Review of Endocrinology

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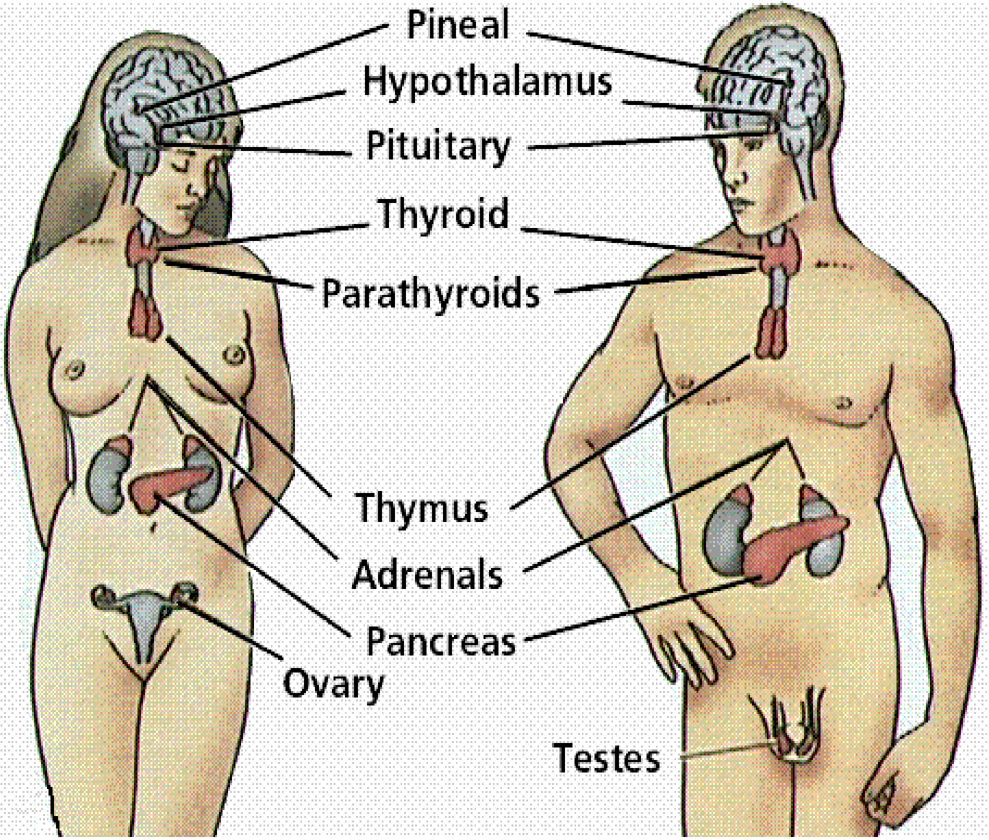
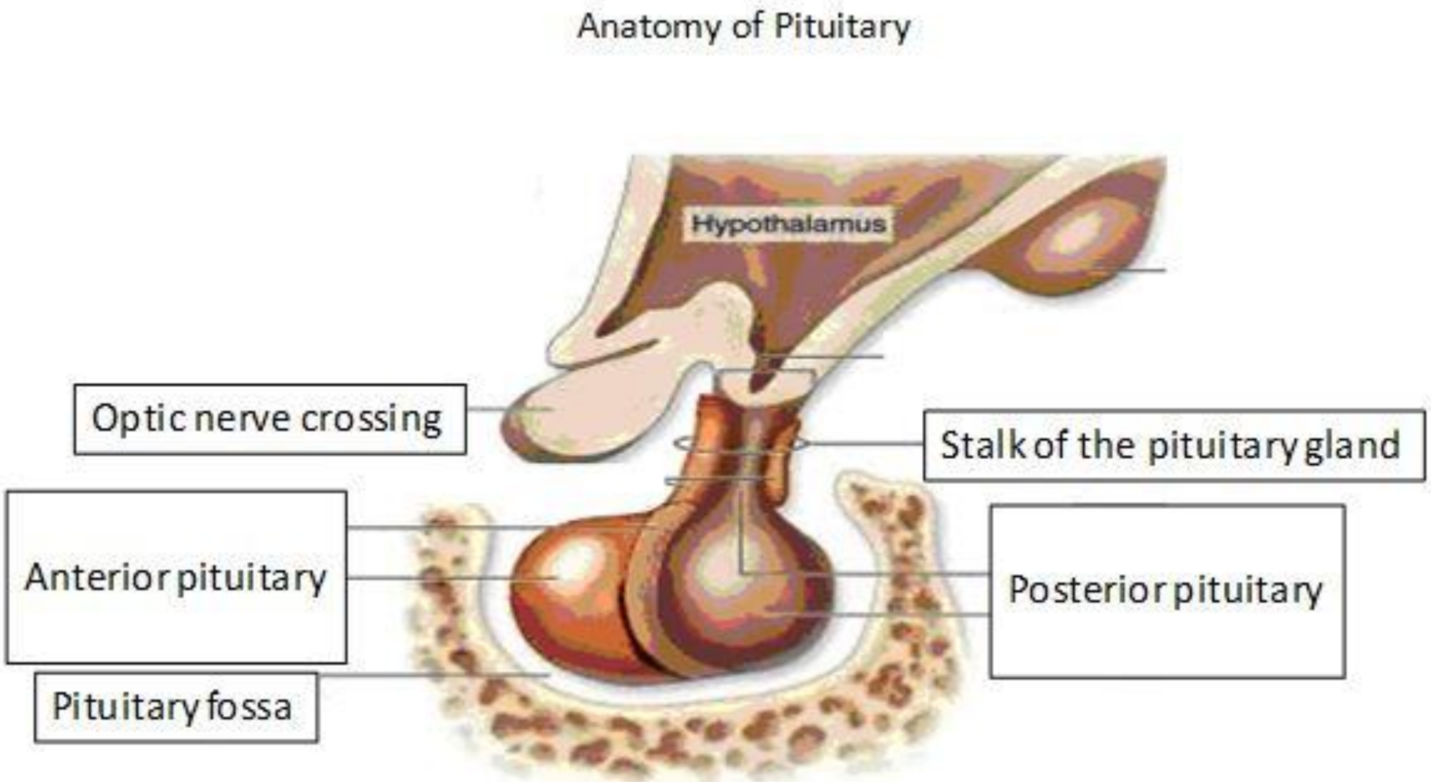


The pituitary gland



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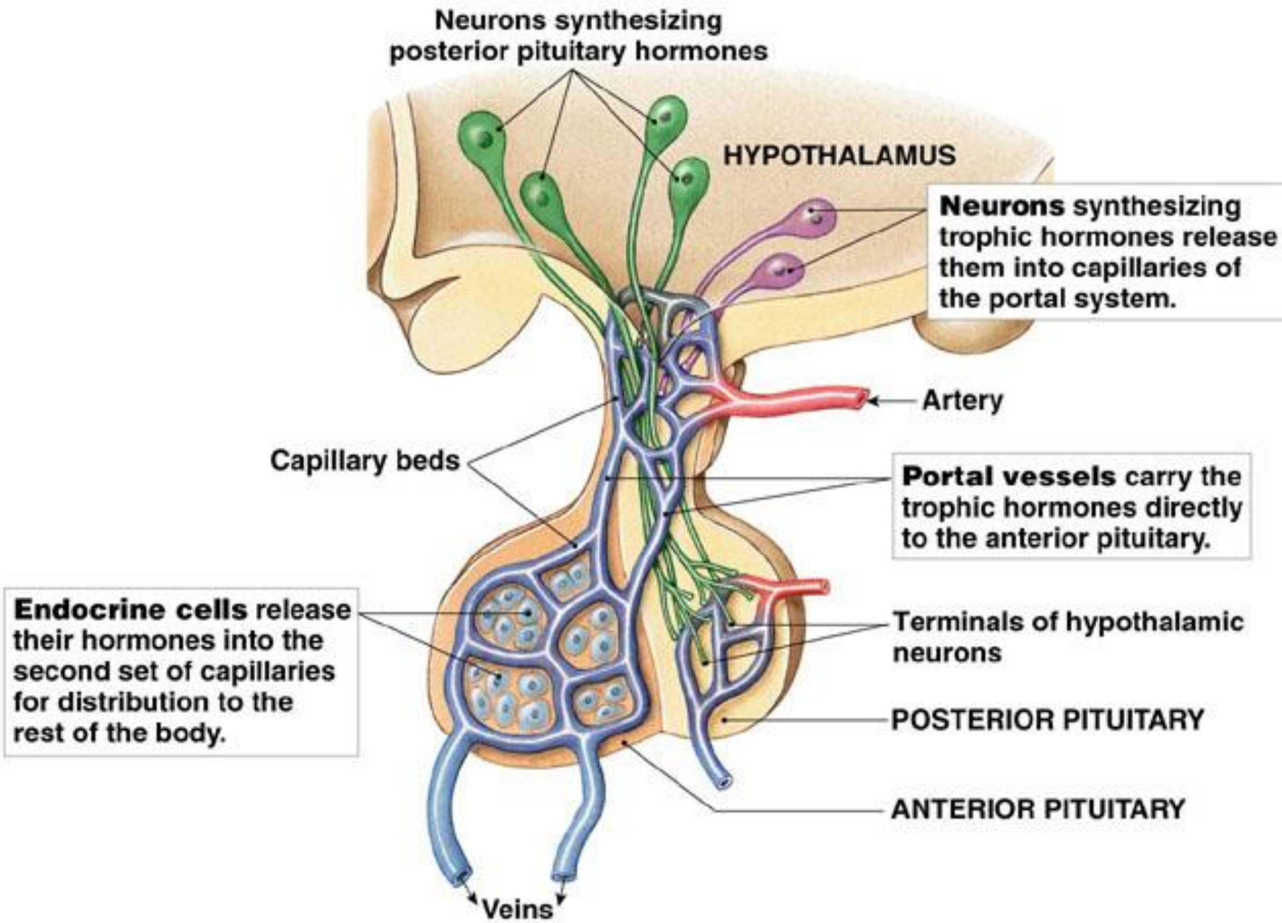


