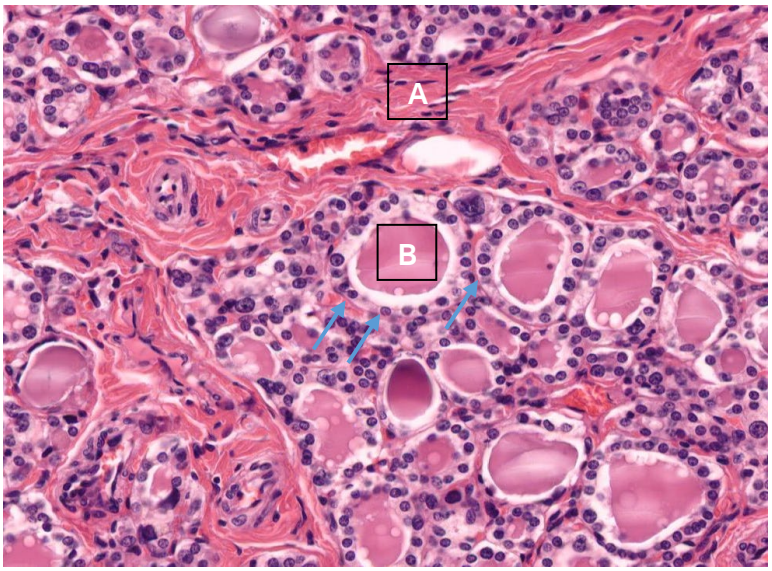
1. **Drinking water is withheld and urine osmolality is monitored until it reaches a steady-state plateau** (representing the maximal concentrating ability of the kidneys): Water deprivation in patients with PP stimulates ADH secretion and leads to a significant rise in urine concentration, whereas urine in patients with DI remains dilute.
2. **Once a plateau is reached, vasopressin is administered:** In DI, exogenous vasopressin causes an increase in urine osmolality; in PP, urine concentration remains unchanged because at this point in the test, the endogenous ADH effect is already at maximum.

F. vasopressin activates urea transporters in the medullary collecting duct, increasing urea reabsorption and decreasing renal urea clearance.

G. Relief of urinary obstruction may result in post-obstructive diuresis as the kidneys act to normalize fluid volume and solute levels. It is mostly seen in patients with a history of reduced urine output from chronic urinary obstruction.

4. Thyroid

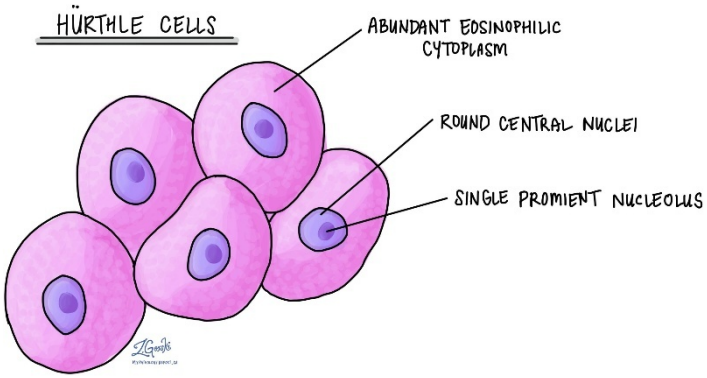
A) Normal Thyroid

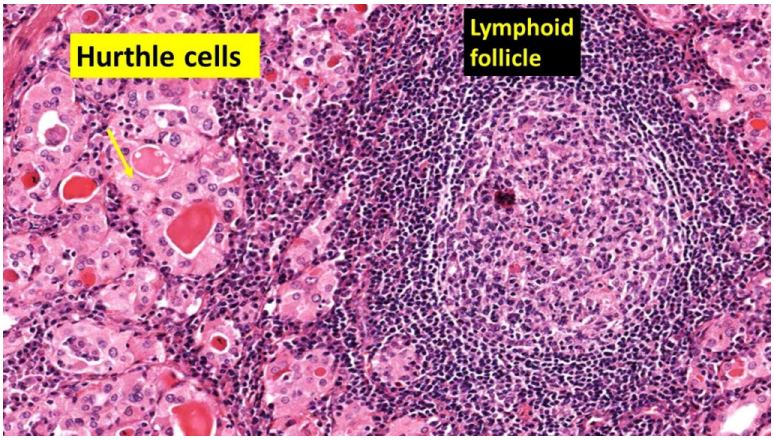


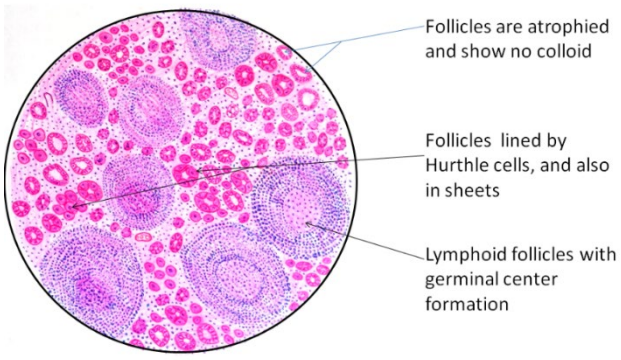
1. Thyroid trabuclae A
2. Thyroid follicules (B)
3. Follicular cells (Arrow)

