Academic lectures for general medicine – 3rd year
2005/2006, 2013/2014

ENDOCRINOLOGY 3

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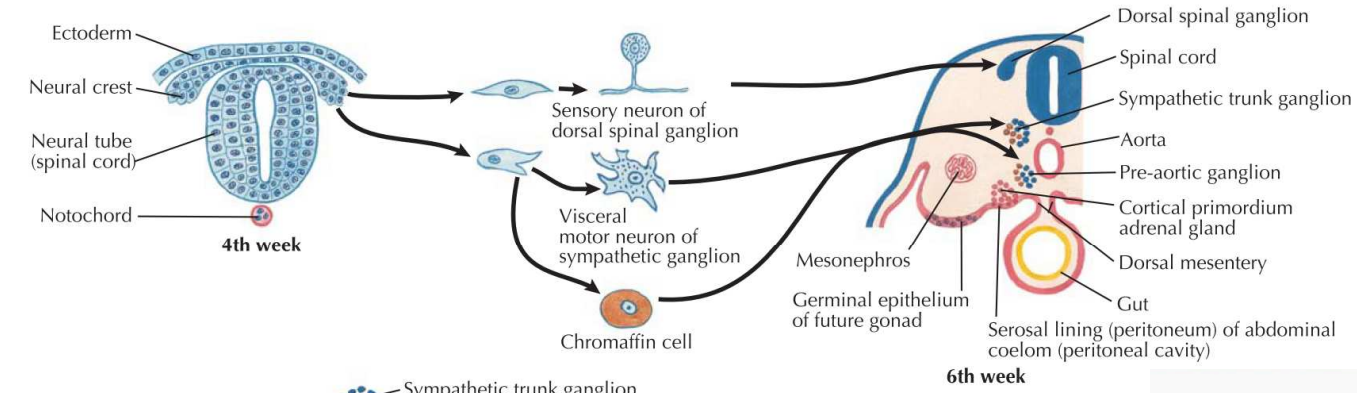
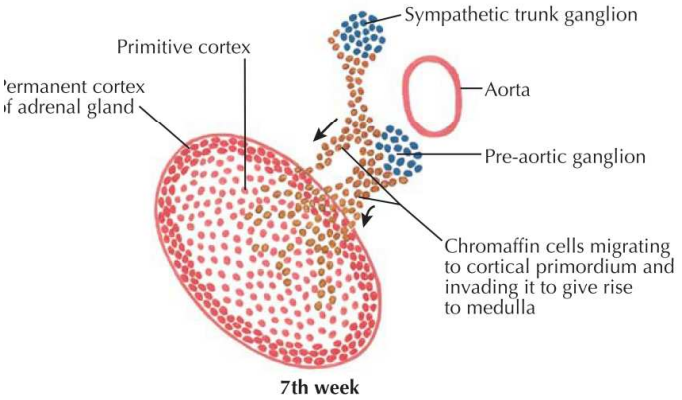
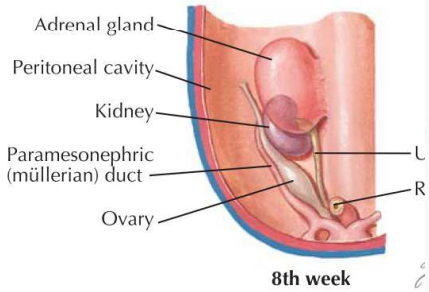
Physiologic overview