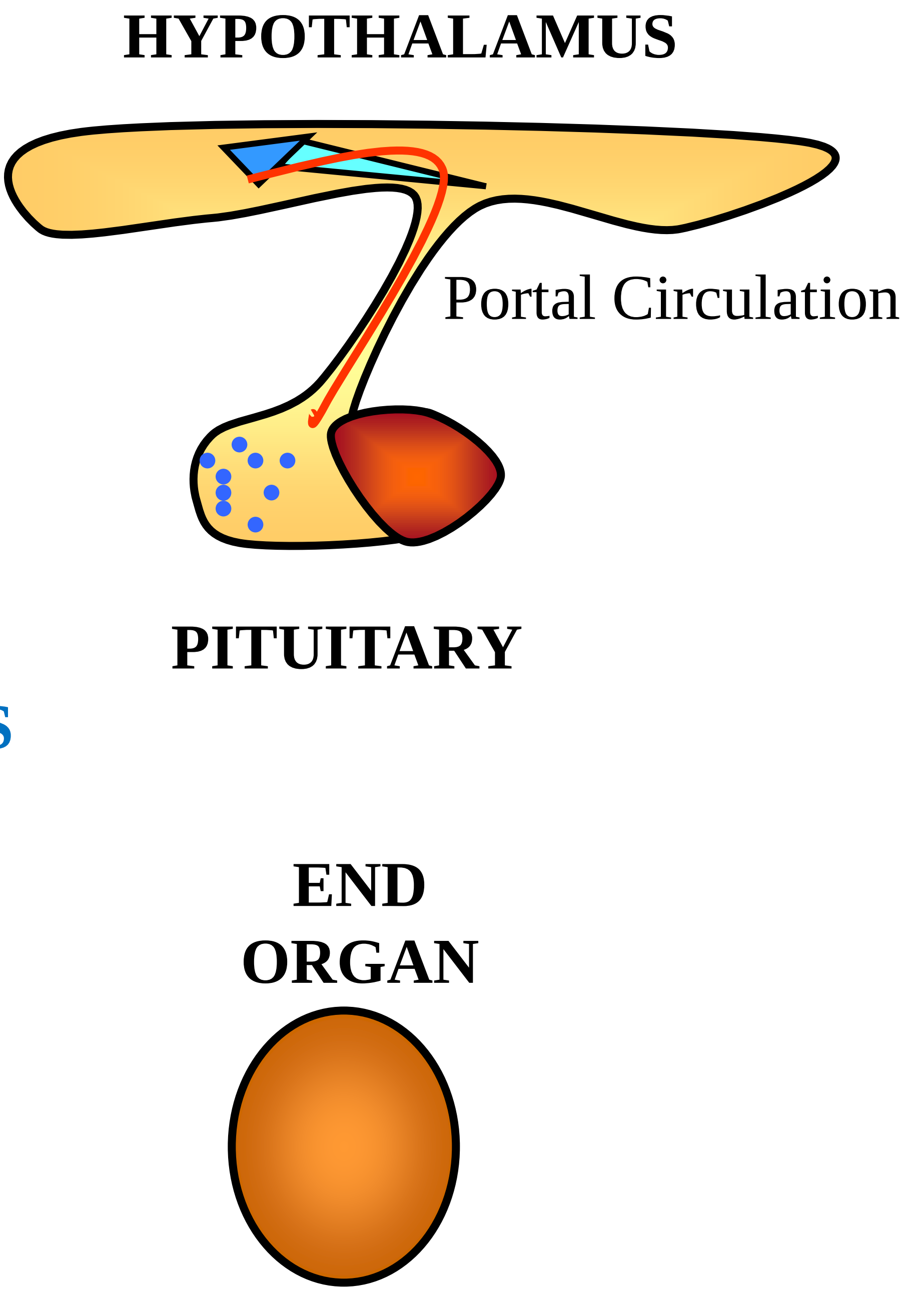
Nomenclature of Anterior Pituitary and Hypothalamic Hormones

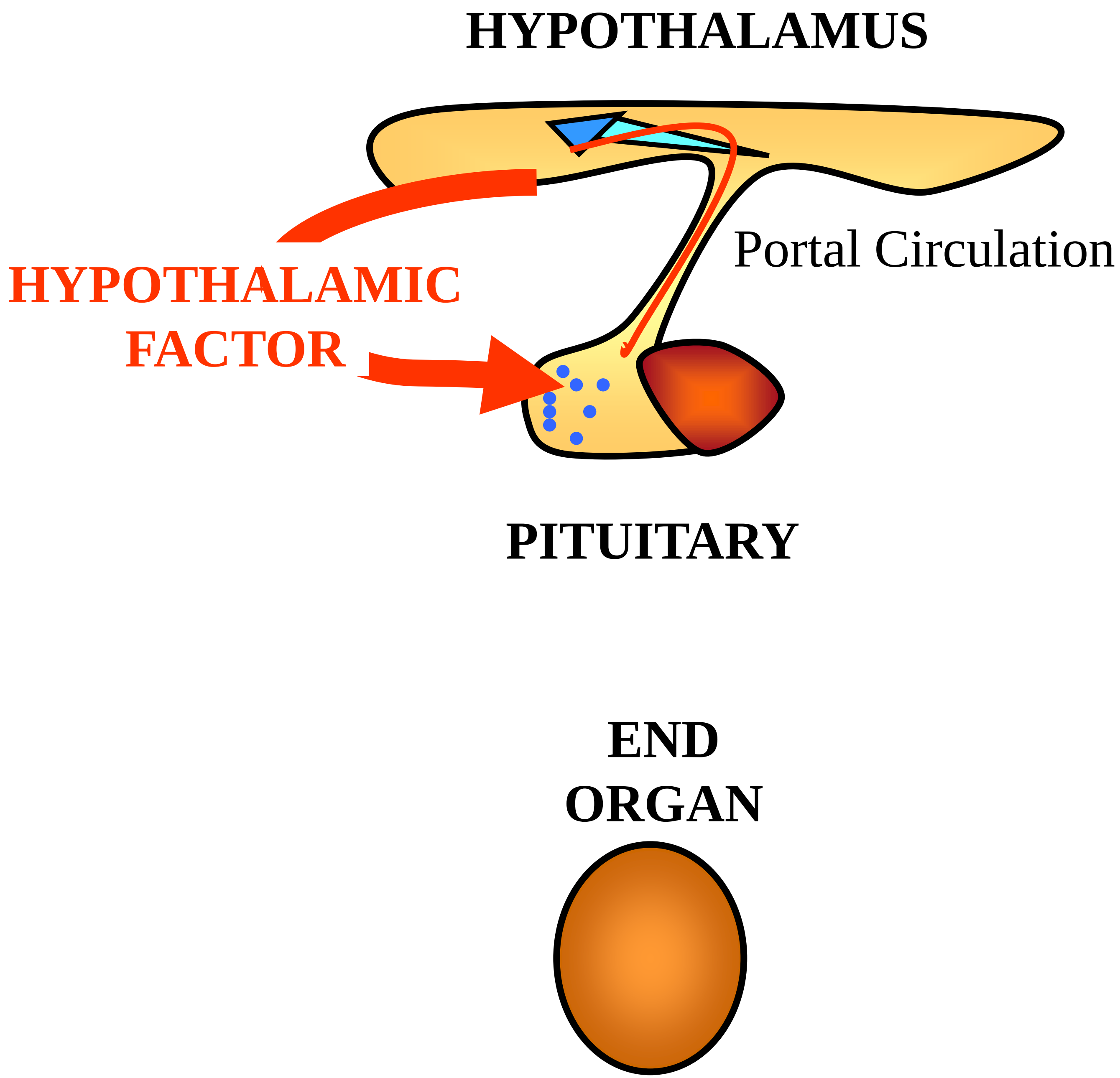
• LH, FSH	Gonadotrophins	Gonadotrophin Releasing Hormone
• GH	Somatotrophin	Growth Hormone Releasing Hormone Somatostatin
• TSH	Thyrotrophin	Thyrotrophin Releasing Hormone
• ACTH	Corticotrophin	Corticotrophin Releasing Hormone
• PRL	Lactotrophin	Dopamine

