HENDOCRINE PHARMACOTHERPY MODULE

OVERVIEW, LEARNING OBJECTIVES, CASES AND READING MATERIAL FOR THYROID SECTION

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DETAILED LEARNING OBJECTIVES

- Review and understand the normal structure and function of the thyroid gland
  - Structure and function of Follicles, colloid and epithelial cells
  - Functions of the follicular cells
  - Differentiation between active and inactive gland structure and function

- Understand the details of thyroid hormone biosynthesis and secretion.
  - Dietary iodine, iodine transport and the iodide pump
  - Formation of MIT and DIT
  - Formation of T_4 and T_3
  - Thyroid hormone secretion
  - Thyroid-hormone binding proteins and hormone transport
  - Peripheral thyroid hormone metabolism: Activation and inactivation
  - Thyroid hormone clearance

- Understand how thyroid hormone production and secretion is regulated by the hypothalamic-pituitary axis.
  - Formation and release of hypothalamic thyrotropin-releasing hormone (TRH)
  - Formation and release of pituitary thyroid-stimulating hormone (TSH):
  - Similarity to other pituitary hormones and normal plasma levels and half-life
  - Thyroidal TSH receptors structure and function

- Describe the role of thyroid hormones in normal human development and regulation of metabolism and physiologic function
  - Maturation
  - Tissue/Organ Systems (CV, Muscle, Liver, Bone, GI, CNS, PNS, Endocrine)

- Describe the etiology and pathophysiology of hyperthyroidism/Thyrotoxicosis.
  - Grave's and TSH-R{stim}ab
  - TSH-secreting tumors
  - Pituitary Resistance
  - Trophoblastic (hCG)
  - Thyroid nodule/multinodular goiter
  - Thyroiditis
  - Ectopic Thyroid
  - Exogenous (Drug-induced)

- Describe the typical clinical presentation for hyperthyroidism and physiologic effects
  - Ocular, Behavioral, GI (Weight, appetite, bowel), CV, Muscular, Skin, hair, nails

- Describe the typical laboratory indicators for hyperthyroidism.
  - TSH, T4, T3, Total TH, Thyroid receptor and enzyme antibodies, RAIU
  - Should thyroid function tests be performed routinely in certain populations?
  - Describe the etiology and pathophysiology of hypothyroidism.
  - Hashimoto's
  - Chronic
  - Lymphocytic thyroiditis
  - Iatrogenic thyroid damage
  - Iodine deficiency
  - Drugs
  - Pituitary/Hypothalamic disorders

- Describe the typical clinical presentation for hypothyroidism and physiologic effects
  - Symptomology and age: infant, pre-teens, teens, young adult, elderly
  - Ocular, Behavioral, GI (Weight, appetite, bowel), CV, Muscular, Skin, hair, nails

- Describe the typical laboratory indicators for hypothyroidism
  - TSH, T4, T3, Total TH, Thyroid receptor and enzyme antibodies, RAIU
  - Should thyroid function tests be performed routinely in certain populations?

- Understand why thyroid function tests may be abnormal in euthyroid states:
- Understand the relationships between thyroid abnormalities and other disease states (hypercholesterolemia, arrhythmias, menstrual abnormalities, osteoporosis, etc.
- Identify and justify goals of therapy for various thyroid disorders.
- Compare and contrast the therapeutic alternatives. Must have full understanding of pharmacologic alternatives (MOA, kinetics, side effects, drug interactions, etc.).
- Understand how drugs, herbal products and food supplements may alter thyroid function tests, thyroid hormone levels and drug therapy for hypo- or hyperthyroidism
- Develop an assessment and plan for treatment and monitoring.
- Describe appropriate counseling points.
- Recognize and assess problems with concomitant diseases.

CASED-BASED PROBLEM OBJECTIVES:

The many manifestations and complexity of Thyroid Disease

- Apply knowledge acquired from mastery of basic learning objectives concerning thyroid function, physiology and pathology.

- Understand the many and varied manifestations of thyroid disease in key sub-populations. *Drug therapy options are limited, but abnormal thyroid function is prevalent in different age groups and impacts on a host of physiologic function and many other disease states. See case problems!*

- Explore and expand the relationships between thyroid disorders and other disease states covered in previous modules (renal: electrolyte imbalances) and in the current (Endocrine) module (OCs, pregnancy, menstruation, menopause, osteoporosis and diabetes): *See case problems!*

- Understand the role of hyperthyroidism/hypothyroidism and other disease states (CAD, arrhythmia, dementia, cancer, etc.) *See case problems!*

- Understand the key differences between hyperthyroidism/hypothyroidism and other disease states with similar clinical manifestations**.** *See case problems!*

Required Readings:

- DiPiro Chapter: *Thyroid Disorders*, pages 1244-1264
- *Thyroid Hormone Tutorial: The Thyroid and Thyroid Hormones* by J. DeRuiter
- *Thyroid Hormone Tutorial: Thyroid Pathology* by J. DeRuiter
- *Thyroid Hormone Tutorial: Drug and Other Therapies* by J. DeRuiter

Drug List:

- Hyperthyroidism (see Tutorial):
  6-n-propyl-2-thiouracil (PTU) and Methimazole
  Radio-iodine, ^{131}I
- Hypothyroidism(see Tutorial):
  Thyroid Hormone Preparations (Levothyroxine and derivatives)
- Adjunctive Therapies (see Tutorials and Dipiro): Beta-blockers and related agents
- Natural Products and Hyperthyroidism and Hypothyroidism (see Tutorial):

Other Approaches

- Surgery
- Radioactive iodine

THYROID DISEASE: PREVALENCE, RISK FACTORS AND SCREENING CRITERIA

Prevalence: As high as 27 million (depending on diagnostic criteria), making thyroid disease most common endocrine disorder in the US. "The prevalence of undiagnosed thyroid disease in the United States is shockingly high - particularly since it is a condition that is easy to diagnose and treat," (Dr. Gharib).

Incidence of thyroid disease related to:

- Age: Increases with age
- Gender: Most forms of thyroid disease more common in women
- Genetic factors and the presence of other immunologic-based disease
- Exposure to head/neck radiation and thyroid cancer
- Hypothalamic/Pituitary abnormalities
- Goiter or thyroid gland abnormalities and infection
- Drug therapies
- Serious illness
- Iodine deficiency

Screening/Monitoring Groups:

- Neonates
- Adolescents with developmental abnormalities
- Women of reproductive age and in pregnancy
- Menopause with primary or secondary symptoms related to thyroid function
- Elderly with primary or secondary symptoms related to thyroid function

Opening Case

AP is a 52yo white male who comes to your hypertension clinic complaining of anxiousness for the last month and increasing swelling of his feet and ankles. He comments that he "is very tired because he has not been able to sleep" and he "feels hot all the time." Upon further questioning, AP admits to increased hunger, weight loss, and some muscle weakness but denies diarrhea or bowel frequency. The physician suspects this patient may have thyroid disease. If so:

- What other signs and symptoms may be present? Are "extra-thyroidal" symptoms present and why is it important to identify such symptoms?
- What information about this patient's PMH may be important and why?
- What information about this patient's FH and SH may be important and why?
- What information this patient's about current medications may be important and why?
- What laboratory information may be important if this patient has thyroid disease and why?
- What information this patient's allergy history may be important and why?
- Why is it important to determine the cause of this patient's apparent thyroid disorder? How could this be accomplished?
- If this patient has thyroid disease, what therapeutic options (drug and non-drug) are available for the management of this patient' thyroid disease? Which is most appropriate for this patient?
- If surgery is appropriate, which adjunctive pretreatment or post-treatment regimes may be required? What are possible complications of thyroid surgery?
- If radioactive iodine therapy is appropriate, which adjunctive pretreatment or post-treatment regimes may be required? What are possible complications of RAI?
- If drug therapy is appropriate, recommend an appropriate dosage regimen? Are there any absolute or relative contraindications that limit drug therapy options in this case?
- If drug therapy is initiated, describe appropriate monitor parameters.
- If drug therapy is initiated, describe monitoring parameters for safety and toxicity. What potential complications should be anticipated?
- If drug therapy is initiated, what are the important counseling issues?
- Are additional drug or non-drug therapies (supportive) appropriate in this case?

