Endocrinology

Outline

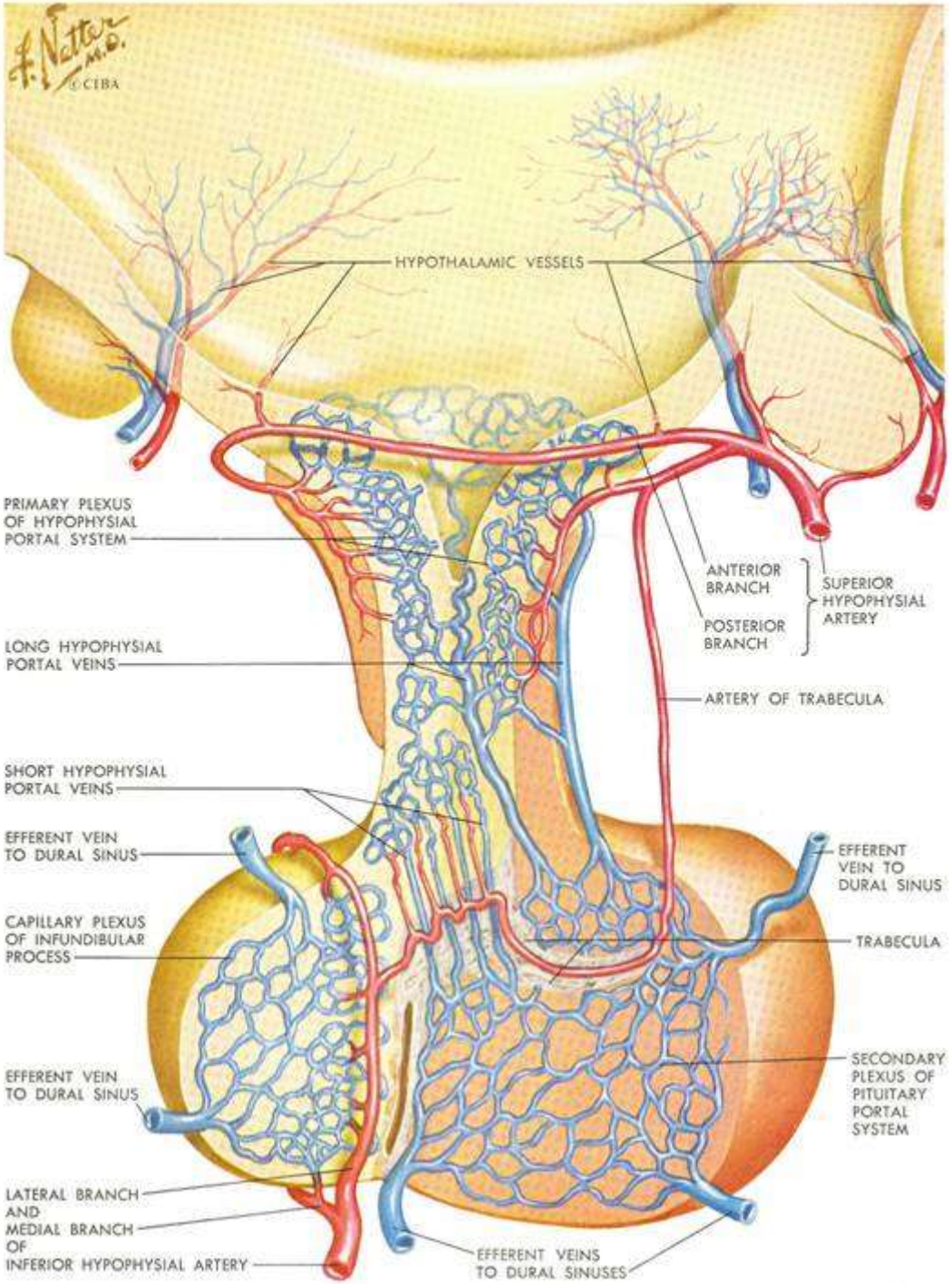
- General Principles of Endocrinology
- Central Axis
  - **HPA**
- Peripheral Axis
  - **Thyroid**
  - **Parathyroid**
  - Adrenal
  - Gonadal
  - Gastrointestinal
- Disorders

Hypophyseal-Pituitary Axis

- Site of Neural – Hormonal interaction
- Sets temporal release of hormones
- Responsible for stress reaction of hormones

HPA Basics

- Hypophysis
  - Third Ventricle
  - GRH, TRH, CRH, GnRH, Dopamine, Somatostatin
- Neurohypophysis
  - Derived from Hypophysis
  - ADH, Oxytocin
- Adenohypophysis
  - Derived from Rathke's pouch
  - ACTH, LH, FSH, TSH, GH, PRL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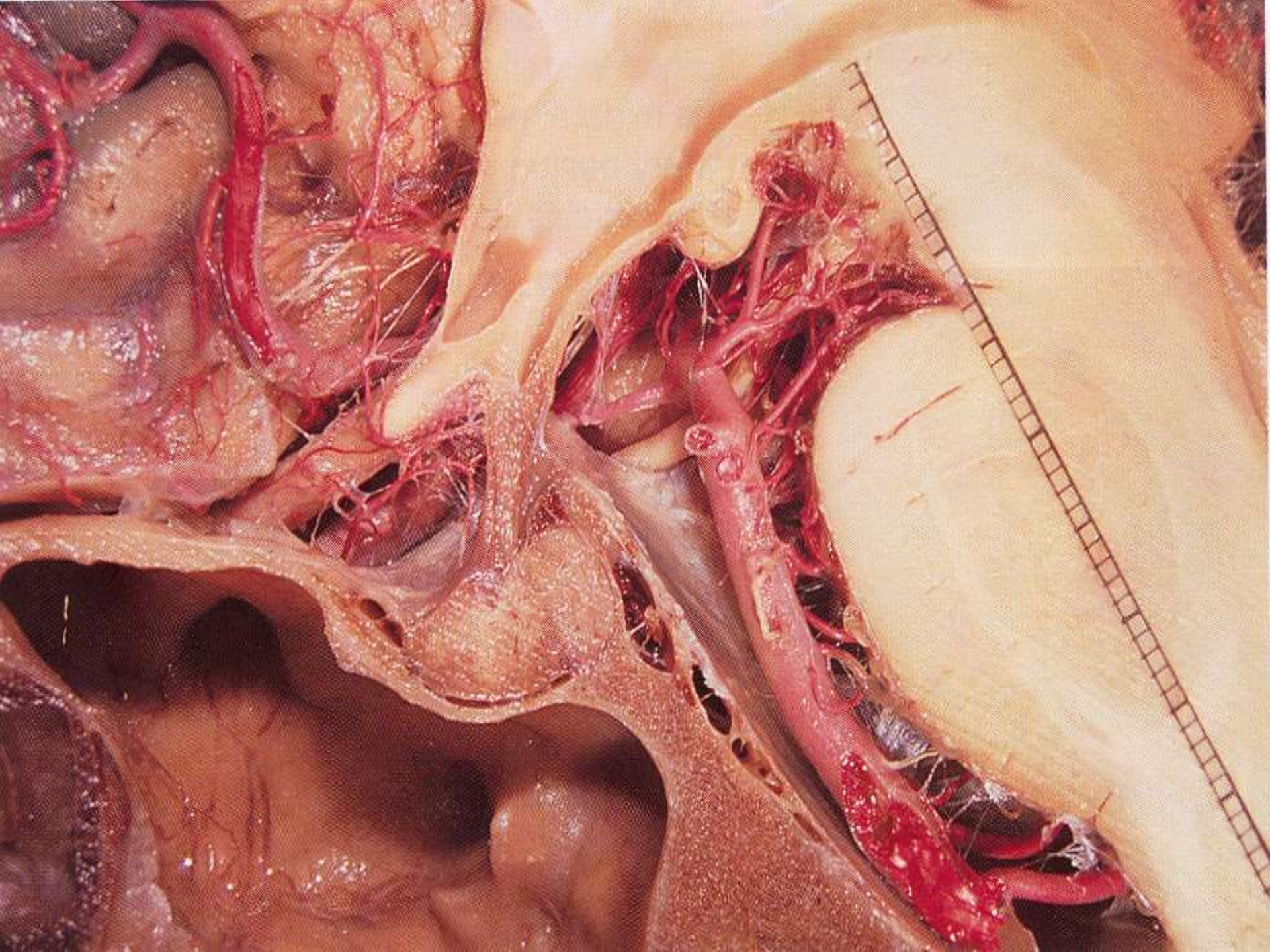
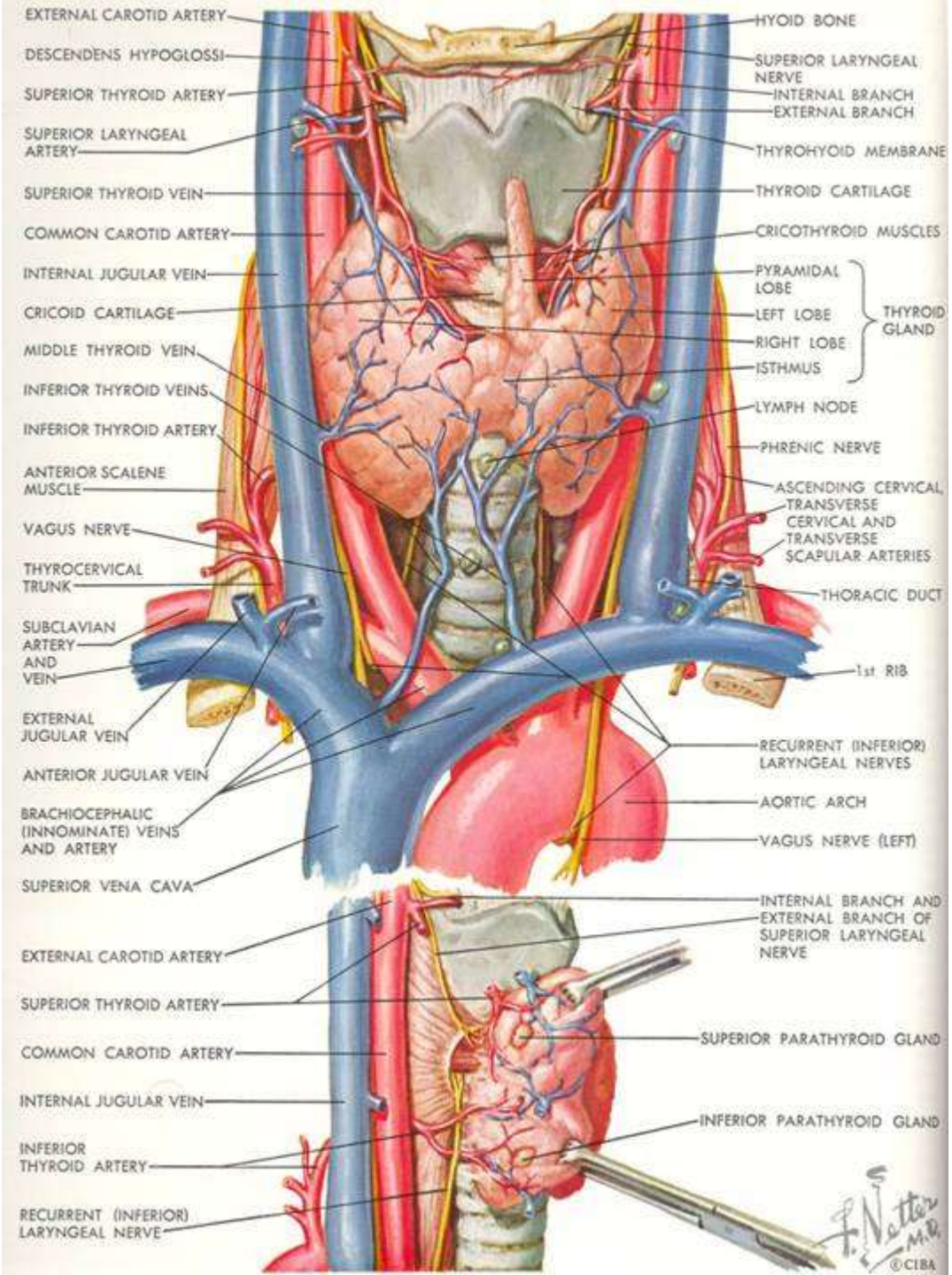
HYPOTHALAMIC VESSELS
PRIMARY PLEXUS OF HYPOPHYSIAL PORTAL SYSTEM
ANTERIOR BRANCH
POSTERIOR BRANCH
SUPERIOR HYPOPHYSIAL ARTERY
LONG HYPOPHYSIAL PORTAL VEINS
ARTERY OF TRABECULA
SHORT HYPOPHYSIAL PORTAL VEINS
EFFERENT VEIN TO DURAL SINUS
EFFERENT VEIN TO DURAL SINUS
CAPILLARY PLEXUS OF INFUNDIBULAR PROCESS
TRABECULA
SECONDARY PLEXUS OF PITUITARY PORTAL SYSTEM
EFFERENT VEIN TO DURAL SINUS
LATERAL BRANCH AND MEDIAL BRANCH OF INFERIOR HYPOPHYSIAL ARTERY
EFFERENT VEINS TO DURAL SINUSES