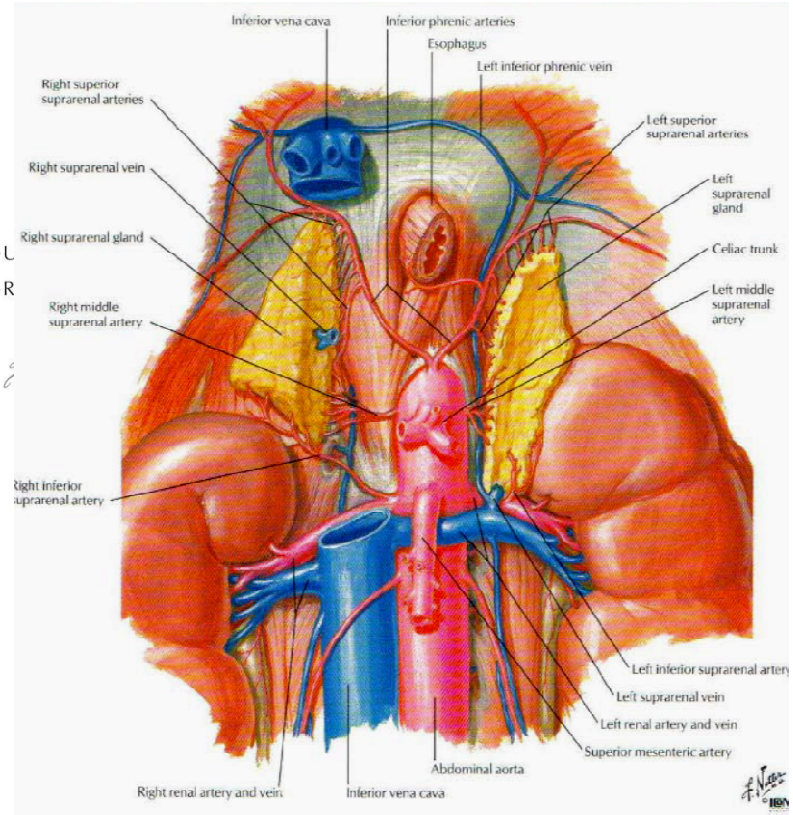
- Physiological overview
- Hypercortisolism- Cushing syndrome
- Hypocortisolism – Addison disease