B)Hypothyroidism

1) Hashimoto Thyroiditis







C. What is the clinical course of Postpartum thyroiditis? (High Yield)

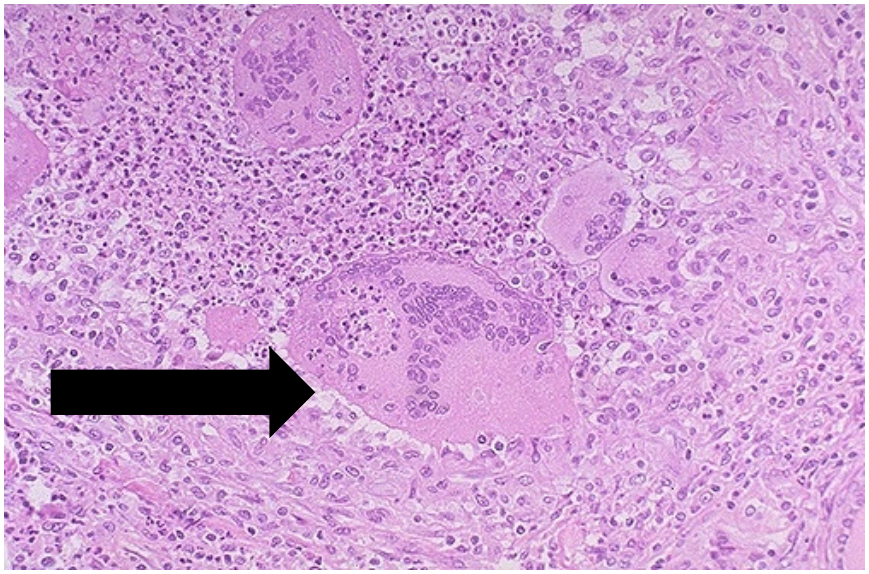
1. Onset ≤12 months after pregnancy
2. Transient hyperthyroid phase (↑ T4 & T3, ↓ TSH): due to release of preformed thyroid hormone after thyroid follicle destruction.
3. Brief hypothyroid phase (↓ T4 & T3, ↑ TSH)
4. Return to euthyroid state

D. Important investigations for post-partum thyroiditis: (High Yield)

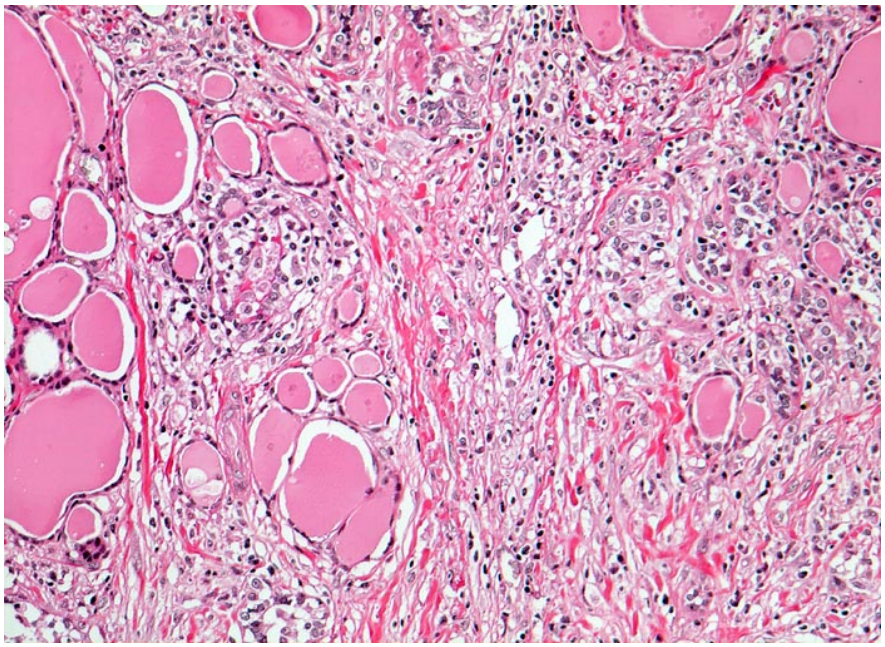
1. ↑ Serum thyroglobulin: destruction of thyroid follicles releases preformed thyroglobulin**,** T3**,** and T4 into the bloodstream**.**
2. ↓ Radioiodine uptake: no production of thyroid hormone
3. Ultrasonography: diffuse thyroid enlargement with ↓ blood flow

