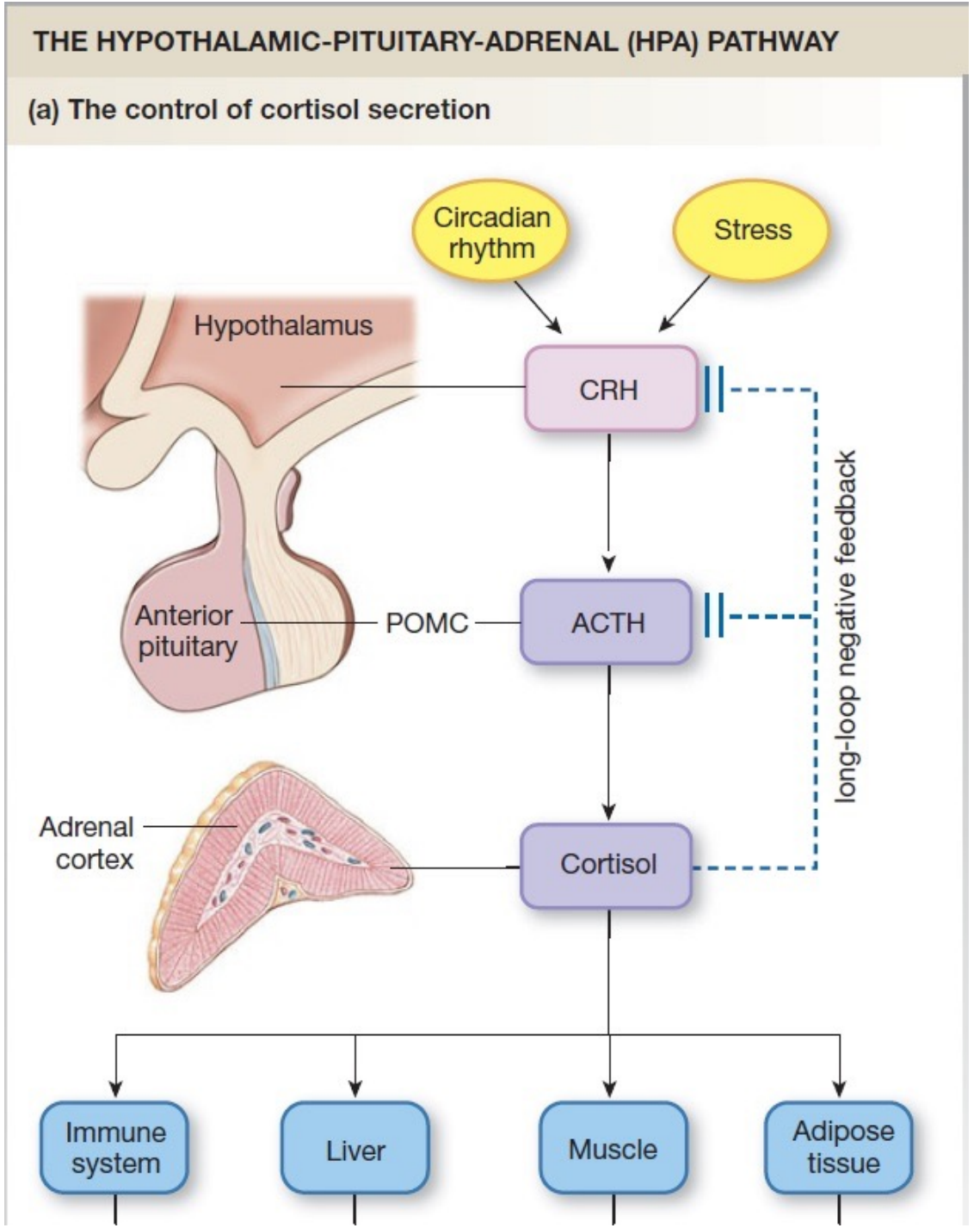
# Pathophysiology of the Endocrine System

# Pathophysiology of the Endocrine System

1. Introduction

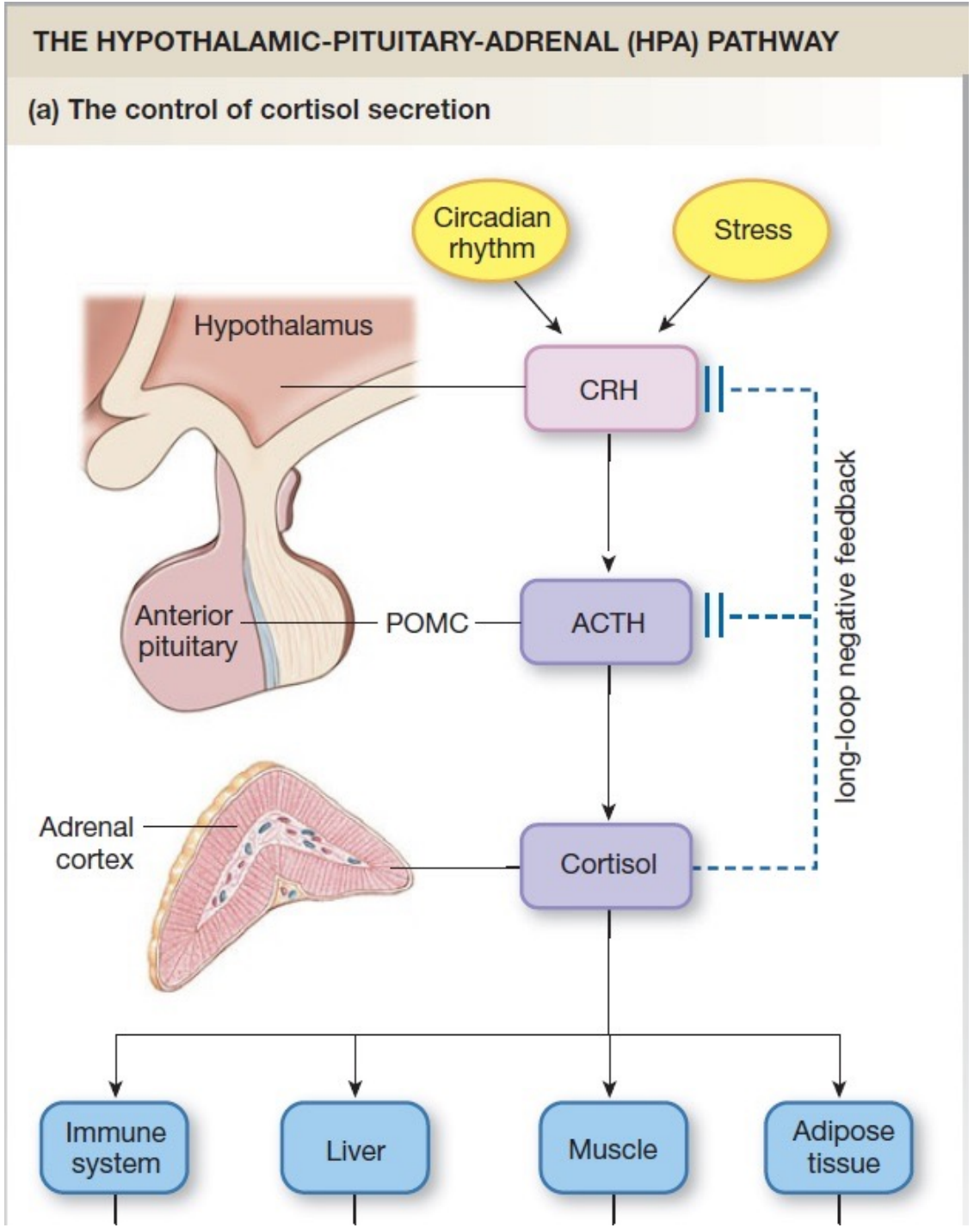
# Introduction

- Disorders are usually related to hyper or hyposecretion
- Disorders related to thyroid hormone, cortisol and growth hormone are usually due to changes in hypothalamic – pituitary axis
- Primary – damage is to the endocrine gland
- Secondary – damage is to the anterior pituitary or hypothalamus



# Introduction

- Etiology
  - Idiopathic / iatrogenic / neoplastic
  - Congenital / autoimmune / infectious
  - Lack of precursors? Age-dependent critical periods?
- Pathophysiology
  - Depends on the cause but hormone secretion is altered
- Clinical Manifestations
  - Usually an exaggeration of normal effects of a hormone system
  - Usually very predictable



