Acute Thyroid disease

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Three Questions

- Is the Biology and biochemistry congruous
- Do I believe biology or biochemistry
- Does this need treatment

Case study-1

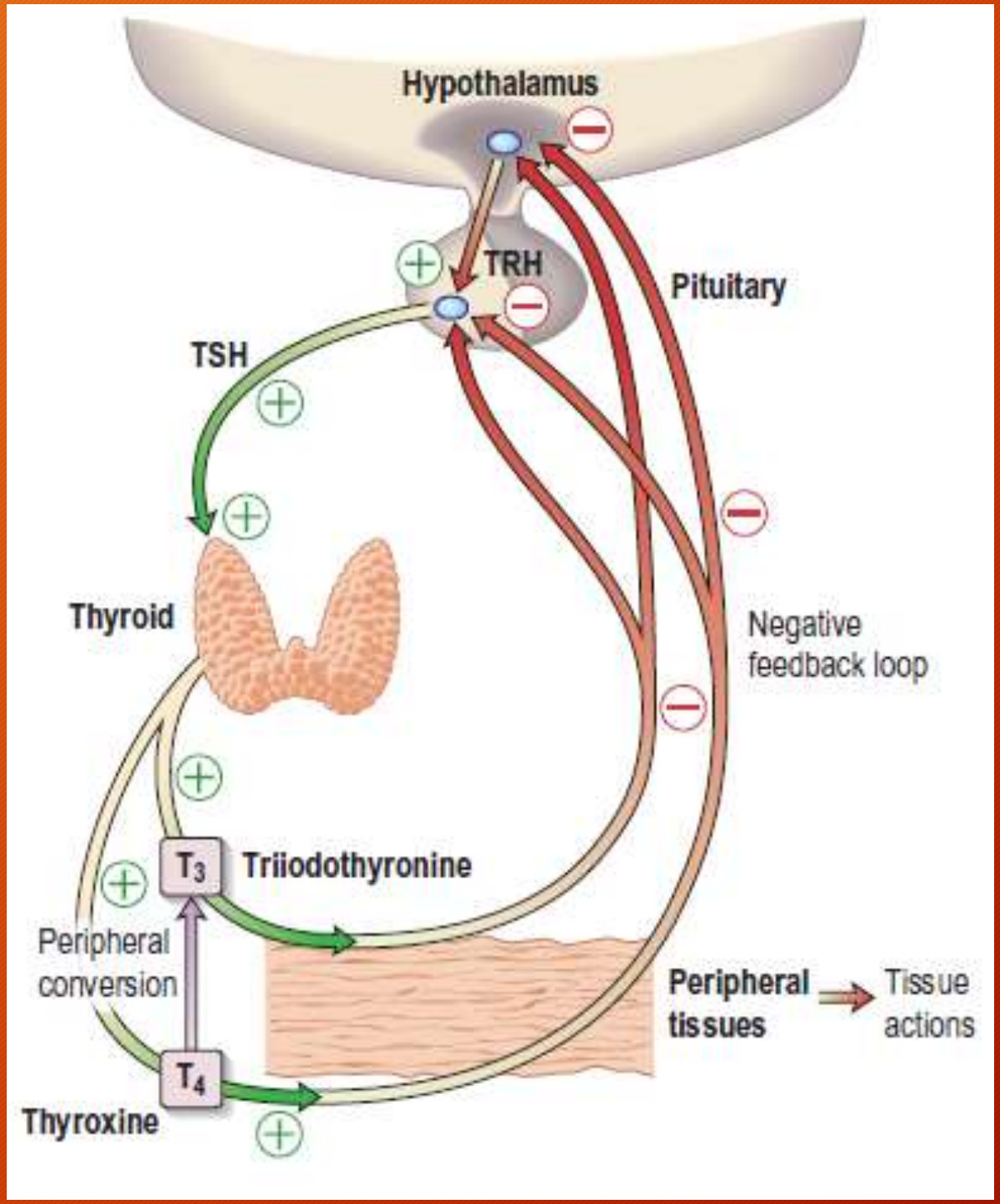
- A 27-year-old male
- Wants to attend gym
- Incidental Tachycardia
- Normal clinical exam, and no relevant clinical history
- All Bloods normal, unsure about TFT: TSH- 3.4, FT4- 21

