Hypothyroidism	**Thyrotoxicosis** (any cause of TH excess) vs **Hyperthyroidism** (subset in which excess TH is 2/2 increased TH production and release)
• **Neuro/Ophtho/Psych**: slowed mental fxn "brain fog", fatigue, increased need for sleep, apathy, depression, diminished hearing, DTRs w/ slow return to relaxed state aka "hung up", ptosis, loss of lateral 1/3 portion of eyebrows • **CV:** bradycardia, systolic HypoTN / diastolic HTN, decreased cardiac contractility, overall decreased CO, pericardial effusion, accelerated atherosclerosis • **Pulm/ENT:** pleural effusion, hoarse, low voice, slow speech • **MS:** weakness, myalgias w/ ↑CK, arthralgia • **Derm:** dry skin, cold intolerance, coarse and brittle hair/nails, myxedema (build up of matrix substances like GAGs in tissue specifically tongue, eye, hand) resulting in enlarged tongue, non-pitting edema throughout esp periorbital area, carpel tunnel syndrome • **Renal**: hyponatremia 2/2 SIADH • **GI**: constipation, peritoneal effusion aka ascites • **Endo**: hypoglycemia, ↑LDL, ↑TG, ↓HDL, decreased metabolic rate, weight gain • **GU**: menorrhagia • **Heme**: N/N anemia NB everything hypo except LDL, TG, menses, sexual activity, for both hypo/hyper you can have Sx due to mass effect resulting in airway/esophageal compression NB higher prolactin	• **Neuro/Ophtho/Psych**: nervousness, insomnia, irritable, anxiety, rapid speech, fatigue (b/c the body is chronically revved up the pt is fatigued), brisk DTRs, increased sympathetic output stimulates the levator palpabre aka wide staring eye (lid retraction) and delay in moving upper lid down as eye moves downward resulting in sclera visible above iris (lid lag) • **CV**: palpitations due to tachy-arrhythmias, HTN • **Pulm/ENT**: decreased capacity due to muscle weakness • **MS:** jittery, tremor, hyperactive, easy fatigability, fractures 2/2 resorption (consider checking a DEXA scan) • **Derm**: warm moist skin, excessive hyperhydrosis, heat intolerance, thin fine hair, hair loss, hyperpigmentation, onycholysis (separation of fingernail from bed) • **GI**: diarrhea • **Endo**: hyperglycemia, ↓LDL, ↓TG, ↑HDL, increased metabolic rate, weight loss despite increased appetite • **GU**: amenorrhea, ED and decreased libido • **Heme**: N/N anemia