2) De Quervain Thyroiditis

A. Arrow shows the giant cells



3) Ridel Thyroiditis



4. Congenital Hypothyroidism

Clinical Manifestations	**Usually Asymptomatic at Birth** ↳ Rarely: delayed meconium passage **Maternal Thyroxine Wanes (Weeks to Months)** Lethargy, poor feeding Enlarged fontanelle Protruding tongue, puffy face, umbilical hernia Constipation Prolonged jaundice Dry skin
Diagnosis	TSH ↑ Thyroxine ↓ Elevated TSH & Low free thyroxine levels. Newborn Screening (critical)
Treatment	* Levothyroxine
Prognosis	No deficits if treatment started in neonatal period. Untreated disease leads to neurocognitive dysfunction (e.g., lower IQ).

5) Why can hypothyroidism be associated with goiter?

Due to chronic thyroid stimulation by TSH which improves with the administration of levothyroxine (as TSH levels are decreased)

6) Why T4 supplementation is preferred more than T3?

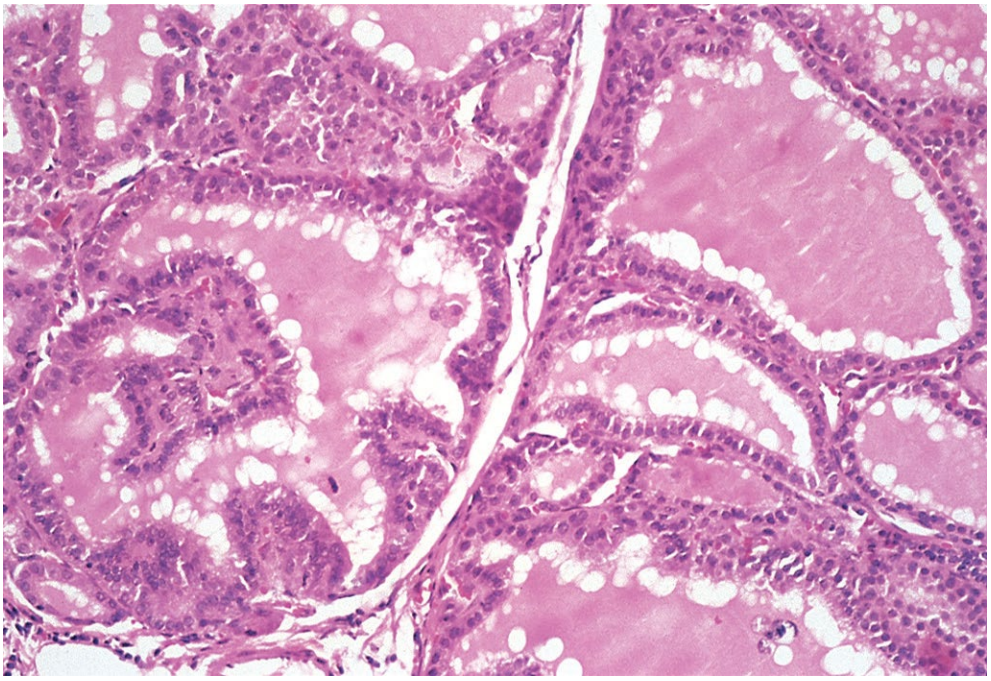
Synthetic T3 (liothyronine) is not recommended for the routine treatment of hypothyroidism, as it has a short half-life, and patients can experience wide fluctuations in plasma T3 levels. T4 (levothyroxine) supplementation provides a more physiologic effect and is preferred.