HYPOTHALAMIC

PITUITARY

END ORGAN AXIS

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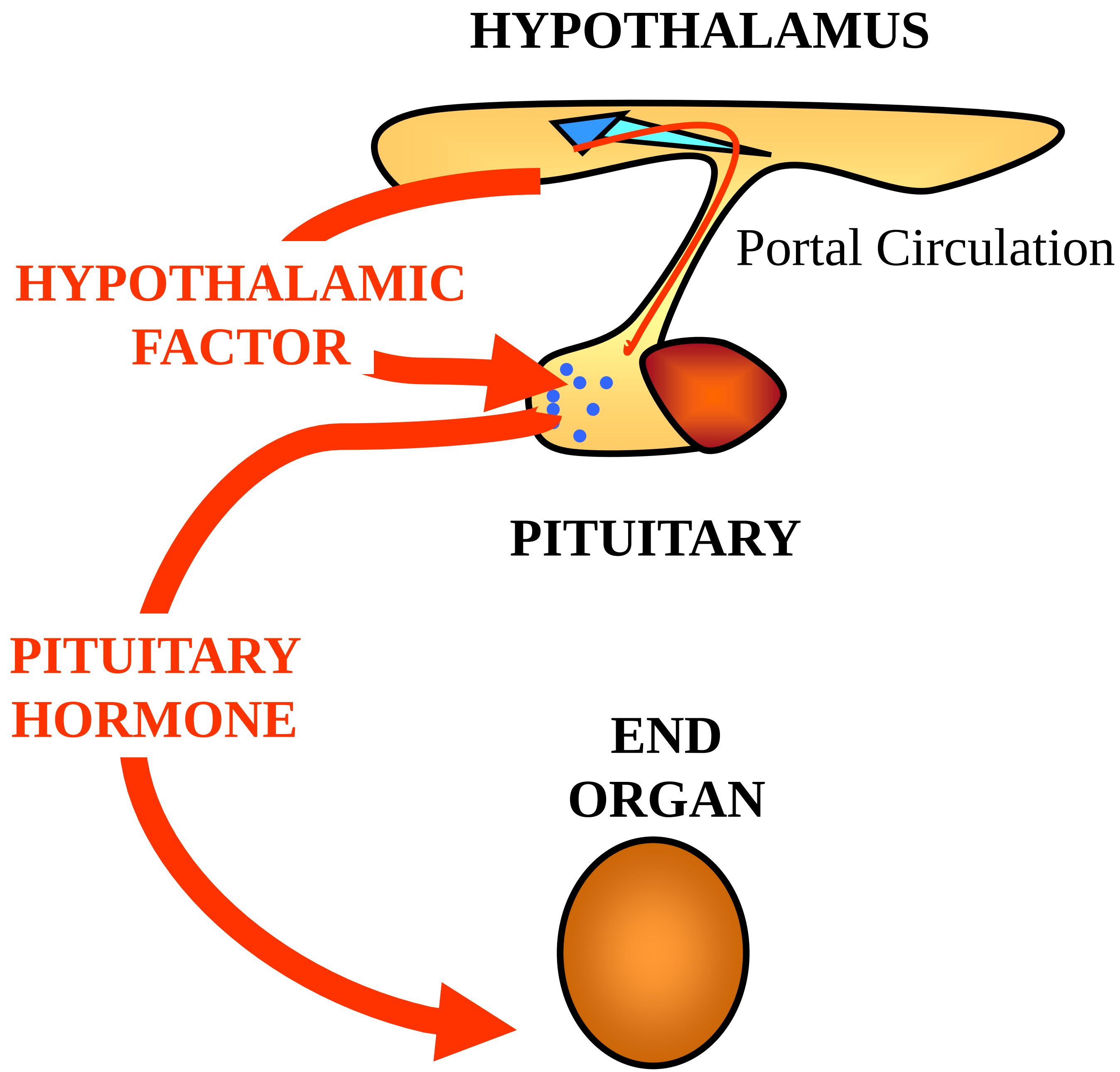
Portal Circulation
HYPOTHALAMIC
FACTOR
PITUITARY
END
ORGAN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PITUITARY
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HORMONE
END
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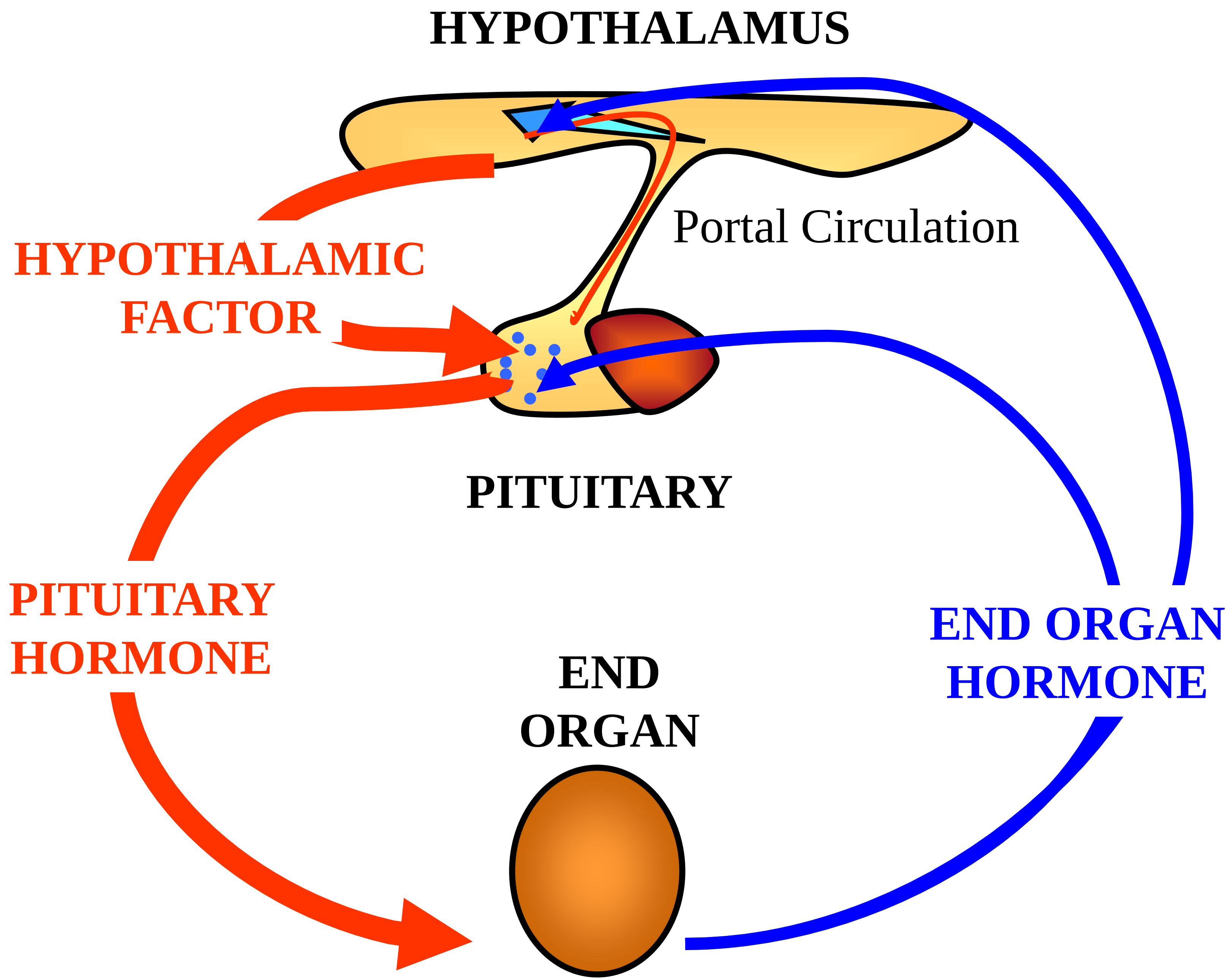
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FACTOR
PITUITARY
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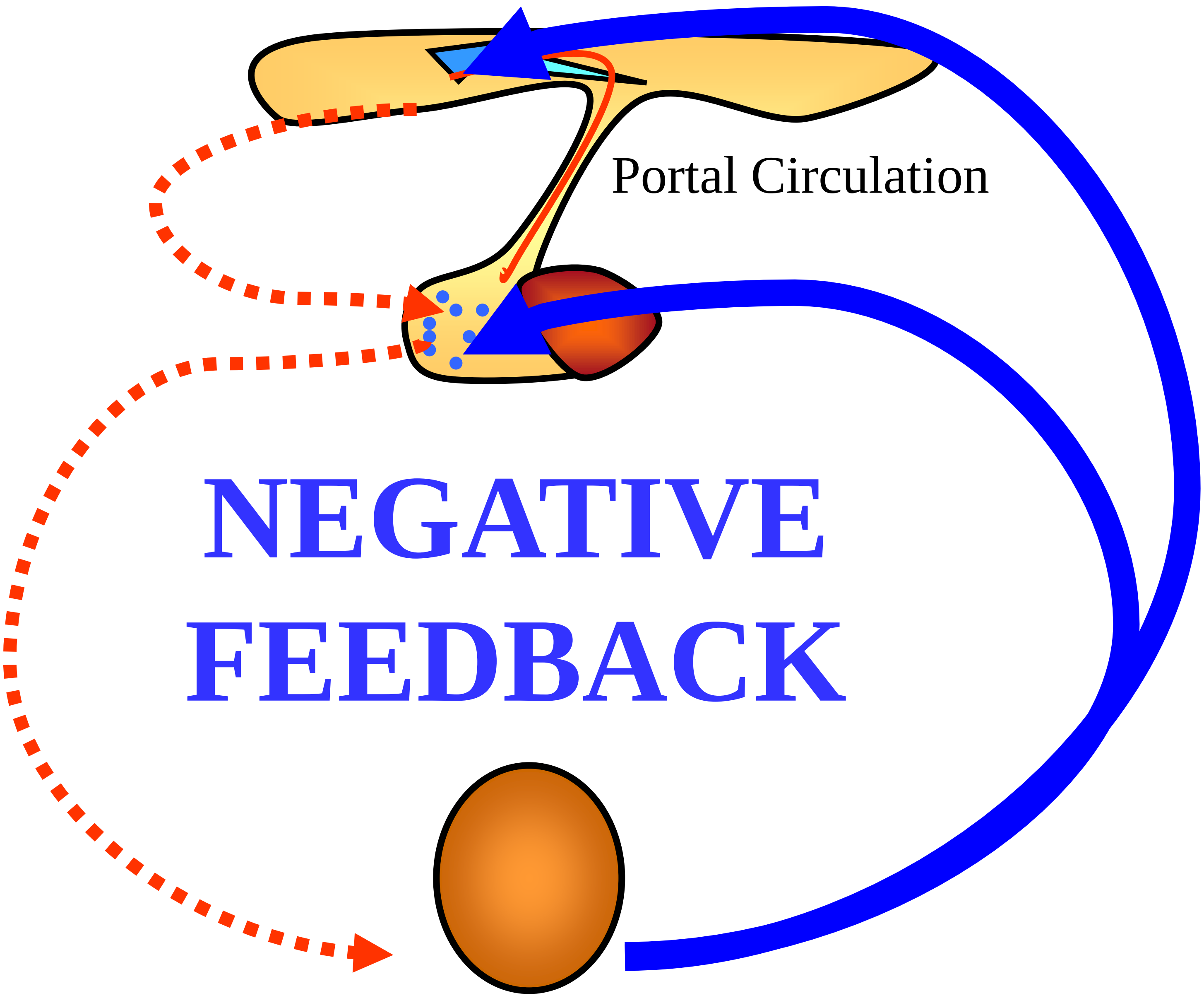
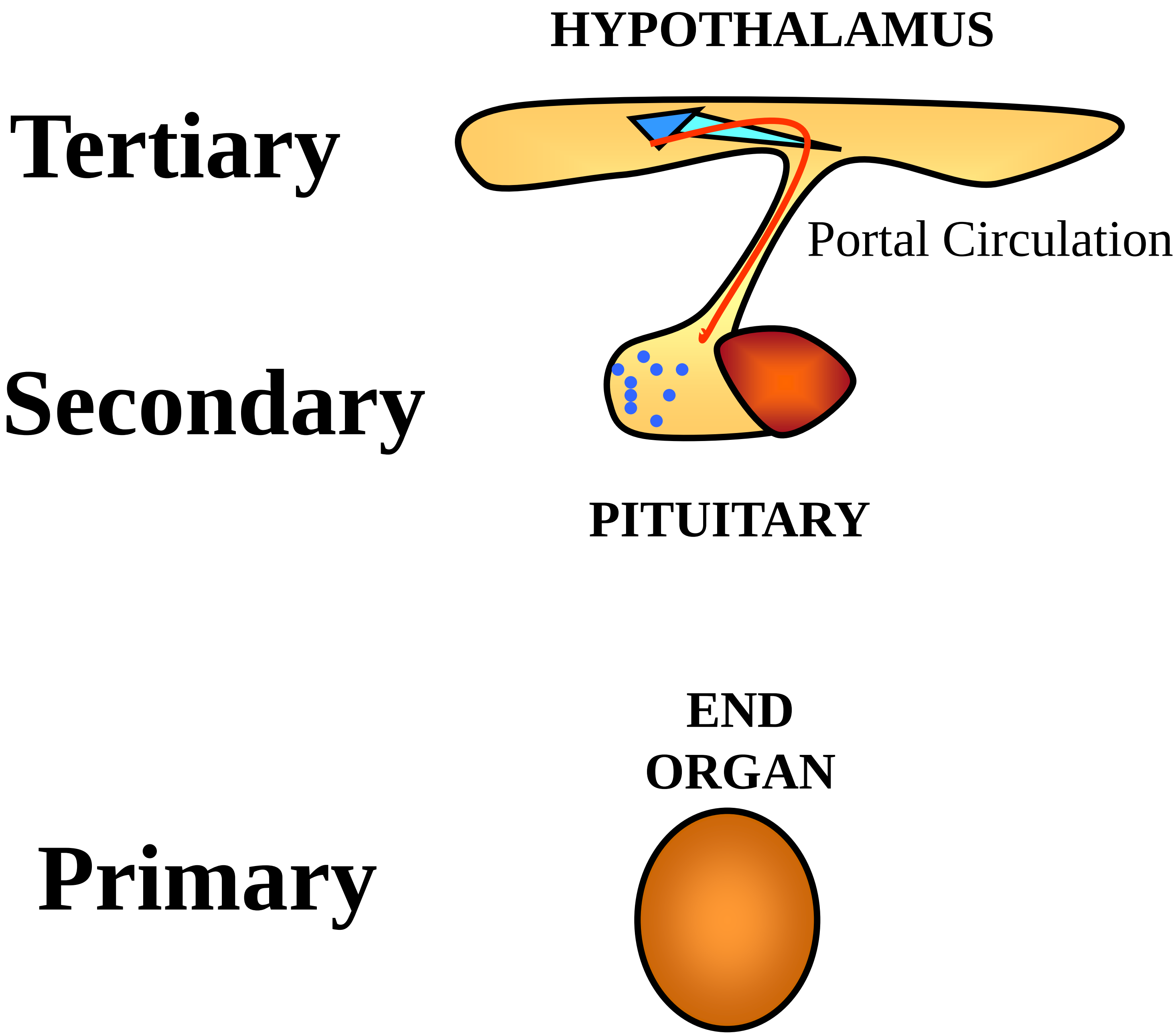
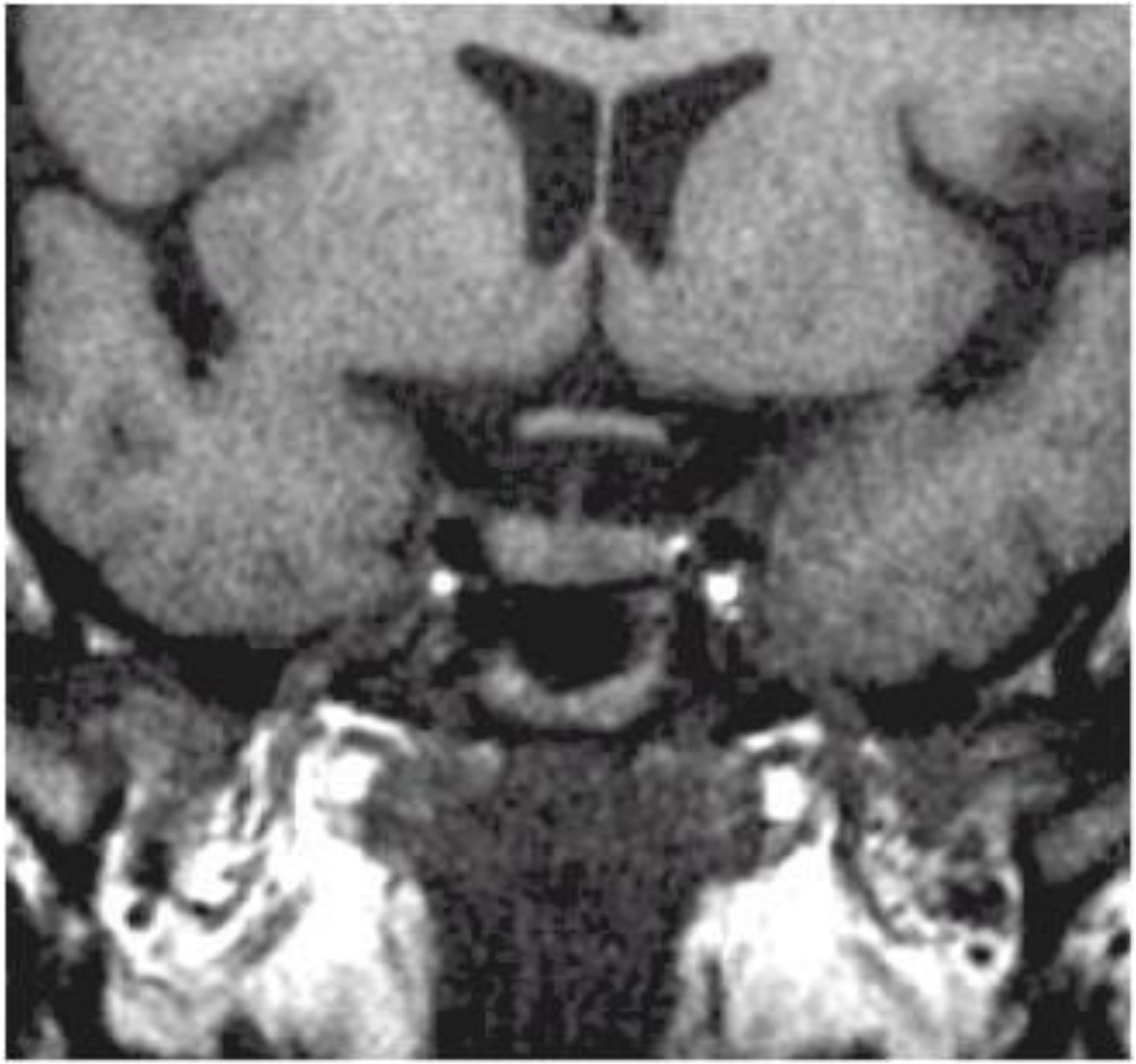
HORMONE
END
ORGAN
END ORGAN
HORMONE