THE THYROID GLAND

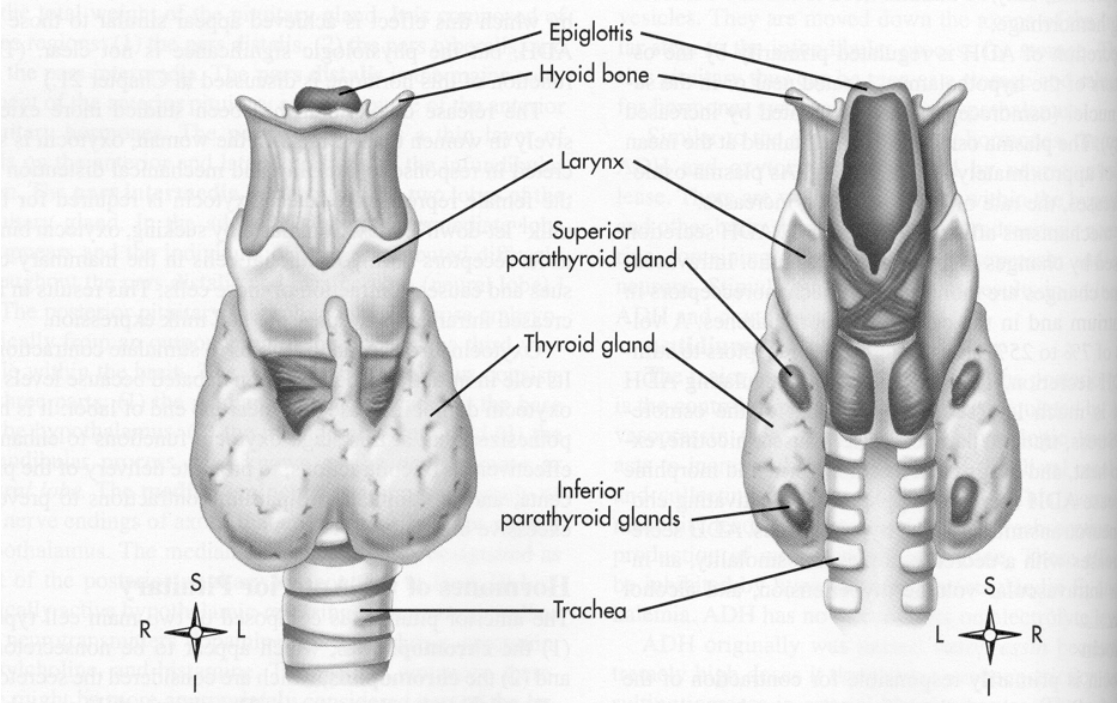


FIG. 19-12 Thyroid and parathyroid glands. Note the relationship of the thyroid and parathyroid glands to each other, to the larynx (voice box), and to the trachea. (From Thibodeau GA, Patton K: *Anatomy & physiology,* ed 4, St Louis, 1999, Mosby.)

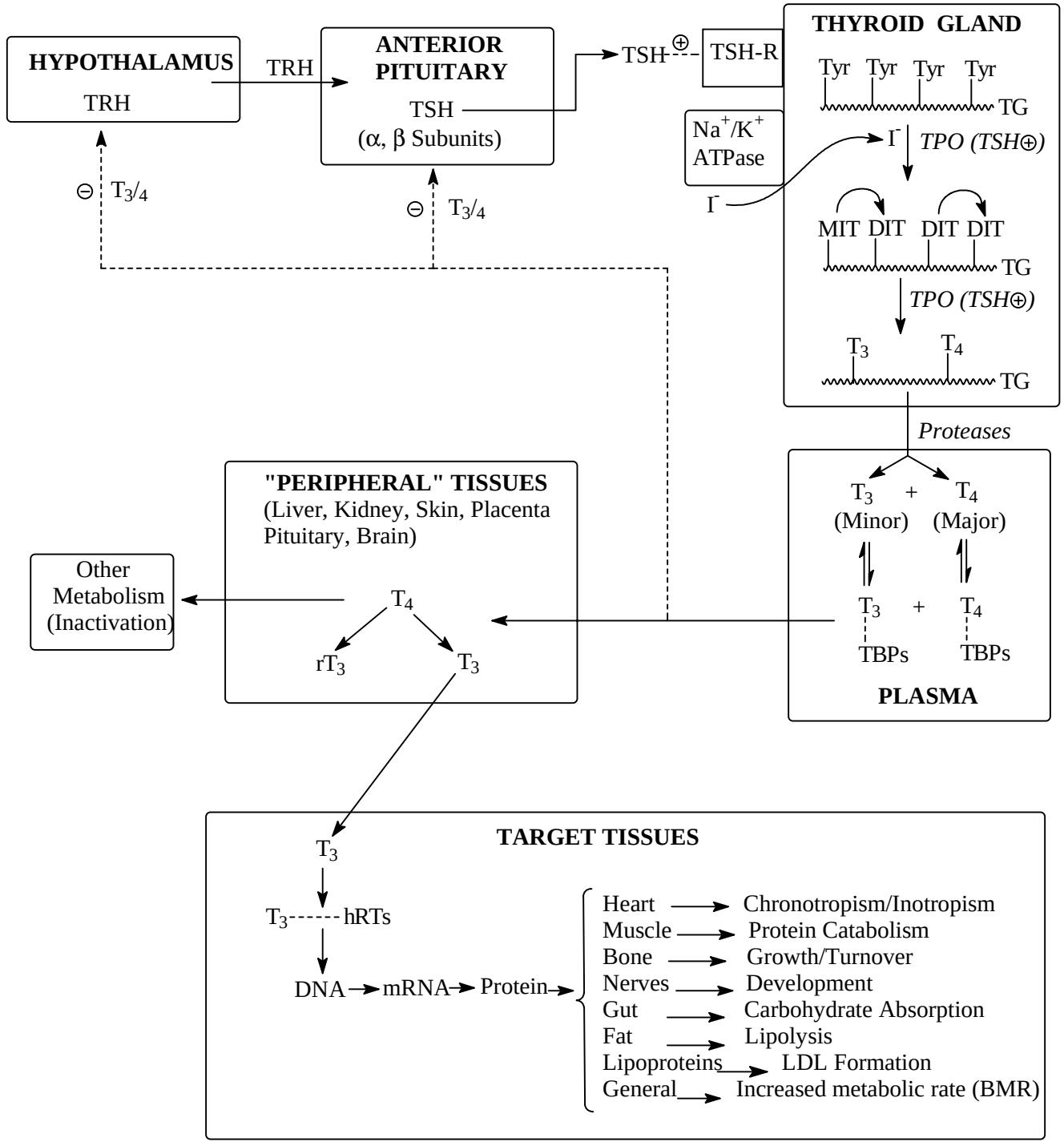
Basic Structure and Function of the Thyroid Gland

- Lobes and the connecting isthmus
- Highly vascularized: Follicles surrounded by capillaries
- Follicle cells filled with colloid
- Colloid is thyroglobulin and stored thyroid hormone
- Follicle cells: Collect iodine, synthesis of thyroglobulin and THs and release of THs

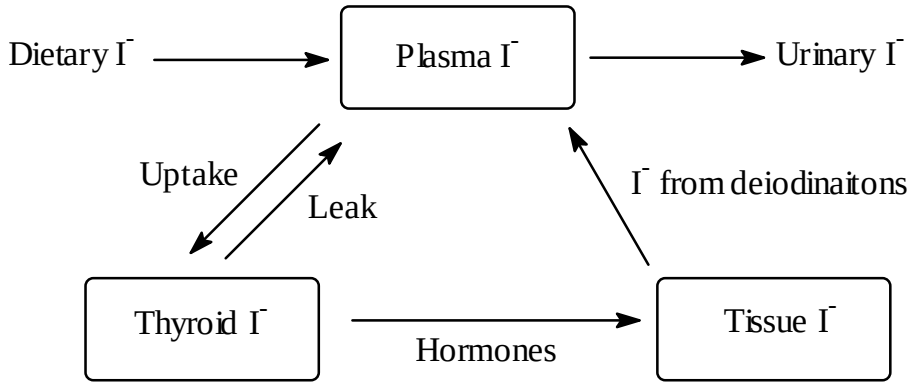
Potential Pathology:

- **General endocrine pathologies: Is hypothalamic and pituitary function normal?**
- **Developmental abnormalities: Did the gland develop normally (aplasia)? Are there genetic defects in thyroid receptors or enzymes? Was the developing gland exposed to maternal antibodies (TSAbs, etc.)?**
- **PMH: Was the patient exposed to radiation (head/neck cancer) or RAI? Was the gland removed in a previous procedure? Is the patient seriously ill?**
- **CC: Does the patient have autoimmune disease or a recent history of infection, inflammation, pregnancy, cancer, etc.?**
- **PE: Is there evidence of a goiter or nodules?**
- **Meds: Is the patient currently taking medications that could alter thyroid function?**