Pituitary Diseases

- Primary Tumors
  - Adenomas
  - Craniopharyngioma
- Metastasis
- Empty Sella
  - Surgical, post-Sheehand's
- Hemorrhage
  - Sheehand's syndrome
- Hyperfunction
  - Prolactin
- Insufficiency

Thyroid


EXTERNAL CAROTID ARTERY
DESCENDENS HYPOGLOSSI
SUPERIOR THYROID ARTERY
SUPERIOR LARYNGEAL ARTERY
SUPERIOR THYROID VEIN
COMMON CAROTID ARTERY
INTERNAL JUGULAR VEIN
CRICOID CARTILAGE
MIDDLE THYROID VEIN
INFERIOR THYROID VEINS
INFERIOR THYROID ARTERY
ANTERIOR SCALENE MUSCLE
VAGUS NERVE
THYROCERVICAL TRUNK
SUBCLAVIAN ARTERY AND VEIN
EXTERNAL JUGULAR VEIN
ANTERIOR JUGULAR VEIN
BRACHIOCEPHALIC (INNOMINATE) VEINS AND ARTERY
SUPERIOR VENA CAVA
HYOID BONE
SUPERIOR LARYNGEAL NERVE
INTERNAL BRANCH
EXTERNAL BRANCH
THYROHYOID MEMBRANE
THYROID CARTILAGE
CRICOTHYROID MUSCLES
PYRAMIDAL LOBE
LEFT LOBE
RIGHT LOBE
ISTHMUS
THYROID GLAND
LYMPH NODE
PHRENIC NERVE
ASCENDING CERVICAL, TRANSVERSE CERVICAL AND TRANSVERSE SCAPULAR ARTERIES
THORACIC DUCT
1st RIB
RECURRENT (INFERIOR) LARYNGEAL NERVES
AORTIC ARCH
VAGUS NERVE (LEFT)
INTERNAL BRANCH AND EXTERNAL BRANCH OF SUPERIOR LARYNGEAL NERVE
EXTERNAL CAROTID ARTERY
SUPERIOR THYROID ARTERY
SUPERIOR PARATHYROID GLAND
COMMON CAROTID ARTERY
INTERNAL JUGULAR VEIN
INFERIOR PARATHYROID GLAND
INFERIOR THYROID ARTERY
RECURRENT (INFERIOR) LARYNGEAL NERVE
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Thyroid

- Largest Endocrine organ in the body
- Involved in production, storage, and release of thyroid hormone
- Function influenced by
  - Central axis (TRH)
  - Pituitary function (TSH)
  - Comorbid diseases (Cirrhosis, Graves, etc.)
  - Environmental factors (iodine intake)

Thyroid (cont)

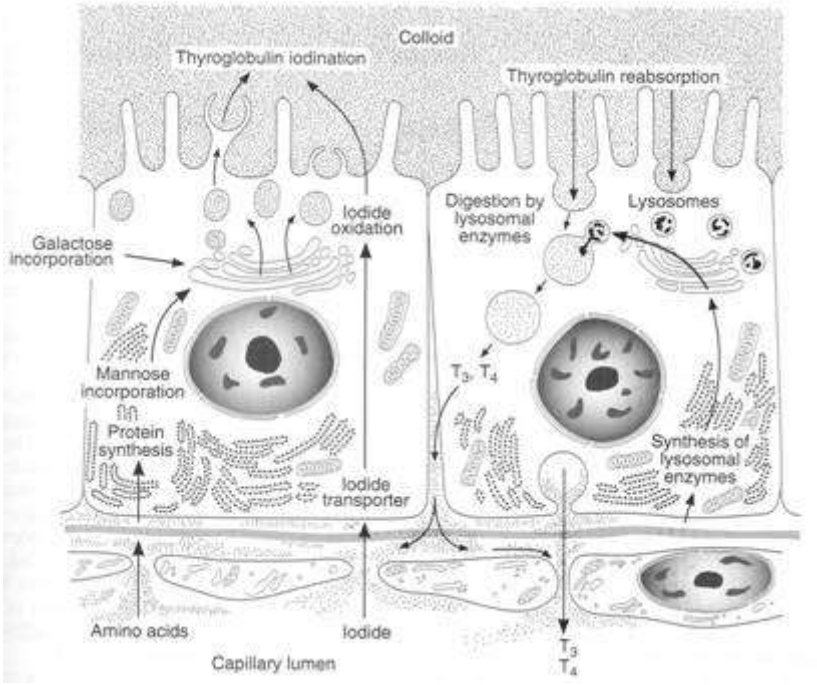
- Regulates basal metabolic rate
- Improves cardiac contractility
- Increases the gain of catecholamines
- Increases bowel motility
- Increases speed of muscle contraction
- Decreases cholesterol (LDL)
- Required for proper fetal neural growth

Thyroid Physiology

- Uptake of Iodine by thyroid
- Coupling of Iodine to Thyroglobulin
- Storage of MIT / DIT in follicular space
- Re-absorption of MIT / DIT
- Formation of T_3, T_4 from MIT / DIT
- Release of T_3, T_4 into serum
- Breakdown of T_3, T_4 with release of Iodine

Iodine uptake

- Na^+/I^- symport protein controls serum I^- uptake
- Based on Na^+/K^+ antiport potential
- Stimulated by TSH
- Inhibited by Perchlorate



MIT / DIT formation

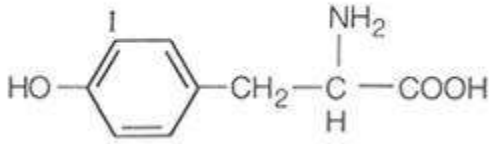
- Thyroid Peroxidase (TPO)
  - Apical membrane protein
  - Catalyzes Iodine organification to Tyrosine residues of Thyroglobulin
  - Antagonized by methimazole
- Iodine coupled to Thyroglobulin
  - Monoiodotyrosine (Tg + one I^-)
  - Diiodotyrosine (Tg + two I^-)
- Pre-hormones secreted into follicular space

Secretion of Thyroid Hormone

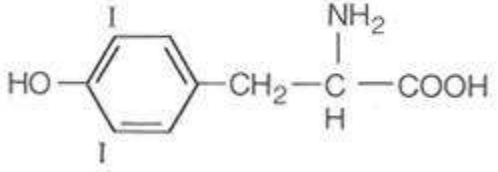
- Stimulated by TSH
- Endocytosis of colloid on apical membrane
- Coupling of MIT & DIT residues
  - Catalyzed by TPO
  - MIT + DIT = T_3
  - DIT + DIT = T_4
- Hydrolysis of Thyroglobulin
- Release of T_3, T_4
- Release inhibited by Lithium

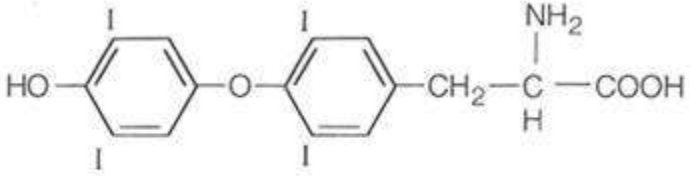
Thyroid Hormones

Monoidotyrosine (MIT)