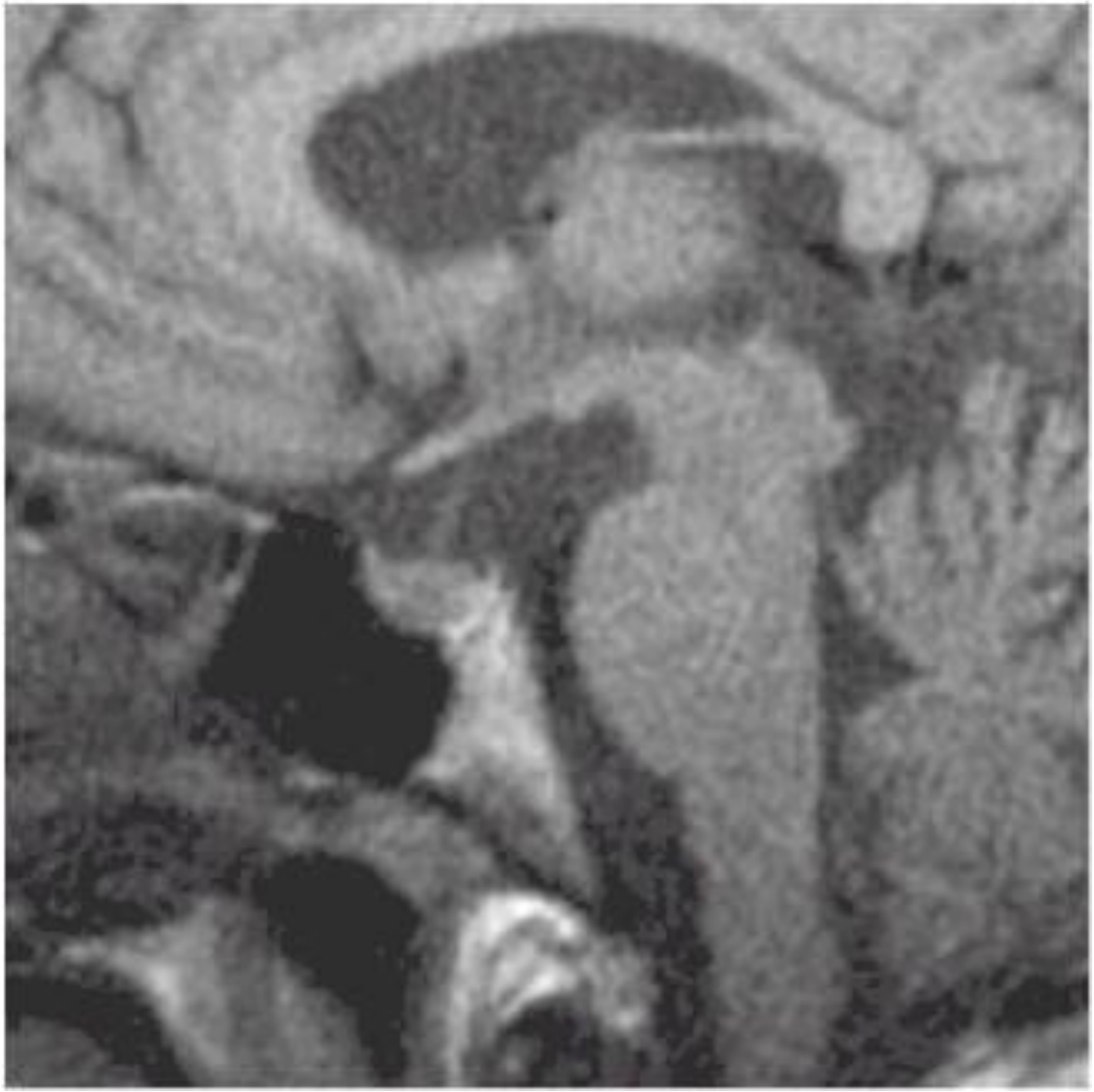

Portal Circulation
NEGATIVE
FEEDBACK


HYPOTHALAMUS
Tertiary
Portal Circulation
Secondary
PITUITARY
END ORGAN
Primary

Normal pituitary gland on MRI scan



Normal pituitary gland on MRI scan



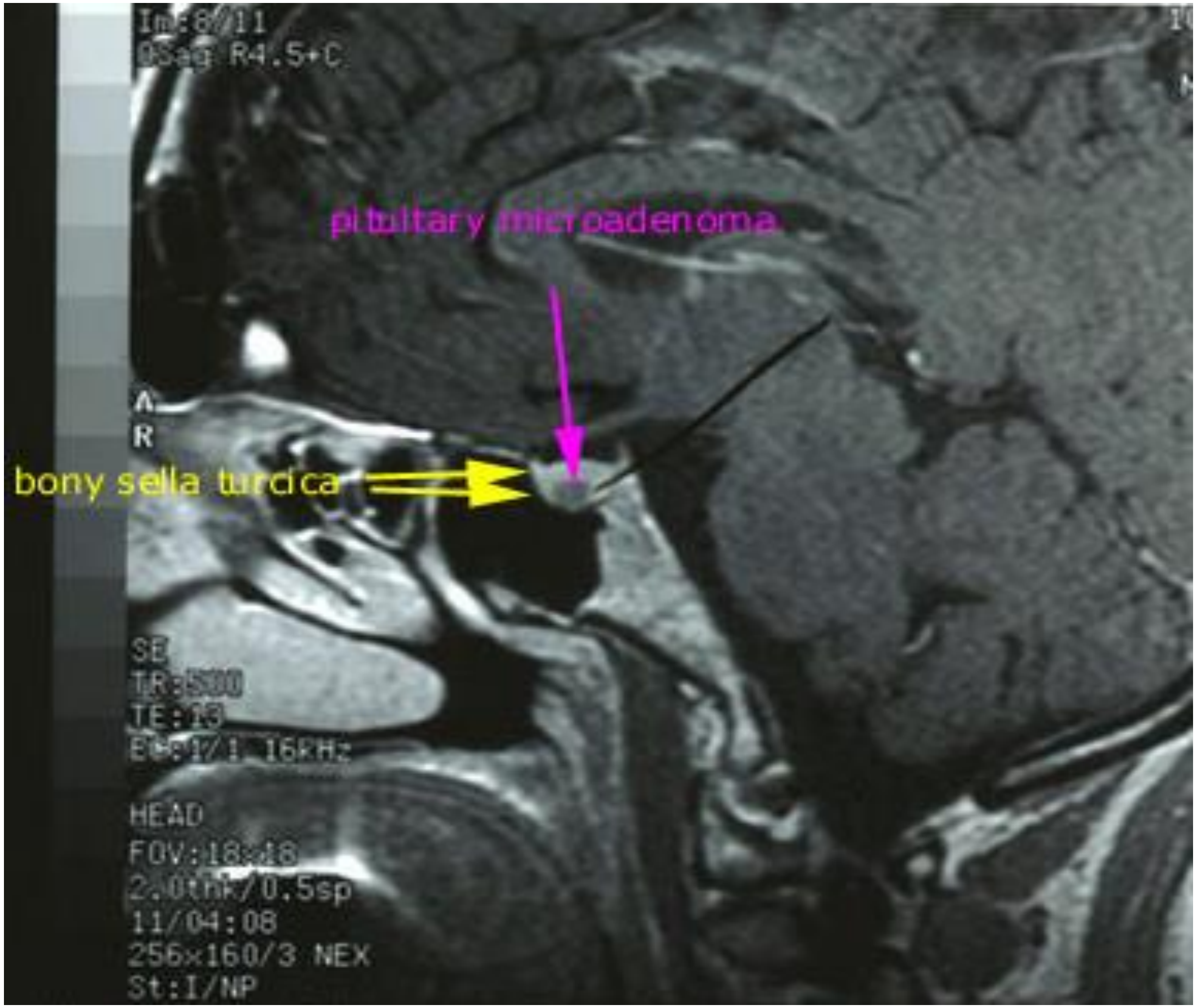
Causes of Pituitary Disease

- Tumour
  - Benign
    - Functional
    - Non functional
  - Malignant
    - Primary
    - Secondary
- Trauma
- Infection
- Inflammation
  - Sarcoidosis
  - Histiocytosis
  - SLE
  - Hypophysitis
- Infiltration
  - Haemochromatosis
- Iatrogenic
- Apoplexy