OVERVIEW OF THYROID FUNCTION



BIOSYNTHESIS OF THYROID HORMONES: IODIDE UPTAKE

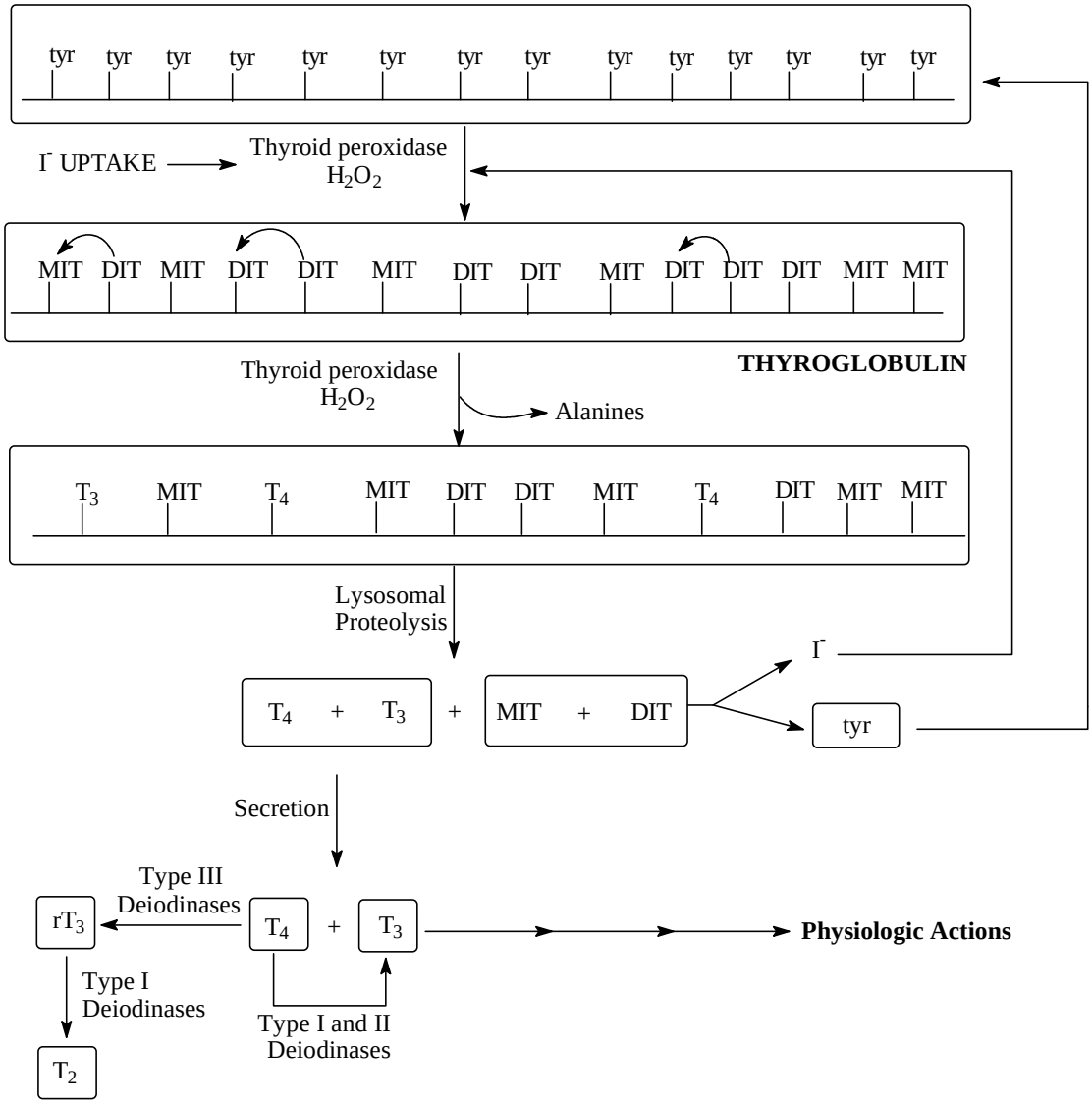


- Dietary iodine uptake required: Normally 500 mcg (salt, flour, etc)
- Active uptake by thyroidal cell membrane pump (Na+-K+ ATPase) which is regulated by TSH: Active and specific uptake is important for imaging studies also!
- Normal uptake: 120 mcg/day with approximately 80 mcg/day incorporated into TH
- Uptake pump can be inhibited by thiocyanate and perchlorate ions, and drugs that interfere with the Na+-K+ ATPase pump (cardiac glycosides).

Significance:

- **Active/specific thyroidal uptake of iodine important for diagnosis (RAIU)!**
- **Active/specific thyroidal uptake of iodine important for treatment with iodides or RAI!**
- **Active/specific thyroidal uptake related to some forms of drug-associated thyroid disease!**

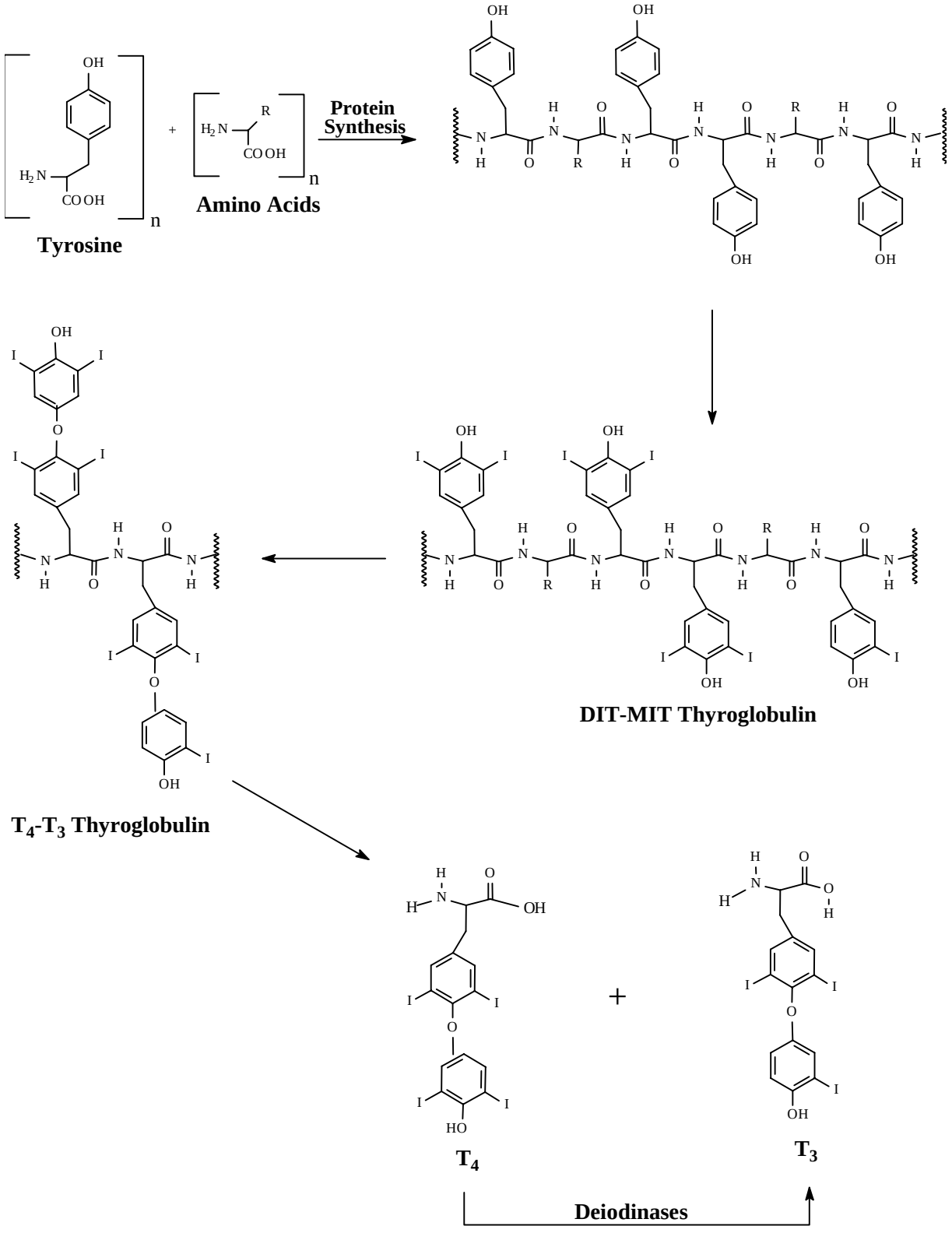
BIOSYNTHESIS OF THYROID HORMONES: TH BIOSYNTHESIS OVERVIEW



Deiodinases:

- Type I (liver and kidney): Inner (T_4 to rT_3) and outer ring (T_4 to T_3) deiodination:
- Type II (Brain and Pituitary): Outer ring deiodination: T_4 to T_3
- Type III (Brain, Skin and Placenta): Inner ring deiodination: T_4 to rT_3

BIOSYNTHESIS OF THYROID HORMONES: DETAILED VIEW OF TH BIOSYNTHESIS



THYROID HORMONE TRANSPORT

Table 1: Plasma proteins involved in thyroid hormone transport:

Protein	Conc (mg/dl)	K_a for T_4	%T_4 Bound	K_a for T_3	%T_3 Bound
TBG	1.5	10^{10}	75	10^9	70
TBPA	25.0	10^7	15	10^6	----
Albumin	4000.0	10^6	10	10^5	30

TBG: thyroxine-binding globulin
TBPA: thyroxine-binding prealbumin

Plasma Half-Life: $T_4 > T_3$ due to:

- **Prohormone function of T_4**
- **Higher protein binding of T_4: Serum retention, slower metabolic inactivation, etc.**

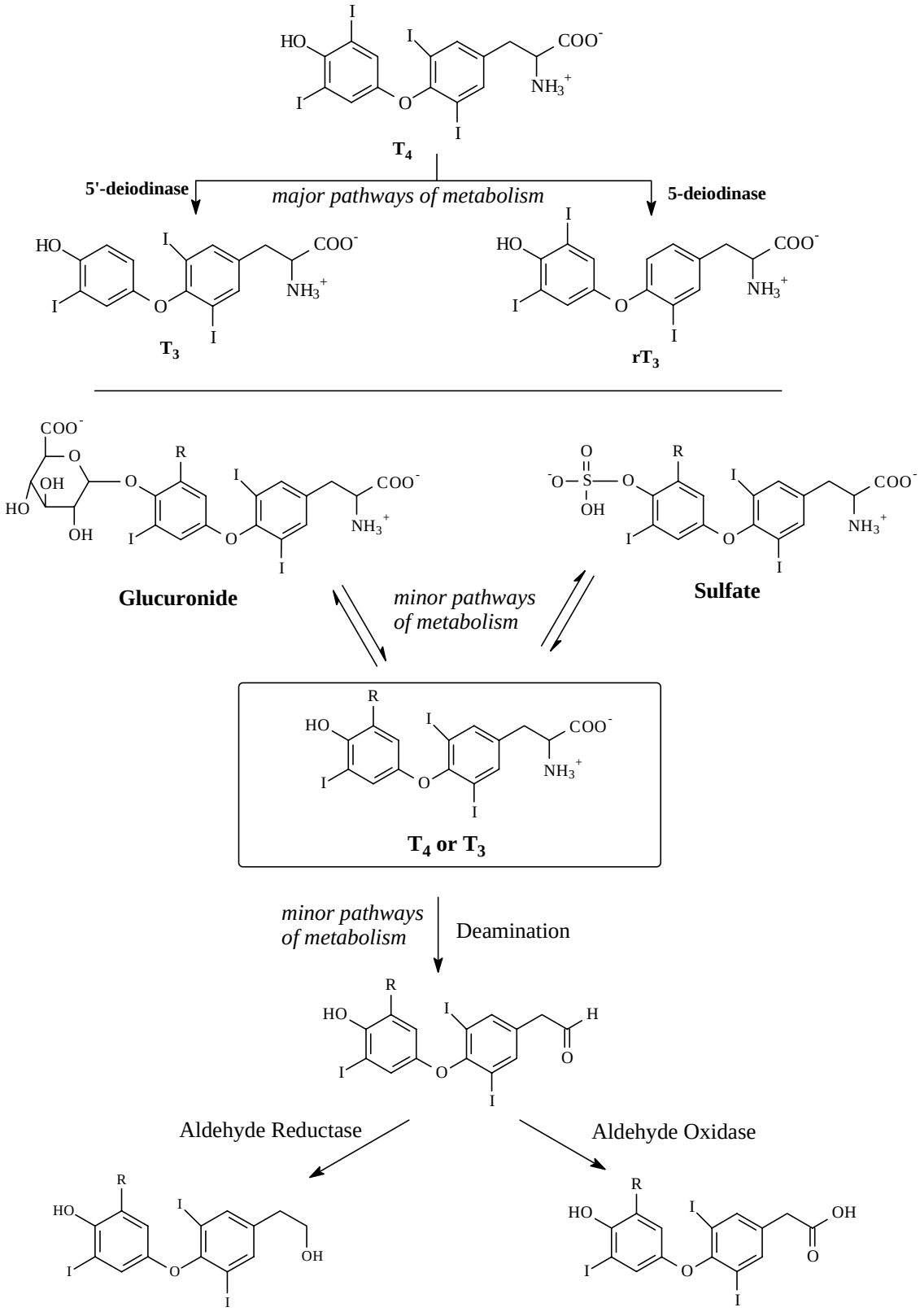
Table 2: Summary of the effects of physiological states on plasma thyroid binding proteins and T_3 and T_4 levels

Condition	Concentrations of Binding Proteins	Total Plasma T_4, T_3, RT_3	Free Plasma T_4, T_3, RT_3	Plasma TSH	Clinical State
Primary hyperthyroidism	Normal	High	High	Low	Hyperthyroid
Primary hypothyroidism	Normal	Low	Low	High	Hypothyroid
Drugs (estrogens, methadone, heroin, perphenazine, clofibrate), pregnancy, acute and chronic hepatitis, acute intermittent porphyria, estrogen-producing tumors, idiopathic, hereditary	High	High	Normal	Normal	Euthyroid
Drugs (glucocorticoids, androgens, danazol, asparaginase), acromegaly, nephrotic syndrome, hypoproteinemia, chronic liver disease (cirrhosis), testosterone-producing tumors, hereditary	Low	Low	Normal	Normal	Euthyroid

- **Be aware that TSH levels are the primary diagnostic indicators for thyroid disease, not TH levels or total TH levels.**

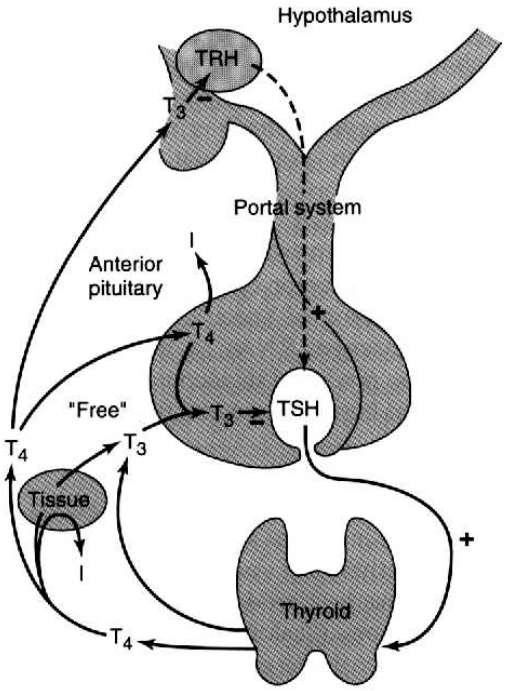
- **Be aware that drugs can alter the concentrations of TH binding proteins (THBPs) and therefore give misleading total TH levels.**

THYROID HORMONE METABOLISM



THYROID HORMONE PHYSIOLOGY: TSH

Thyroid Stimulating Hormone (TSH) Production and Control



- TSH composition: Alpha (like FSH and LH) and beta-subunits: Also, structural homology between hCG and TSH! Elevated levels of these hormones may stimulate the thyroid gland and produce symptoms suggestive of thyroid disease
- Normal plasma concentrations: Approximately 0.3 to 3 mU/L
- TSH half-life: 60 minutes
- TSH Receptor actions:

  ➔ Iodine uptake
  ➔ Iodination of Thyroglobulin by TPO
  ➔ Synthesis of MIT and DITs
  ➔ Thyroid gland atrophy - goiter (continual receptor stimulation by TSH)

THYROID HORMONE PHYSIOLOGY: TH ACTIONS

- Circulating THs (especially T_3) enter cells and bind to different TH receptors nuclear receptors designated as hTR-α1 and hTR-β1. The T_3-receptor complex then binds DNA via "zinc fingers" and this produces a change in the expression of a variety of genes that encode enzymes that control cellular functions (dependent on tissues):

T_3 + hTR-α/β → T_3----hTR-α/β → T_3----hTR-α/β---DNA → mRNA → Proteins

Target Tissue	Effect	Mechanism
Heart	Chronotropic	Increase number and affinity of beta-adrenergic receptors.
	Inotropic	Enhance responses to circulating catecholamines. Increase proportion of alpha myosin heavy chain (with higher ATPase activity).
Adipose tissue	Catabolic	Stimulate lipolysis.
Muscle	Catabolic	Increase protein breakdown.
Bone	Developmental and metabolic	Promote normal growth and skeletal development; accelerate bone turnover.
Nervous system	Developmental	Promote normal brain development.
Gut	Metabolic	Increase rate of carbohydrate absorption.
Lipoprotein	Metabolic	Stimulate formation of LDL receptors.
Other	Calorigenic	Stimulate oxygen consumption by metabolically active tissues (exceptions: adult brain, testes, uterus, lymph nodes, spleen, anterior pituitary). Increase metabolic rate.