• **Myxedema Coma** (Medical Emergency w/ 40% Mortality)
  ○ Mech: severe hypothyroidism in a chronically untreated hypothyroid pt that experiences a precipitating event (trauma, infection, cold exposure, narcotics) esp seen in elderly women during winter time
  ○ S/S
  ▪ General: hypothermia
  ▪ CNS: depressed state of consciousness to coma
  ▪ GI: hypoNa (b/c ~SIADH), hypoGlu
  ▪ CV: LO CHF, bradycardia, hypoTN, pericardial effusion
  ▪ Resp: resp depression, hypoventilation, pleural effusion
  ○ Tx
  ▪ ABCs
  ▪ warm blankets but slowly to prevent vasodilation and subsequent hypotension
  ▪ pressors to maintain BP
  ▪ intubation to maintain RR
  ▪ IV T4 (5-8mcg/kg x1 then 50-100mcg IV Qd) and b/c peripheral conversion is impaired consider giving T3 5-10mcg/kg Q8hrs
  ▪ **dexamethasone b/c of adrenal insufficiency**
  ▪ **broad culture and empiric broad spectrum abx**
• **Cretinism**
  ○ Mech: 1/4000 newborns hence part of newborn screen, it is one of the metabolic disorders that is routinely checked at birth, unique causes (congenital problems, mother's diet deficient in I, autoimmune mother transfers Abs to fetus, prenatal exposure to radioiodine or antithyroid meds aka "goitrogens")
  ○ S/S
  ▪ at birth usually look normal (sometimes they have low Apgar's, prolonged jaundice, and hypotonia) regardless newborn screen is done
	• **Thyrotoxic Storm** (Medical Emergency w/ 20% Mortality)
	  ○ Mech: severe hyperthyroidism in a chronically untreated hyperthyroid pt that experiences a precipitating event (emotional stress, trauma, infection, DKA, surgery, MI, stroke, PE, childbirth, radioiodine, iodinated contrast dyes, abrupt cessation of antithyroids, vigorous thyroid palpation)
	  ○ S/S
	  ▪ General: hyperthermia, exhaustion, flushing, sweating
	  ▪ CNS: mild (agitation) mod (delirium, psychosis, lethargy) severe (seizure, coma)
	  ▪ GI: N, V, D, ab pain, jaundice (late ominous complication)
	  ▪ CV: HO CHF, tachycardia, HypoTN (not HTN)
	  ○ Tx
	  ▪ cooling blankets and acetaminophen for F
	  ▪ Propranolol to maintain BP
	  ▪ IV fluids and glucose
	  ▪ PTU
	  ▪ Na Iodide (very large [ ]) to inhibit further T4 release (only start 1hr after antithyroid drugs) via Wolff-Chaikoff Effect, this effect only lasts for a few days
	  ▪ dexamethasone to inhibit conversion of T4 to T3, prophylaxis against relative adrenal insufficiency
	  ▪ DO NOT GIVE salicylates b/c increase conversion of T4 to T3 and O2 consumption
	  ▪ **broad culture and empiric broad spectrum abx**

b/c not overtly apparent early on ▪ if not caught then… Physical: developmental delay, wide fontanel, enlarged tongue, abdominal distension, coarse facial features, umbilical herniation (everything is "big") and Mental: developmental delay, mental retardation	