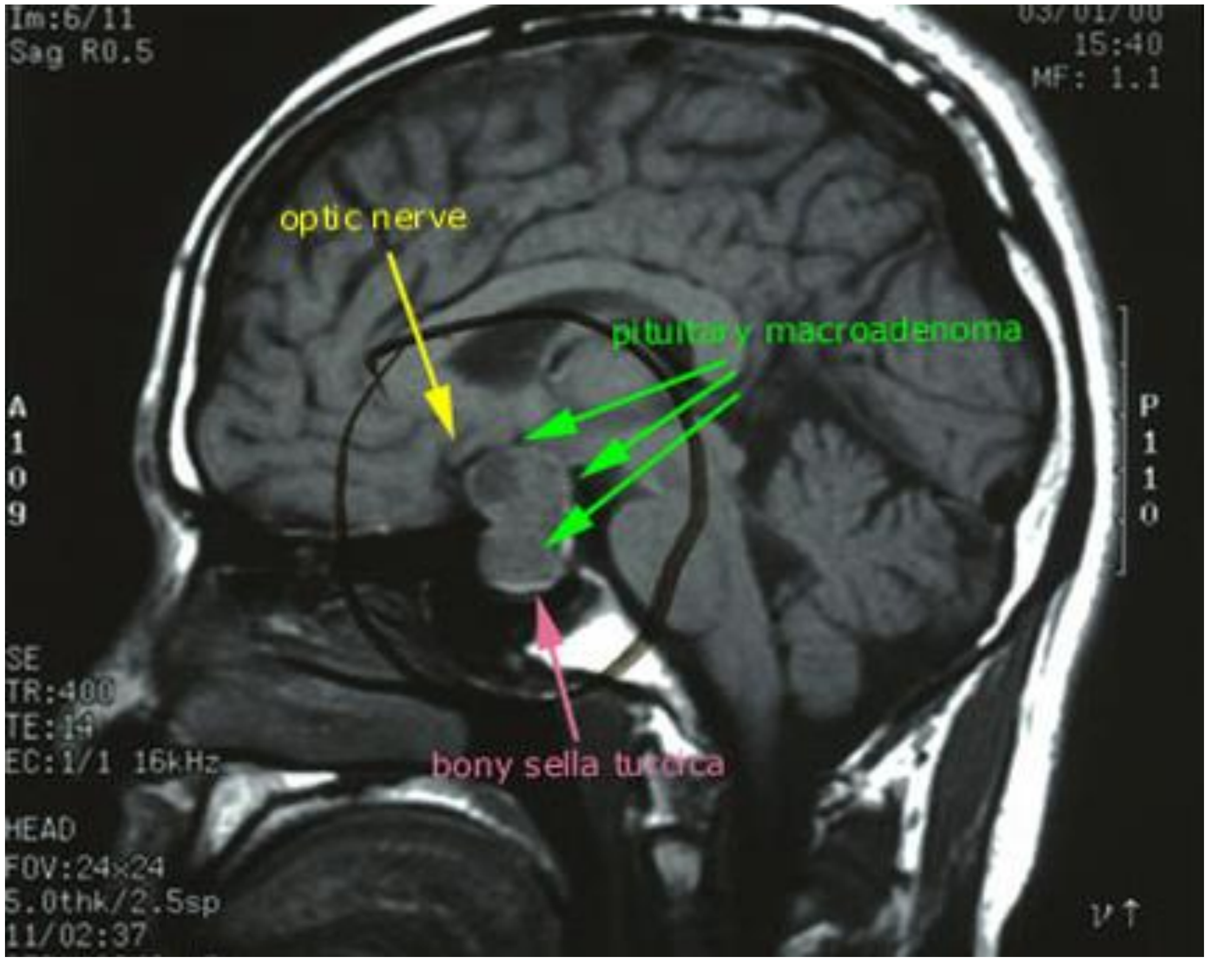
Benign Pituitary Tumours

- Functional
  - Effects of hormone excess
- Functional or Non functional
  - Effects on rest of pituitary function
  - Effects on surrounding structures

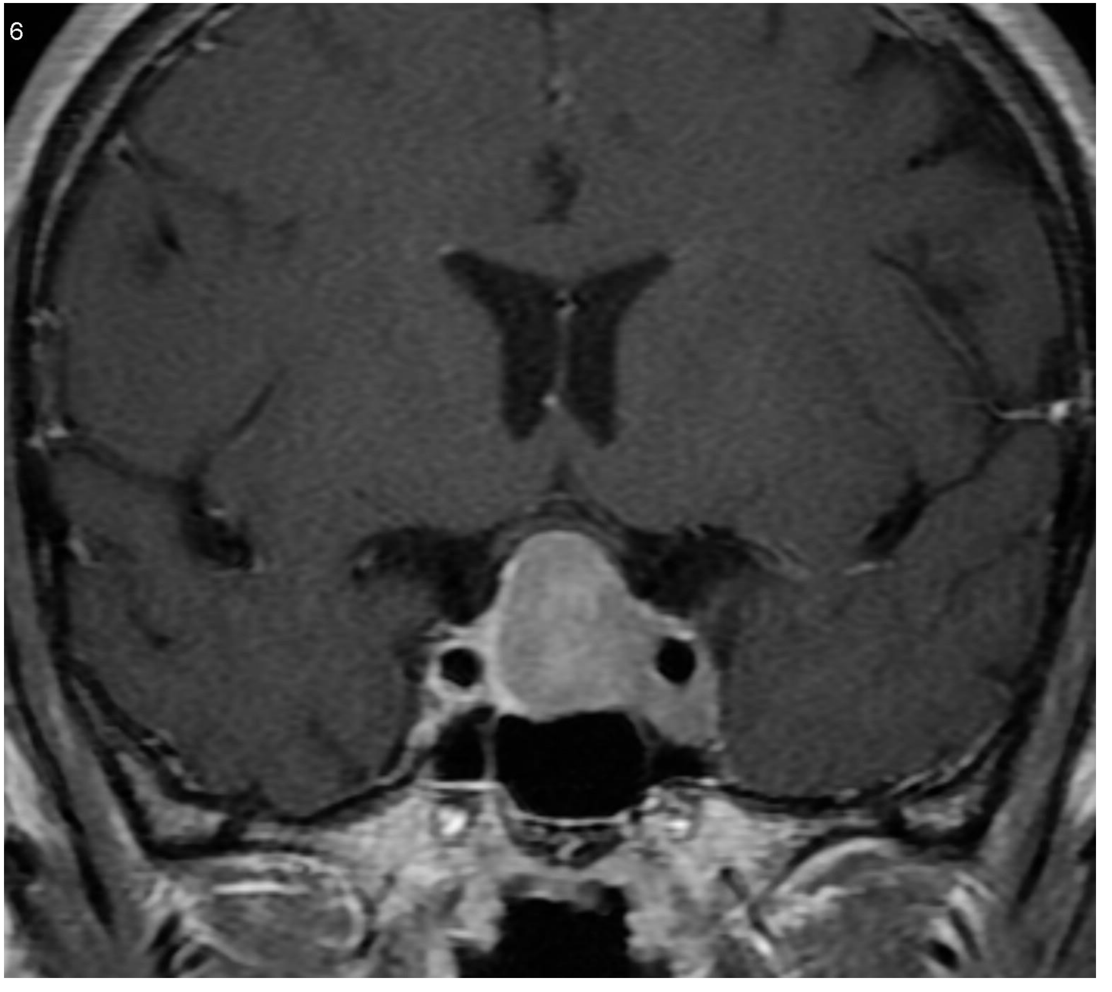
Pituitary microadenoma



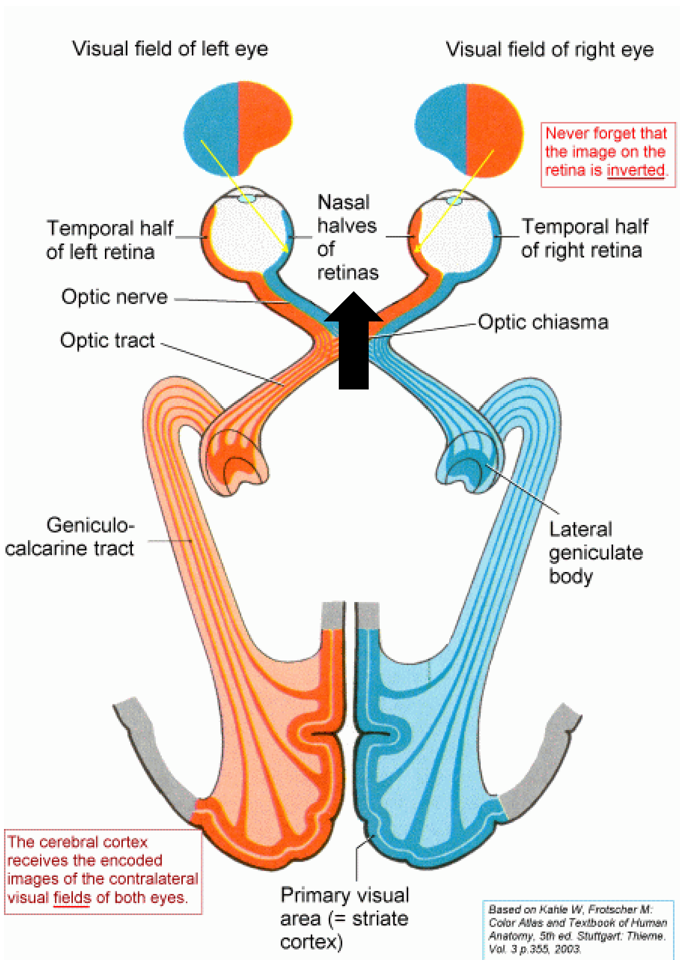
Pituitary macroadenoma

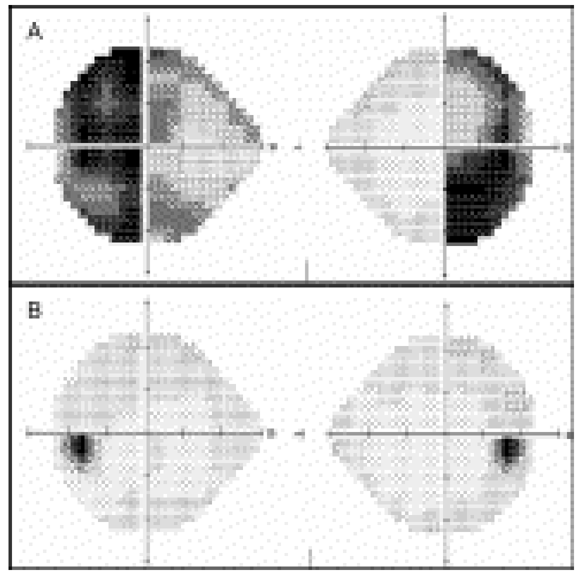


Compression of the optic chiasm



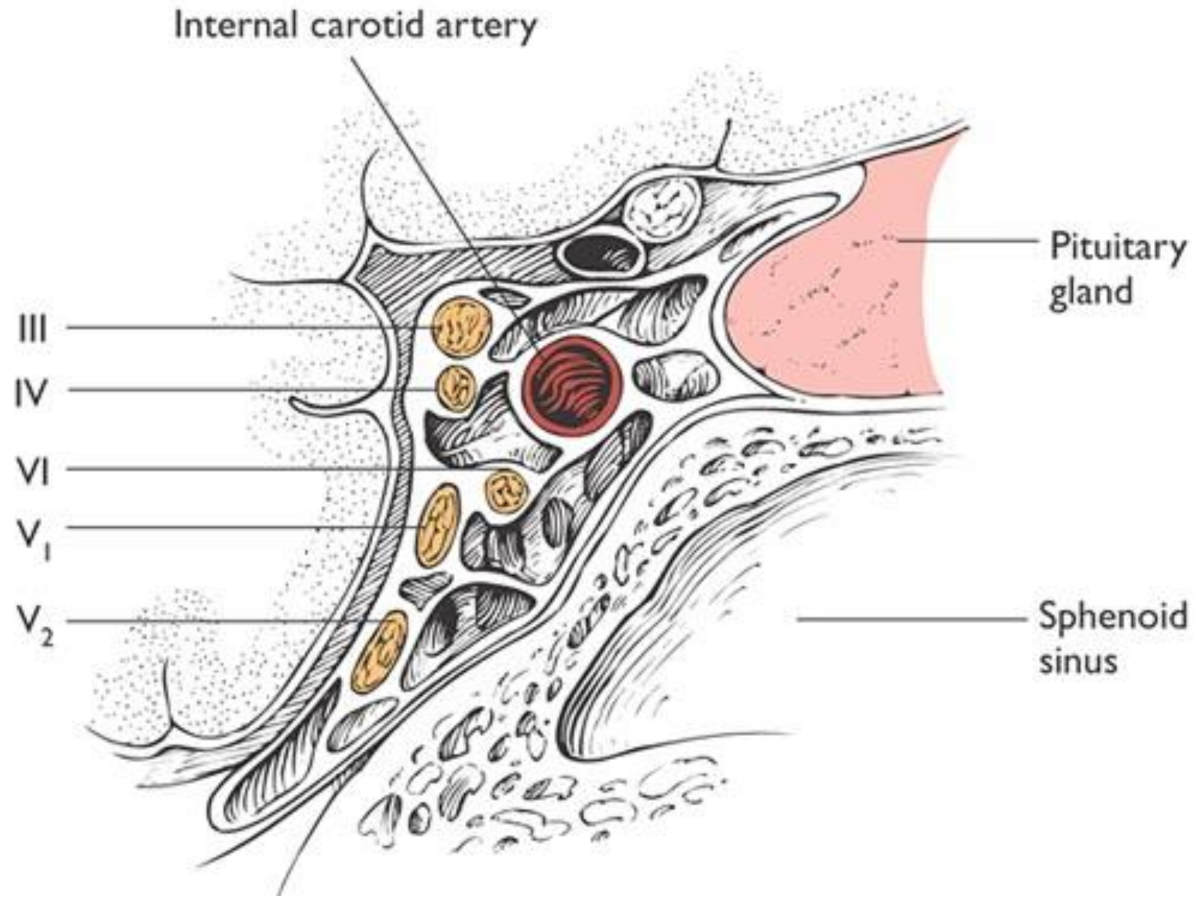
Compression of the optic chiasm and effect on visual fields