Complex physiologic actions of the THs means that patients with thyroid disease may manifest an array of metabolic and structural symptoms!!!!!

NOW……BACK TO THE CASE:

PMH
Hypertension diagnosed 3 years ago.
BPH x 1 year

FH
Mother, one sister all with HTN; Father had HTN; deceased age 75 - MI

SH
Occ. EtOH (2-3 beers on weekends); smokes ½ ppd x 32 yrs.

Current Medications
HCTZ 25mg po qd
Doxazosin 4mg po qd

ALL
NKDA

PE

Gen – A excitable thin man in NAD
VS – BP 156/92, P 120, RR 18, T 37°C
HEENT – NC; PERRLA; EOMI; lid lag bilaterally and downward gaze; mild exopthalmus bilaterally; oropharynx clear
Neck – Supple; diffusely enlarged thyroid, surface smooth and firm; no bruits noted; no nodules, masses, or lyphadenopathy
Cor – tachycardic, regular rhythm, S_1/S_2 normal, no murmurs
Resp – CTA bilaterally
Abd – Soft, NT, ND, hyperactive bowel sounds, no HSM
Ext – no edema; pulses equal and bounding
Skin and Hair – skin warm and moist; onycholysis bilaterally; fine hair
Neuro – A & O x 3, Cranial nerves intact; hyperreflexia

Labs
Na 136 mEq/L, K 4.0 mEq/L, CL 102 mEq/L, CO_2 30 mEq/L, BUN 15 mg/dl, SCr 1.0 mg/dl, glucose 95 mg/dl, TSH <0.1 mIU/ml, free T_4 4.2 ng/dl

EKG
Sinus tachycardia with ventricular rate = 120; no ST/T wave abnormalities; no LVH

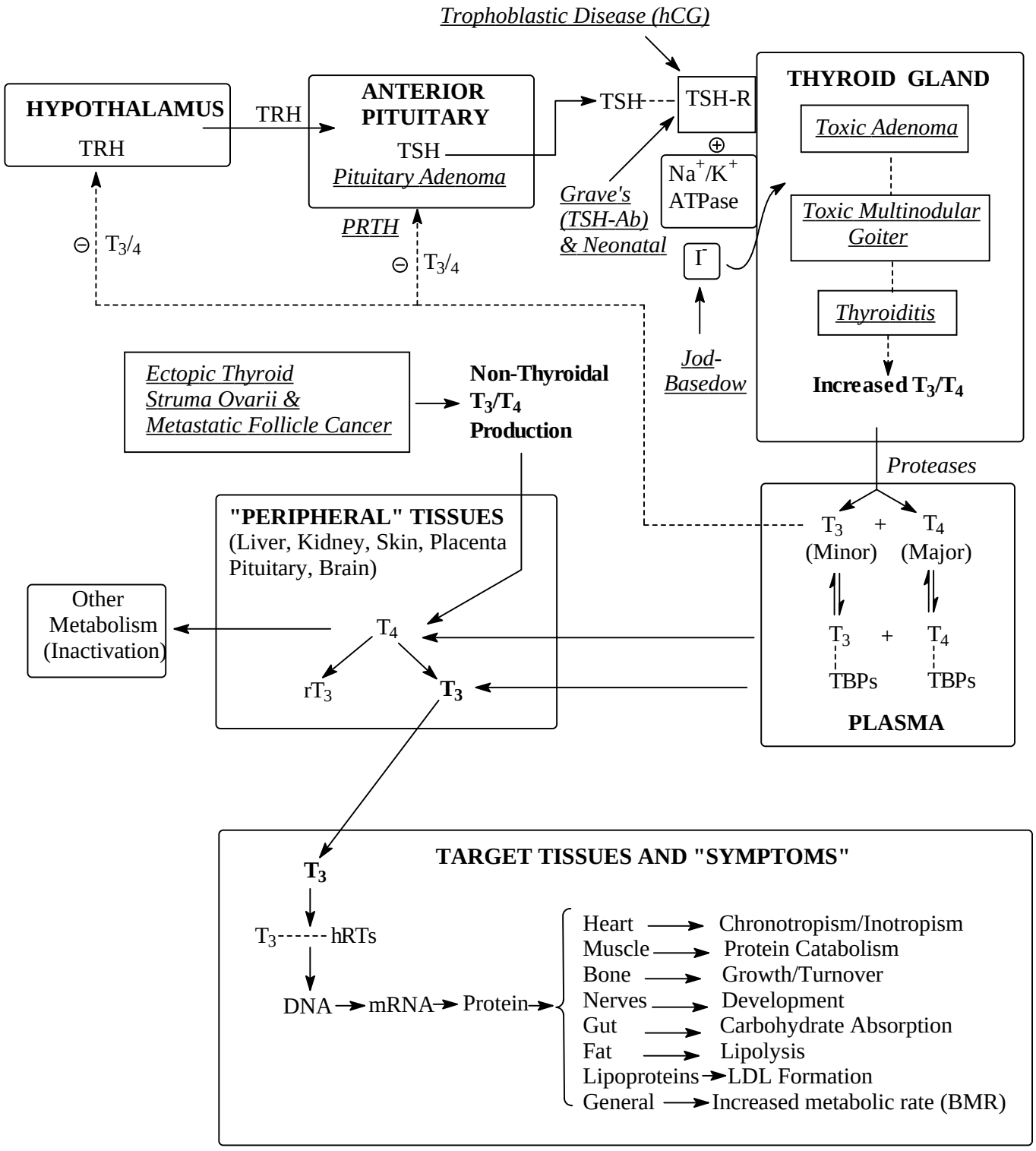
THYROID PATHOLOGY: SIGNS AND SYMPTOMS OF HYPERTHYROIDISM

Organ System	Symptoms/Physical Findings
Thyroidal Symptoms	- **Diffusely enlarged goiter (3-4X) in "True" hyperthyroidism** - Systolic or continuous bruit over thyroid
Ocular (most – but not infiltrative - are "functional" due to increased sympathetic nerve stimulation)	- Proptosis - Periorbital edema ("puffiness") - Lid lag and lid retraction - Decreased blinking: Staring - **Infiltrative changes (Exophthalmos of Graves'): Autoimmune**
Reproductive Tract	- Oligomenorrhea or amenorrhea - Erectile dysfunction (males) - Impotence
Integumentary (Skin) Hyperdynamic cirulation	- Excessive sweating - Flushing, Warm skin - Heat intolerance - Fine, soft, straight hair, Temporary hair loss - Nails that grow away from their beds - Pedal edema - **Pretibial myxedema (Graves' dermopathy)**
Gastrointestinal	- Increased appetite - Nausea, vomiting, abdominal pain - Increased peristalsis leading to diarrhea, frequent bowel movements
Pulmonary	- Exertional dyspnea - Reduced vital capacity
Cardiovascular	- Increased cardiac output - Decreased peripheral resistance - Palpitations, loud heart sounds - Tachycardia at rest - Supraventricular dysrhythmias (***especially in elderly***) - Ventricular dilation and hypertrophy
Muscular	- Tremor - Muscle weakness to total paralysis in extreme cases (hypokalemic periodic paralysis) - Brisk deep tendon reflexes
General CNS	- Fatigue - Nervousness, restlessness, irritability - Short attention span - Insomnia - Emotional lability - Depression, confusion, withdrawal: ***"Apathetic thyrotoxicosis"/elderly***
Metabolic Increased catabolism!	- Increased bone resorption resulting in hypercalcemia and decreased PTH secretion (decreased bone mineral density and osteoporosis) - Increased glycogen utilization: Increased catabolism - Decrease in serum lipids (CH&TG): Increased CH metabolism/elim - Decreased insulin sensitivity and increased insulin degradation - Increased cortisol degradation - Increased serum estrogens levels, but lower levels of free estrogens - Decreased vitamin stores: Slow formation