• **T4 aka Levothyroxine (Synthroid, Levothyroid, Levoxyl, Unithroid)** (mcg) different brands of levothyroxine are not always interchangeable and bioequivalent therefore if you switch then check TSH, 1/2IV = PO, even though T3 is 5x more potent than T4, T4 is better b/c it has ~8x the half life hence can take QD (t1/2 T4 = 8d, t1/2 T3 = 1d) ○ Interfered Absorption w/ PPIs and cations (iron, antacids, calcium, sucrulfate, cholestyramine) therefore take 4hrs before or after ○ Enhanced Metabolism w/ rifampin and AEDs therefore increase dose ○ NB when a pt suddenly needs more HRT consider drug interaction • **T4+T3 aka Levo + Lio (Armour, Thyrolar)** (grain) because TH in the blood is a mixture of T4 (80%) and T3 (20%) it was theorized that it would be best to administer HRT with this ratio but studies indicate there is little benefit except for treating fatigue and that there is actually an increased r/o arrhythmias • **T3 aka Liothyroxine (Cytomel, Triostat)** (mcg) • Treatment Strategy (adjust at 12.5mcg amounts Q4-8wks, 50mcg of levo = 65mg/1grain of lio + levo = 25mcg of lio) ○ Sub-Clinical (very controversial, all based on risk of osteoporosis/tachyarrhythmias if pt is Tx vs risks of remaining hypoTH) ▪ >65yo OR Heart Dz OR Osteoporosis • TSH 4.5-10 (mild) = NO Tx • TSH >10 (severe)/Symptoms/Goiter/Pregnancy/Infertility = Low Dose Tx (1.4mcg/kg/d) w/ Goal TSH (1.0) ▪ <65yo AND NO Heart Dz AND NO Osteoporosis = Tx • TSH 4.5-10 (mild) = Med Dose Tx (1.5mcg/kg/d) w/ Goal TSH (0.75) • TSH >10 (severe)/Symptoms/Goiter/Pregnancy/Infertility = High Dose Tx (1.6mcg/kg/d) w/ Goal TSH (0.50) ▪ NB subclinical is usually 2/2 early Hashimoto's therefore check anti-TPO Ab and if high then follow pt closely b/c pt will likely become clinical in a very short period of time ○ Clinical (always treat w/ 1.7mcg/kg/d)	• **BB:** used to treat CV symptoms of hyperTH and has also been found to inhibit a deiodinase converting T4 to T3 ○ **Propranolol** • **Thionamides**: inhibit (1) thyroperoxidase which iodinates and conjugates tyrosines together and (2) deiodinase (only PTU) ○ **Propyl-Thio-Uracil (PTU)** ▪ Fasting Acting BUT Short Half-Life (Q7hrs) therefore TID dosing ▪ Less Milk/Placenta Penetration hence "PTU ok in Pregnancy" ▪ Other SEs: tastes bad ○ **Methi-Ma-Zole (MMZ)** ▪ Long Half-Life BUT Slow Acting (Q12hrs) therefore QD dosing ▪ More Milk/Placenta Penetration ▪ Other SEs: congenital newborn scalp malformation, aplasia cutis and GI defects ○ SEs: PTU/MMI have same SE profile, check CBC/LFTs/TFTS Q1-3mo ▪ Rare Severe (0.5%) (cannot switch to other agent) • Agranulocytosis and Aplastic Anemia (warn pt of any fever, sore throat, mouth ulcers, etc, seen in 0.2%, since Sx of granulocytosis are acute surveillance with CBC is not recommended just tell pts to tell you about Sx, can occur at any time, higher risk in older pts and at higher doses) • Hepatic Necrosis (warn pt of jaundice) • Vasculitis ▪ Common Mild (5%) (can switch to other agent) • Transient Leucopenia • LFTs/cholestasis • Rash/pruritis/urticaria/arthralgias • Treatment Strategy ○ Sub-Clinical (very controversial, all based on risk of Tx vs risks of osteoporosis/tachyarrhythmias if pt remains hyperTH) ▪ <65yo AND NO Heart Dz AND NO Osteoporosis • TSH 0.1-0.45 = NO Tx • TSH <0.1 = Low Dose Tx ▪ >65yo OR Heart Dz OR Osteoporosis = Tx • TSH 0.1-0.45 = Med Dose Tx • TSH <0.1 = Large Dose Tx ○ Clinical (always treat)