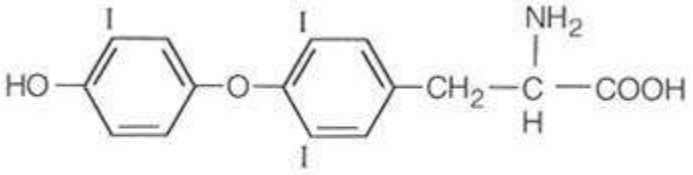


Diiodotyrosine (DIT)





3,5,3',5' - Tetraiodothyronine (L-thyroxine) (T_4)



3,5,3' - Triiodothyronine (T_3)

Thyroid Hormone

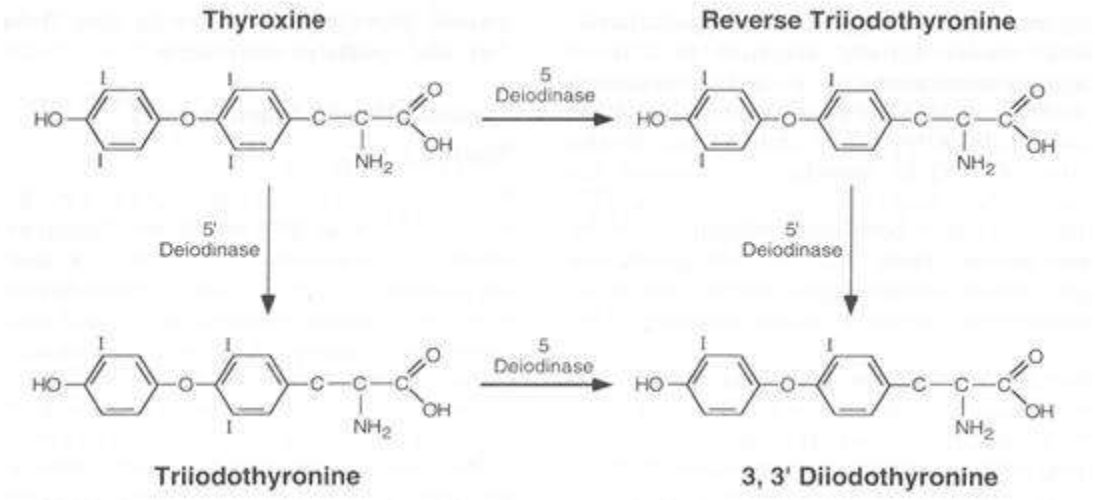
- Majority of circulating hormone is T_4
  - 98.5% T_4
  - 1.5% T_3
- Total Hormone load is influenced by serum binding proteins (TBP, Albumin, ??)
  - Thyroid Binding Globulin 70%
  - Albumin 15%
  - Transthyretin 10%
- Regulation is based on the free component of thyroid hormone

Hormone Binding Factors

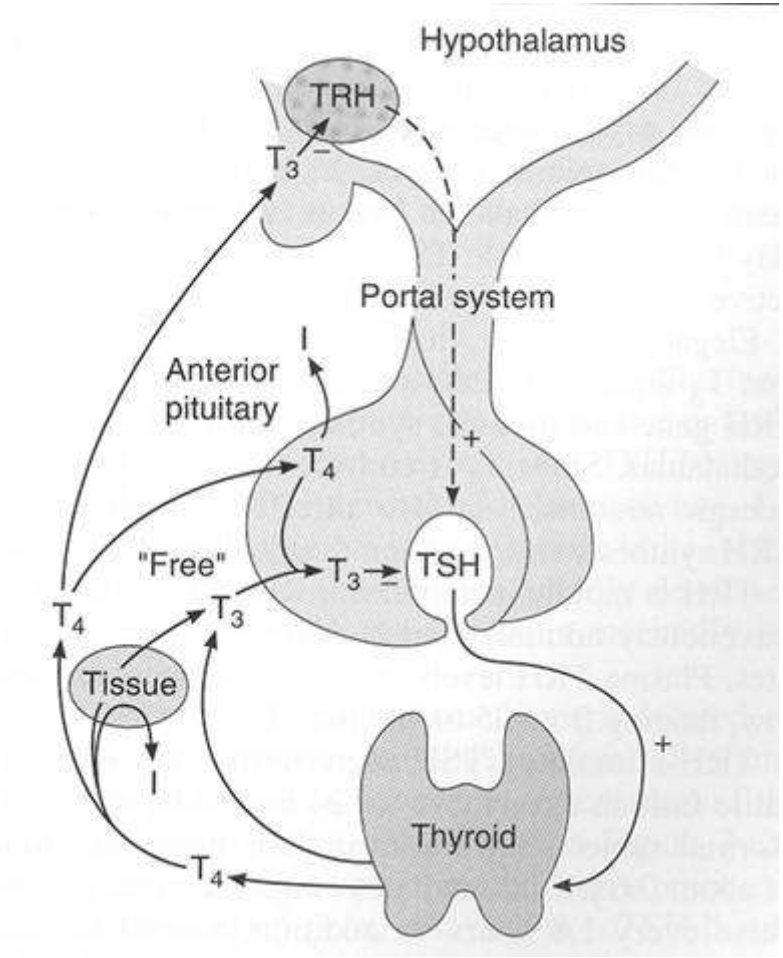
- Increased TBG
  - High estrogen states (pregnancy, OCP, HRT, Tamoxifen)
  - Liver disease (early)
- Decreased TBG
  - Androgens or anabolic steroids
  - Liver disease (late)
- Binding Site Competition
  - NSAID's
  - Furosemide IV
  - Anticonvulsants (Phenytoin, Carbamazepine)

Hormone Degredation

- T_4 is converted to T_3 (active) by *5' deiodinase*
- T_4 can be converted to rT_3 (inactive) by *5 deiodinase*
- T_3 is converted to rT_2 (inactive)by *5 deiodinase*
- rT_3 is inactive but measured by serum tests



Thyroid Hormone Control



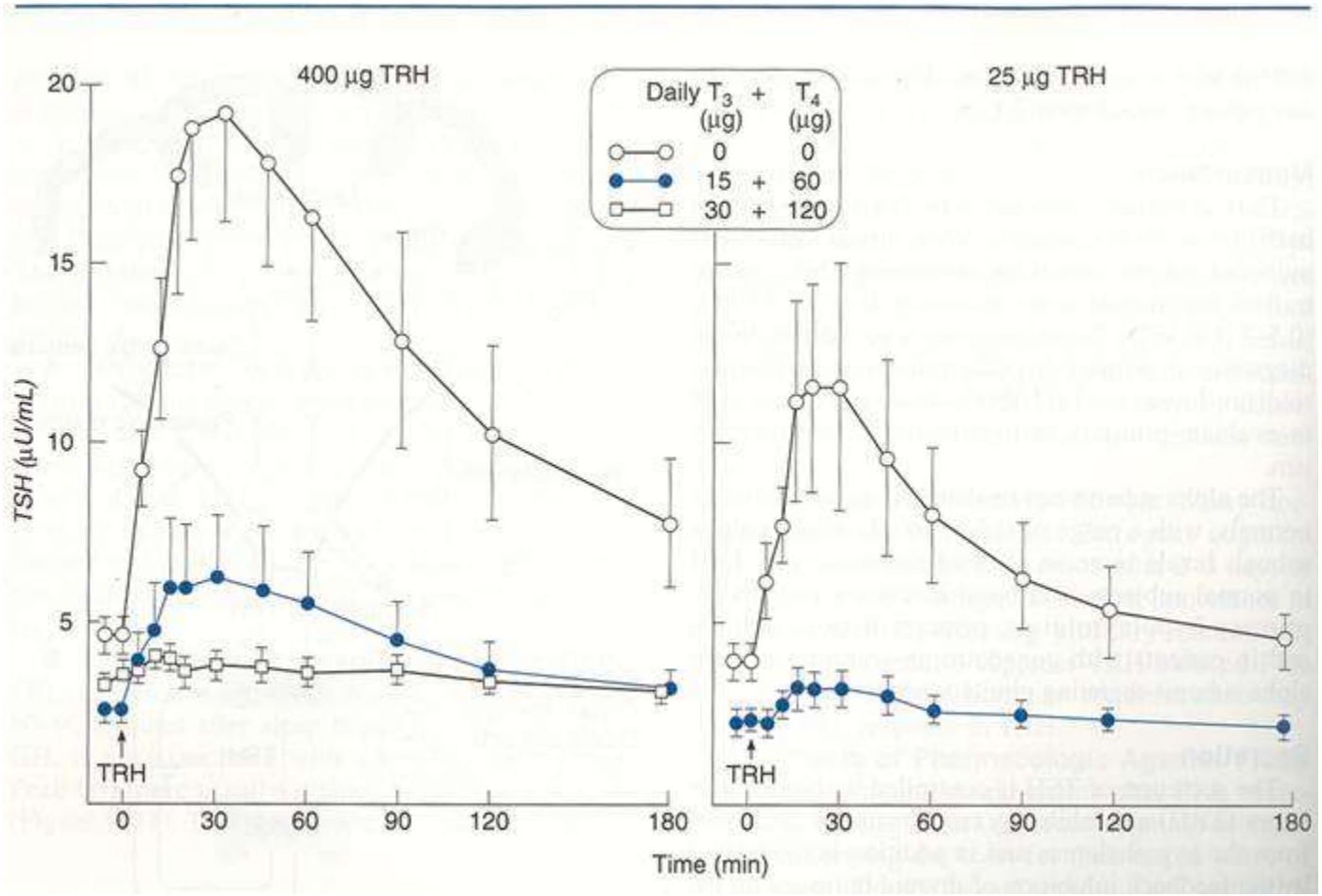
TRH

- Produced by Hypothalamus
- Release is pulsatile, circadian
- Downregulated by T_4, T_3
- Travels through portal venous system to adenohypophysis
- Stimulates TSH formation

TSH

- Produced by Adenohypophysis Thyrotrophs
- Upregulated by TRH
- Downregulated by T_4, T_3
- Travels through portal venous system to cavernous sinus, body.
- Stimulates several processes
  - Iodine uptake
  - Colloid endocytosis
  - Growth of thyroid gland