Summary of Thyroid Function Tests and Diagnostic Procedures

Test	Measures	Normals	Interference	Comments
Measurements of circulating thyroid hormone levels				
FT_4	Direct measure of free T_4	0.7-1.9 ng/mL (Analog)	Altered TBG do not interfere	Most accurate measure of free T_4
FT_4I	Calculated free T_4 level	6.5-12.5 T_4 (1.3-3.9)	Euthyroid sick syndrome	Estimates direct free T_4, compensates for altered TBG
TT_4	Total free + bound T_4	5.0-12 mg/dL	Alterations of TBG	Adequate if TBG is not altered
TT_3	Total free + bound T_3	70-132 ng/dL	Alterations of TBG; Euthyroid sick syndrome	Useful to detect early, relapsing and T_3 toxicosis
RT_3U	Indirect measure of TBG saturation	26-35%	Alterations of TBG	Used to calculate FT_3I and FT_4I
Tests of Thyroid Gland Function				
RAIU	Thyroid uptake of iodine	24 hr: 15-35%	< with Excess Iodine and > with iodine deficiency	Different. of hyperthyroidism
Scan	Size, shape & activity	----------	Thyroid and antithyroid drugs	Detect “Hot” vs “cold” nodules
Test Hypothalamic-Pituitary-Thyroid Axis				
TSH	Pituitary TSH levels	0.3-3.04 U/L	DA, glucocort-coids, TH, amiodarone	Most sensitive index for hyper-thyroidism & to monitor therapy
Tests of Autoimmunity				
ATgA	Antibodies to thyroglobulin	<8%	Non-thyroidal immune disease	Present in auto-immune thyroid disease; not present in remission
TPO	Thyroperoxidase antibodies	<100IU/mL	Non-thyroidal immune disease	More sensitive test; detectable during remission
TRab (TSAb)	Thyroid receptor IgG antibody	Titers negative	----------	Confirms Graves’ incl. neonatal
Thyroglobulin	Colloid protein of gland	5-25 mg/dL	Goiters, Inflam thyroid	Thyroid cancer marker

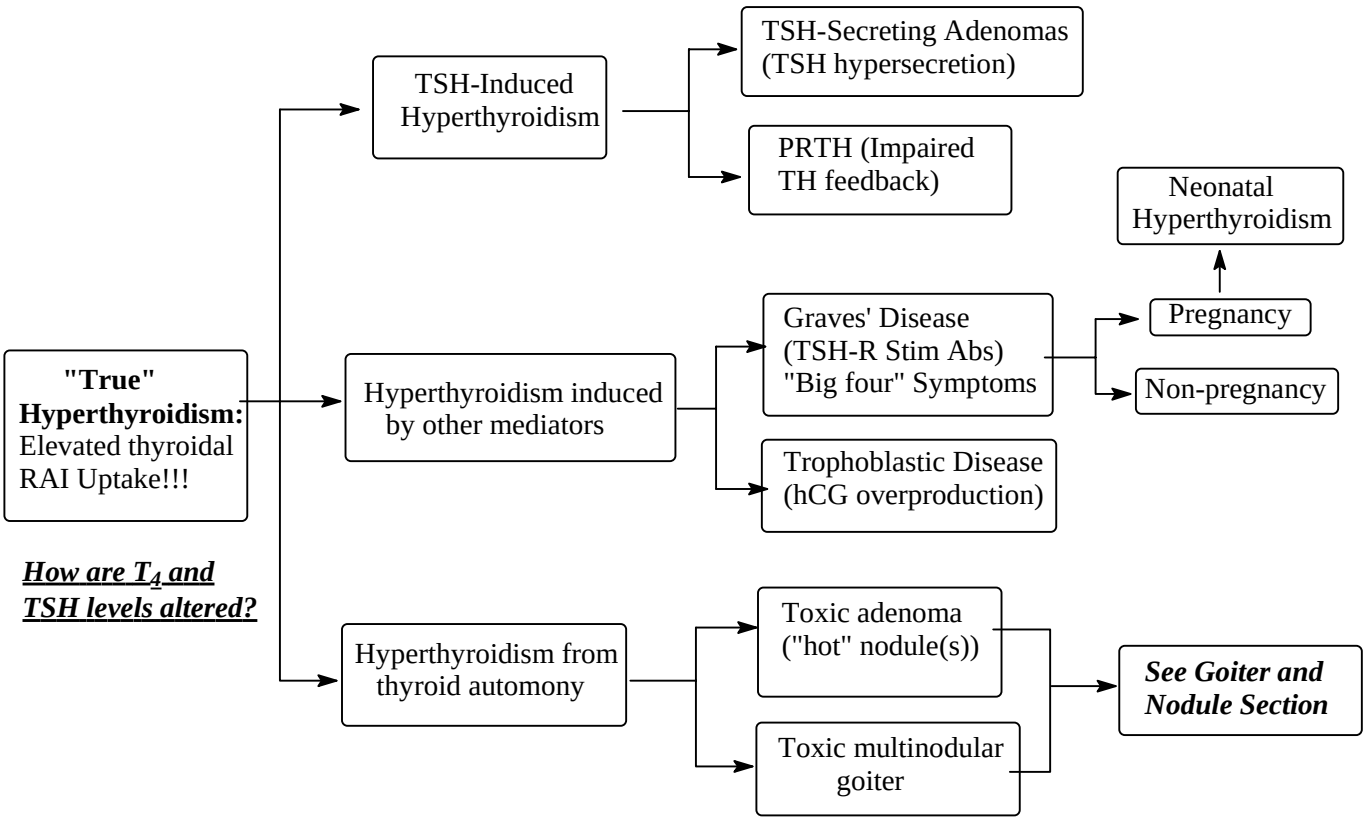
OVERVIEW OF HYPERTHYROIDISM

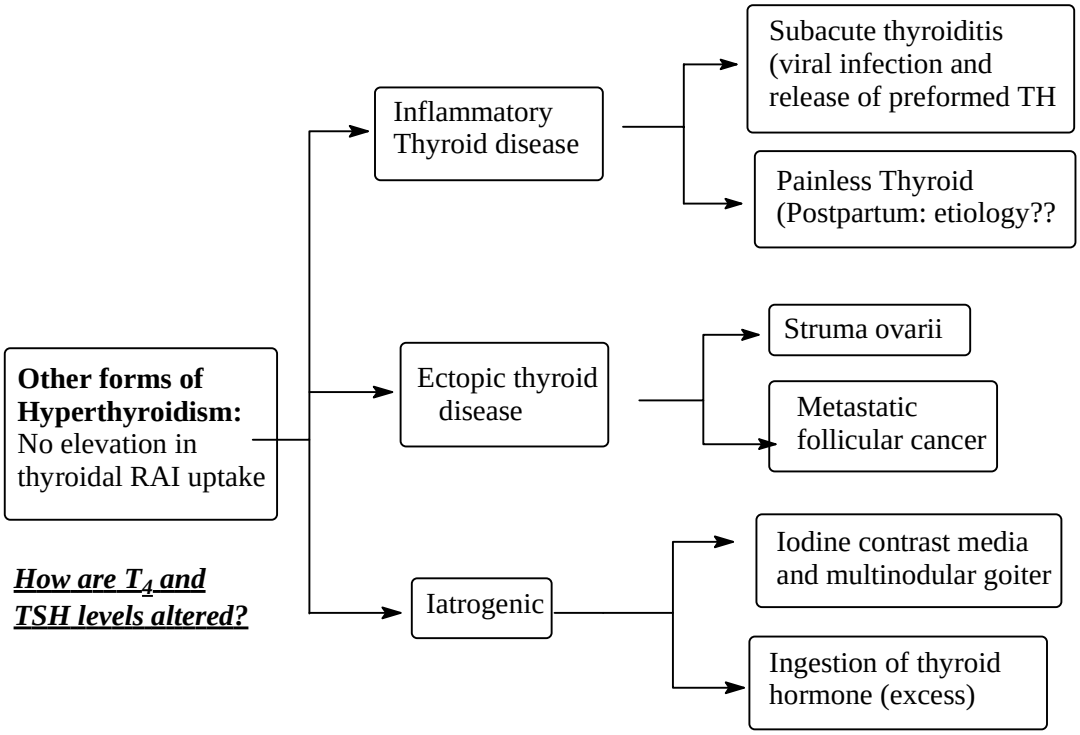


"True Hyperthyrpoidism" characterized by elevated RAIU: TSH and TH levels?
Pituitary adenomas, PRTH, Grave's, Trophoblastic Disease, Toxic Adenoma, Multinodular Goiter