# Pathophysiology of the Endocrine System

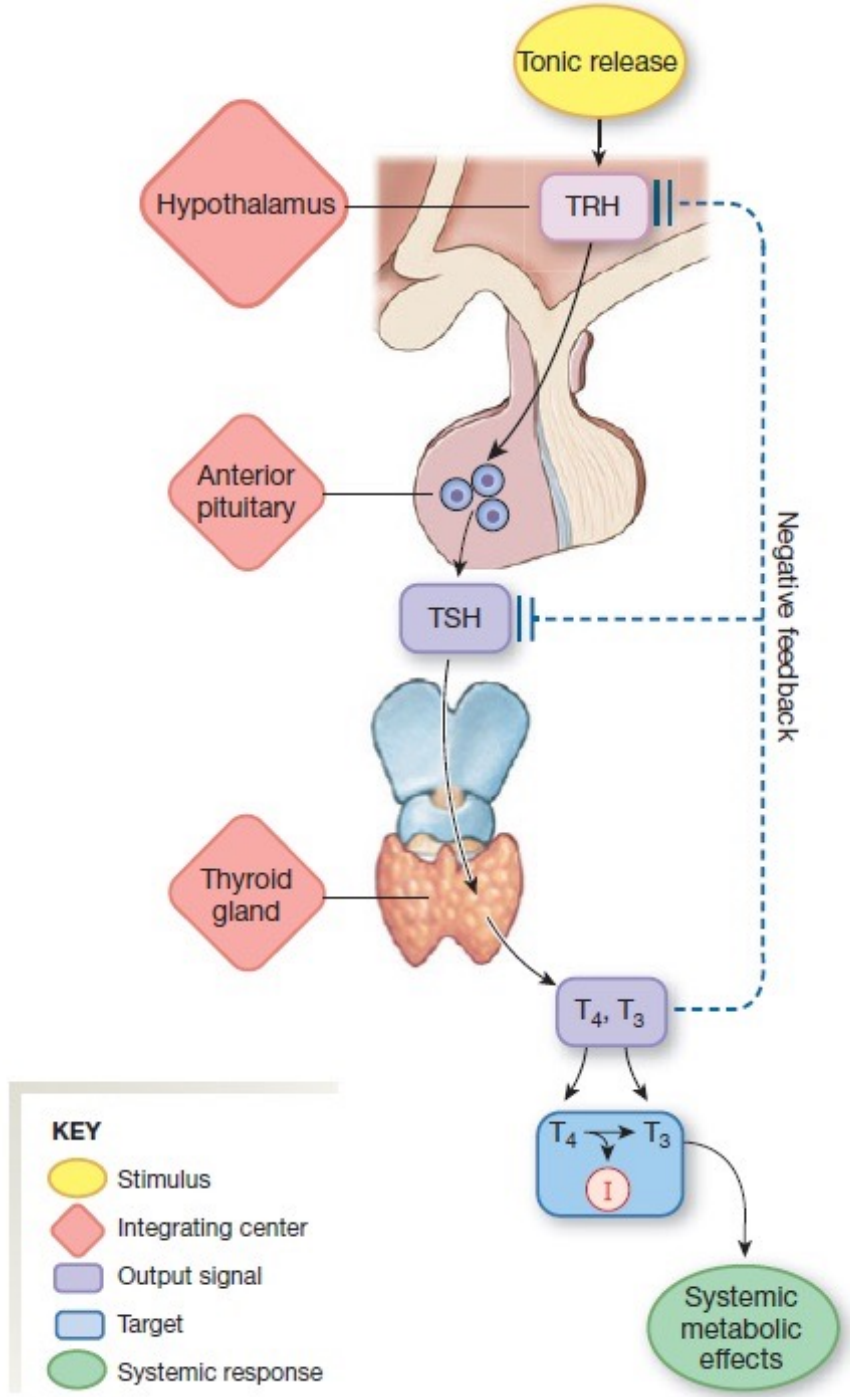
2. Disorders in the secretion of hormones of the thyroid gland

# Effects of T3 & T4

- Increase basal metabolic rate (BMR; consumption of O2 and energy to meet minimum requirements to survive)
- Increases protein synthesis and protein degradation
- Increases rate of glycogenolysis and gluconeogenesis
- Increases lipolysis
- Increases HR, FoC and cardiac output

- In neonate, essential for normal neurologic development (particularly myelin, axon development & neurotransmitter production)

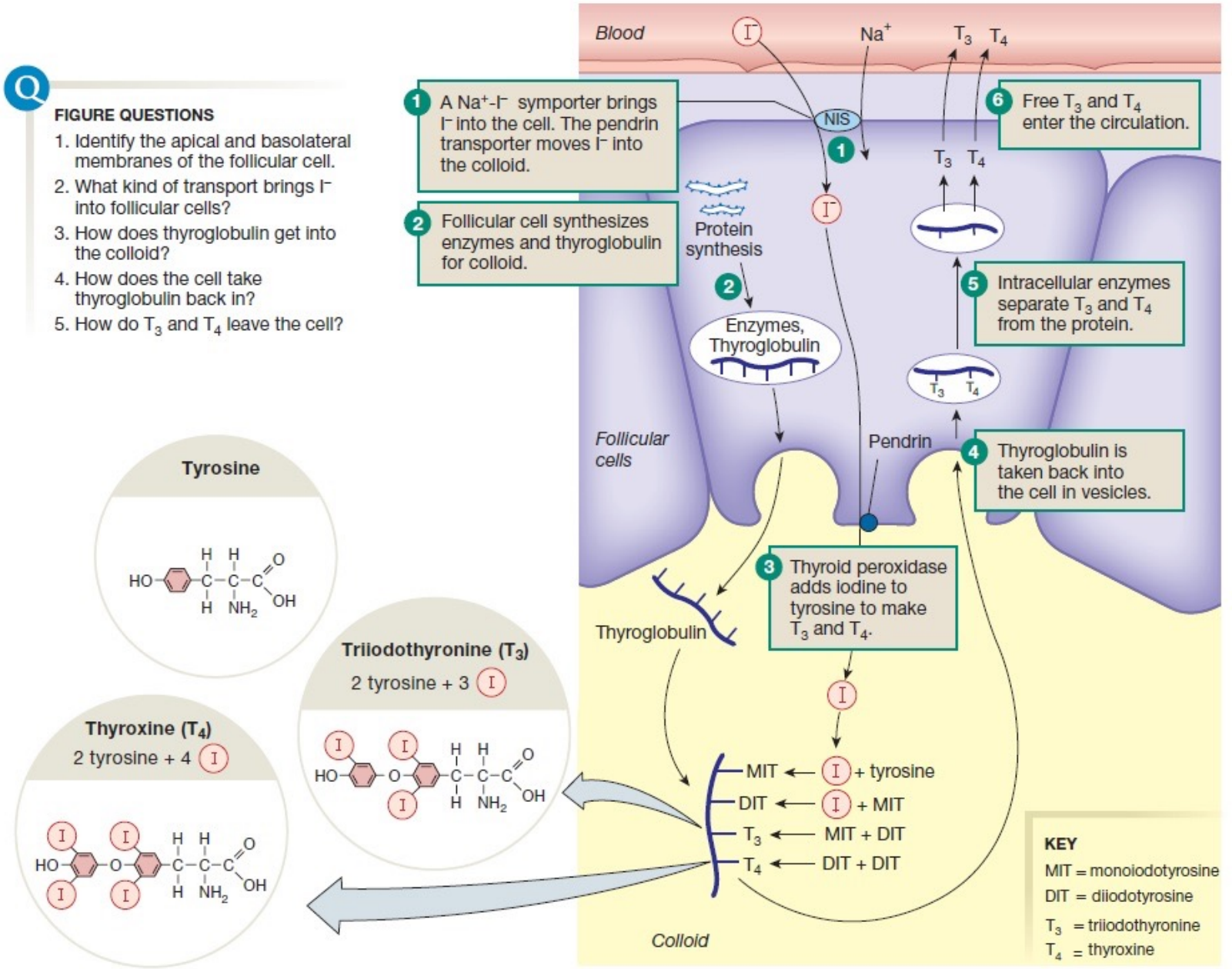
# Regulation of Secretion of T3 & T4




| Thyroid Hormones | |
|---|---|
| **Cell of origin** | Thyroid follicle cells |
| **Chemical nature** | Iodinated amine |
| **Biosynthesis** | From iodine and tyrosine. Formed and stored on thyroglobulin in follicle colloid. |
| **Transport in the circulation** | Bound to thyroxine-binding globulin and albumins |
| **Half-life** | 6-7 days for thyroxine ($T_4$); about 1 day for triiodothyronine ($T_3$) |
| **Factors affecting release** | Tonic release |
| **Control pathway** | TRH (hypothalamus) → TSH (anterior pituitary) → $T_3$ + $T_4$ (thyroid) → $T_4$ deiodinates in tissues to form more $T_3$ |
| **Target cells or tissues** | Most cells of the body |
| **Target receptor** | Nuclear receptor |
| **Whole body or tissue reaction** | ↑ Oxygen consumption (thermogenesis). Protein catabolism in adults but anabolism in children. Normal development of nervous system |
| **Action at cellular level** | Increases activity of metabolic enzymes and $Na^+$-$K^+$-ATPase |
| **Action at molecular level** | Production of new enzymes |
| **Feedback regulation** | $T_3$ has negative feedback on anterior pituitary and hypothalamus. |