7) **TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism:** TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism); In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction **(High Yield)**

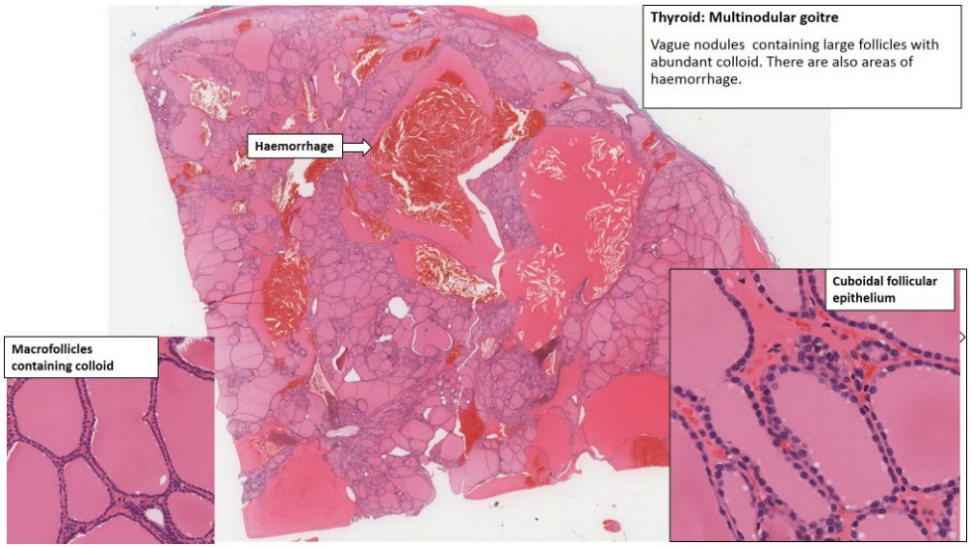
C)Hyperthyroidism

1) Graves disease

Tall, crowded follicular cells and scalloped colloid



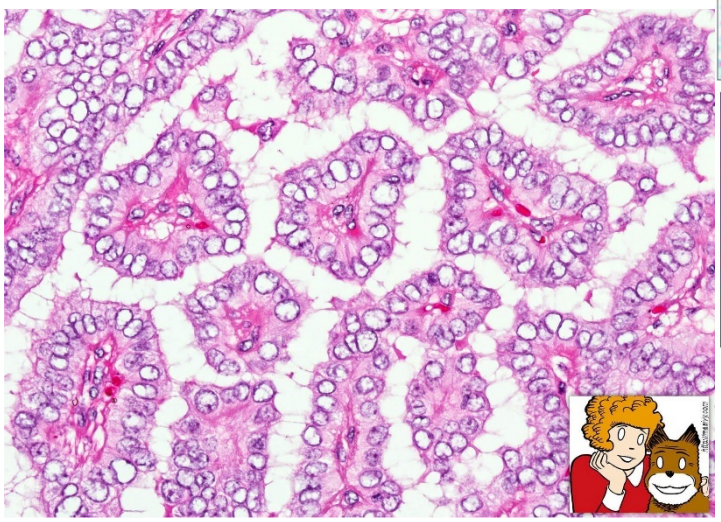
2) Toxic Multinodular Goiter

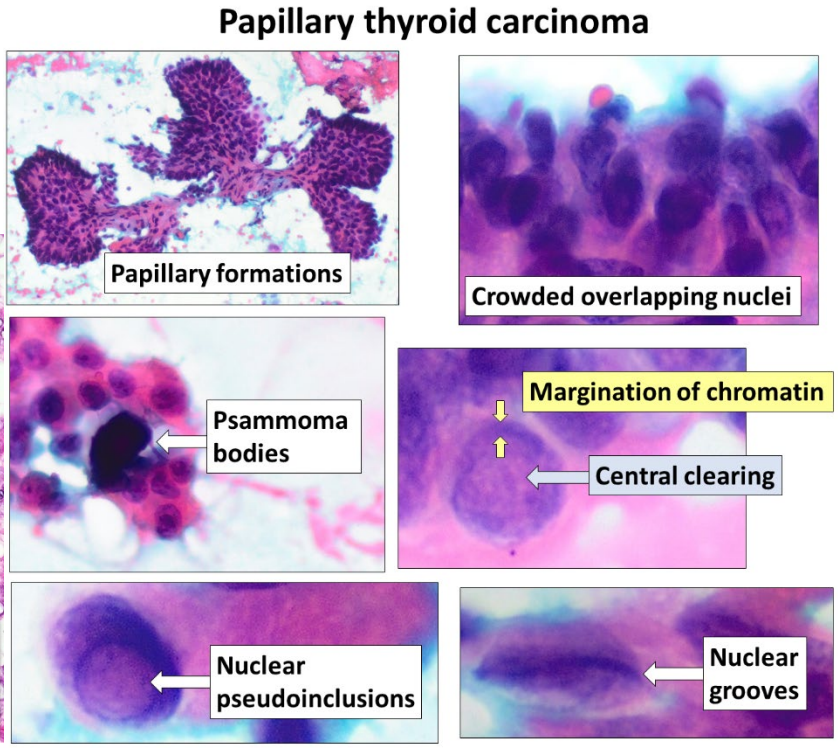


D. Thyroid Neoplasm

1. Papillary carcinoma

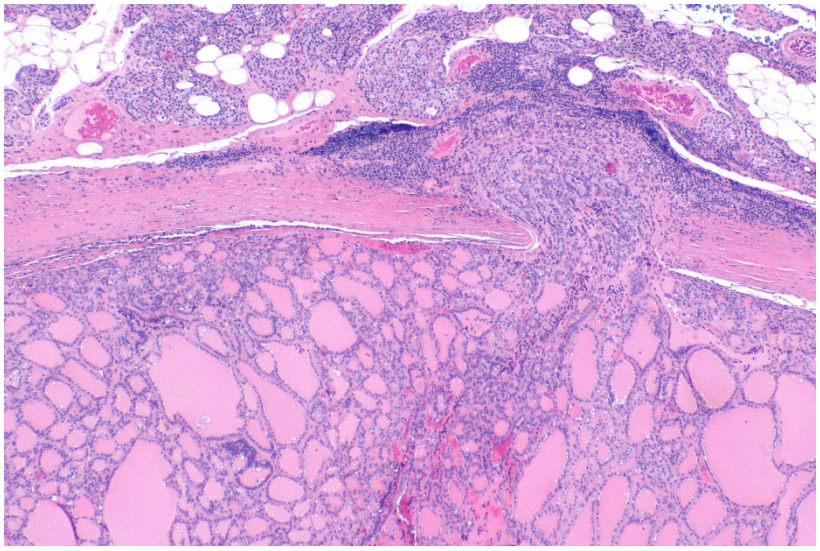
Orphan annie eyes