TSH Response



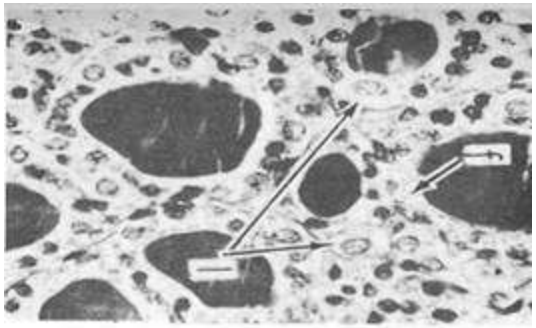
Thyroid Lab Evaluation

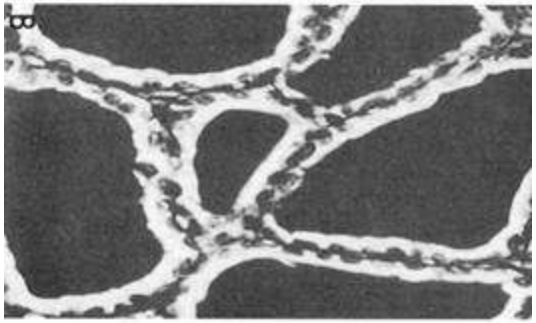
- TRH
- TSH
- TT_3, TT_4
- FT_3, FT_4
- RAIU
- Thyroglobulin, Thyroglobulin Ab
- Perchlorate Test
- Stimulation Tests

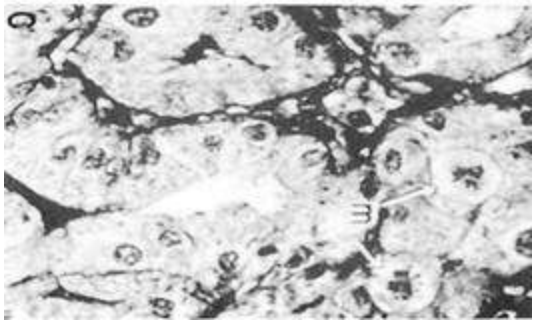
RAIU

- Scintillation counter measures radioactivity 6 & 24 hours after I^{123} administration.
- Uptake varies greatly by iodine status
  - Indigenous diet (normal uptake 10% vs. 90%)
  - Amiodarone, Contrast study, Topical betadine
- Symptomatic elevated RAIU
  - Graves'
  - Toxic goiter
- Symptomatic low RAIU
  - Thyroiditis (Subacute, Active Hashimoto's)
  - Hormone ingestion (Thyrotoxicosis factitia, Hamburger Thyrotoxicosis)
  - Excess I^- intake in Graves' (Jod-Basedow effect)
  - Ectopic thyroid carcinoma (Struma ovarii)

Iodine states



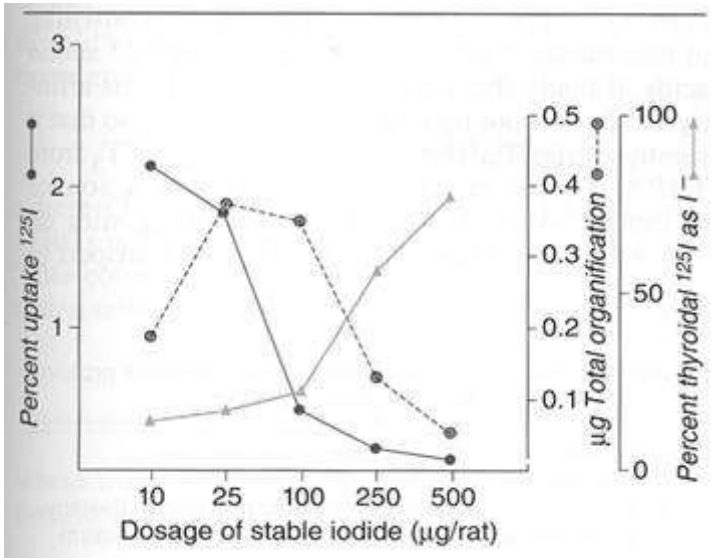




- Normal Thyroid
- Inactive Thyroid
- Hyperactive Thyroid

Wolff-Chaikoff

- Increasing doses of I^- increase hormone synthesis initially
- Higher doses cause cessation of hormone formation.
- This effect is countered by the Iodide leak from normal thyroid tissue.
- Patients with autoimmune thyroiditis may fail to adapt and become hypothyroid.

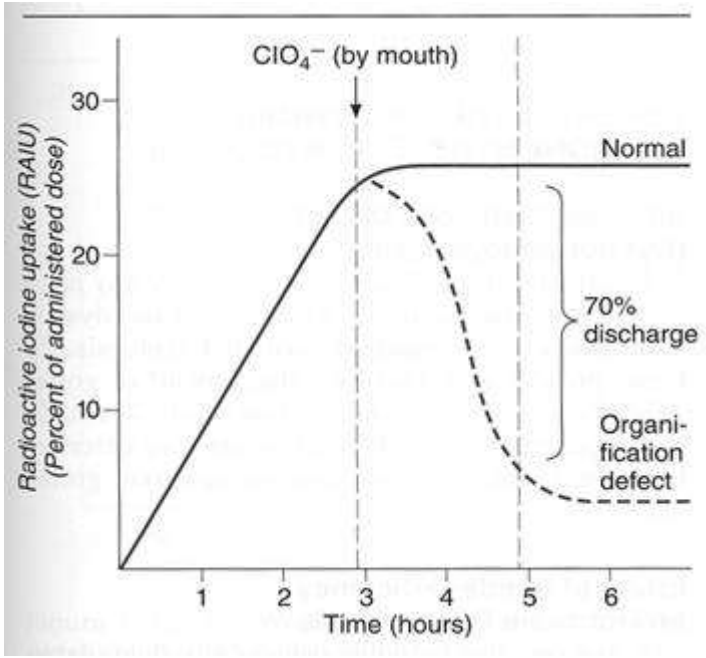


Jod-Basedow

- Aberration of the Wolff-Chaikoff effect
- Excessive iodine loads induce hyperthyroidism
- Observed in several disease processes
  - Graves' disease
  - Multinodular goiter

Perchlorate

- ClO_4^- ion inhibits the Na^+ / I^- transport protein.
- Normal individuals show no leak of I^{123} after ClO_4^- due to organification of I^- to MIT / DIT
- Patients with organification defects show loss of RAIU.
- Used in diagnosis of Pendred syndrome



Hypothyroid

- Symptoms – fatigability, coldness, weight gain, constipation, low voice
- Signs – Cool skin, dry skin, swelling of face/hands/legs, slow reflexes, myxedema
- Newborn – Retardation, short stature, swelling of face/hands, possible deafness
- Types of Hypothyroidism
  - Primary – Thyroid gland failure
  - Secondary – Pituitary failure
  - Tertiary – Hypothalamic failure
  - Peripheral resistance

Hypothyroid

- Cause is determined by geography
- Diagnosis
  - Low FT_4, High TSH (Primary, check for antibodies)
  - Low FT_4, Low TSH (Secondary or Tertiary, TRH stimulation test, MRI)
- Treatment
  - Levothyroxine (T_4) due to longer half life
  - Treatment prevents bone loss, cardiomyopathy, myxedema

Primary:

1. Hashimoto's thyroiditis:
   a. With goiter.
   b. "Idiopathic" thyroid atrophy, presumably end-stage autoimmune thyroid disease, following either Hashimoto's thyroiditis or Graves' disease.
   c. Neonatal hypothyroidism due to placental transmission of TSH-R blocking antibodies.
2. Radioactive iodine therapy for Graves' disease.
3. Subtotal thyroidectomy for Graves' disease or nodular goiter.
4. Excessive iodide intake (kelp, radiocontrast dyes).
5. Subacute thyroiditis.
6. Rare causes in the USA:
   a. Iodide deficiency.
   b. Other goitrogens such as lithium; antithyroid drug therapy.
   c. Inborn errors of thyroid hormone synthesis.

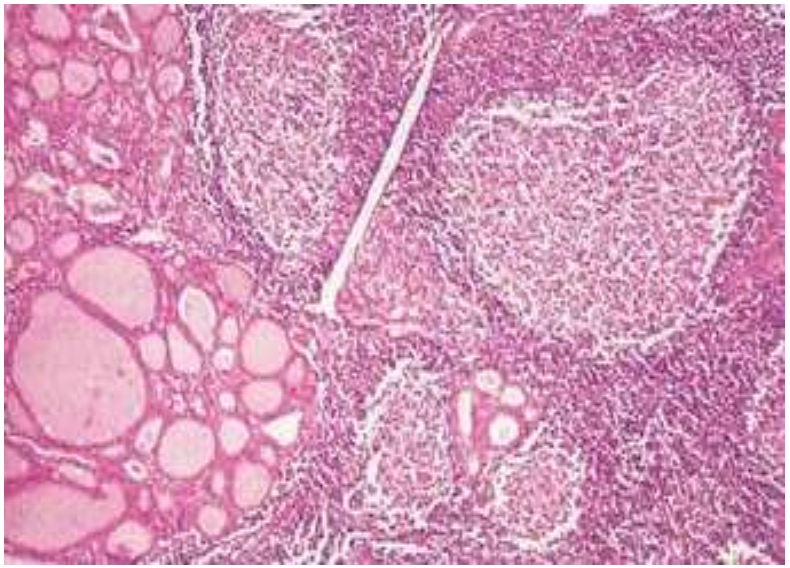
Secondary: Hypopituitarism due to pituitary adenoma, pituitary ablative therapy, or pituitary destruction.

Tertiary: Hypothalamic dysfunction (rare).

Peripheral resistance to the action of thyroid hormone.