# Hypothyroidism – Etiology

- Congenital – thyroid dysgenesis
- Lack of precursors – non-iodinated salt
- Receptors on thyroid gland (TSH receptors) are insensitive to TSH
- Surgical removal / irradiation due to cancer



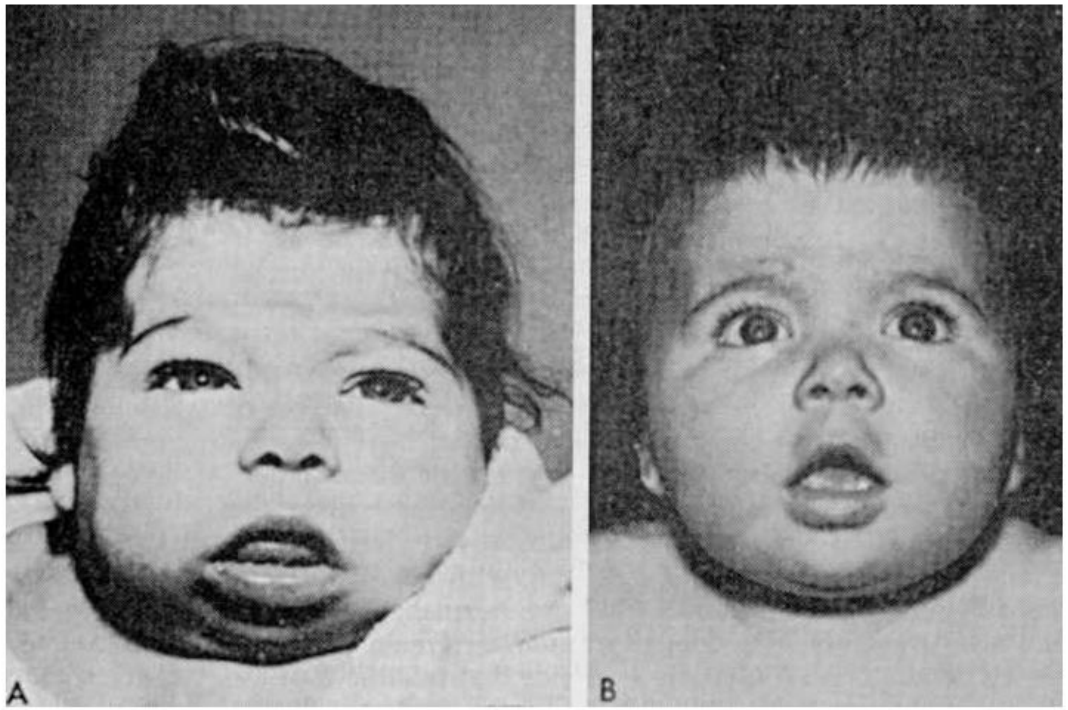
# Generalized Clinical Manifestations of Hypothyroidism

- Decreased basal metabolic rate (BMR)
- Bradycardia, decreased blood pressure
- Weight gain despite decreased appetite
- Hyperlipidemia
- Constipation
- Cold intolerance; difficulty staying warm
- Lethargy / feeling of weakness
- Difficulty with memory & concentration; mentally slow
- Decreased T3 / T4 (if $1^{o}$) but increased TSH & TRH – why?

# Hypothyroidism During Early Development

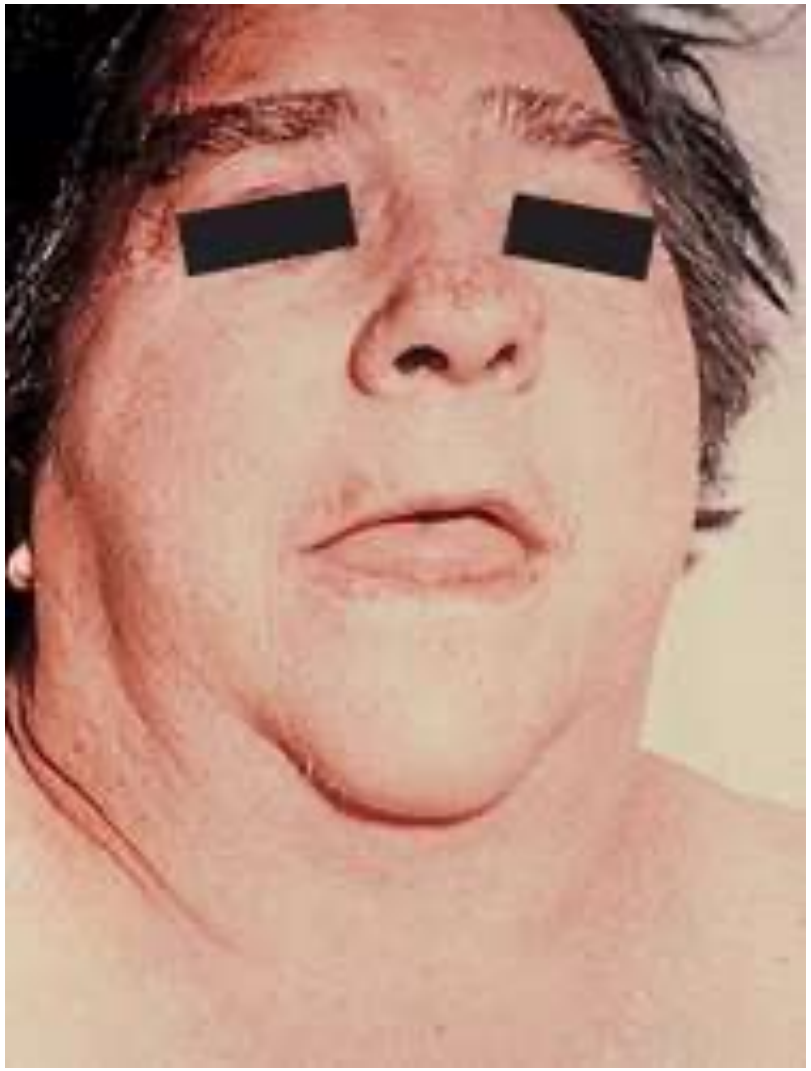
- T3 /T4 are critical for proper neurological development
- Cretinism
  - Signs appear at about 1 month of age
  - Thickened tongue & lips
  - Bradycardia
  - Poor muscle tone
  - Neonatal jaundice
  - Neurological delays
  - Irreversible damage if not treated
  - Managed with supplemental T3 /T4

**6 MONTHS OLD BOY with CRETINISM & 4 MONTHS AFTER TREATMENT STARTED**



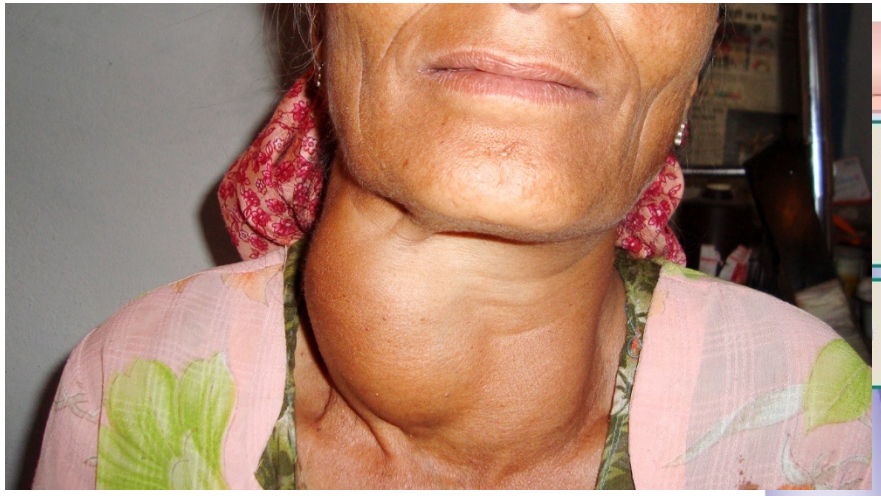
# Hypothyroidism During Adulthood

- Myxedema (if not managed)
  - Prolonged lack of T3 / T4
  - Generalized non-pitting edema
  - Altered mental state; slow; flat
  - Cold intolerance / difficulty with maintaining body temperature
  - Managed with T3 / T4 supplements