Supraren – gross anatomy

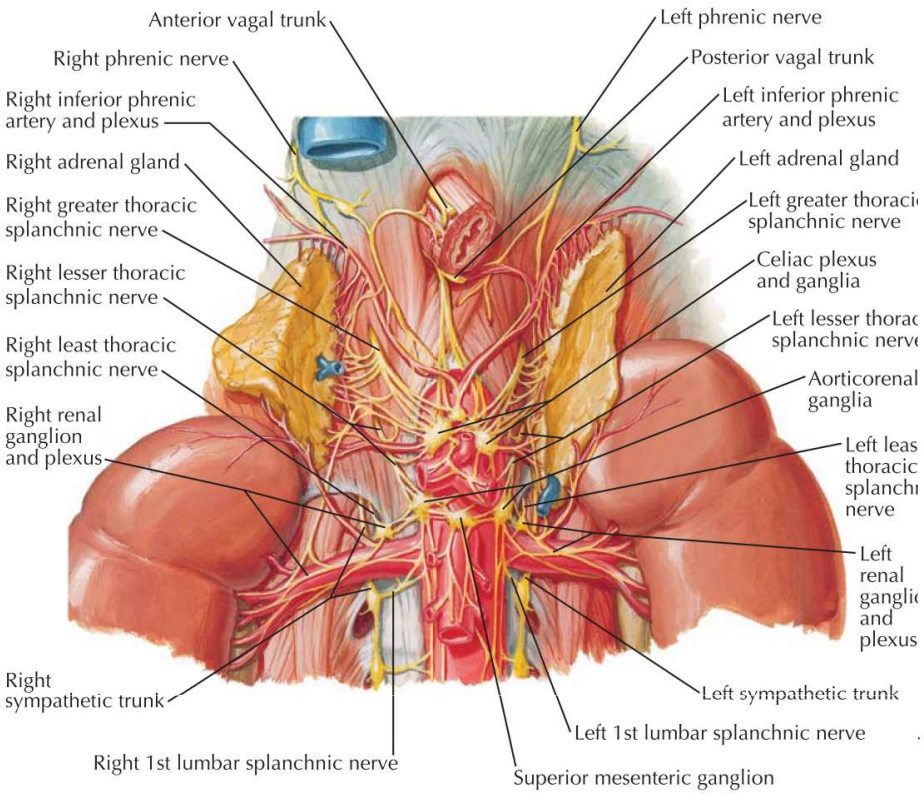


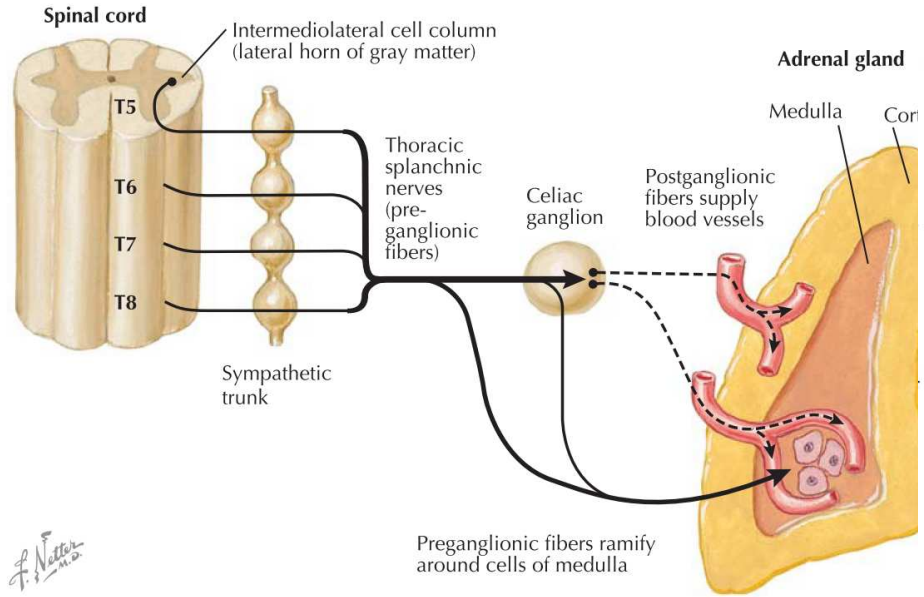


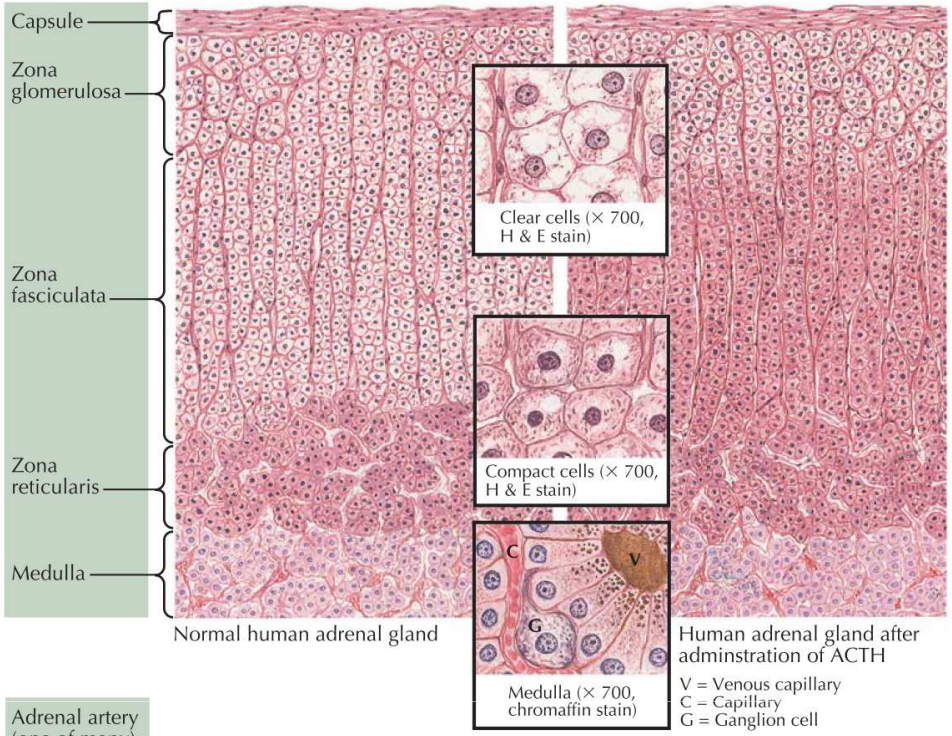


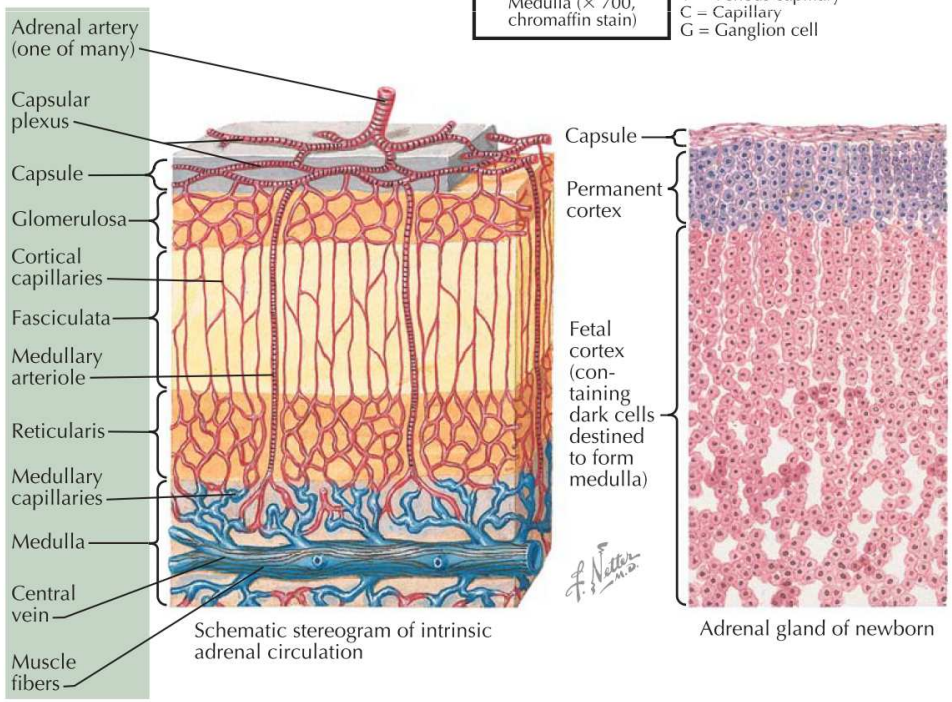


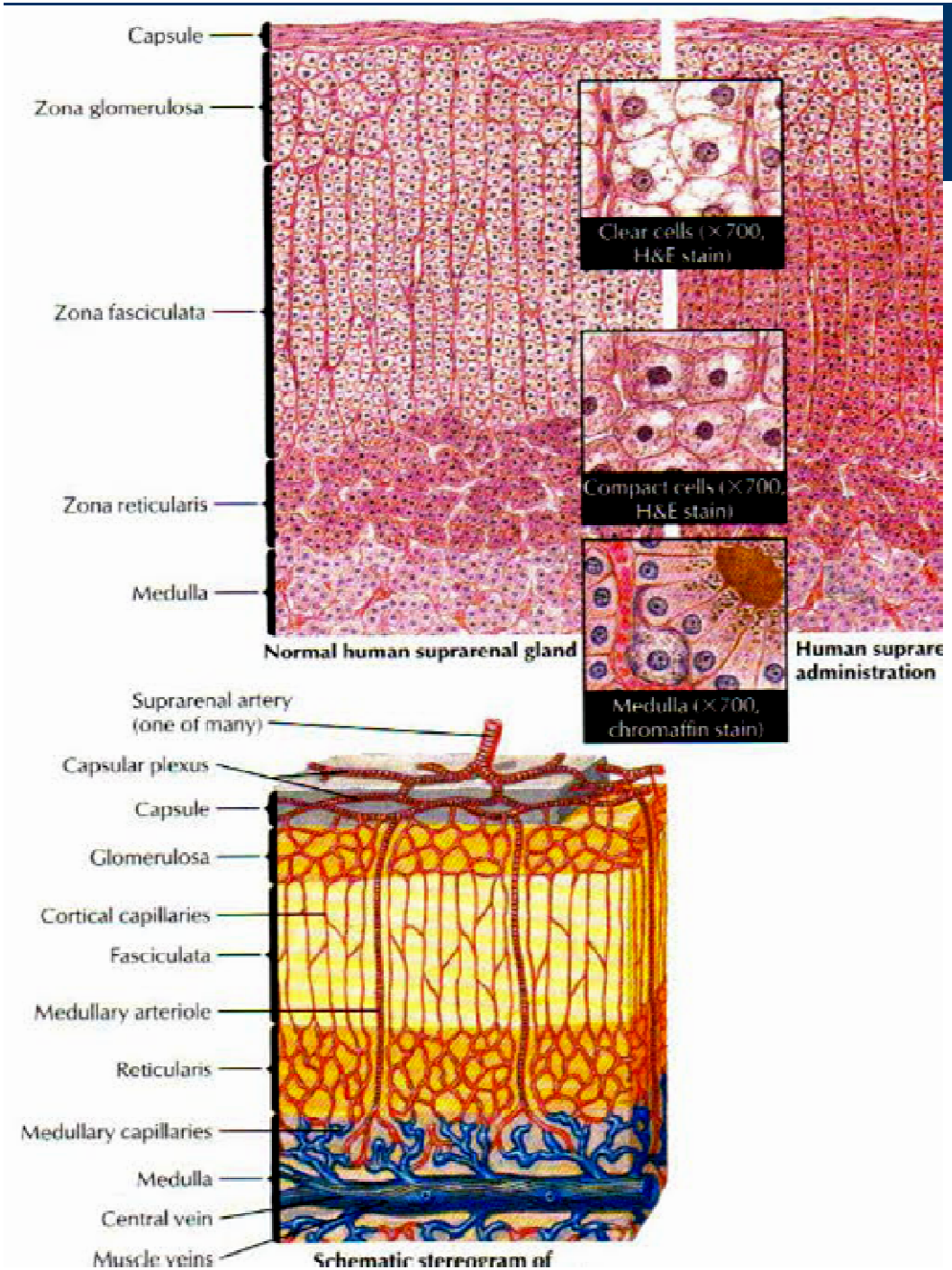
- pyramidal organs found anteriorily above each kidney
- each gland is 4 to 6 cm in greatest dimension and weighs about 4 g


Anterior vagal trunk
Right phrenic nerve
Right inferior phrenic artery and plexus
Right adrenal gland
Right greater thoracic splanchnic nerve
Right lesser thoracic splanchnic nerve
Right least thoracic splanchnic nerve
Right renal ganglion and plexus
Right sympathetic trunk
Right 1st lumbar splanchnic nerve
Left phrenic nerve
Posterior vagal trunk
Left inferior phrenic artery and plexus
Left adrenal gland
Left greater thoraci splanchnic nerve
Celiac plexus and ganglia
Left lesser thorac splanchnic nerv
Aorticorenal ganglia
Left leas thoracic splanchi nerve
Left renal ganglic and plexus
Left sympathetic trunk
Left 1st lumbar splanchnic nerve
Superior mesenteric ganglion


Spinal cord
Intermediolateral cell column (lateral horn of gray matter)
T5
T6
T7
T8
Thoracic splanchnic nerves (pre-ganglionic fibers)
Sympathetic trunk
Celiac ganglion
Postganglionic fibers supply blood vessels
Adrenal gland
Medulla
Cor
Preganglionic fibers ramify around cells of medulla


Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Clear cells (× 700, H & E stain)
Compact cells (× 700, H & E stain)
C
V
G
Medulla (× 700, chromaffin stain)
Normal human adrenal gland
Human adrenal gland after adminstration of ACTH
V = Venous capillary
C = Capillary
G = Ganglion cell