	Thyroiditis (REMEMBER LOW RAUI)			
Type	**Autoimmune Hashimoto's**	**De Quervain's**	**Sporadic-PostPartum** (SOME SAY A VARIANT OF HASHIMOTOS)	**Suppurative**
Course	Chronic	Subacute	Subacute	Acute
Histology	Lymphocytic	Granulomatous	Lymphocytic	Neutrophilic
Pt Mechanism	Pt: +FHx, F>M, any age but peaks at ~40yo, other autoimmune conditions: PGA-II, Addison's, DM, Pernicious Anemia,	Mechanism: **summer time URT** viral infection with coxsackie, adeno, measles, mumps during the summer	Mechanism: idiopathic/sporadic or post-partum (10% of post-partum	Mechanism: radiation, Amio, trauma, infection: bacterial, fungal, parasitic,

	Sjogren's, Primary Biliary Cirrhosis, etc Mechanism: autoimmune antibodies bind peroxidase, thyroglobulin and TSH-receptor but do not stimulate activity just attract complement → thyroid inflammation results in leakage of stored hormone (rare transient HYPERthryoidism) "Hashitoxicosis" → as hormone begins to deplete (transient EUthyroidism) → as hormone depletion becomes more severe (permanent HYPOthyroidism) Complication: thyroid lymphoma	time → **prodromal phase** (F, flu-like illness) for 2wks → thyroid inflammation results in leakage of stored hormone (transient HYPERthryoidism) → as hormone begins to deplete (transient EUthyroidism) → as hormone depletion becomes more severe (transient HYPOthyroidism) → immune system removes virus → full recovery of thyroid function (permanent EUthryoid) **w/ typical course lasting 2-12 months**	mothers (autoimmunity that unmasks as immune surveillance rebounds after pregnancy, increased risk if mother has + anti-TPO during pregnancy) → Hyperthyroid 0-6mo after delivery → Euthyroid 6-8mo → Hyothyroid 8mo-10mo → Euthyroid w/ typical course lasting ~10mo NB 50% will develop Hashimoto's if +anti-TPO	TB
Unique Features	Goiter	**Diffusely Painful Thyroid w/ pain radiating to the ears**		Painful
Labs **(increased TG)**	• variable TFTs (recheck TSH to ensure chronic thyroiditis vs. transient acute/subacute thyroiditis) • **Anti-Tyrosine Peroxidase (TPO) aka Anti-Microsomal Ab** (95% sens) unlike anti-TSH-receptor for Graves, anti-TPO is checked because its level (also TSH) is predictive for progression to overt hypothyroidism • Anti-Thyroglobulin (85% sens) • Anti-TSH-Receptor aka Thyroid Stimulating Ig (15% sens)	• variable TFTs • **high APRs**	• variable TFTs	• variable TFTs • **high APRs**
Tx	HRT	beta-blockers, NSAIDs to SAIDs if severe, HRT is recommended for 3-6mo after which it should be withdrawn to see if the pt has fully recovered	" "	" " + Abx

Hypothyroidism

- **Late Thyroiditis** (refer above)
- **Meds (Type II Amiodarone, Lithium, Hyperthyroidism Meds, Iodine Deficiency)**
  - **Amiodarone** (can cause two very different disease (one hyper the other hypo) and some pts can have elements of both, check TFTs prior and at 4mo intervals and for 1yr after amio stopped)
    - Type I (Goitrous, 3% of pts, increased/homogenous RAIU/Scan, tends to occur in pts w/ pre-existing thyroid disease) Mech: high iodine content upregulates sodium-iodide symporter resulting in thyroid stimulation (Jodbasedow Effect), Tx: similar to Graves
    - Type II (Non-Goitrous, 10% of pts, decreased/homogneous RAIU/Scan, tends NOT to occur in pts w/ pre-existing thyroid disease) Mech: high iodine content downregulates sodium-iodide symporter resulting in thyroid rest (Wolf-Chaikoff Effect), but this effect lasts ~1mo unless pt has underlying thyroid disease, NB Wolf–Chaikoff Effect can be used as a treatment against hyperthyroidism by infusion of a large amount of iodine to shut down the hyperfunctioning thyroid gland, NB there can also be a destructive effect of amiodarone on the thyroid resulting in a thyroiditis, Tx: similar to De Quervain's
- **Infiltration** (**Malignant Thyroid Cancer, Metastatic, Riedel's** w/ scar tissue, **Amyloidosis, Hemachromatosis, Sarcoidosis, Scleroderma,** etc, firm gland on PEx, can compress trachea/esophageal/parathyroids)
- **Head & Neck Surgery/Radiation**
- **Congenital** (Problem with Formation: **Agenesis** (does not form) vs **Dysgenesis** (forms improperly), Hormone Enzyme Synthesis Disorder: **Pendred Syndrome** (+ hearing loss), **Peripheral Thyroid Gland Hormone Resistance**, Genetic Syndromes: **Down's, Turner's, Kleinfelter's**)
- **Secondary** (Hypothalamic-Pituitary Failure)

Hyperthyroidism

- **Early Thyroiditis** (in general the thyrotoxicosis caused by thyroiditis is less severe than that seen with causes below, RAIU is low, only treatment during these brief thyrotoxic states is beta-blocker to mainly treat symptoms otherwise do not use thionamides b/c not helpful b/c it is not a problem of over production but of destruction and spilling out of TH)
- **Autoimmune Grave's Disease**
  - Pt: other autoimmune disease, 0.5% of the population, ~50yo (but in general younger than Plummer's), F>M, +HLA, often triggered by childbirth, life stressors, infection, et al, if + maternal relatives then increased incidence and at a younger age
  - Mechanism: antibodies bind TSH receptor and actually act as an agonist → EVERY follicular cell is hyperfunctioning → HYPERthyroidism
  - PEx