Bitemporal hemianopia

Normal visual fields


Internal carotid artery
Pituitary gland
III
IV
VI
V_1
V_2
Sphenoid sinus

Effect of an Expanding Tumour on Pituitary Function

• ↓ LH FSH	secondary hypogonadism
• ↓ GH	GH deficiency
• ↓ TSH	secondary hypothyroidism
• ↓ ACTH	secondary hypocortisolism
• ↑ Prolactin	stalk effect
• ↓ ADH	cranial diabetes insipidus

Female Infertility Causes

Anovulatory

- Central
  - Kallman’s syndrome
  - Anorexia nervosa
  - Hyperprolactinaemia
  - Pituitary destruction
- Ovarian
  - Polycystic ovarian syndrome
  - Ovarian failure
  - Ovarian dys/agenesis (Turner’s syndrome)

Ovulatory

- Cervical hostility
- Uterine malformation
  - Congenital
  - Fibroids
- Uterine infection
- Fallopian tube blockage
- Unexplained

Female Infertility Tests

Tests

- Gonadotrophins
- Oestradiol
- Progesterone
- LHRH test
- Prolactin
- Pelvic ultrasound
- Karyotype

Male Infertility Causes

- **Central**
  - Kallman's Syndrome
  - Anorexia Nervosa
  - Hyperprolactinaemia
  - Pituitary Destruction
- **Testicular**
  - Varicocele
  - Tumour
  - Torsion
  - Orchitis
  - Trauma
  - Undescended testes
  - Surgery / DXT
  - Testicular dys/agenesis (Klinefelter's syndrome)
- **Post Testicular**
  - Post infective ejaculatory duct obstruction
  - Congenital absence of the vas deference (Cystic fibrosis)
- **Miscellaneous**
  - Alcohol
  - Smoking
  - Strenuous riding
  - Drugs
  - Obesity

Male Infertility Tests

Tests

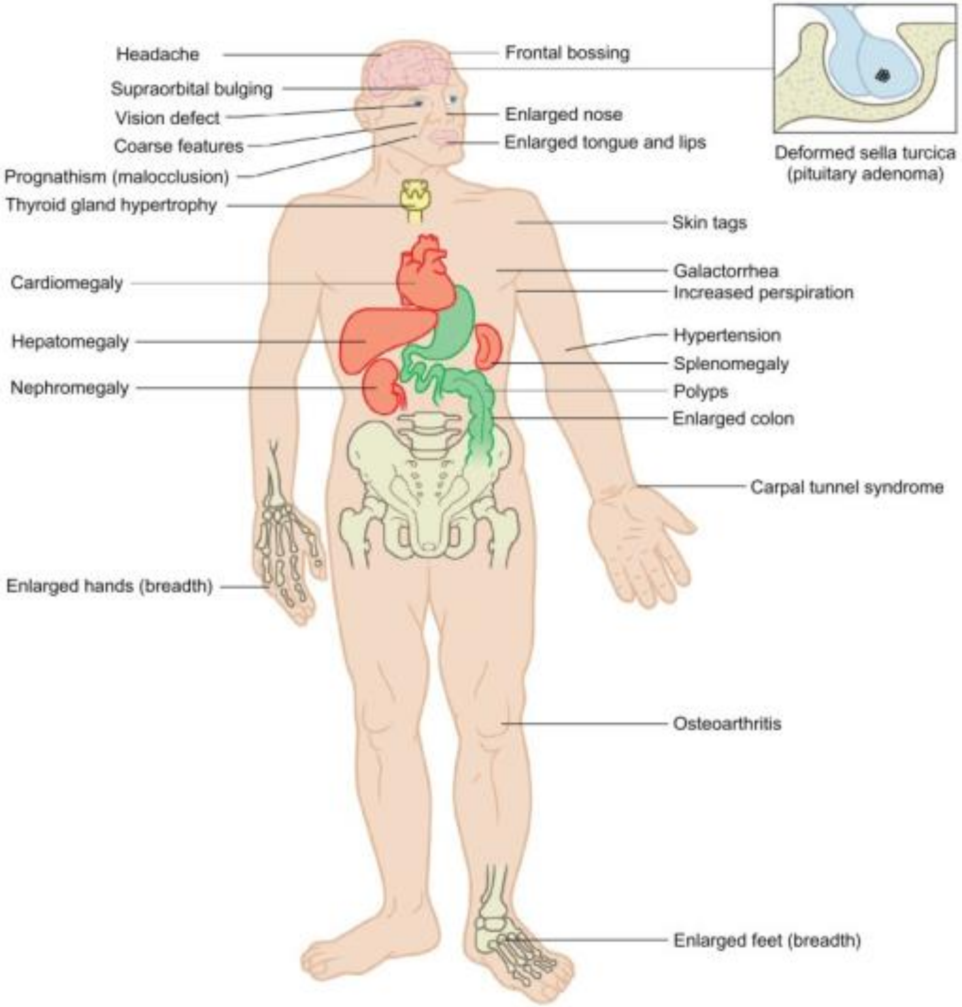
- Gonadotrophins
- Testosterone
- LHRH test
- Prolactin
- Testicular ultrasound
- Karyotype

Acromegaly

- GH-secreting pituitary adenomas present as acromegaly

- The somatic and metabolic effects in acromegaly are mediated by high levels of IGF-1 secreted by the liver

- Acromegaly causes hypertension, insulin resistance and left ventricular hypertrophy leading to increased mortality due to cardiovascular disease



Diagnosis of Acromegaly

- History and examination
  - Retrospective photographs
  - Clinical features
  - Co-morbidities

- Biochemical
  - Lack of GH suppression during OGTT with nadir GH level > 1 µg/L
  - Elevated IGF-1 level
  - Evaluation of overall pituitary function
- Structural
  - MRI scan pituitary
  - Visual field testing

Treatment of Acromegaly

- Surgery
  - Usually transsphenoidal
  - Cures 65% (better with smaller tumours)
- Radiotherapy
  - Very slow
  - Requires adjuvant therapy
- Drugs
  - Somatostatin analogues
  - Dopamine agonists
  - Growth hormone receptor antagonists

Prolactin excess

- Prolactinoma
- Expanding tumour with stalk effect
- Hypothyroidism
- Oestrogens
- Antidepressants
- Stress
- Exercise

Prolactinomas

- Their presentation depends on the patient's age and sex
  - Women of reproductive age

  Oligo/amenorrhoea, decreased libido, vaginal dryness, infertility

  Galactorrhoea

  Early presentation with small tumours
  - Men and post-menopausal women

  Decreased libido, erectile dysfunction, infertility, muscle weakness in men

  May present with galactorrhoea

  Mass effects such as visual disturbance or headache

  Late presentation with large tumours

- Treatment

  Dopamine agonists (bromocriptine, cabergoline)

  Surgery (usually transsphenoidal)

  Radiotherapy

Hyperthyroidism Aetiology

Common

- Graves' disease (~80%) – autoimmune with stimulating antibodies to the TSH receptor.
- Toxic multinodular goitre (~ 15%).

Uncommon

- Toxic adenoma ('hot' nodule, ~ 2%).
- Thyroiditis (~ 1%).

Rare

- TSH secreting pituitary tumor (<0.01%) – biochemically this must be distinguished from thyroid hormone resistance when TSH secretion is high due to loss of negative feedback effects.
- Trophoblastic tumors (<0.001%) – high concentrations of the homologous chorionic gonadotrophin hormone interacting with the TSH receptor.
- Thyrotoxicosis factitia (<1%) – excess thyroxine ingestion in patients who perceive weight loss and other benefits.
- Thyroid follicular carcinoma (<0.01%).

Hyperthyroidism Investigation

Serum assays –

fT4	High
fT3	High
TSH	Suppressed

Hyperthyroidism

due to Graves' or MNG

Serum assays –

fT4	High
fT3	High
TSH	High

Hyperthyroidism

due to TSH secreting tumour

Hyperthyroidism Management

Medical

Drug	Use	Advantages	Disadvantages/side effects
Thiocarbamides e.g. PTU, carbimazole	Patients with mild thyroid disease and small goiter or those with eye disease, cardio-respiratory disease, pregnancy, children	Cheap, effective	Rashes, pruritis (~ 4%), neutropenia (~ 0.4%), hepatitis or pneumonitis (~ <0.1%)
β-adrenergic receptor blockers (e.g. propranolol)	Symptomatic relief (especially cardiac), hyperthyroid storm	Propranolol inhibits hepatic conversion of T_4 to T_3	Asthma, heart failure
Glucocorticoids (e.g. prednisolone)	Hyperthyroid storm	Prednisolone inhibits hepatic conversion of T_4 to T_3	Iatrogenic Cushing's syndrome
Iodine (e.g. Lugol's solution)	Hyperthyroid storm Prior to surgery to reduce blood flow	Rapid inhibition of thyroid hormone synthesis (Wolff-Chaikoff effect)	'Escape' occurs with time
Perchlorate	Iodine-induced hyper-thyroidism	Discharge iodide excess from thyroid gland	Rash, gastric upset, lymphadenopathy (~ 5%). Agranulocytosis or aplastic anaemia (~ 0.5%)
Lithium	Second-line alternative to thiocarbamides	Inhibits T_4 and T_3 release	Lithium toxicity* (tremor, ataxia, coma); polydipsia, polyuria (~10%)

Thyroid surgery

Radioactive iodine

Hypothyroidism
Aetiology

Primary disorders

Common (~ 95%)

- Hashimoto's disease – autoimmune thyroid destruction
- Primary (atrophic) hypothyroidism (Probably endstage Hashimoto's disease)
- Post-radioiodine therapy which destroys thyroid tissue
- Post-surgery of the gland

Uncommon (~ 5%)

- Thyroiditis (non-lymphocytic)
- Impaired T_4 synthesis due to genetic defect
- Antithyroid drugs

Rare (<1%)

- Loss of function TSH receptor mutations
- Thyroid hormone resistance

Secondary (or pituitary, ~ 1%) disorders

- Hypopituitarism caused by e.g. tumors, surgery, radiotherapy
- Impaired TSH synthesis

Tertiary (or hypothalamic, ~ <1%) disorders

- Hypothalamic damage due to tumors, radiotherapy or trauma

*In most Western countries iodide deficiency is not a cause of hypothyroidism. It is a major cause in known deficient areas.