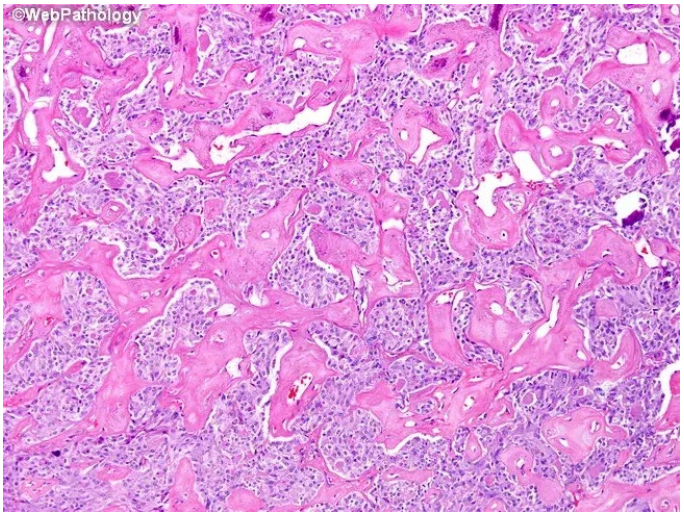
2. Follicular Carcinoma

Follicular carcinoma and adenoma looks like a normal Thyroid gland but separated by a capsule (carcinoma invades the capsule while adenoma doesn't)

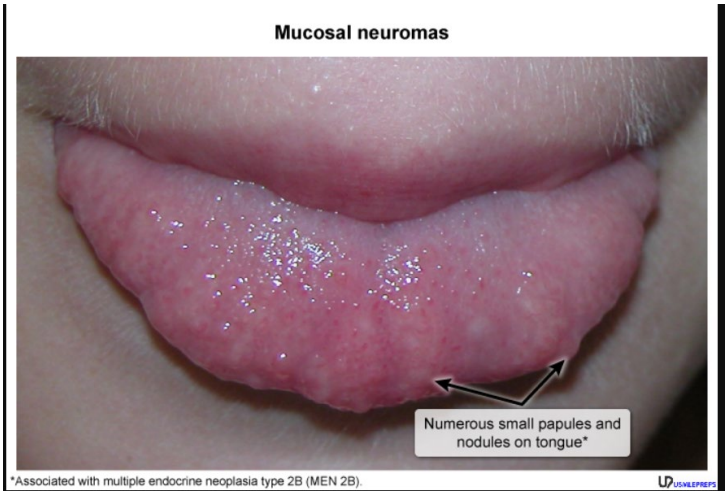


3.Medullary carcinoma

A. Amyloid stroma



B. In association with mucosal neuromas and marfanoid habitus (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B (MEN2B).** (High Yield)



unlike true Marfan syndrome, patients with MEN 2B do not develop aortic malformations (eg, dilation) or ocular malformations (eg, ectopia lentis).