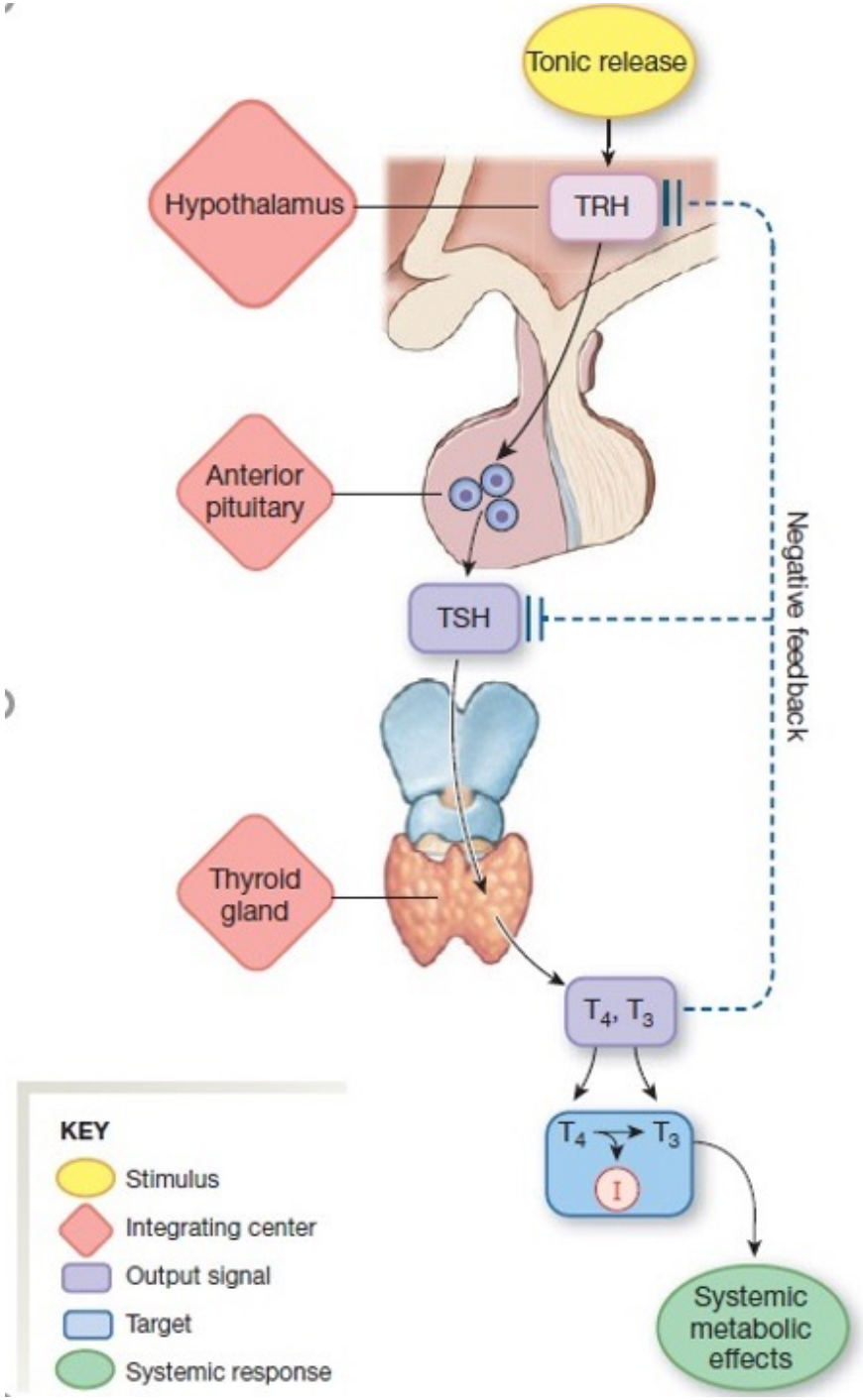
# Hypothyroidism – lack of iodine

- Goiter develops
- TSH stimulates thyroid to produce T3 / T4
- No iodine so no T3 / T4 but thyroglobulin continues to be produced and enter colloid
- No T3/T4 thus TSH remains hgh
- Managed by adding iodide to the diet



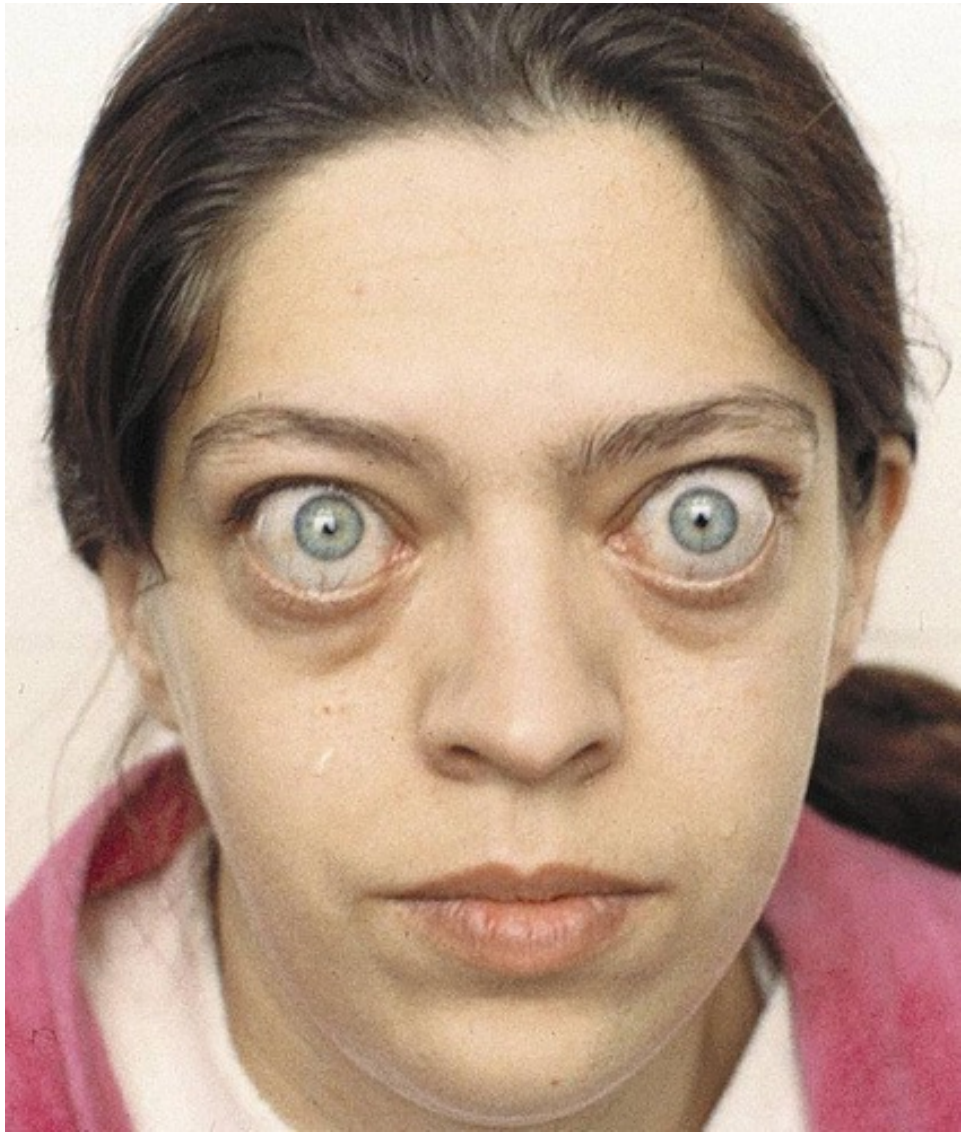
# Hyperthyroidism – Etiology

- Primary
  - Graves Disease
    - Antibody is produced that stimulates TSH receptors on follicular cells stimulating them to produce more T3 / T4
  - Thyroid gland tumour
- Secondary
  - Usually related to tumour of the anterior pituitary gland
  - How will this affect secretion of TRH & TSH?



# Hyperthyroidism – General Clinical Manifestations

- Increased basal metabolic rate (BMR)
- Increased sympathetic nervous system activity
  - Tachycardia, diaphoresis
- Restlessness, insomnia, “spun”, hand tremors
- Weight loss despite increased appetite / N, V, D
- Heat intolerance
- Amenorrhea in females
- Thyromegaly – due to constant production of T3 / T4
- Exopthalmos
- High T3 / T4; primary → almost no TRH, TSH – why?