Hypothyroidism Investigation

Serum assays –

fT4	Low	
fT3	Low	**Primary hypothyroidism**
TSH	High	

Serum assays –

fT4	Low	
fT3	Low	**Secondary hypothyroidism**
TSH	Low	

Hypothyroidism Management

- Primary hypothyroidism

Appropriate thyroxine dose aiming to normalise TSH

- Secondary hypothyroidism

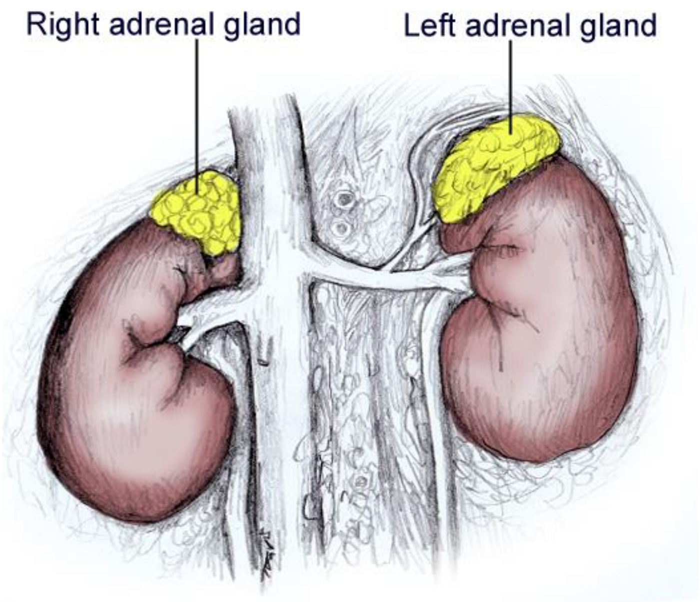
Appropriate thyroxine dose aiming to keep fT4 in the middle of the normal range

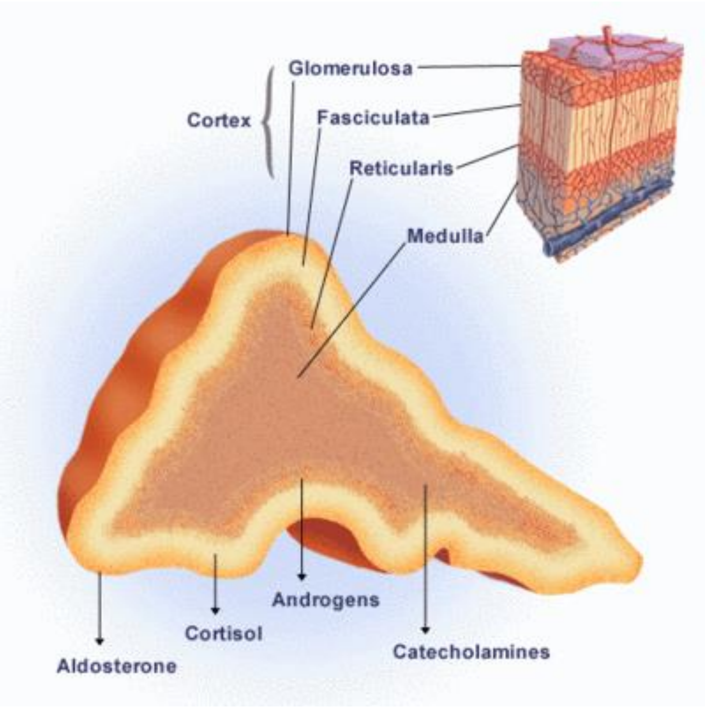
- Cautions

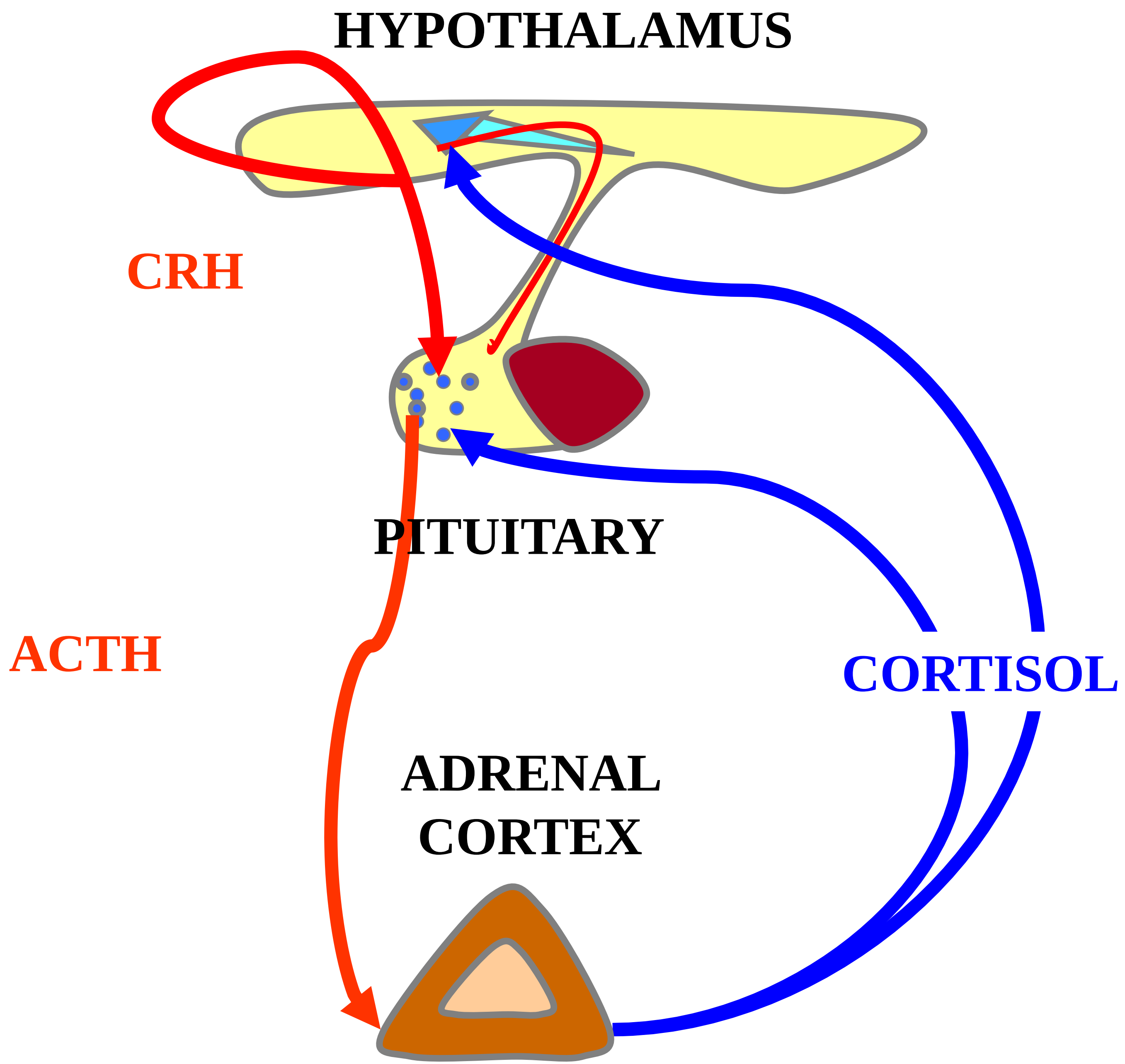
In the elderly and in patients with known IHD introduce thyroxine gradually

In certain cases exclude or treat adrenal insufficiency first before the introduction of thyroxine

The adrenal glands

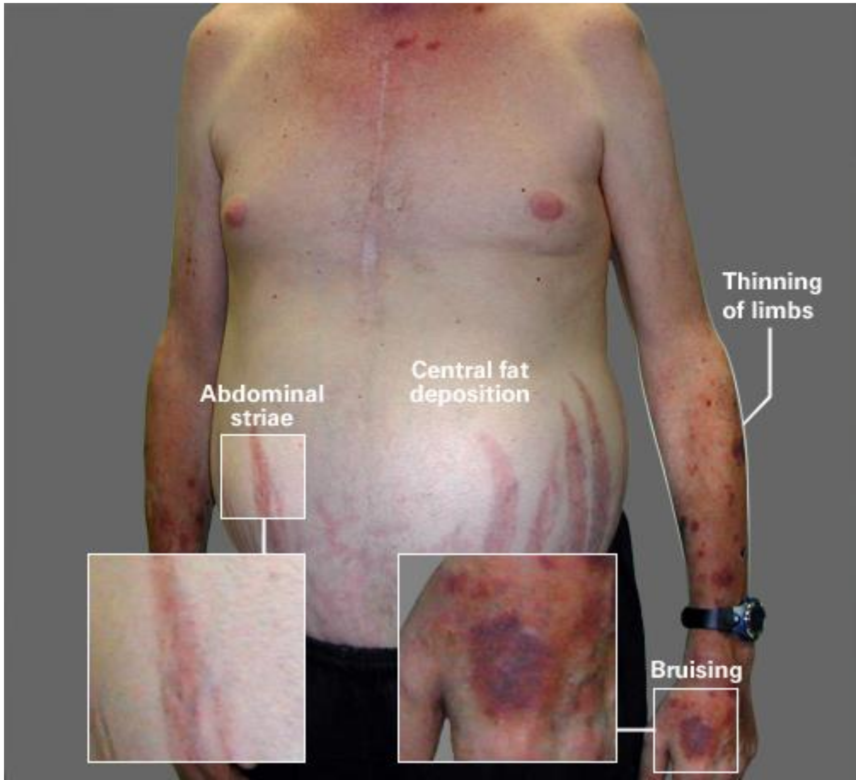





HYPOTHALAMUS
CRH
PITUITARY
ACTH
CORTISOL
ADRENAL
CORTEX

Cushing's syndrome

- Weight gain
- Central obesity
- Buffalo hump
- Moon face
- Hyperhidrosis
- Telangiectasiae
- Easy bruising
- Purple or red striae
- Proximal muscle weakness
- Hirsutism
- Acne



Cushing’s syndrome

- Insomnia
- Reduced libido
- Erectile dysfunction
- Amenorrhoea/oligomenorrhoea
- Infertility
- Psychological disturbances (euphoria, psychosis, depression and anxiety)
- Hypertension
- Diabetes mellitus
- Osteoporosis

The Investigation of Cushing's Syndrome is in Three Stages

- Screening
- Confirmation of the Diagnosis
- Differentiation of the Cause

Screening for Cushing's Syndrome

- 24h urinary free cortisol
- Midnight cortisol
- Overnight dexamethasone suppression test
  - Dexamethasone 1mg is given at 11pm
  - Cortisol is measured at 8am the next morning
  - Cortisol suppression to <50nmol/l is normal

Confirmation of the Diagnosis

- Low dose dexamethasone suppression test
  - Dexamethasone 0.5mg is given six hourly for 48h
  - Cortisol suppression to <50nmol/l at 48h is normal

Causes of Cushing's Syndrome

- ACTH - dependent 80%

  Pituitary adenoma (Cushing's disease) 80%

  Ectopic ACTH syndrome 20%

- ACTH - independent 20%

  Adrenal adenoma 60%

  Adrenal carcinoma 40%

Differentiation of the Cause of Cushing's Syndrome

- ACTH level < 5pg/mL → ACTH – independent
- ACTH level normal or high → ACTH – dependent
- High dose dexamethasone suppression test

  Dexamethasone 2mg is given six hourly for 48h

  Cortisol suppression by > 50% of the basal value at 48h → Cushing's disease

  No cortisol suppression at 48h → Ectopic ACTH syndrome

Differentiation of the Cause of Cushing's Syndrome

- CRH test

0.1 µg/kg of human CRH is given

Blood is assayed for cortisol and ACTH at -15, 0, 15, 30, 60, 90, 120 minutes

Cortisol rises by > 20% and ACTH by > 50% of the basal value → Cushing's disease

No stimulation → Ectopic ACTH syndrome

- Bilateral inferior petrosal sinus sampling

ACTH central to peripheral ratio > 2 → Cushing's disease

Differentiation of the Cause of Cushing's Syndrome

The place of radiology is confirmatory only after a clinical and biochemical diagnosis of Cushing's syndrome and its cause has been made

- MRI scan pituitary
- CT scan/MRI scan adrenals
- CT scan/MRI scan thorax/abdomen
- Octreotide scan

Treatment of Cushing’s Syndrome

- Surgery

- Trans-sphenoidal selective adenomectomy
- Unilateral adrenalectomy open or laparoscopic
- Bilateral adrenalectomy open or laparoscopic (Nelson’s syndrome may develop)
- Removal of source of ectopic ACTH