What would you do

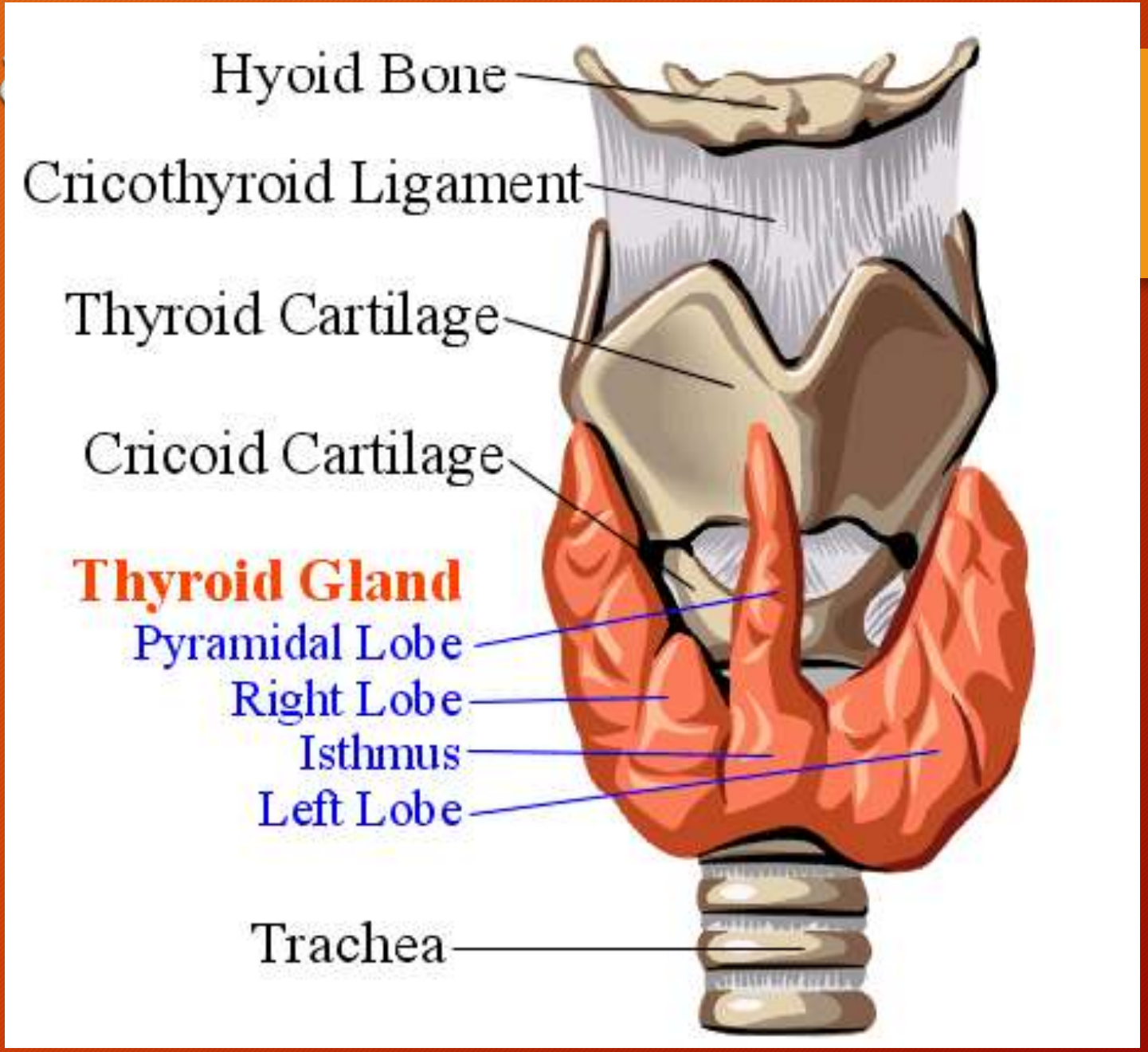
- A-Repeat TFT in 3-4 months
- B-Encourage mindfulness training
- C-Refer to cardiology
- D-Refer to Endocrinology

Differntial diagnosis?