# Hyperthyroidism – Treatment

- Depends on the cause
- General
  - Beta blockers to address SNS related clinical manifestations
  - Drugs that inhibit T3 /T4 production
  - Removal of gland + T3 / T4 replacement therapy
  - Radioactive I-
- Secondary tumour
  - Removal of anterior pituitary

# Pathophysiology of the Endocrine System

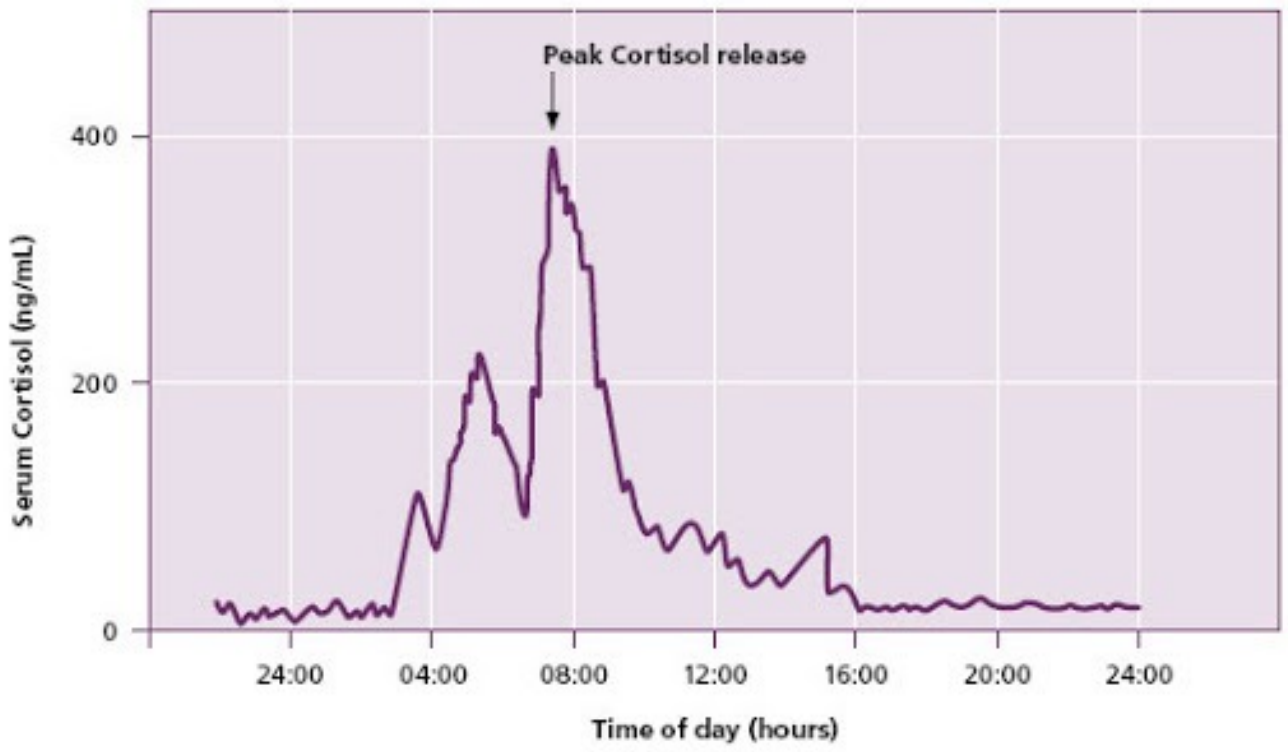
3. Disorders in the secretion of hormones by the adrenal cortex

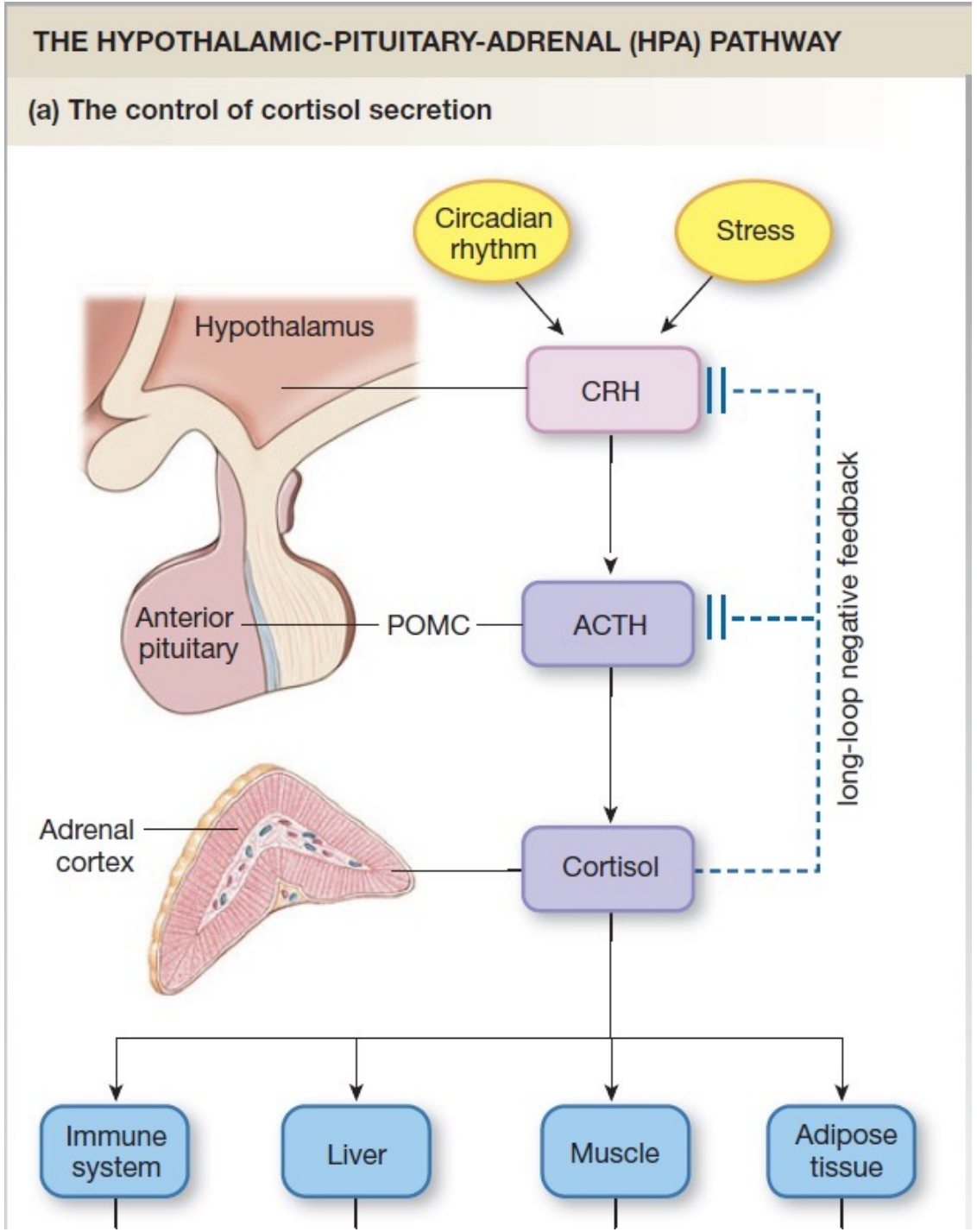
# Glucocorticoid – Cortisol

- What does it do?
  - Increases blood glucose, AA and FA by altering metabolism of fats and proteins
  - Gluconeogenesis ← RELEVANT
  - Vasoconstriction (increases BP)
  - Anti-inflammatory
  - Stress hormone