- Pituitary radiotherapy

- Medical therapy

- Metyrapone inhibits cortisol synthesis
- Ketoconazole inhibits cortisol synthesis
- Mifepristone glucocorticoid receptor antagonist

Primary Adrenal Failure

- Tiredness
- Weakness
- Anorexia
- Weight loss
- Postural hypotension
- Myalgia
- Salt craving
- Nausea and vomiting
- Hyperpigmentation
- Vitiligo

- Hyponatraemia
- Hyperkalaemia
- Acidosis
- Hypercalcaemia
- Hypoglycaemia
- ↑ urea and creatinine
- Eosinophilia
- Lymphocytosis

Causes of Primary Adrenal Failure

- Autoimmune (Addison’s disease)
- Steroid withdrawal
- Metastases
- Infiltration

  Amyloidosis

  Haemochromatosis
- Waterhouse- Friderichsen syndrome
- Apoplexy
- Infection

  TB

  Viral

  Fungal
- Enzyme defect

  Congenital Adrenal hyperplasia

Diagnosis of Primary Adrenal Failure

- 9am cortisol ↓ Possible adrenal failure

- Short synacthen test

Test should start at 9am

Blood is assayed for cortisol and ACTH at at 0 minutes

250μg synthetic ACTH is injected IM or IV

Blood is assayed for cortisol at 30, 60 minutes post injection

Cortisol should double from baseline within 60 minutes in normal individual

ACTH ↑ at baseline and cortisol fails to double from baseline within 60 minutes Primary adrenal failure

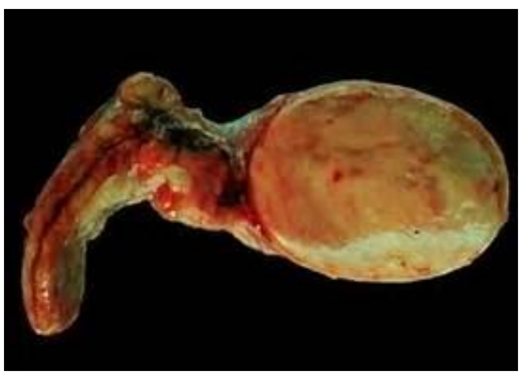
Treatment of Primary Adrenal Failure

- Hydrocortisone
  - 10mg on rising, 5mg at 12pm, 5mg at 5pm
  - Mimics the diurnal rhythm
  - Last dose before 6pm
- Fludrocortisone
  - 50-200μg o.d.

Primary aldosteronism

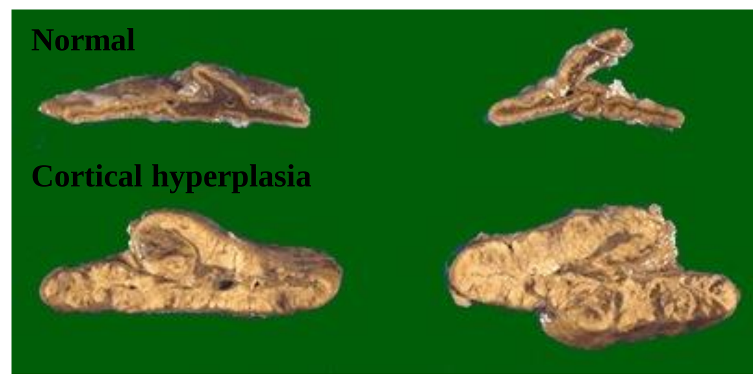
- Excessive aldosterone production by the zona glomerulosa of the adrenal cortex

- It is usually caused by



Aldosterone-producing adrenal cortical adenoma

Conn's syndrome



Bilateral adrenal cortical hyperplasia

Treatment of Conn’s Syndrome

- Spironolactone
- Amiloride / Triamterene
- Potassium Supplementation
- Surgical resection of the Primary Tumour

Phaeochromocytoma

Neuroendocrine tumour of the adrenal medulla secreting high amount of catecholamines

- ↑ Vasoconstriction → ↑ TPR → ↑ BP
- ↑ Heart rate → ↑ CO → ↑ BP

Clinical features

- Throbbing headache, excessive sweating, palpitations
- Treatment resistant hypertension
- Anxiety, pallor, chest pain
- Glucose intolerance with elevation of blood glucose
- Increased metabolic rate with weight loss

Phaeochromocytoma

The tumour is the same brown colour as the adrenal medulla

An attenuated rim of orange adrenal cortex is present around the edge

Phaeochromocytomas Diagnosis

- Plasma free metanephrines
- 24-h urinary catecholamines
- Chromogranin A
- Tumour localisation by
  - CT or MRI scan
  - MIBG scan
  - PET/CT

Phaeochromocytomas Treatment

- Surgical resection of the tumour is the treatment of choice, either open or laparoscopic

- Surgical resection requires prior treatment with an α-adrenoceptor blocker (phenoxybenzamine). This minimises the likelihood of severe intra-operative hypertension that might occur when the tumour is manipulated. A β-adrenoceptor blocker (propranolol) can be added to control the pulse rate. However, it should never be used alone as β-adrenoceptor blockade without concurrent α-adrenoceptor blocker may lead to severe hypertension

- It is usually advised to "salt load" patients prior to surgery in order to avoid severe hypotension once the tumour has been resected

Causes of hypercalcaemia

- 1^o Hyperparathyroidism
- 3^o Hyperparathyroidism
- Malignancy
- Hypervitaminosis D

  Excess intake

  Granulomatous disease

  (increased renal conversion of 25-OH D → 1,25-OH D)
- High bone turnover

  Hyperthyroidism

  Immobilisation
- Familial hypocalciuric hypercalcemia

  (inactivating mutation of CaSR)
- Milk-alkali syndrome
- Thiazide diuretics

Causes of the hypercalcaemia of malignancy

- PTH
  - Small cell lung cancer
- PTHrP
  - Lung
  - Lymphoma
  - Multiple myeloma
- Osteoclast-activating factor
  - Lymphoma
  - Multiple myeloma
- Metastatic solid tumours
  - Lung
  - Breast
  - Kidney
  - Prostate

Symptoms and signs of hypercalcaemia

"Stones, Bones, Groans, Thrones and Psychiatric Overtones"

Stones (renal or biliary)
Bones (pain, erosions)
Groans (abdominal pain, nausea, vomiting, anorexia, constipation, fatigue, muscle weakness)
Thrones (polyuria)
Psychiatric overtones (depression, anxiety, hallucinations, lethargy, confusion, fitting, coma)

ECG findings

Arrhythmias, shortened QT interval, widened T wave

Investigation of hypercalcaemia

- Calcium, phosphate, U&E
- PTH
- Vitamin D
- Urinary calcium excretion
- CXR
- ACE
- Myeloma Screen
- Thyroid function tests

Investigation of hypercalcaemia

- ***Inc PTH***
  - – US scan of the renal tract
  - – DEXA scan
  - – Sestamibi scan
  - – US scan of the neck

- ***Dec PTH***
  - – Bone scan
  - – Localisation of primary tumour

Treatment of 1^{o} Hyperparathyroidism

- Surgery
- Medical
  - Observation
  - Bisphosphonates
  - “Calcimimetics”

Treatment of severe hypercalcaemia

- Saline rehydration
- Frusemide
- Pamidronate infusion
- Calcitonin
- Prednisolone
- Dialysis

Causes of hypocalcaemia

- Low PTH/Action

Hypoparathyroidism

- Parathyroid agenesis
- Parathyroid destruction

Activating mutation of CaSR

PTH resistance

- Pseudohypoparathyroidism
- Hypomagnesaemia

- High PTH

Vitamin D deficiency

- Renal disease
- Liver disease
- Dietary insufficiency
- Malabsorption
- Poor exposure to sunlight
- Sun block

Symptoms and signs of hypocalcaemia

- Paraesthesias
- Laryngospasm
- Bronchospasm
- Tetany
- Seizures
- Chvostek’s sign
- Trousseau sign
- Prolonged QT interval on ECG

Investigation of hypocalcaemia

- Calcium
- Phosphate
- U&E
- Magnesium
- Vitamin D
- PTH
- 1,25 dihydroxy vitamin D

- Malabsorption
  - B12
  - Folate
  - Ferritin
  - Coeliac screen
- Amylase
- Plain X rays

Treatment of Hypocalcaemia

- Treat underlying cause
  - Discontinue offending drugs
  - Correct other electrolyte disorders

- Oral (enteral): Up to 2g per day
- Vitamin D supplementation

Treatment of severe hypocalcaemia

- iv 10ml 10% Calcium gluconate diluted in 200ml N saline over 10 minutes

  Carpopedal spasm

  Fitting

  Arrhythmias

  Calcium < 1.7 mmol/l

Hyponatraemia
Causes

- Can be classified based on volume status

  Hypovolaemic
  - True volume depletion (i.e. bleeding)
  - Adrenal insufficiency
  - Thiazide diuretics
  - Exercise induced hyponatraemia

  Euvolaemic
  - SIADH
  - Psychogenic polydipsia

  Hypervolaemic
  - Effective circulating volume depletion (i.e. heart failure and cirrhosis)

Work up of Hyponatraemia

- **Mandatory lab tests**
  - Serum osmolality
  - Urine osmolality
  - Urine sodium concentration

- **Additional lab tests depending on clinical suspicion**

Syndrome of inappropriate ADH secretion (SIADH)

- Euvolaemic
- Normotensive
- Hyponatraemia
- Serum Osmolality < 280 mOsm/Kg
- Urine Osmolality > 100 mOsm/kg
- Urine Sodium > 20 mmol/L

SIADH Causes

- Tumours
  - Small cell lung cancer
  - Lymphoma
  - Mesothelioma
- Respiratory disease
  - Pneumonia
  - Lung abscess
  - Pneumothorax
  - Invasive positive pressure ventilation
- Metabolic disease
  - Porphyria
- Neurological disease
  - Meningoencephalitis
  - Brain abscess
  - Head injury
  - Subarachnoid haemorrhage
  - Guillain-Barre syndrome
- Drugs
  - Vincristine
  - Phenothiazines
  - Carbamezapine
  - Chlopropamide
  - Clofibrate
  - Cyclophosphamide
  - SSRIs

SIADH Treatment

- Treating underlying cause when possible
- Fluid restriction
- Drugs

Demeclocycline – induces nephrogenic diabetes insipidus

Tolvaptan – antagonist of V_2 vasopressin receptor

Conivaptan – antagonist of V_{1A} and V_2 vasopressin receptor

Diabetes Insipidus

- Polyuria and polydipsia
- Dehydrated
- Urine Output > 3 L/day
- Hypernatraemia
- Serum Osmolality ↑
- Urine Osmolality ↓
- Water deprivation test – to confirm the diagnosis and distinguish between cranial DI and nephrogenic DI

DI Causes

- Cranial DI

  ADH Deficiency

- Genetic
- Idiopathic
- Trauma
- Infection
- Iatrogenic
- Infiltration
  - Haemochromatosis
- Tumour
  - Craniopharyngioma
- Inflammation
  - Sarcoidosis
  - Histiocytosis X
  - Lymphocytic hypophysitis
- Apoplexy
  - Sheehan's syndrome

- Nephrogenic DI

  Insensitivity of the kidneys to ADH

- Genetic
- Infection
- Amyloidosis
- Sickle cell disease/trait
- Sjogren's syndrome
- Polycystic kidney disease
- Post obstructive polyuria
- Metabolic
  - hypercalcaemia
  - hypokalaemia
- Drugs
  - Lithium
  - Demeclocycline

DI Treatment

- Cranial DI

  Treating underlying cause when possible

  Desmopressin (DDAVP)

  – Vasopressin analogue

  – Nasal, oral, subcutaneous

- Nephrogenic DI

  Treating underlying cause when possible

  Hydrochlorthiazide

  Amiloride