"Other" forms of hyperthyroidism characterized by suppressed RAIU: TSH and TH levels?
Inflammatory Thyroid diseases, Ectopic Thyroid Disease, Exogenous Thyroid Excess

HYPERTHYROIDISM



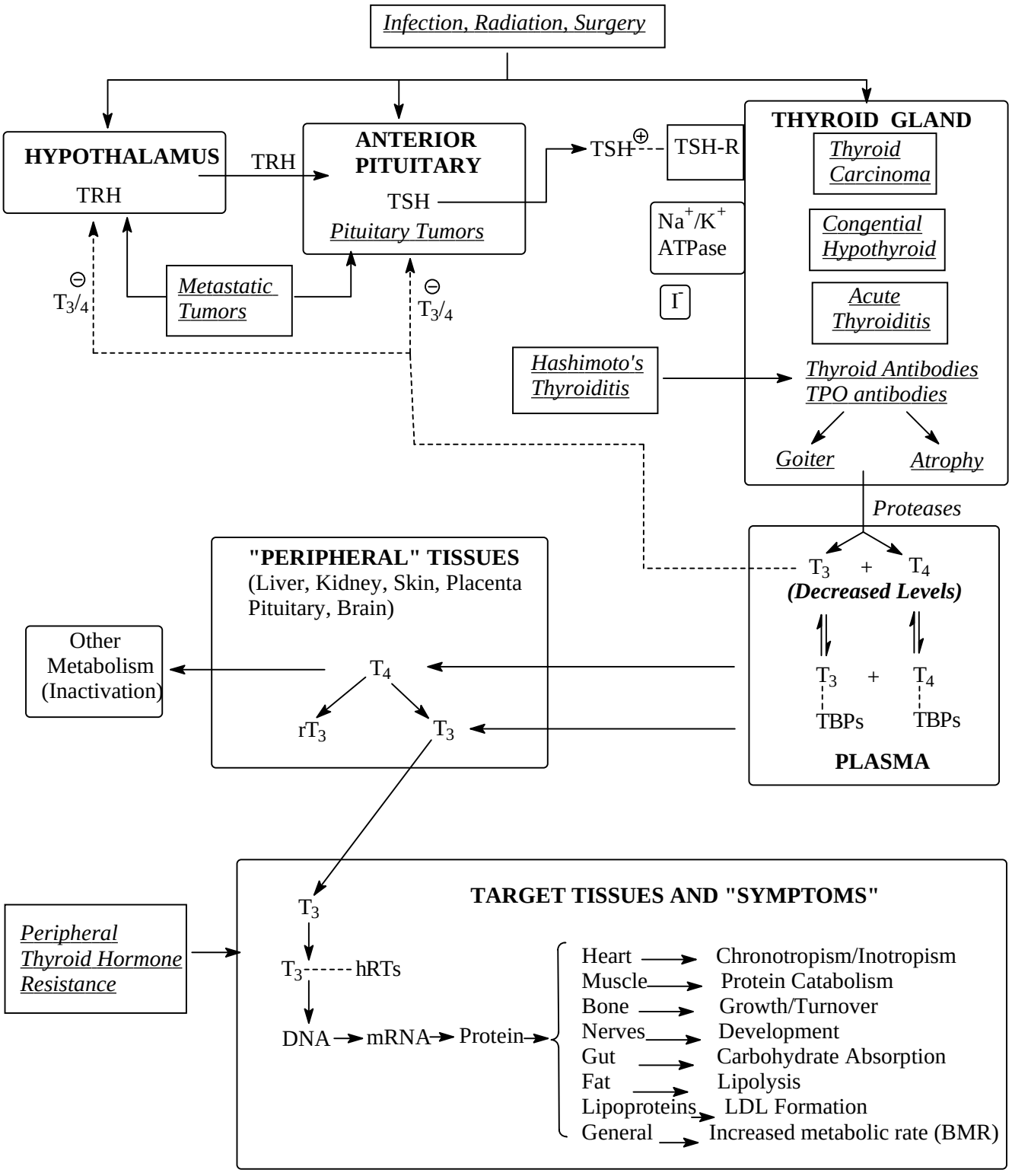


Thyrotoxic crisis (Thyroid storm) in patients with undiagnosed or inadequately treated severe hyperthyroidism

THYROID PATHOLOGY: SIGNS AND SYMPTOMS OF HYPOTHYROIDISM

Organ System	Symptoms/Physical Findings
Thyroidal Symptoms	- Goiter may be present (elevated TSH in response to low TH levels may result in stimulation of thyroid gland)
Ocular	- Minimal symptoms
Reproductive Tract	- Anovulation - Decreased libido - High incidence of spontaneous abortion - Decreased androgen production in males - Increased estrogen production in females - Erectile dysfunction and oligospermia in males
Integumentary (Skin)	- Dry, flaky skin: reduced circulation and glandular secretions - Dry, brittle hair - Cool skin and Cold intolerance - Reduced nail growth - Slow wound healing - **Myxedema (**accumulation of hyalurnic acid and water accumulation)
Gastrointestinal	- Decreased appetite, but weight gain - Constipation and fluid retention - Decreased absorption of nutrients (delayed glucose absorption) due to reduced peristalsis
Pulmonary (symptoms contribute to myxedema coma)	- Dyspnea: Pleural effusions - Hypoventilation: Myxedemic changes in respiratory muscles - Carbon dioxide retention
Cardiovascular	- Decreased cardiac output: Reduced stroke volume and heart rate - Increased peripheral resistance: Maintain BP - Prolonged circulation time, decreased blood flow: (See skin) - Decreased intensity of heart sounds - ECG changes: pericardial effusions - Enlarged heart
Muscular	- Muscle/Joint aching and stiffness - Slow deep tendon reflexes: Decreased muscle contractility
General CNS	- Confusion; slowed speech and thinking - Headaches - Lethargy and syncope - Cerebellar ataxia
Hematologic	- Decreased RBCs: normcytic, normochromic anemia - Macrocytic anemia: Decreased vitamin B12 and folate uptake from gut
Renal	- Reduced renal blood flow and GFR - Dilutional hyponatremia - Reduction erythropoietin production
Metabolic	- Increased serum prolactin levels - Decreased cortisol turnover (but normal levels) - Elevated serum lipid levels: Decreased degradation - Decreased bone remodeling: increased bone density - Decreased insulin degradation