# Regulation Mechanisms

- Hypothalamic pituitary axis
- Circadian rhythms
- Stress



# Hypocortisolemia

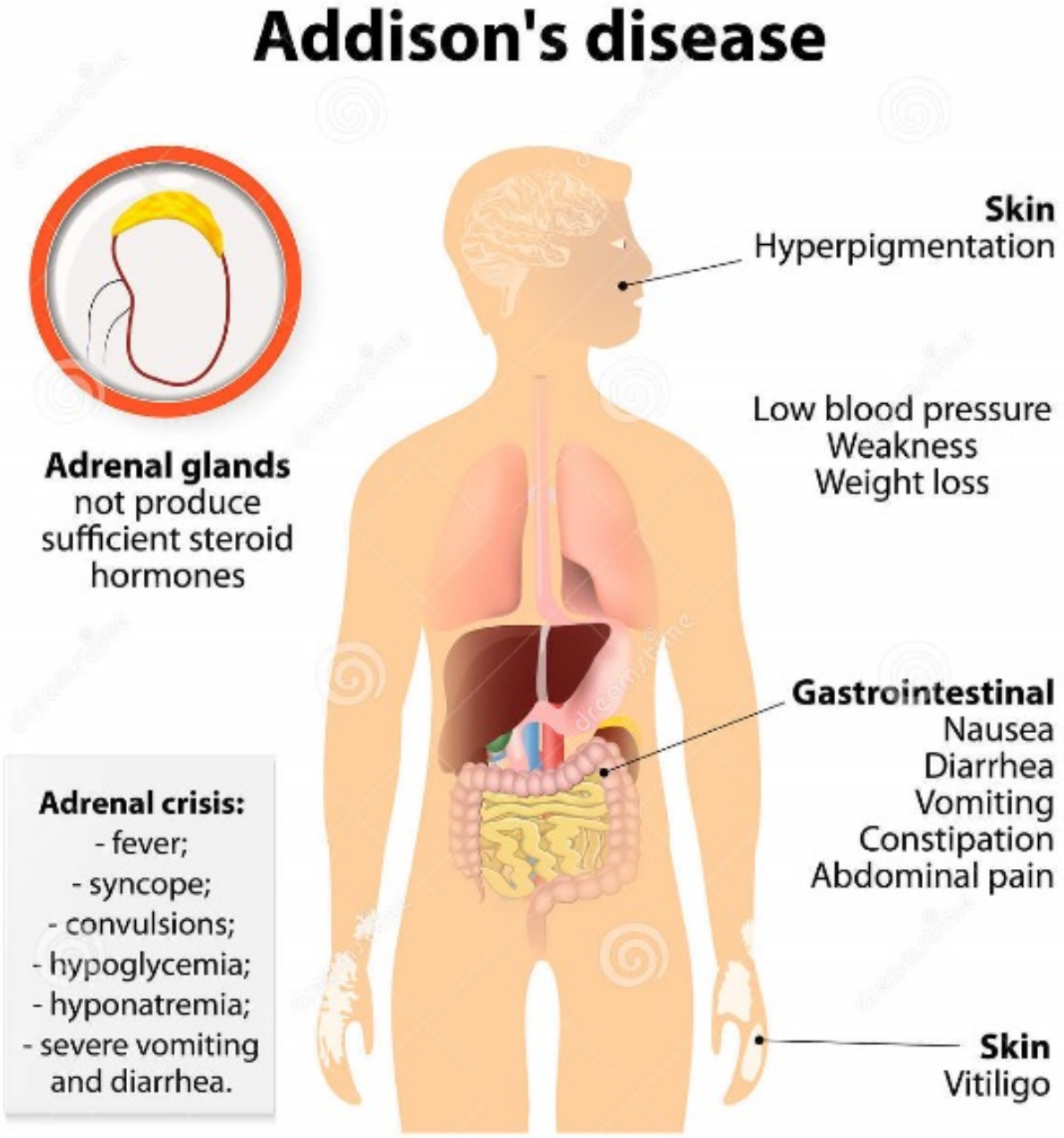
Caused by healthcare

- Etiology
  - Primary – Addison's disease – decreased production of cortisol and aldosterone
  - Secondary – due to reduced output of anterior pituitary (decreased ACTH)
  - Iatrogenic – prolonged exogenous cortisol or related steroid
- Pathophysiology (Addison's disease) / Clinical Manifestations
  - Too little aldosterone
    - Hyponatremia and hypovolemia
    - Hyperkalemia
  - Too little cortisol Adrenal Crisis/Addisonian Crisis
    - Decreased blood glucose
    - GI – N V D C
    - Increased pigmentation of skin – related to increased ACTH (POMC precursor) – but can sometimes lead to vitiligo (autoimmune Addison's disease)

and hypoglycemia

# Addison's Disease - Treatment

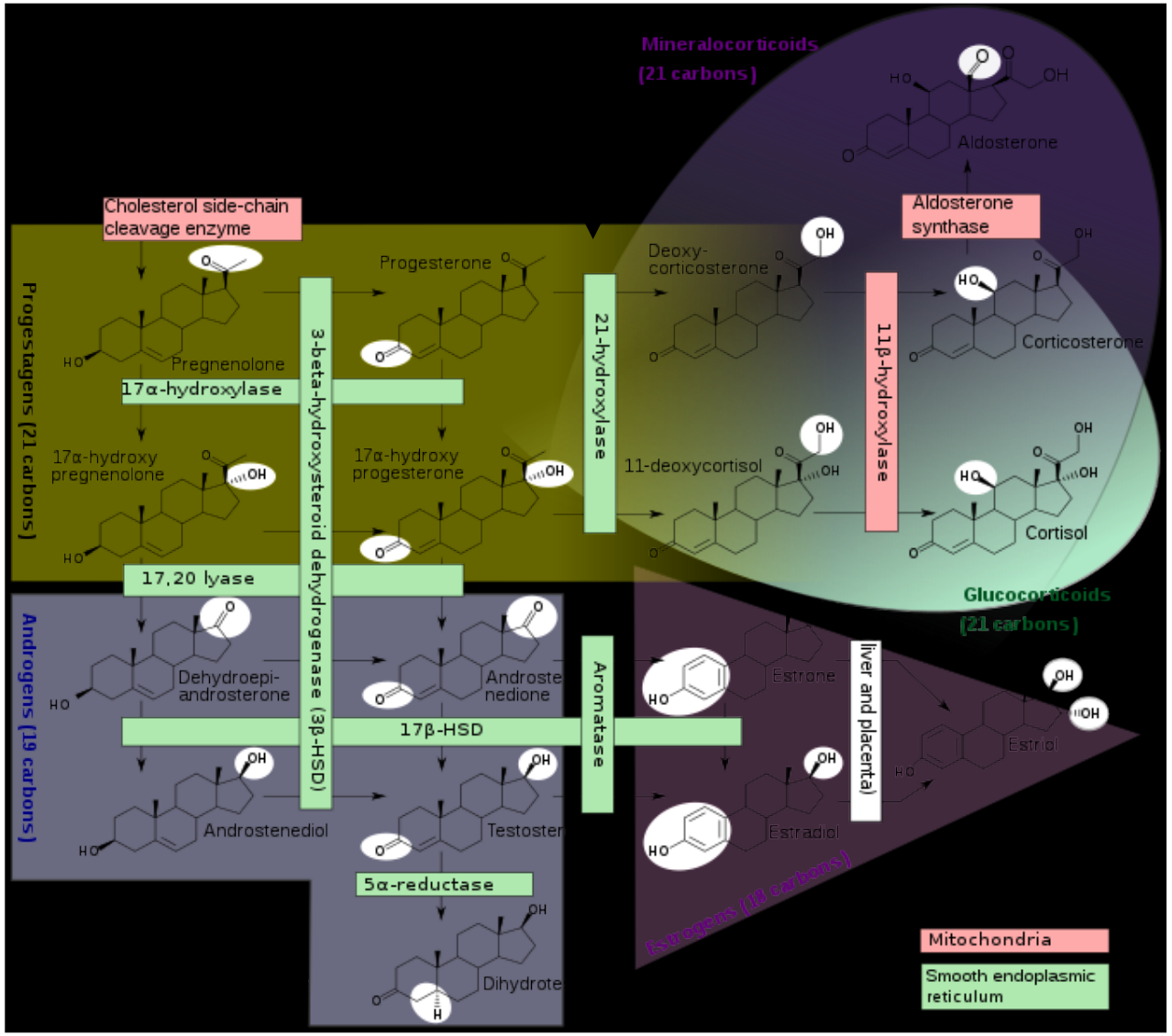
- Hormone replacement therapy with aldosterone and cortisol as required




https://healedbybacon.files.wordpress.com/2015/11/addisons.png?w=607&h=661

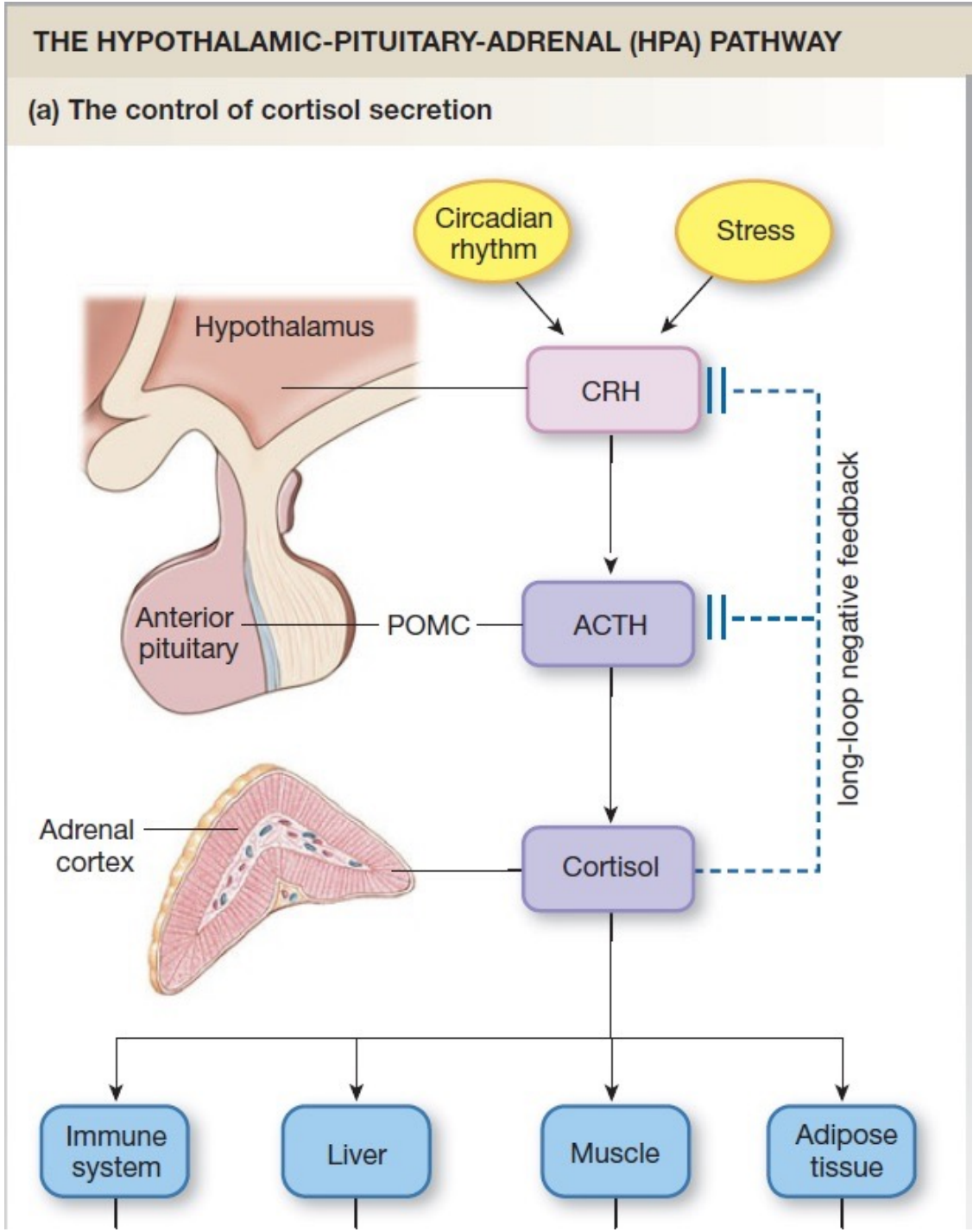
# Congenital Adrenal Hyperplasia (Adrenogenital Syndrome)