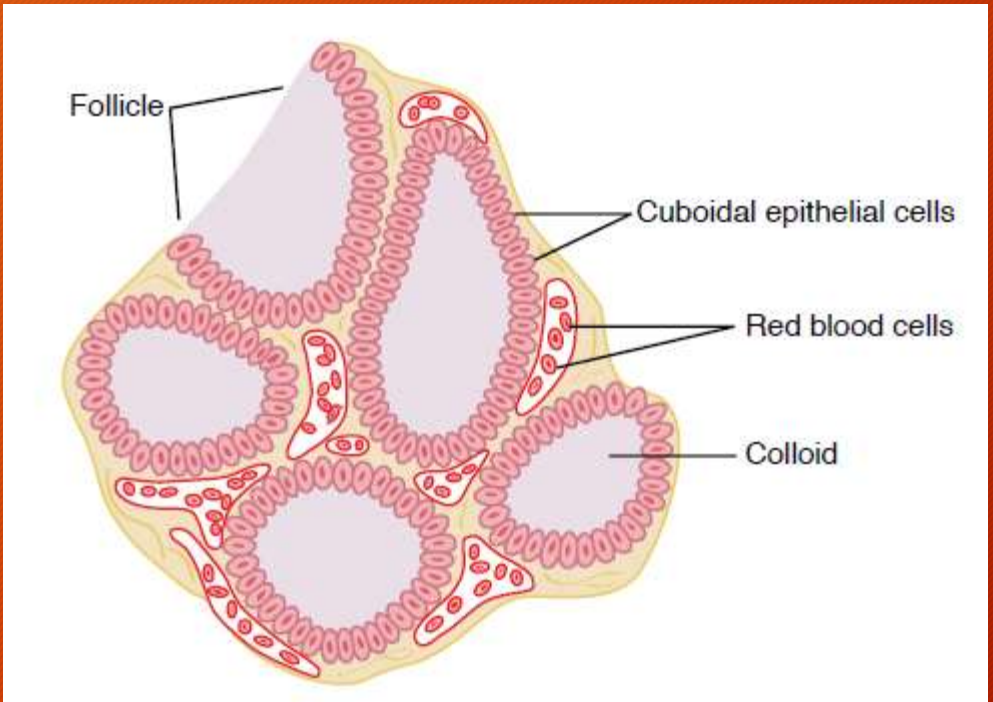
- Auto-immune disease?
- Primary thyroid disease?
- Hypothalamic- pituitary disease?