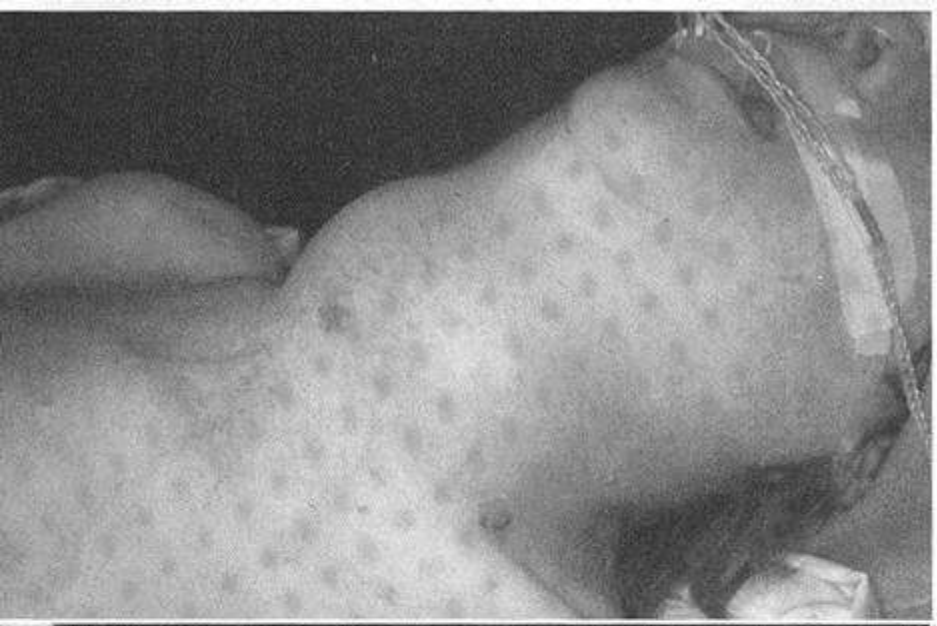
Hashimoto's
(Chronic, Lymphocytic)

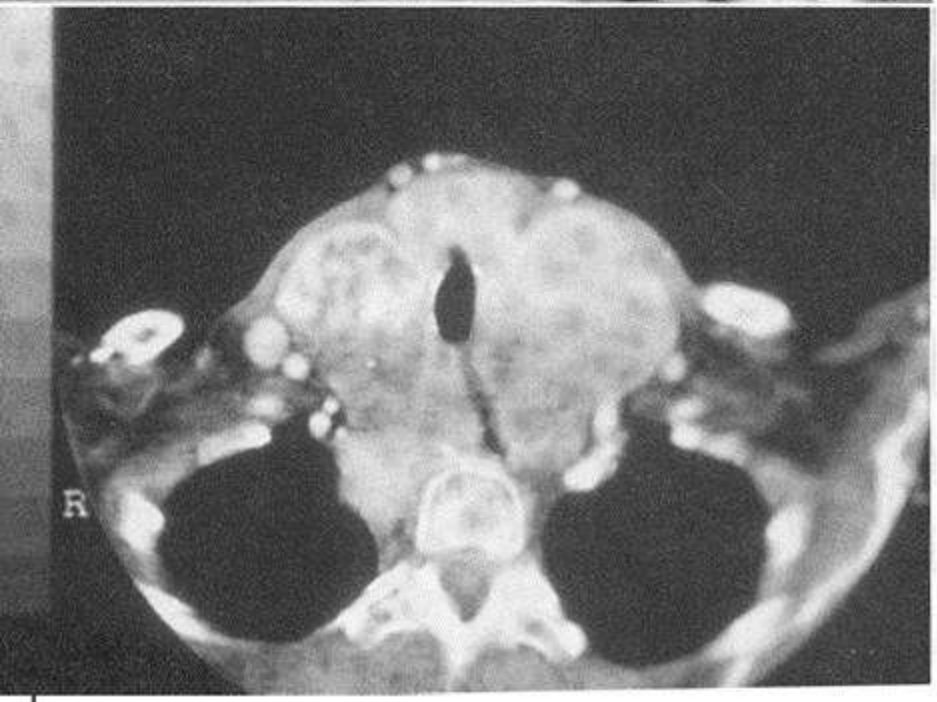
- Most common cause of hypothyroidism
- Result of antibodies to TPO, TBG
- Commonly presents in females 30-50 yrs.
- Usually non-tender and asymptomatic
- Lab values
  - High TSH
  - Low T_4
  - Anti-TPO Ab
  - Anti-TBG Ab
- Treat with Levothyroxine



Goiter

- Endemic goiter
  - Caused by dietary deficiency of Iodide
  - Increased TSH stimulates gland growth
  - Also results in cretinism
- Goiter in developed countries
  - Hashimoto's thryoiditis
  - Subacute thyroiditis
- Other causes
  - Excess Iodide (Amiodarone, Kelp, Lithium)
  - Adenoma, Malignancy
  - Genetic / Familial hormone synthesis defects

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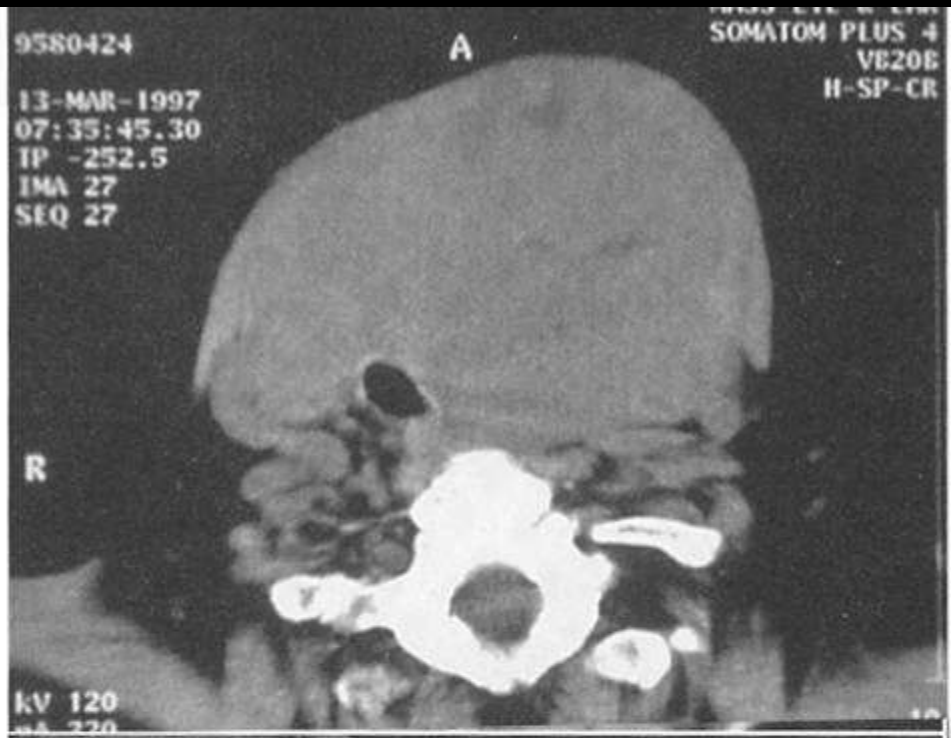
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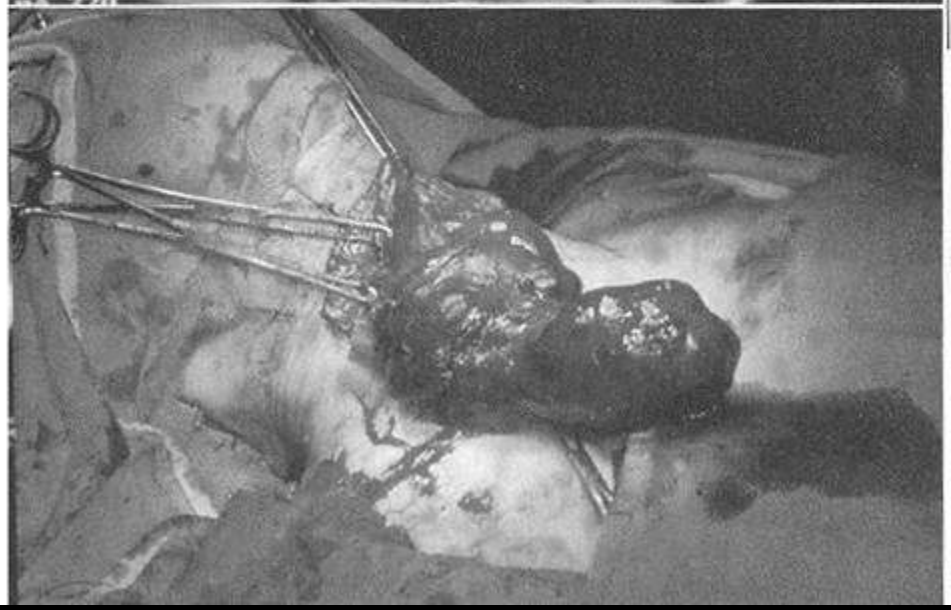