4)Radioactive material such as iodine-131 (131I) can be released into the environment following nuclear reactor accidents, breach-of-containment at waste disposal sites, or atomic bomb blasts.131I is preferentially taken up and concentrated within the thyroid gland. There it can cause significant tissue damage that may result in radiation-induced hypothyroidism and thyroid carcinoma (particularly in younger patients). **In the event of a nuclear accident, potassium iodide is given prophylactically to protect the thyroid from excessive accumulation of radioactive 131I.**

Special Key Words to approach a USMLE Thyroid Case: (High Yield)

1. ⊕ antithyroid peroxidase (antimicrosomal) and antithyroglobulin antibodies= **Hashimoto or Postpartum thyroiditis**

2. Hypo + Painful =**de Quervain thyroiditis**

3. Normal TSH, normal or low T4, low T3, high rT3 in a critically ill **= euthyroid sick syndrome**

4. Hyper + Exophthalmos plus Thyroid-stimulating immunoglobulin= **graves**

5. **Patients with thyroid carcinoma** will be either euthyroid or hypothyroid; they will not be hyperthyroid however their TSH will be low, and uptake is high because those conditions are tumorous, where the gland is autonomously producing and secreting thyroid hormones without the need for TSH.

6. **In subclinical hypothyroidism**, the patient will be asymptomatic (hence subclinical) and will have normal T3 and T4, despite an elevated TSH.

7. **If patient intakes Thyroxine:** Low TSH, high T3, high T4, low 123 I uptake (T4 is high due to intake and T3 is high due to T4 conversion leading to:

    - low TSH
    - decreased 123 I uptake: decreased gland production because of high levels of T3 and T4

8. **If patient intakes Triiodothyronine**: Low TSH, high T3, low T4, low 123 I uptake low rT3 (T3 can't be converted to T4 and high T3 will decrease TSH and thus lower T4; rT3 also decreases because less T4 is available for conversion)

9. Increased levels of thyroxine (T4), triiodothyronine (T3), and TSH are concerning for **thyroid hormone resistance**

10. **Normal TSH, normal T3, normal free T4, increased total T4, decreased free/total T4 ratio** in a pregnant woman is due to TBG because of estrogen (total T4 is free plus bound: more TBG will increase the total bound and thus increased T4)

11. **Normal TSH, normal T3, normal free T4, low total T4, increased free/total T4 ratio** (thyroid binding globulin deficiency)

E. Thyroid Pharmacology

1) Why do we give patients Calcitriol and calcium Post thyroidectomy?

To treat and prevent postoperative hypocalcemia.

N.B. Calcitriol, the active form of vitamin D, should be chosen over calcidiol as the conversion of calcidiol to calcitriol is dependent on parathyroid hormone, and patients with hypoparathyroidism can have inadequate production of calcitriol.

2) What are the symptoms of neutropenia and How is PTU associated with Neutropenia?

A) Symptoms

- Oropharyngeal ulcers and fever
- Laboratory evaluation usually shows isolated leukopenia

B) How is PTU associated:

Interaction of the thionamide with reactive oxidative products leading to generation of drug metabolites (eg, propyl thioester, sulfonic acid) that covalently attach to the neutrophil surface. Antibodies then form against these new antigens (haptens), resulting in antibody-dependent cellular cytotoxicity.

3) What is the function of Beta blockers (eg, propranolol) in hyperthyroidism management? (High Yield)

- Blunt the adrenergic manifestations of hyperthyroidism
- Reduce conversion of T4 to triiodothyronine (T3) by inhibiting 5'-monodeiodinase in peripheral tissues.

4)What drugs decrease the Peripheral conversion of T4 to T3? (High Yield)

- Beta blockers
- Glucocorticoids
- Propylthiouracil.

5.Adrenal gland

1) Hypothalamic-pituitary-adrenal (HPA) axis Physiology

A. What is the physiology of the metyrapone stimulation test?

It is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity: metyrapone blocks cortisol synthesis by inhibiting 11-β-hydroxylase, which converts 11-deoxycortisol to cortisol in the zona fasciculata. Because 11-deoxycortisol lacks glucocorticoid activity, it does not inhibit pituitary ACTH secretion. As a result, the reduction in cortisol levels following metyrapone administration cause an increase in pituitary ACTH secretion. This leads to increased production of 11-deoxycortisol, which is further metabolized by the liver to 17-hydroxycorticosteroids that accumulate in the urine. Serum 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels will normally rise in response to metyrapone, indicating an intact HPA axis. Failure of these steroid levels to increase implies primary or secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

3)Adrenal Insufficiency

A. Bilateral adrenal hemorrhage (**Waterhouse-Friderichsen syndrome [WFS]**) can cause PAI and adrenal crisis but is typically seen acutely in the setting of bacterial sepsis (eg, Neisseria meningitidis). However, hyperpigmentation occurs in chronic adrenal insufficiency and therefore would not be expected with WFS. **(High Yield)**

B. What are the causes of Hyponatremia in primary adrenal insufficiency?

1. **Reduced aldosteron**e leads to markedly decreased sodium absorption by the renal collecting tubule principal cells. The decrease in total body sodium results in hypovolemia which stimulates Antidiuretic hormone (ADH) secretion leading to hypnonatremia.
2. Decreased cortisol (normal inhibits the ADH) also stimulates ADH Secretion.