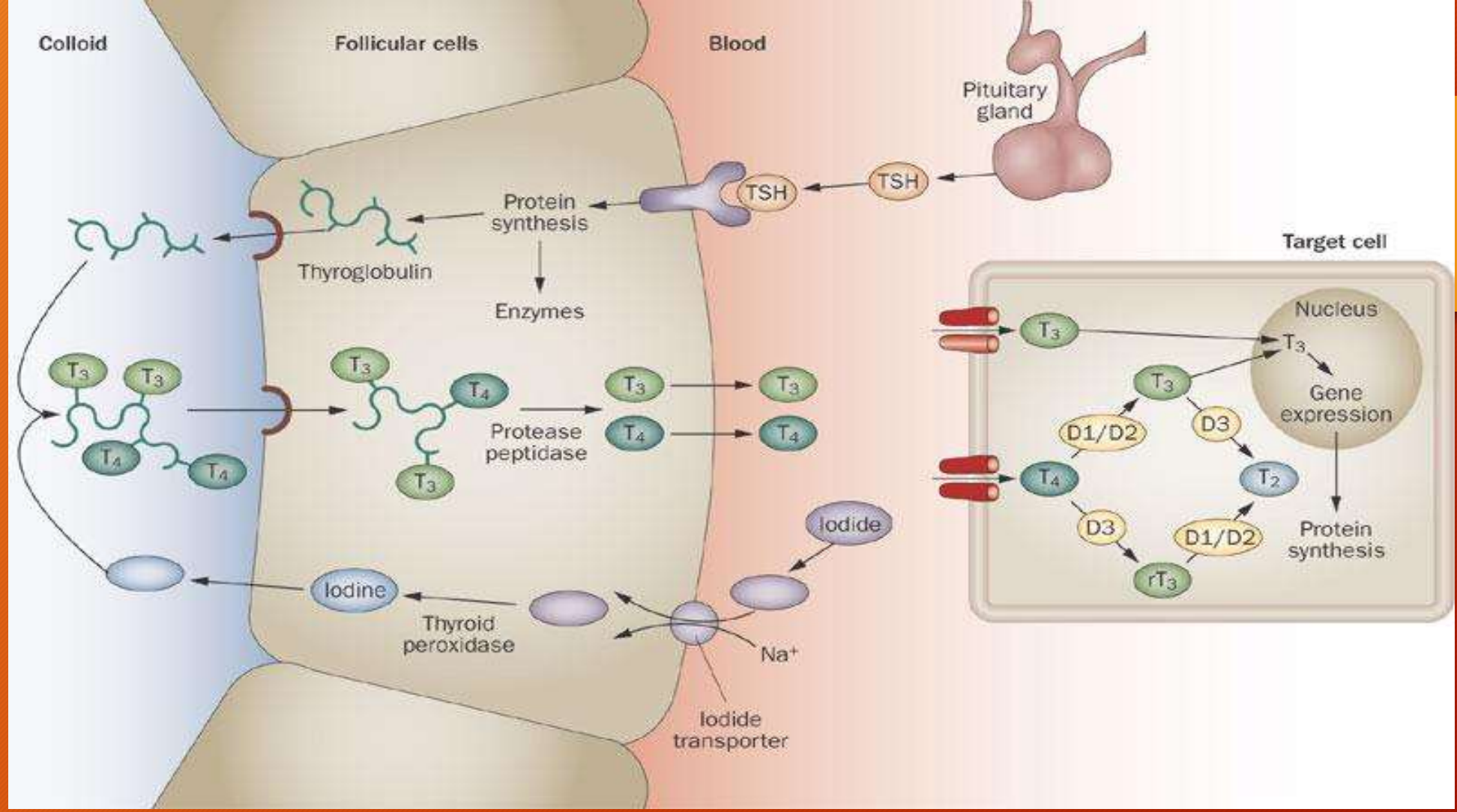

Hypothalamus
TRH
Pituitary
TSH
Thyroid
Negative
feedback loop
T3
Triiodothyronine
Peripheral
conversion
Peripheral
tissues
Tissue
actions
T4
Thyroxine