Hyperthyroid

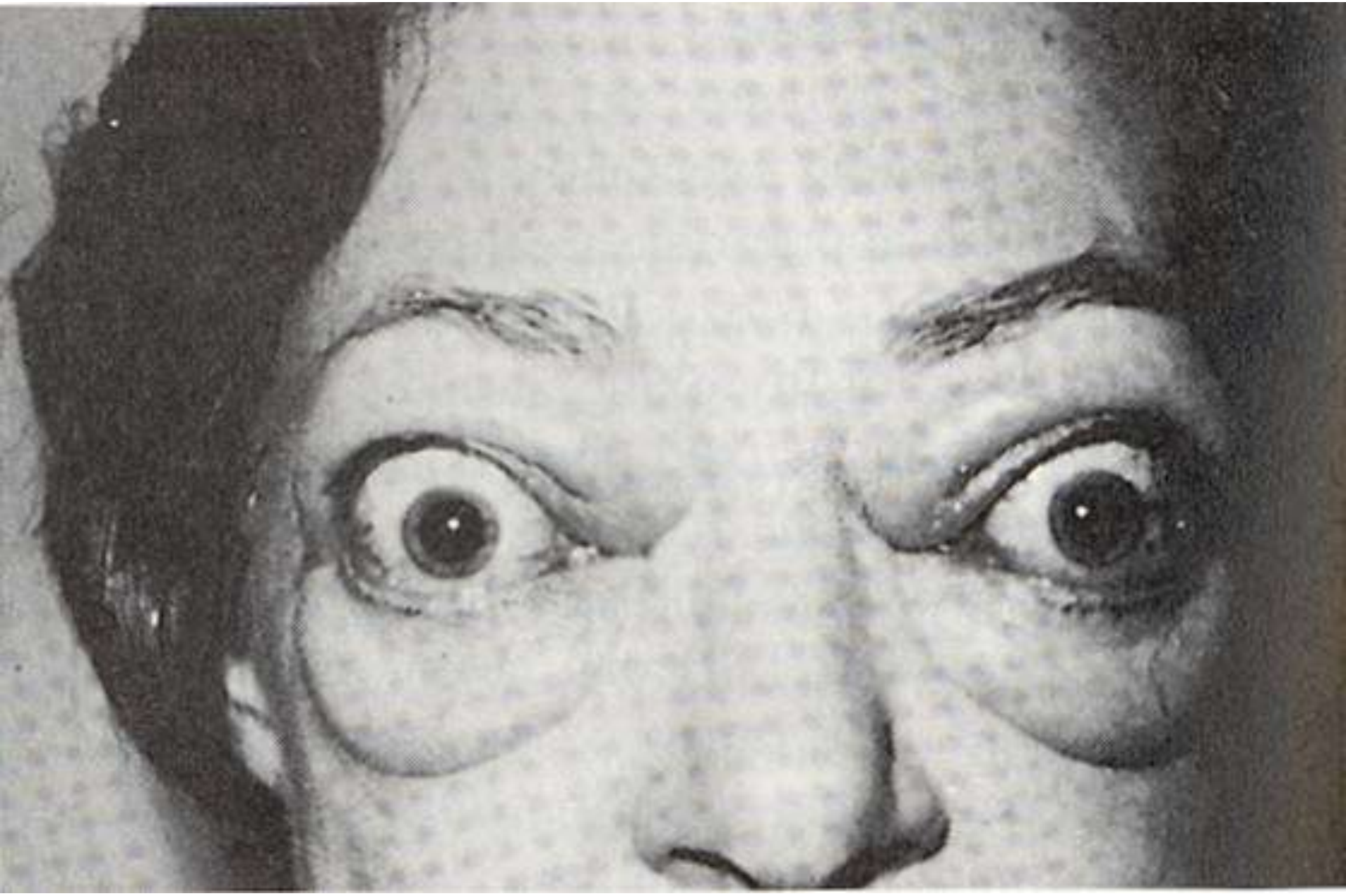
- Symptoms – Palpitations, nervousness, fatigue, diarrhea, sweating, heat intolerance
- Signs – Thyroid enlargement (?), tremor
- Lab workup
  - TSH
  - FT4
  - RAIU
- Other Labs
  - Anti-TSH-R Ab, Anti-TPO Ab, Anti-TBG Ab
  - FT3
  - FNA
  - MRI, US

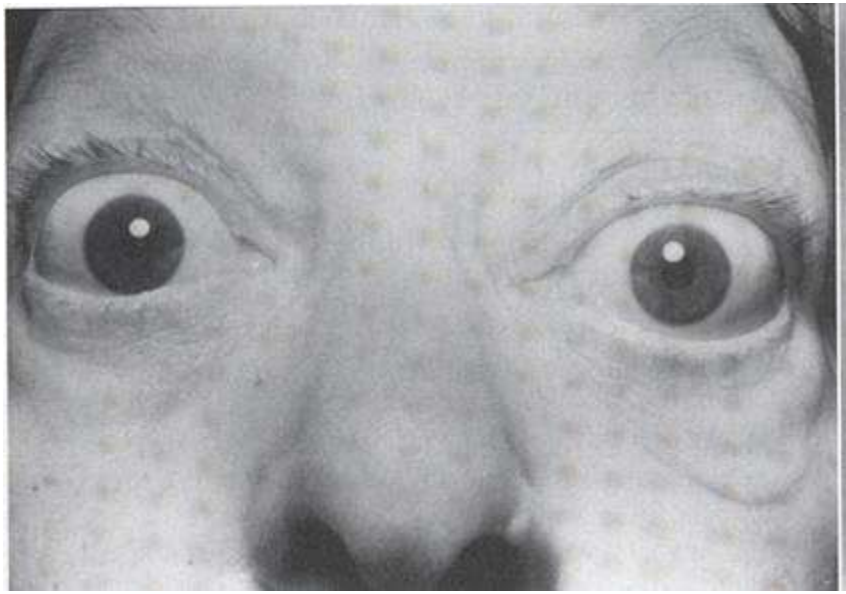
Hyperthyroid

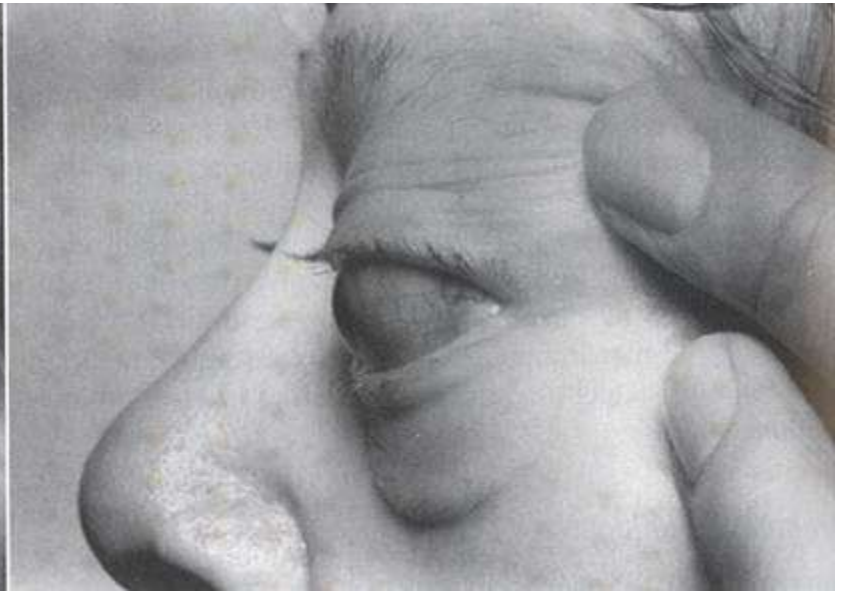
- Common Causes
  - *Graves
  - Adenoma
  - Multinodular Goiter
  - *Subacute Thyroiditis
  - *Hashimoto's Thyroiditis
- Rare Causes
  - Thyrotoxicosis factitia, struma ovarii, thyroid metastasis, TSH-secreting tumor, hamburger

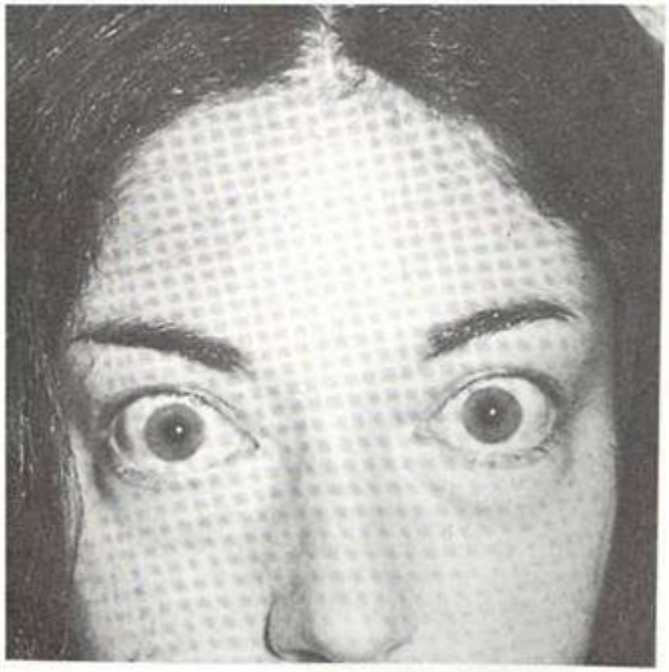
Graves

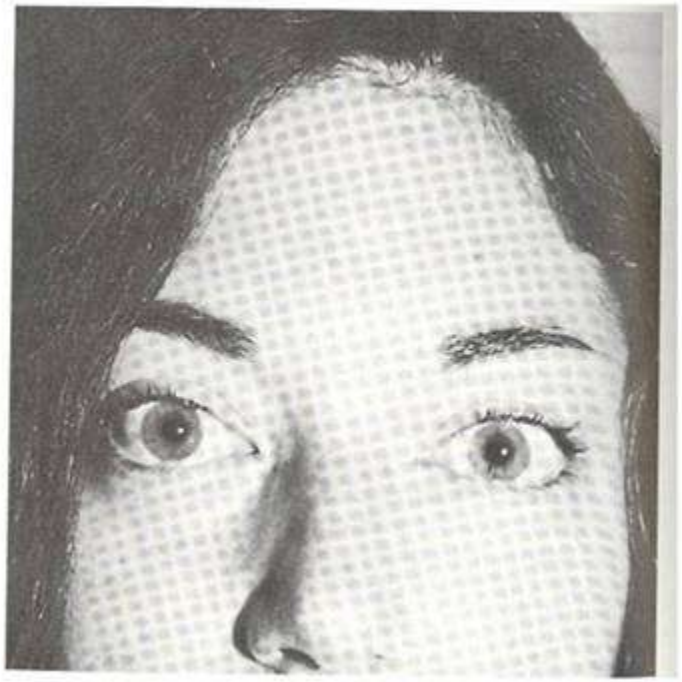
- Most common cause of hyperthyroidism
- Result of anti-TSH receptor antibodies
- Diagnosis
  - Symptoms of hyperthyroidism
  - Clinical exopthalmos and goiter
  - Low TSH, normal/high FT_4, anti-TSH Ab (Optional)
- If no clinical findings I^{123} may demonstrate increased uptake.
- Treatments
  - Medical – Propothyouracil, Methimazole, Propranolol
  - Surgical – Subtotal Thyroidectomy
  - Radiation – RAI ablation [I^{131}(μCi/g) x weight / %RAIU]