- Etiology
  - Autosomal recessive condition; can't produce 21-hydroxylase, an enzyme necessary for the production of cortisol
- Pathophysiology
  - Causes increase production of androgens
  - Lack of cortisol → ↑ CRH & ACTH
- Clinical Manifestations
  - Virilization of females; enhanced maleness
- Treatment
  - Replacement therapy with cortisol



# Cushing's Syndrome / Disease

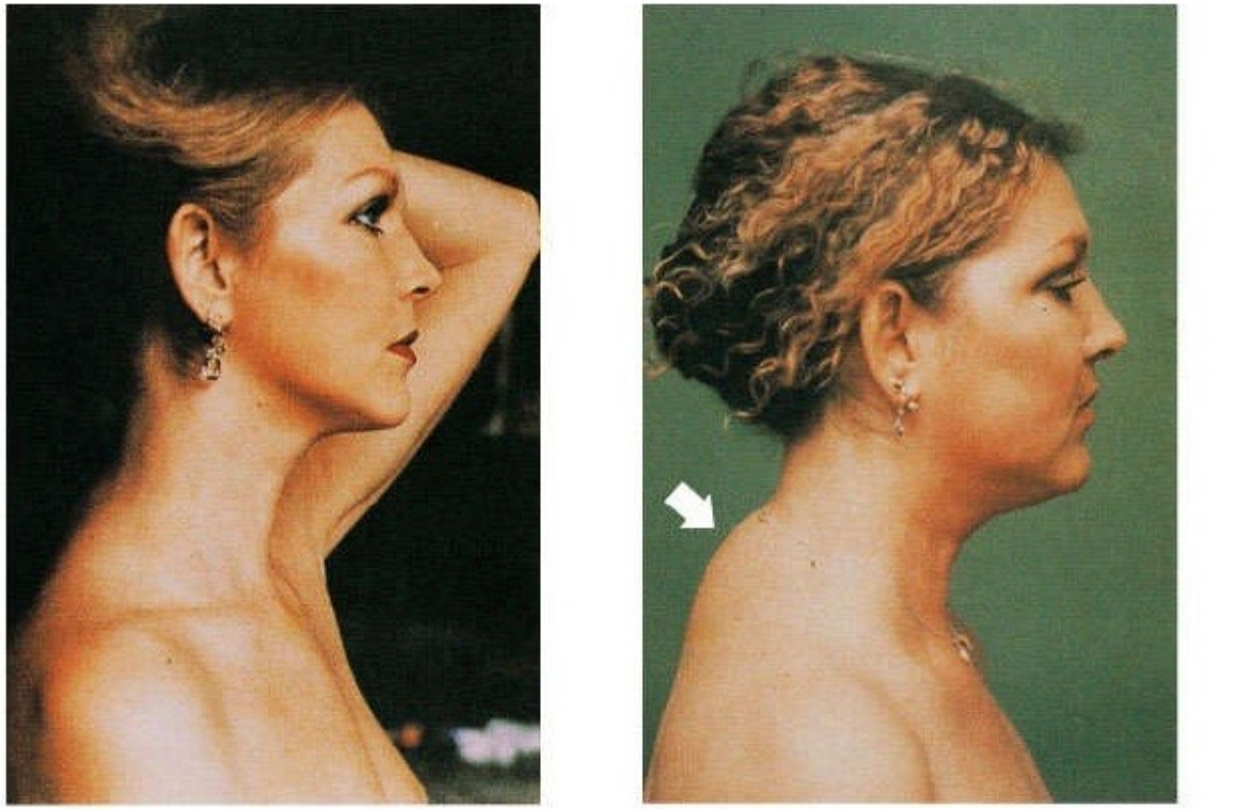
- Etiology
  - Disease – primary or secondary → increased cortisol secretion; onset around age 40 depending on cause
  - Syndrome – iatrogenic
- Pathophysiology
  - In either case, hypercortisolemia can impact secretion of CRH and ACTH
  - Cushing's syndrome can sometimes completely stop endogenous production of CRH and ACTH
    - Pattern of delivery is usually on for a short period of time and then off for a period of time



# Cushing's

- Clinical Manifestations
  - Fat depositions – buffalo hump, moon face, abdomen, weight gain
  - Decreased muscle mass; muscle weakness
  - Bone demineralization
  - Aldosterone –like effects
  - Increased production of androgens
  - Hyperglycemia (loss of sensitivity to insulin
  - Poor concentration and memory
- Treatment
  - Reduce exogenous
  - Deal with primary problem