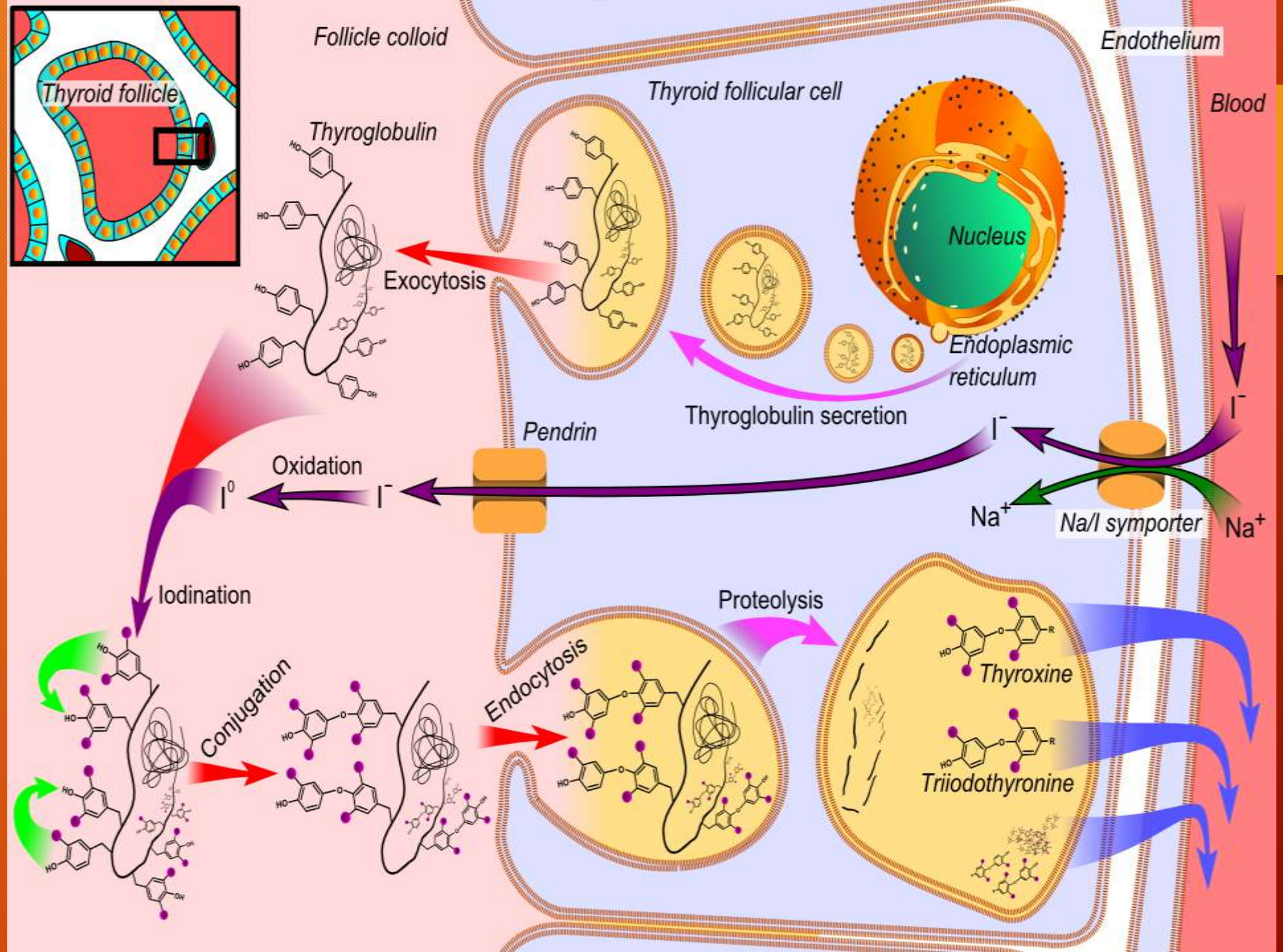
Thyroid

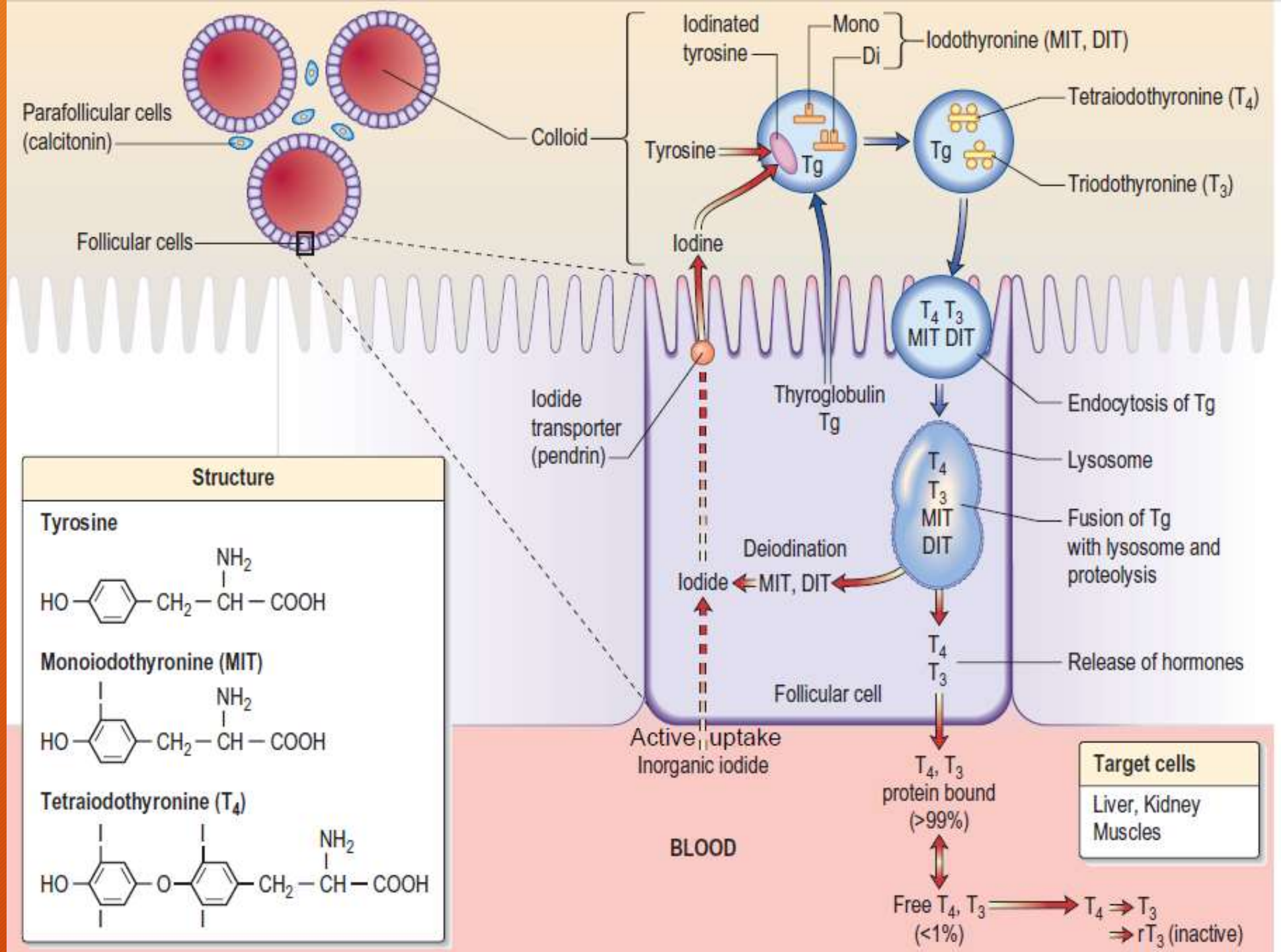

Hyoid Bone
Cricothyroid Ligament
Thyroid Cartilage
Cricoid Cartilage
Thyroid Gland
Pyramidal Lobe
Right Lobe
Isthmus
Left Lobe
Trachea

Microanatomy




Colloid
Follicular cells
Blood
Pituitary gland
TSH
TSH
Protein synthesis
Thyroglobulin
Enzymes
Target cell
Nucleus
Gene expression
Protease peptidase
Iodide
Iodine
Thyroid peroxidase
Na+
Iodide transporter
D1/D2
D3
D3
D1/D2
Protein synthesis


Thyroid follicle
Follicle colloid
Endothelium
Blood
Thyroid follicular cell
Thyroglobulin
Exocytosis
Nucleus
Endoplasmic reticulum
Thyroglobulin secretion
Pendrin
Oxidation
I^0
I^-
I^-
I^-
Na^+
Na^+
Na/I symporter
Iodination
Conjugation
Endocytosis
Proteolysis
Thyroxine
Triiodothyronine


Parafollicular cells
(calcitonin)
Follicular cells
Colloid
Iodinated
tyrosine
Mono
Di
Iodothyronine (MIT, DIT)
Tyrosine
Tg
Tg
Tetraiodothyronine (T_4)
Triodothyronine (T_3)
Iodine
T_4 T_3
MIT DIT
Endocytosis of Tg
Iodide
transporter
(pendrin)
Thyroglobulin
Tg
Lysosome
T_4
T_3
MIT
DIT
Fusion of Tg
with lysosome and
proteolysis
Deiodination
Iodide
MIT, DIT
T_4
T_3
Release of hormones