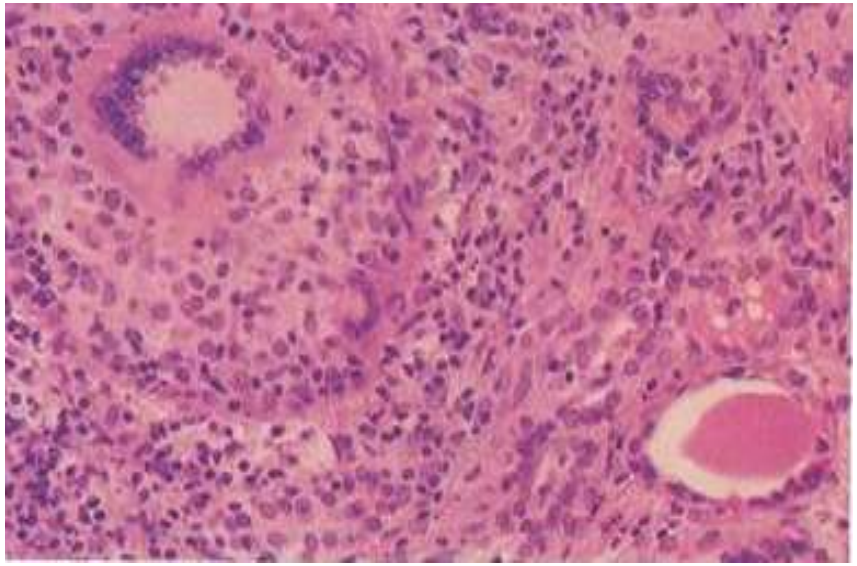




Subacute Thyroiditis

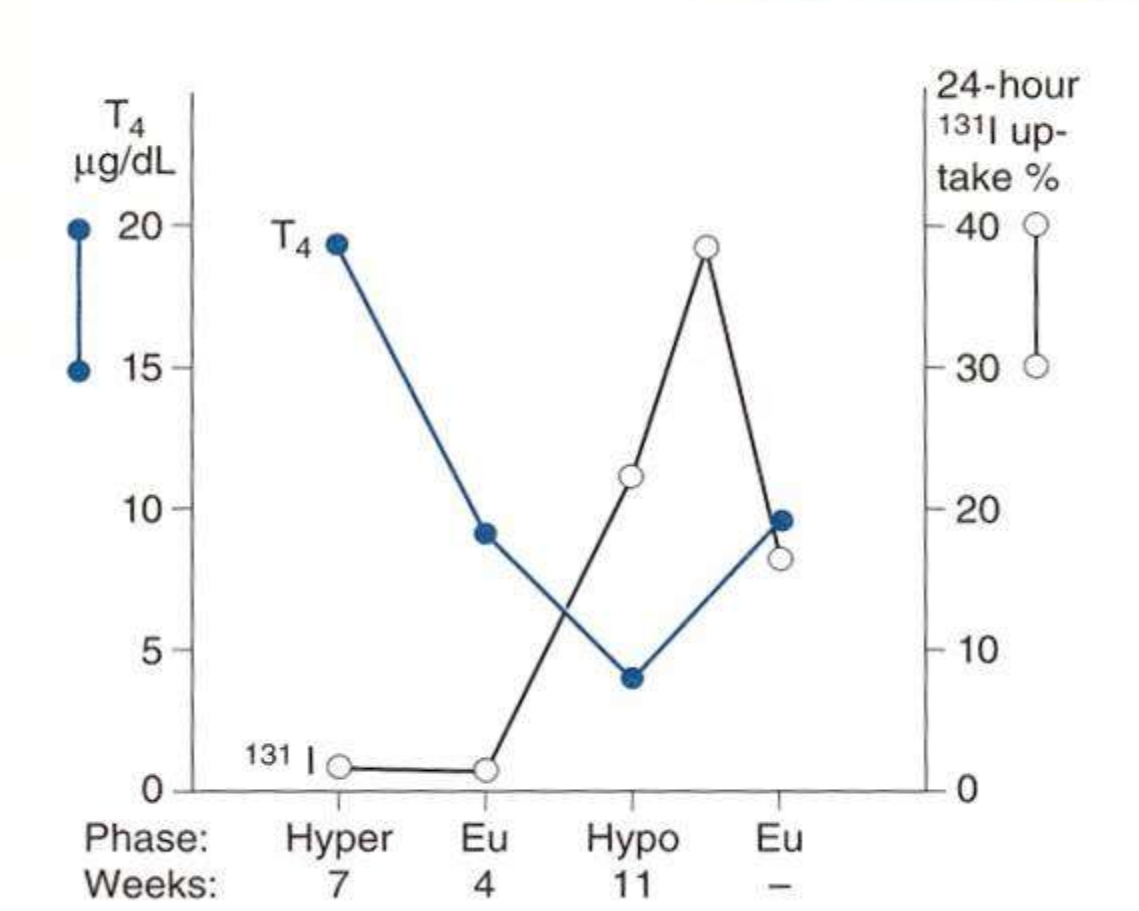
(DeQuervain's, Granulomatous)

- Acute viral infection of thyroid gland
- Presents with viral prodrome, thyroid tenderness, and hyperthyroid symptoms
- Lab values
  - Variable TSH, T_4
  - High ESR
  - No antibodies
- Treatment
  - APAP, NSAID
  - Prednisone (?)
  - Levothyroxine (?)



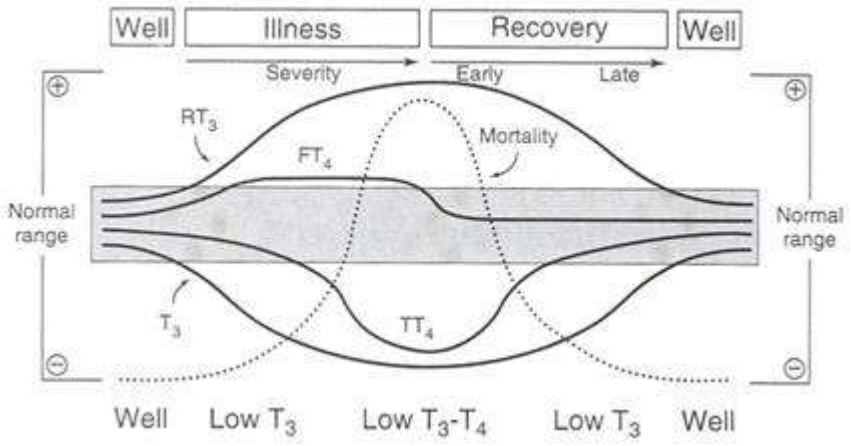
Subacute Thyroiditis

(DeQuervain's, Granulomatous)



Euthyroid Sick

- Results from inactivation of 5'-Deiodinase, resulting in conversion of FT_4 to rT_3.
- Generally occurs in critically ill patients, but may occur with DM, malnutrition, iodine loads, or medications (Amiodarone, PTU, glucocorticoids)
- Treatment
  - Avoid above medications
  - Treat primary illness
  - T_3, T_4 not helpful



Thyroid Storm

- Causes
  - Surgery
  - Radioactive Iodine Therapy
  - Severe Illness
- Diagnosis
  - Clinical – tachycardia, hyperpyrexia, thyrotoxicosis symptoms
  - Labs (Low TSH, High T4, FT4)
- Treatment
  - Propranolol IV vs. Verapamil IV
  - Propylthiouracil, Methimazole
  - Sodium Iodide
  - Acetamenophen, cooling blankets
  - Plasmapheresis (rare)
  - Surgical (rare)

Calcium Regulation

Parathyroid

Calcium

- Required for muscle contraction, intracellular messenger systems, cardiac repolarization.
- Exists in free and bound states
  - Albumin (40% total calcium)
  - Phosphate and Citrate (10% total calcium)
- Concentration of iCa++ mediated by
  - Parathyroid gland
  - Parafollicular C cells
  - Kidney
  - Bone

Parathyroid Hormone

- Produced by Parathyroid Chief cells
- Secreted in response to low iCa^{++}
- Stimulates renal conversion of 25-$(OH)D_3$ to 1,25-$(OH)_2D$ which increases intestinal Ca^{++} absorption
- Directly stimulates renal Ca^{++} absorption and PO_4^{3-} excretion
- Stimulates osteoclastic resorption of bone

Calcitonin

- Produced by Parafollicular C cells of Thyroid in response to increased iCa^{++}
- Actions
  - Inhibit osteoclastic resorption of bone
  - Increase renal Ca^{++} and PO_4^{3-} excretion
- Non-essential hormone. Patients with total thyroidectomy maintain normal Ca^{++} concentrations
- Useful in monitoring treatment of Medullary Thyroid cancer
- Used in treatment of Pagets', Osteoporosis

Vitamin D

- Sources
  - Food – Vitamin D_2
  - UV light mediated cholesterol metabolism – D_3
- Metabolism
  - D_2 and D_3 are converted to 25(OH)-D by the liver
  - 25(OH)-D is converted to 1,25$(OH)_2$-D by the Kidney
- Function
  - Stimulation of Osteoblasts
  - Increases GI absorption of dietary Ca^{++}

Hypocalcemia

- Decreased PTH
  - Surgery
  - Hypomagnesemia
  - Idiopathic
- Resistance to PTH
  - Genetic disorders
  - Bisphosphonates
- Vitamin D abnormalities
  - Vitamin D deficiency
  - Rickets (VDR or Renal hyroxylase abnormalities)
- Binding of Calcium
  - Hyperphosphate states (Crush injury, Tumor lysis, etc.)
  - Blood Transfusion (Citrate)

Hypercalcemia

- Hyperparathyroidism
  - Primary, Secondary, Tertiary
  - MEN Syndromes
- Malignancy
  - Humoral Hypercalcemia
  - PTHrP (Lung Cancer)
  - Osteoclastic activity (Myeloma, Lymphoma)
- Granulomatous Diseases
  - Overproduction of 1,25 $(OH)_2D$
- Drug-Induced
  - Thiazides
  - Lithium
  - Milk-Alkali
  - Vitamin A, D
- Renal failure

Hypercalcemia

- Signs & Symptoms
  - Bones (Osteitis fibrosa cystica, osteoporosis, rickets)
  - Stones (Renal stones)
  - Groans (Constipation, peptic ulcer)
  - Moans (Lethargy, depression, confusion)
- Medical Treatment
  - SERM's (Evista)
  - Bisphosphonates (Pamidronate)
  - Calcitonin (for severe cases)
  - Saline diuresis
  - Glucocorticoids (for malignant/granulomatous diseases)
  - Avoid thiazide diuretics
- Surgical Treatment
  - Single vs. Double adenoma – simple excision
  - Multiple Gland hyperplasia – total parathyroid with autotransplant vs. 3½ gland excision