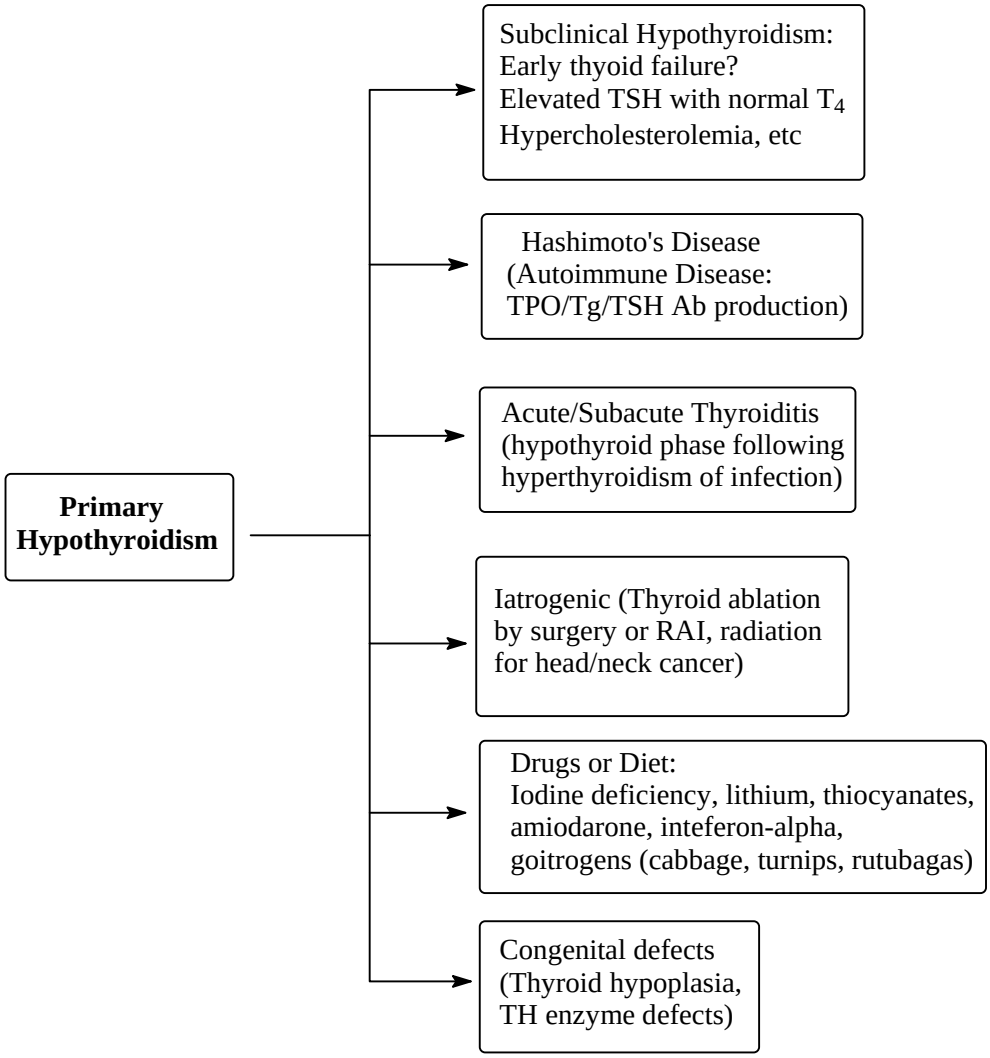
OVERVIEW OF HYPOTHYROIDISM

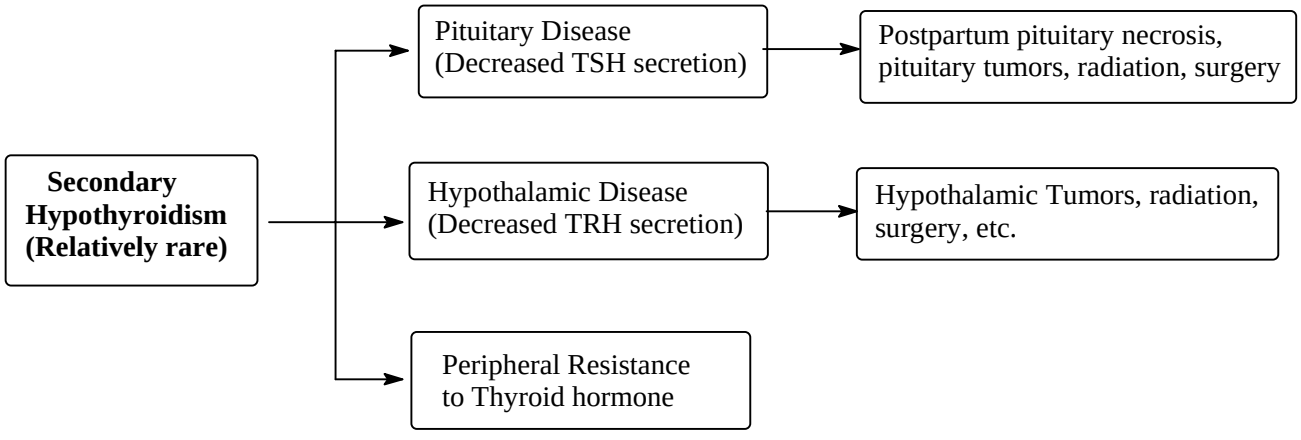


Primary Hypothyroidism: Hashimoto's or other thyroiditis, I- deficiency, antithyroid drugs, congenita
Surgery or radiation

Secondary Hypothyroidism: Hypothalamic or pituitary disease/dysfunction, peripheral resistance to thyroid hormones

HYPOTHYROIDISM SUMMARY

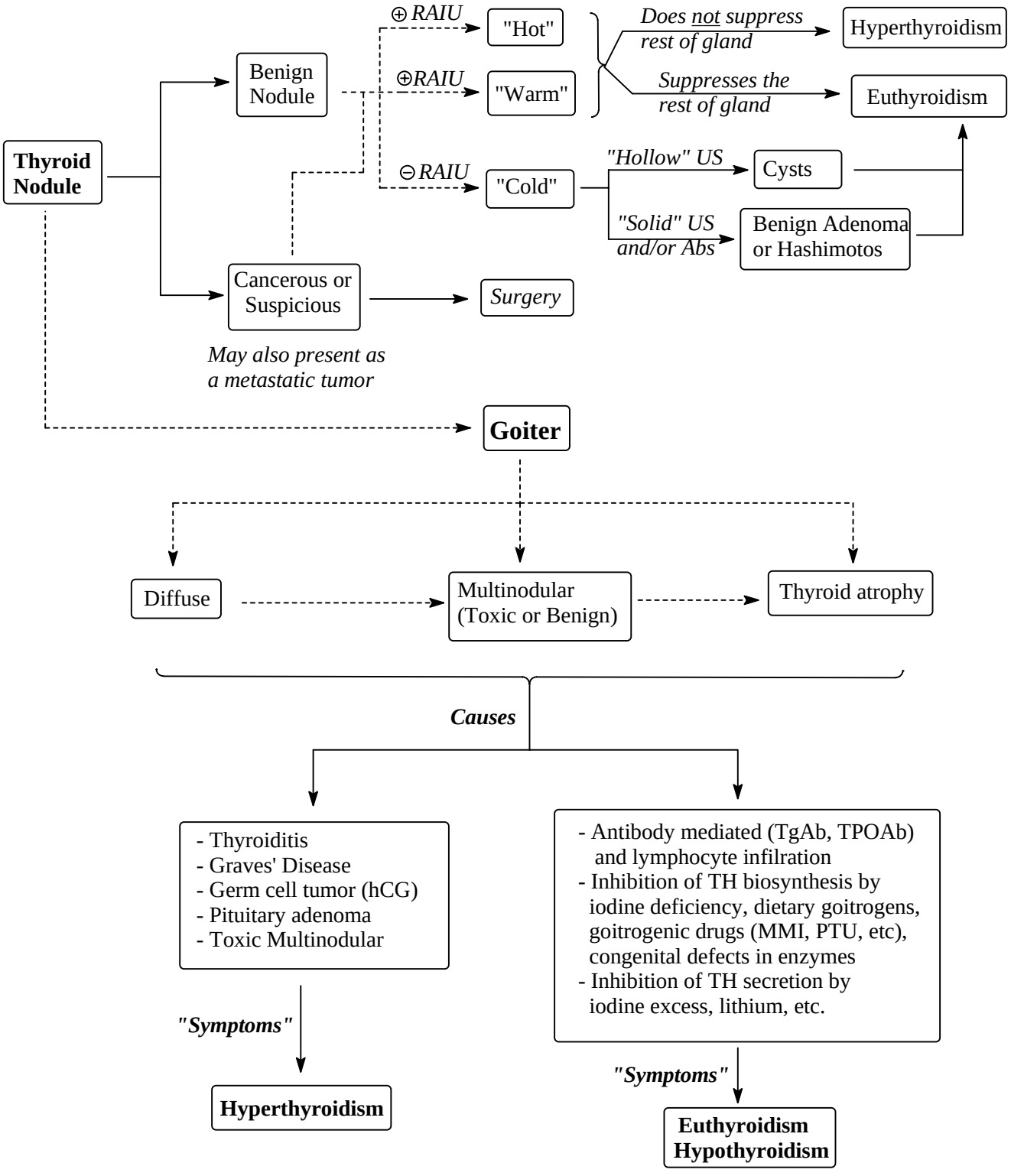




Myxedema coma from severe, long-standing hypothyroidism. Medical intervention required to correct hypothyroidism, hypothermia, hypoventilation, hypoglycemia, lactic acidosis, etc.

GOITER AND NODULES

Nodule Properties: Most nodules cold (85%) and 85% of cold nodules are benign and 90-95% of warm and hot nodules are benign



EUTHYROID SICK SYNDROME

Associated with <u>non-thyroidal</u> severe illness including heart failure, chronic renal failu liver disease, stress, starvation, surgery, trauma, infection, autoimmune diseas, and in patients receiving certain drugs (a significant number of hospitalized patients)

Inhibited conversion of T_4 to T_3:
IL-6 production (surgery, respiratory illness) inhibits deiodinase
Low T_3 , high rT_3 with normal T_4 and TSH:

Decreased TBPs or presence of TBP inhibitor:
Low T_3 and T_4; normal to low TSH

Decreased pituitary or hypothalamic response to THs:
Low T_3 and T_4; low to undetectable TSH

Increased TBP levels: Biliary cirrhosis, hepatitis
High TT_4 and normal or high $T_{3;}$ TSH normal of high