Follicular cell
Active uptake
Inorganic iodide
T_4, T_3
protein bound
(>99%)
BLOOD
Free T_4, T_3
(<1%)
$T_4 \Rightarrow T_3$
$\Rightarrow rT_3$ (inactive)
Target cells
Liver, Kidney
Muscles
Structure
Tyrosine
Monoiodothyronine (MIT)
Tetraiodothyronine (T_4)

Formation of thyroid hormone

- ER and golgi synthesise and secrete thyroglobulin
- Each thyroglobulin contains 70 tyrosine, combine with iodine T4/ T3 - within thyroglobulin
- Thyroperoxidase- apical membrane & hydrogen peroxide convert iodide to iodine which can combine with tyrosine

Formation of thyroid hormone

- Step 2: Tyrosine is iodised by iodinase to monoiodotyrosine and diiodotyrosine.
- The iodotyrosine residues become coupled.
- DIT + DIT → T4 | MIT + DIT → T3 15:1
- Each thyroglobulin molecule contains up to 30 thyroxine (T4) and a few T3.
- Enough stored to supply 2-3months

Release of T4 + T3 from Thyroid

- T4 (85%)+ T3 (15%) released into blood, cleaved and released as free hormones
- The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form pinocytic vesicles
-
- Then lysosomes fuse with these vesicles to form digestive vesicles- lysosomes mixed with the colloid.