Primary Hyperparathyroidism

- Diagnosis
  - Signs & Symptoms
  - Elevated serum calcium
  - Elevated PTH
- Etiology
  - Solitary Adenoma (80-85%)
  - Double Adenomas (2-4%)
  - Muliple Gland Hyperplasia (10-30%)
  - Parathyroid Carcinoma (0.5%)
  - MEN syndromes (10% of MGH have MEN 1)

Multiple Endocrine Neoplasia

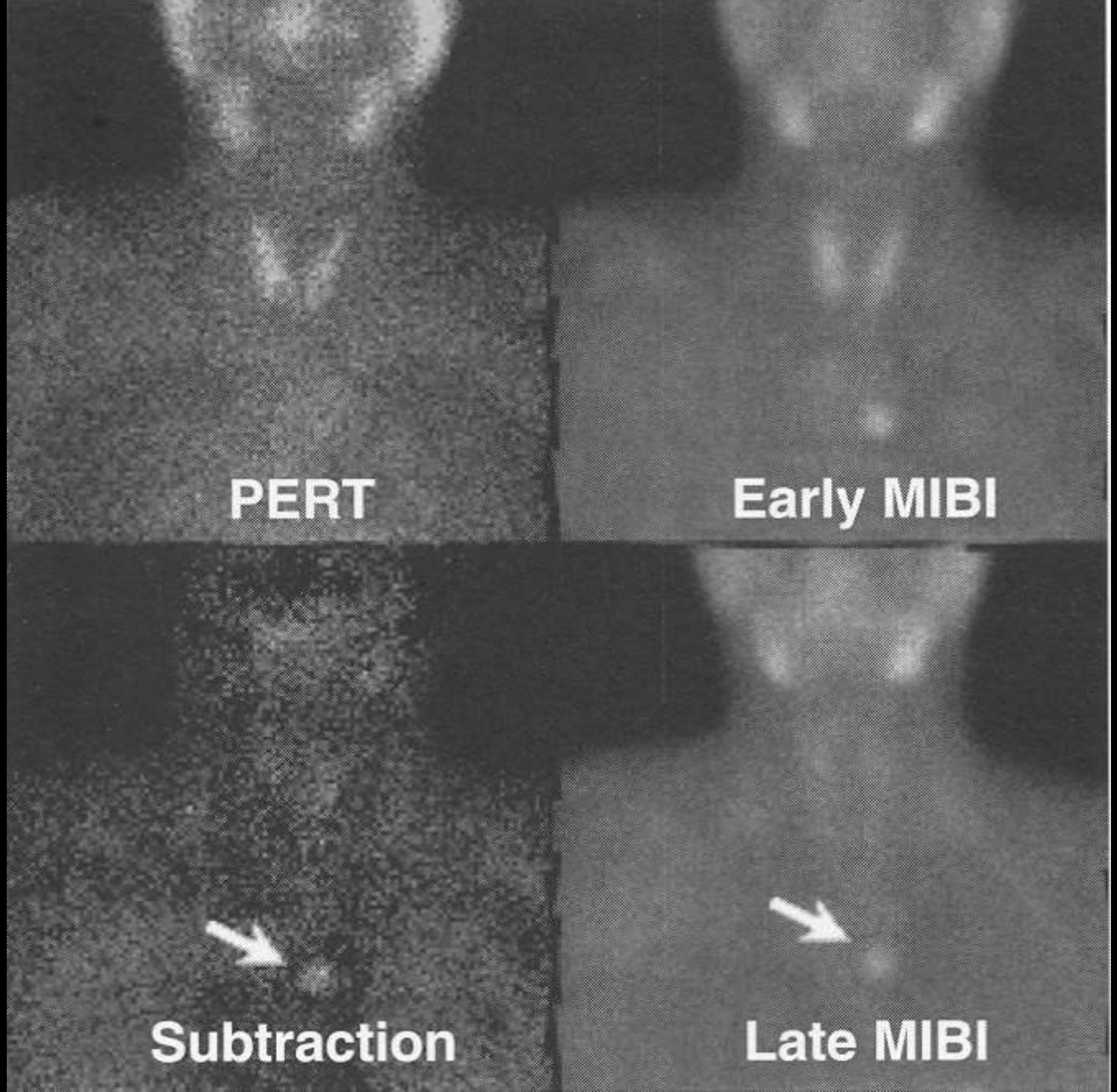
- MEN 1
  - Pituitary adenoma
  - Pancreatic endocrine tumor
  - Parathyroid neoplasia (90%)
- MEN 2a
  - Medullary thyroid cancer (100%)
  - Pheochromocytoma (50%)
  - Parathyroid neoplasia (10-40%)
- MEN 2b
  - Medullary thyroid cancer (100%)
  - Pheochromocytoma (50%)
  - Neuromas (100%)

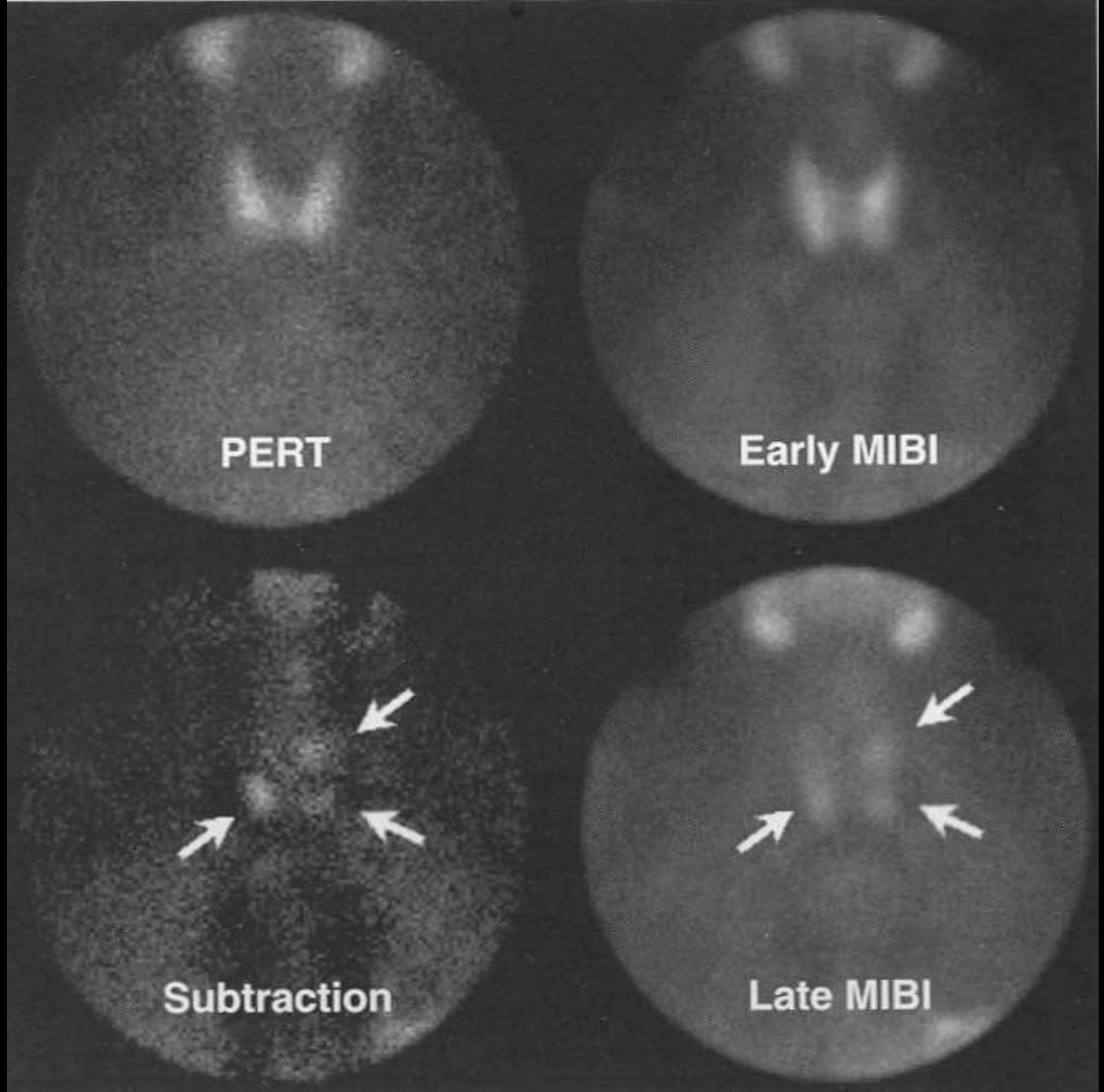
Parathyroidectomy

- 1990 NIH Guidelines
  - Serum Ca++ > 12 mg/dl
  - Hypercalciuria > 400 mg/day
  - Classic symptoms
    - Nephrolithiasis
    - Osteitis fibrosa cystica
    - Neuromuscular disease
  - Cortical bone loss with DEXA Z score < -2
  - Reduced creatinine clearance
  - Age < 50
- Other considerations
  - Vertebral osteopenia
  - Vitamin D deficency
  - Perimenopause

Preoperative Localization

- Thallium / Pertechnetate
  - Based on subtraction of Tc 99 which concentrates only in thyroid from background Thallium which is absorbed by thyroid and parathyroid
  - Moderate sensitivity and specificity
  - Thyroid pathology reduces effectiveness
- Technetium 99m Sestamibi
  - Absorbed by thyroid and abnormal parathyroid
  - Early washout from thyroid leaves residual parathyroid signals in later images
  - Higher sensitivity and specificity
- Single Photon Emission Computed Tomography
  - Creates a three dimensional representation to allow for ectopic localization
  - Not commonly used


PERT
Early MIBI
Subtraction
Late MIBI


PERT
Early MIBI
Subtraction
Late MIBI

Intraoperative Hormone Assays

- Garner, S., Leight, G. *Surgery* 1999; 126: 1132-8.
  - Intraoperative PTH assays found highly sensitive for remaining disease (98.4%)
  - All cases of false positives were in multiple gland disease
  - The incidence of MGH was low in this study
- Weber, C., Ritchie, J. *Surgery* 1999; 126: 1139-44.
  - Intraoperative PTH assays work well in solitary adenomas
  - Multiple gland disease often gives false results due to “adenoma effect” of the dominant gland
  - Recomends bilateral exploration with any evidence of multiple gland disease

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Source from

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