        - Goiter w/ Bruit (increased blood flow on Doppler US)
        - Thyroid Associated Ophthalmopathy (TAO) (50% clinically and 90% on imaging) abs against TSH-receptor cross react with periorbital connective tissue, retroorbital fat, and extraocular muscles resulting in exophthalmos/proptosis (eyes bulge out w/ sclera visible b/t lower iris and lower lid), lagophthlamos (inability to close eyes), optic neuritis, diplopia [TAO DOES NO DISAPPEAR AFTER YOU TREAT AND FIX THE THYROID PROBLEM B/C THE PROBLEM IS NOT ELEVATED T3/T4 BUT THE ANTIBODY] Tx options include intraocular steroid, antiinflammatory, immunosuppressive injections, radiation, and surgery, refer to ophthalmologist
        - Pretibial Myxedema (1%) scaly, doughy, indurated, non-pitting edema skin overlying shins with violaceous nodules vs Eye, Hand, Tongue Myxedema seen in hypoTH
        - Acropachy (0.1%) aka digital clubbing
    - Studies
        - Ig
            - **Anti-TSH Receptor aka TSI (Thyroid Stimulating Ig)** (sens 90%, very expensive and not needed to make dx thus not checked only during pregnancy b/c high titers is linked to neonatal hyperTH)
            - TBII (Thyroid Binding Ig)
            - Anti-Thyroglobulin (sens 60%)
            - Anti-TPO (sens 60%, if + more associated w/ TAO) aka Anti-Microsomal-Ab
        - RAUI/Scan: Increased/Homogenous
    - Tx: you can be cured w/ meds but after 1yr of Tx there was a 50% relapse rate if meds are stopped therefore lifelong vs another option is surgery or radioactive ablation. After diagnosis you start a thionamide and a beta-blocker, then taper off beta-blocker after 1-2mo, continue thionamide until euthyroid which takes ~1yr so that thyroid storm does not occur during the surgery or ablation, then proceed with surgery or ablation.
        - 1° Radioactive Ablation: **everyone except pregnant, child, suspect cancer b/c of nodule, compressive symptoms, TAOs** (NB for some reason after radiation 15% of Grave's pts get worse eye symptom for a few months which is mild, returns to normal in 2 mo, effect may be decreased with corticosteroid use, if preexisting TAO is severe do surgery, smoking cessation decreases risk), single oral capsule 10-30 mCi of ^{131}I, ionizing iodine causes cancer but radioactive iodine does not, hypothyroid in 2mo, 7d pre-op stop thionamide, 20% relapse rate, SEs: transient neck tenderness, transient decrease in testosterone, there was some concern that there were increased episodes of CV disease and certain cancers but that was never confirmed
        - 2° Surgery: **for the exceptions, subtotal** (keep ~4-5g to prevent hypoTH), 5% relapse rate, Pre-Op: continue drugs, give KI (Wolff-Chaikoff Effect) 7-10d before surgery to decrease r/o thyroid storm and to decrease size/vascularity as much as possible, Post-Op Complications: HypoTH, HypoPTH (many times you can transplant the glands to the SCM and forearm if vascular supply is compromised), Hemorrhage leading to airway obstruction, Recurrent Laryngeal Nerve (Uni Damaged: hoarse x3mo, Bi Damaged: hoarse x6mo, Uni Cut: hoarse lifelong, Bi Cut: airway obstruction 2/2 vocal cord paralyzed in the midline adducted position, Tx: emergency intubation followed by lateral fixation of arytenoids cartilage)
- **Plummer's Disease aka Toxic Multinodular Goiter**
    - Pt: elderly
    - Mechanism: autonomous hyperfunctioning of SOME follicular cells → HYPERthyroidism (BUT the non functioning normal follicular cells actually atrophy b/c the increased TH from the hyperfunctioning cells feedback and inhibits TSH release)
    - PEx
        - **Multinodular**
        - **Apathetic Thyrotoxicosis**: very slow progression unlike Graves, thyroid goes from euthyroid to subclinical hyperthyroid to clinical hyperthyroid to overt thyrotoxicosis over many years hence it really manifests clinically when old and when they do the pt is usually lethargic, depressed, decreased appetite, etc aka opposite of what you would think hence called "apathetic thyrotoxicosis"
        - **Pemberton's Sign**: goiter extends into the mediastinum compressing substernal contents trachea (dyspnea), esophagus (dysphagia), great vessels (venous congestion, facial flushing, and lightheadedeness)
    - Studies
        - RAIU/Scan: normal/heterogenous (some parts nl/cold/hot)
    - Tx: **similar treatment to Graves but unlike in Graves where the entire gland is ablated in Plummers the hypofunctioning tissue returns back to normal and pt might not need HRT (if Pemberton's Sign than surgical removal is necessary)**
    - NB **increased risk for iodine-induced thyrotoxicosis** and thus should be monitored after exposure to iodinated contrast or iodine rich medications
- **Functioning Adenoma** (hot single nodule, usually an activating mutation of the TSH receptor, TH production is proportional to size such that overt hyperthyroidism manifests when nodule is **>3cm**, Normal-Increased RAIU "Hot/nl" + Single Nodular Scan, develop very slowly (like Plummer's) manifesting in the elderly, Tx: **hemi**thyroidectomy)
- **Ectopic**
    - **Struma Ovarii** (autonomous thyroid tissue in ovarian teratoma)
    - **HCG-Secreting Tumor** (HCG is similar to T4 in structure and action)
- **Exogenous**
    - **Prescribed**
    - **Factious**
- **Iodine (Jodbasedow Effect)**
- **Secondary**