Release of T4 + T3 from Thyroid

- Proteases digest the thyroglobulin and release T3 and T4, diffuse through the base into the surrounding capillaries.
- 75% of the iodinated tyrosine in the thyroglobulin never becomes thyroid hormones but remain MIT and DIT.
- During digestion of the thyroglobulin molecule to release T4 and T3, iodinated tyrosines are also freed from thyroglobulin molecules. The iodine is cleaved from them by a deiodinase, that makes virtually all this iodine available for recycling within the gland

Physiological effects of T3

- CVS- Increased HR, cardiac output, AF
- T3 up-regulates myosin Ca2+-ATPase activity- myocardial contractility and sensitivity to noradrenaline/ adrenaline- up-regulation of beta adrenoceptors
- Skeletal - increased bone turnover, bone resorption
- Respiratory - maintains hypoxic and hypercapnic drive in respiratory centre

Physiological effects of T3

- Blood - increase RBC 2,3-BPG facilitating oxygen release to tissues
- Neuromuscular - increases speed of muscle contraction and relaxation and muscle protein turnover
- Metabolism - increased oxygen consumption and heat production which increases the basal metabolic rate (BMR).

Physiological effects of hormones

- Increased hepatic gluconeogenesis/glycolysis and intestinal glucose absorption, increased lipolysis and cholesterol synthesis and degradation. This effect is an important response to living in a cold environment.

- 30-40% of the increased oxygen consumption is due to the stimulation of cardiac motility, Sympathetic nervous tissue - increases catecholamine sensitivity and beta-adrenergic receptor numbers in heart, skeletal muscle, adipose cells and lymphocytes.

Decreases cardiac alpha-adrenergic receptors.

A patient presents with hyperthyroidism. Which of the following interventions will mostly likely interrupt the greatest number of steps in thyroid hormone synthesis?

A. *B*-blocker
B. Steroid (i.e. dexamethasone)
C. Radiation
D. Surgery
E. Methimazole
F. Propylthiouracil
G. 131 Iodine

A patient is taking propylthiouracil for hyperthyroidism, which of the following will decrease first?

A. Thyroglobulin
B. Thyroid binding globulin
C. T3 & T4
D. Newly made T3 & T4
E. Size of the thyroid gland

Management of hyperthyroidism

- Block and replace/ Reducing regimen- CBZ/ PTU
- Radio Iodine
- Thyroid surgery
- Lugol’s Iodine

Management of Hyperthyroidism

- Timing of Surgery
- Management of hyperthyroidism in pregnancy
- Aetiology of hyperthyroidism in pregnancy

Case 2

- 45 year old lady presents with menorrhagia, lethargy and constipation for 4 months
- What further history would you like to know
- What examination findings would help guide management?

Case 2

- TSH- 6.7 mU/L (NR: 0.34- 3.45 mU/L), FT4- 12.5 (NR 11.2-21 pmol/L)
- What further investigations would help guide management
- What other Blood test should you consider?

Case 2

- Thyroxine replacement: what options do we have
- Should we always replace T3
- When would T3 replacement be beneficial?

Hypothyroidism

Primary hypothyroidism - 95% of all cases

- a. Hashimoto's disease - autoimmune destruction of the thyroid gland.
- Associated with anti-thyroglobulin & anti-microsomal antibodies
- b. Iatrogenic - radioiodine therapy, thyroidectomy, medications

. Secondary & tertiary hypothyroidism - less than 5% of all cases. Deficiency of TSH or TRH

Clinical Symptoms

1. Cretinism in infants
2. Bradycardia
3. Decreased deep tendon reflexes
4. Cold intolerance
5. Weight gain
6. Menorrhagia
7. Constipation
8. Slow mentation

Signs

1. Dry Skin
2. Coarse hair
3. Hoarse voice c c c
4. Nonpitting edema
5. Carpal tunnel syndrome
6. Goiter
7. Puffy features

Case 3

- Young female, 8 weeks pregnant; palpitations, weight loss, hyperemesis, fidgety
- Bloods: TSH- 0.12 mU/L (NR 0.34-3.45 mU/L), FT4- 21.2 (NR11.2-21 pmol/L)
- Next: 1) Monitor 2) B-blocker 3)Refer to endocrinology

Pregnancy

- Hyperthyroid picture in first trimester- physiological: HCG/ FSH/LH homology- guided by biochemistry
- Oestrogen effects in second and third trimester of pregnancy: binding proteins: Free T4/ Free T3, and pituitary response- guided by biology, only in patients on Thyroxine replacement
- On the whole Pituitary assay is most reliable, guided by TSH 99% of time

Treatment and references

1. Levothyroxine (T4), Triiodothyronine, and Armour thyroid
2. Sattar, H. (2011) *Fundamentals of Pathology*. Chicago, IL: Pathoma
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4. McCance, K. (2010) *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. Maryland Heights, MO: Mosby