N.B. The tubular salt wasting reduces total body sodium but does not directly affect serum sodium concentration instead the increased ADH levels increases water retention and lowers the serum sodium.

C. Why does High levels of Cortisol cause Hypertension? (High Yield)

- Increased peripheral vascular sensitivity to adrenergic stimuli (Permissive **effect of cortisol on catecholamine)**
- Increased hepatic production of renin substrate (angiotensinogen)
- Activation of renal tubular mineralocorticoid receptors

D. Adrenal crisis: (High Yield)

1. **C/P:**

- Severe hypotension and refractory shock
- Abdominal pain, vomiting, weakness, and fever.

2. **Treatment**

Fluid resuscitation + glucocorticoid supplementation with hydrocortisone or dexamethasone.

How to approach any Cushing syndrome USMLE Case? (High Yield)

Dexamethasone suppression test:

- Failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes down; answer = Cushing disease.

- Failure of cortisol suppression with low-dose dex; high-dose dex administered + patient's cortisol goes not go down; answer = either primary adrenal secretion (Low ACTH), or small cell bronchogenic carcinoma secreting ACTH (High ACTH)

- If a patient is on exogenous glucocorticoids, we do not do dexamethasone suppression test because the Cushing syndrome is clearly due to the exogenous steroids. We use the dexamethasone suppression test to identify endogenous causes of Cushing syndrome.

- Cushing disease (Pituitary ACTH-secreting tumor)
- Cushing syndrome (Any case of increased cortisol)

E. What are the DD of Hypertension + hypokalemia?

1. **1ry hyperaldosteronism**
2. **2ndry hyperaldosteronism**
3. **Non-aldosterone causes:**

    - Congenital adrenal hyperplasia
    - Deoxycorticosterone producing adrenal tumor
    - Cushing syndrome
    - Exogenous mineralocorticoids

F) What are the side effects of Glucocorticoids on pituitary hypothalamic axis? (High Yield)

1. **Long-term suppression leads to atrophy of:**

- hypothalamic CRH-releasing neurons
- pituitary corticotrophic cells
- adrenal zona reticularis and zona fasciculata

2. **Glucocorticoids accelerate the development of osteoporosis by a number of mechanisms:**

- **Decreased osteoblast:**

    - Inhibit the proliferation and differentiation of osteoblast precursor cells
    - Increased rates of apoptosis in mature osteoblasts

- **Increased osteoclast effect:**

  Osteoclast differentiation and activity are promoted by the receptor activator of nuclear factor kappa B (RANK)/RANK-ligand; this effect is inhibited by osteoprotegerin, which acts as a decoy receptor. Glucocorticoids increase the expression of RANK and RANK-ligand and decrease the expression of osteoprotegerin , leading to increased bone resorption.

- **Renal and intestinal calcium wasting:** Glucocorticoids suppress intestinal calcium absorption and renal calcium reabsorption, requiring increased release of calcium from bone to maintain calcium homeostasis.

6.Insulin and DM

1) What enzyme deficiency is associated with maturity-onset diabetes of the young (MODY)? (High Yield)

Glucokinase mutations are one cause of maturity-onset diabetes of the young (MODY), an autosomal dominant disorder characterized by mild hyperglycemia that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus, patients with MODY are typically younger and nonobese, and the condition is nonprogressive, even without treatment.

2)What is the pathogenesis of stress hyperglycemia?

- Secretion of cortisol, catecholamines, glucagon & proinflammatory cytokines
- Increased hepatic glycogenolysis & gluconeogenesis

4)What is the type of insulin receptor? (High Yield)

The surface receptor for insulin is a transmembrane protein with intrinsic tyrosine kinase activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). **IRS-1** then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the **MAP kinase pathway** promotes mitogenic functions such as DNA synthesis and cell growth.

3) Is smoking cessation or dietary modification more important in decreasing risk of cardiovascular disease?

Dietary modification and exercise reduce the risk of cardiovascular disease to a lesser extent than smoking cessation.