Before and after onset of Cushing's disease

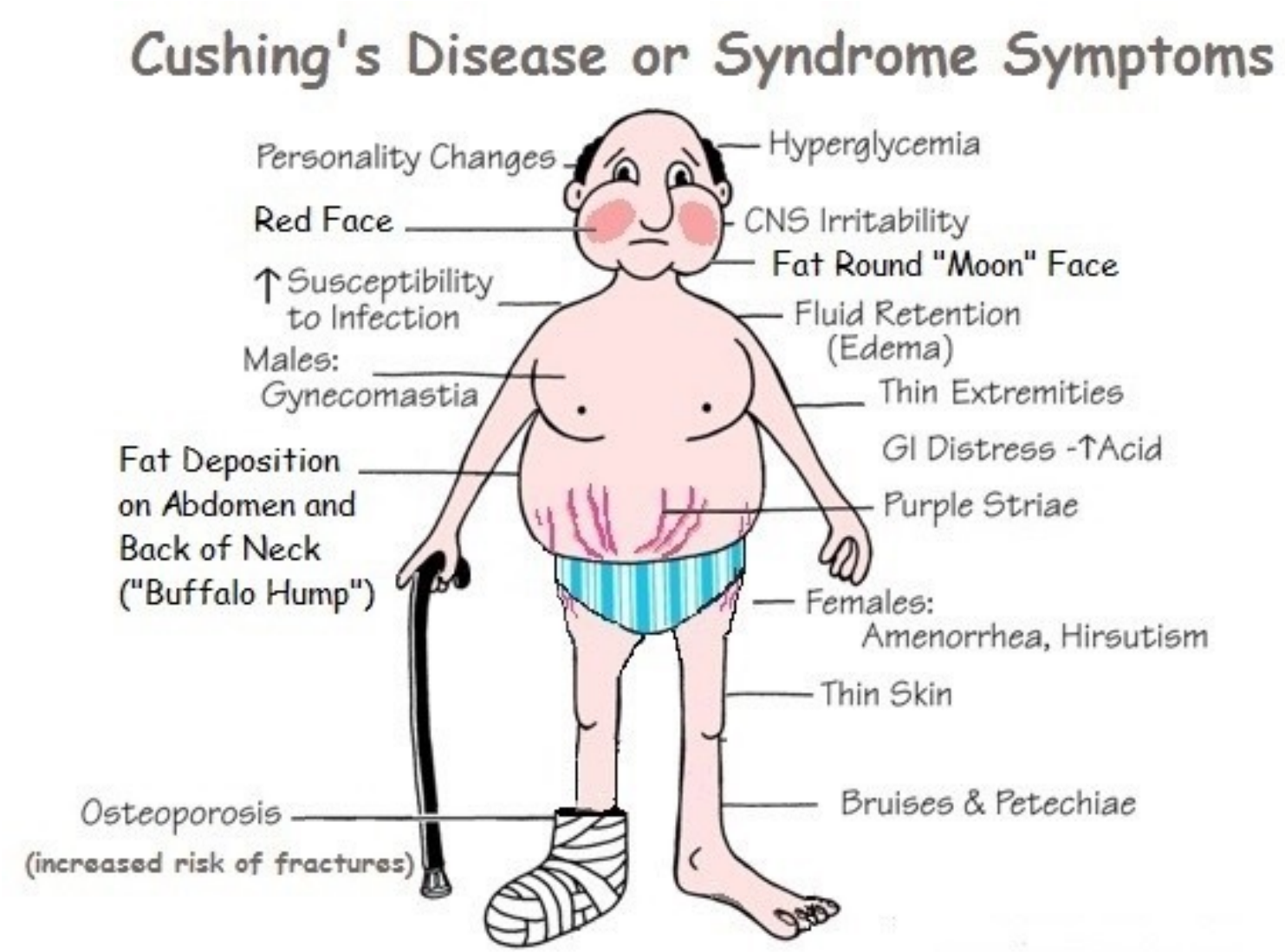


(a) Before (b) After



https://www.google.ca/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwje5dTc9o3fAhVEnuAKHUm1ByUQjRx6BAgBEAU&url=http%3A%2F%2Fbulk.medicalcertificate.me%2Fcjc-1295%2F02190-moon-face-steroids.html&psig=AOvVaw0gA7X00ShwMaTMk418KHWB&ust=1544279088928398

# Cushing's



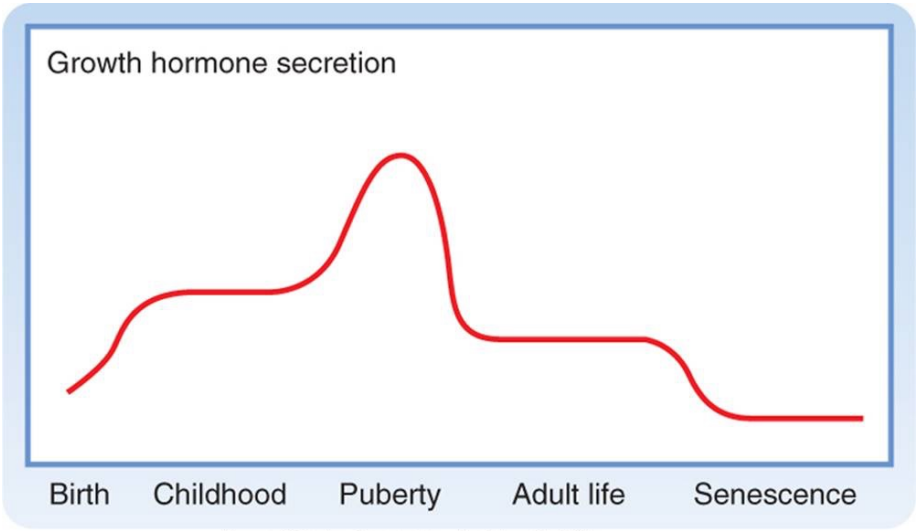

https://www.google.ca/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=2ahUKEwjZqdX-9o3fAhXhTN8KHfVKAJIQjRx6BAgBEAU&url=https%3A%2F%2Fwww.quora.com%2FWhat-is-Cushing-syndrome&psig=AOvVaw0gA7X00ShwMaTMk418KHWB&ust=1544279088928398

# Pathophysiology of the Endocrine System

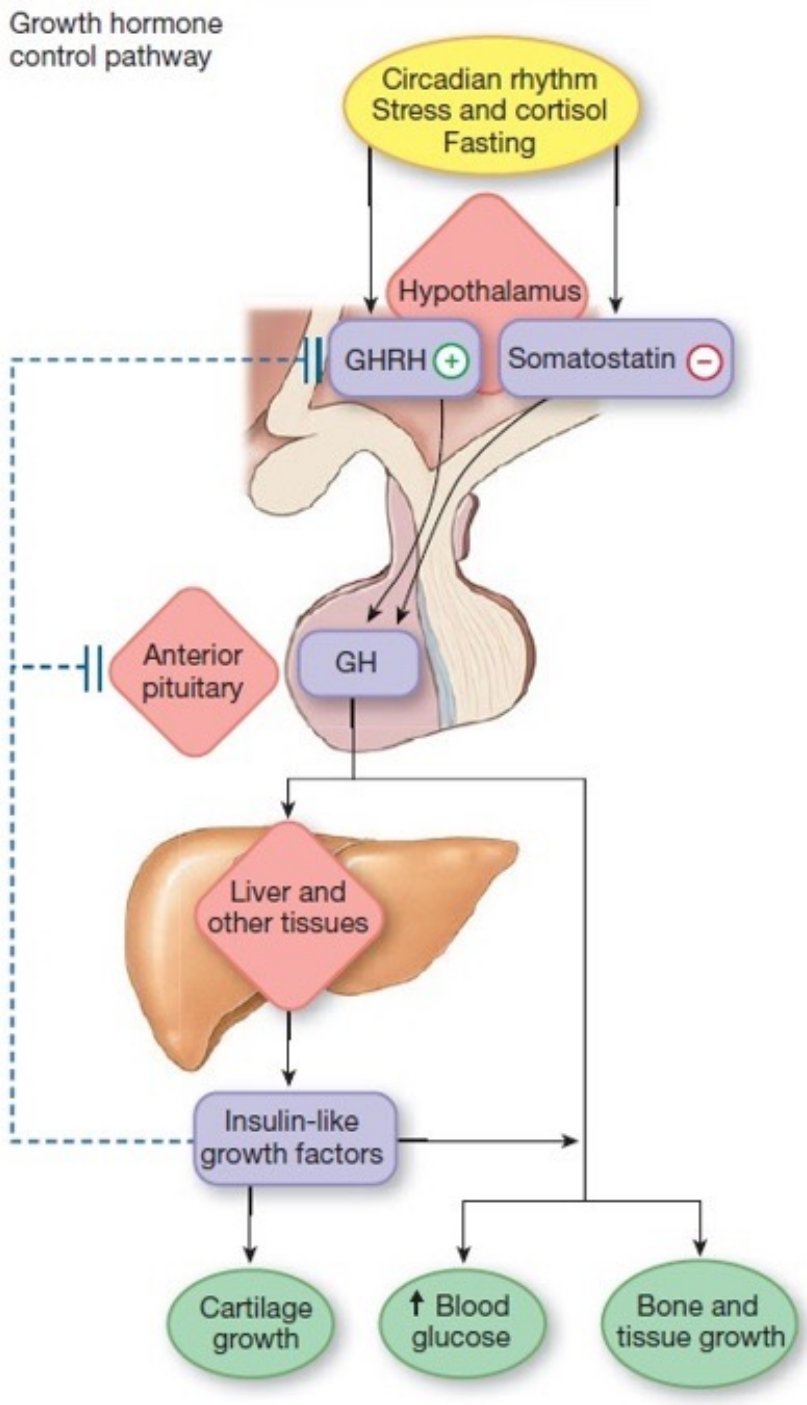
4. Disorders in the secretion of growth hormone

# Growth Hormone

- Growth Hormone is produced by anterior pituitary
- GHRH promotes secretion; IGF negative feedback to anterior pituitary and hypothalamus reduces GH and GHRH secretion
- Somatostatin reduces secretion of GH
- GH can act directly on target tissues promoting bone and tissue growth or indirectly through IGF to also promote cartilage growth







# Hyposecretion of GH

- Etiology
  - Usually a congenital condition but can be acquired
- Pathophysiology
  - Lack of GH production; GH receptors don't respond; lack of IGF production
- Clinical Manifestations
  - Normal birthweight / length
  - Reduced growth of long bones; normal proportions
  - Shorter axial skeleton; poor joint mobility
  - Hypoglycemia
  - Increased fat mass, decreased muscle mass
- Treatment – hormone replacement

# Hypersecretion of GH

- Gigantism
  - Etiology
    - Pituitary gland tumour (benign) before epiphyseal plates stop growth
  - Pathophysiology
    - Increased GH & IGF secretion → increased bone growth and cartilage increased
  - Clinical Manifestations
    - Extremely tall individuals
    - Delayed puberty
    - Excessive bone deposition in face and hands
    - Cardiomegaly and CV disorders
  - Treatment
    - Removal of tumour

# Hypersecretion of GH

- Acromegaly
  - Etiology
    - Pituitary gland tumour (benign) after epiphyseal plates stop growth; onset between age 20 and 40
  - Pathophysiology
    - Increased GH & IGF secretion → increased bone growth and cartilage increased
  - Clinical Manifestations
    - Excessive bone deposition in face and hands
    - Overgrowth of mandible → underbite
    - Arthritis, peripheral neuropathies
    - Cardiomegaly and CV disorders
  - Treatment
    - Removal of tumour