- TSH Secreting Pituitary Adenoma (TSH is a dimer of alpha/beta, in adenomas there is an increase in ratio of alpha to beta, Tx: resection then somatostatin analogues then XRT)
- Resistance to Thyroid Hormone (TH receptor in pituitary is mutated resulting in constantly increased TSH)

Type (Frequency) NB unlike most other cancers thyroid cancer continues to rise in incidence over the past few decades	**Malignancy 10yr Survival**	**Grade**	**Mutation**	**Notes**	**Metastasis** • Pre-Op: Neck US and CT Chest to check for LAD	**Treatment** • Surgery (below) then • PostOp Radiation w/ ^{131}I that is 5-10x higher than ablation used for Graves (except for MTC) • HRT to suppress TSH (~0.3mU/L not 0) effects on hidden cancer (except for MTC) • Follow markers (thyroglobulin/calcitonin) and/or whole body scanning using tracer doses of ^{131}I (except for MTC)
Papillary Carcinoma (80%)	+ 98%	I	RET	• 0-30yo • Cytology: Orphan Annie Eye Nuclei • Histology: Psommoma Bodies • 3F:1M due to expression of ER • RFs: radiation and familial colon cancer syndromes	Spread via lymphatics to palpable cervical LNs (no organ involvement)	**<1cm: Lobectomy** **>1cm or Radiation Exposure: Total Thyroidectomy**
Follicular Carcinoma (15%)	++ 92%		RAS	• 30-40yo • Cytology: NORMAL hence diagnosis cannot be made on FNA you need a large needle biopsy to look at histology • Histology: capsular/vascular invasion • 3F:1M due to expression of ER • RFs: iodine deficient areas	Spread via blood to 1° bone, 2° brain, lung, liver (no LN involvement)	
Hurthle Carcinoma						
Medullary Thyroid Carcinoma (MTC) (5%)	+++ 80%	II	RET	• 40-50yo • Cytology: ? • Histology: amyloid deposition • all others are tumors of follicular cells, this one is a tumor of the PARA-follicular C-cells that secrete calcitonin • RFs: 25% sporadic vs 75% genetic (MEN IIa/b)	Spread via both lymphatics AND blood	**Total Thyroidectomy w/ Central LN Dissection**
Anaplastic Carcinoma (~0%)	++++ 13%	III	P53	• >50yo • Cytology: very anaplastic, giant cells, spindle cells • Histology: ?	Literally just eat through all adjacent tissue	**Total Thyroidectomy w/ Surrounding Tissue Resection**