4) Why is hemoglobin A1c misleading in Beta thalassemia?

Increased erythrocyte turnover results in a misleadingly low hemoglobin A1c level. In such cases, measurement of glycated serum proteins (ie, fructosamine) is sometimes used to estimate glycemic control.

5. Why are Patients with type 1 diabetes mellitus are at increased risk of hypoglycemia?

- Exogenous insulin is not subject to the same regulation as endogenous insulin and will continue to be absorbed from the injection site despite falling glucose levels.
- Those with long-standing diabetes (ie, >5 years) and those with pancreatogenic DM (Chronic Pancreatitis) frequently also have alpha cell failure with decreased glucagon secretion and therefore have an even greater risk of rapid hypoglycemia.

6. What drugs can be used for diabetic gastroparesis? (High Yield)

- **Metoclopramide**, a dopamine 2 receptor antagonist, can improve symptoms but is occasionally associated with extrapyramidal side effects and tardive dyskinesia.
- For patients with gastroparesis who cannot tolerate metoclopramide, **erythromycin**, a macrolide antibiotic, activate the motilin receptor in the smooth muscle of the upper digestive tract, which results in coordinated peristaltic contractions that begin in the stomach and move through the entire upper digestive system (thereby propelling food into the colon). However, the agonist effects of erythromycin diminish over time (tachyphylaxis) so it is generally used for short periods (<4 weeks).

7) Mention 2 drugs that binds to PPAR-α? (High Yield)

Thiazolidinediones (TZDs) (Pioglitazone) and fibrate medications

8)Why is Nonselective beta blockers contraindicated in DM? (High Yield)

Because they attenuate the norepinephrine/epinephrine-mediated symptoms of hypoglycemia, but cholinergic symptoms (eg, hunger) are unaffected.

9) Why is short term weight loss hard to preserve?

Caloric restriction and falling fat stores, lead to increased ghrelin levels along with decreased insulin and leptin levels. This causes an increase in appetite and, typically, regain of weight.

7.PTH and Calcium

1. why does patients with granulomatous diseases have hypervitaminosis D? (High Yield)

Due to expression of 1-α-hydroxylase in activated macrophages (A similar process can occur in Hodgkin disease and some non-Hodgkin lymphomas)

2. What is the side effect of excessive vitamin D intake?

- **Symptomatic hypercalcemia** with impaired depolarization of neuromuscular membranes (eg,
  muscle weakness, constipation, confusion)
- **Impaired concentration of urine in the distal tubule** (polyuria/polydipsia).
- **Renal stone formation**
- **Bone demineralization with associated bone pain**

3. What is the mechanism of action of PTH analog (teriparatide)?

Promote bone remodeling by inducing increased resorption of old bone while stimulating a corresponding increase in new bone production, resulting in a net increase in total bone mass.

3. What is the mechanism of action of pyrophosphate analogs or Bisphosphonates (eg, alendronate, risedronate)? (High Yield)

They attach to **hydroxyapatite binding sites on bone surfaces and inhibit osteoclast-mediated bone resorption.**

4. What is the mechanism of action of Denosumab? (High Yield)

It is a monoclonal antibody that decreases bone resorption by binding to RANK-L and blocking the interaction between RANK-L and RANK on osteoclast surfaces.

8.Pharmacology

1. what medications cause Medication-induced body fat redistribution (lipoatrophy or lipodystrophy)? (High Yield)

Nucleoside reverse transcriptase inhibitors (mainly stavudine and zidovudine) and protease inhibitor.

2. What medications are commonly used for weight loss?

- **Sympathomimetic amines**
- **Orlistat:** Intestinal lipase inhibitor
- **Bupropion/naltrexone** antidepressant + opioid antagonist

3. What medications are associated with drug-induced neutropenia?

1. **Antithyroid**
    - Propylthiouracil
    - Methimazole
2. **Anti-inflammatory**
    - Methotrexate
    - Sulfasalazine
3. **Antimicrobial**
    - Acyclovir
    - Trimethoprim-sulfamethoxazole
    - Quinine
4. **Psychotropic or anticonvulsant**

- Clozapine
- Carbamazepine
- Phenytoin

5. **Cardiovascular**

- Ticlopidine and Antiarrhythmic agents (eg, procainamide)

4.What is the tratment of irritable bowel syndrome (IBS)?

- **Antispasmodic medications** (eg, dicycloverine), block gastrointestinal muscarinic receptors, for gastrointestinal bloating symptoms.
- **Lubiprostone**, a chloride channel activator to increase intestinal fluid secretion, for constipation-predominant IBS.