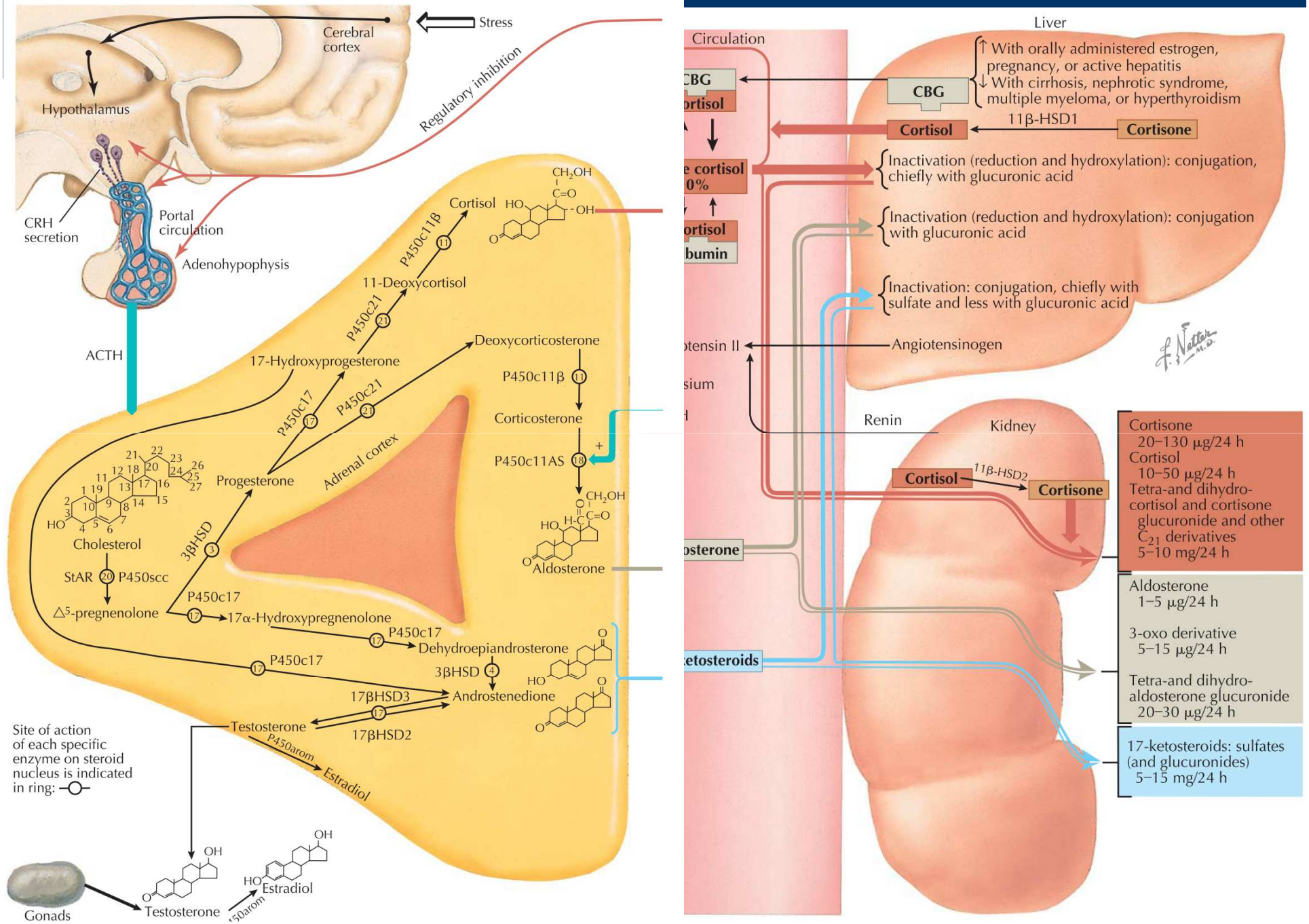

Adrenal artery (one of many)
Capsular plexus
Capsule
Glomerulosa
Cortical capillaries
Fasciculata
Medullary arteriole
Reticularis
Medullary capillaries
Medulla
Central vein
Muscle fibers
Schematic stereogram of intrinsic adrenal circulation
Capsule
Permanent cortex
Fetal cortex (containing dark cells destined to form medulla)
Adrenal gland of newborn



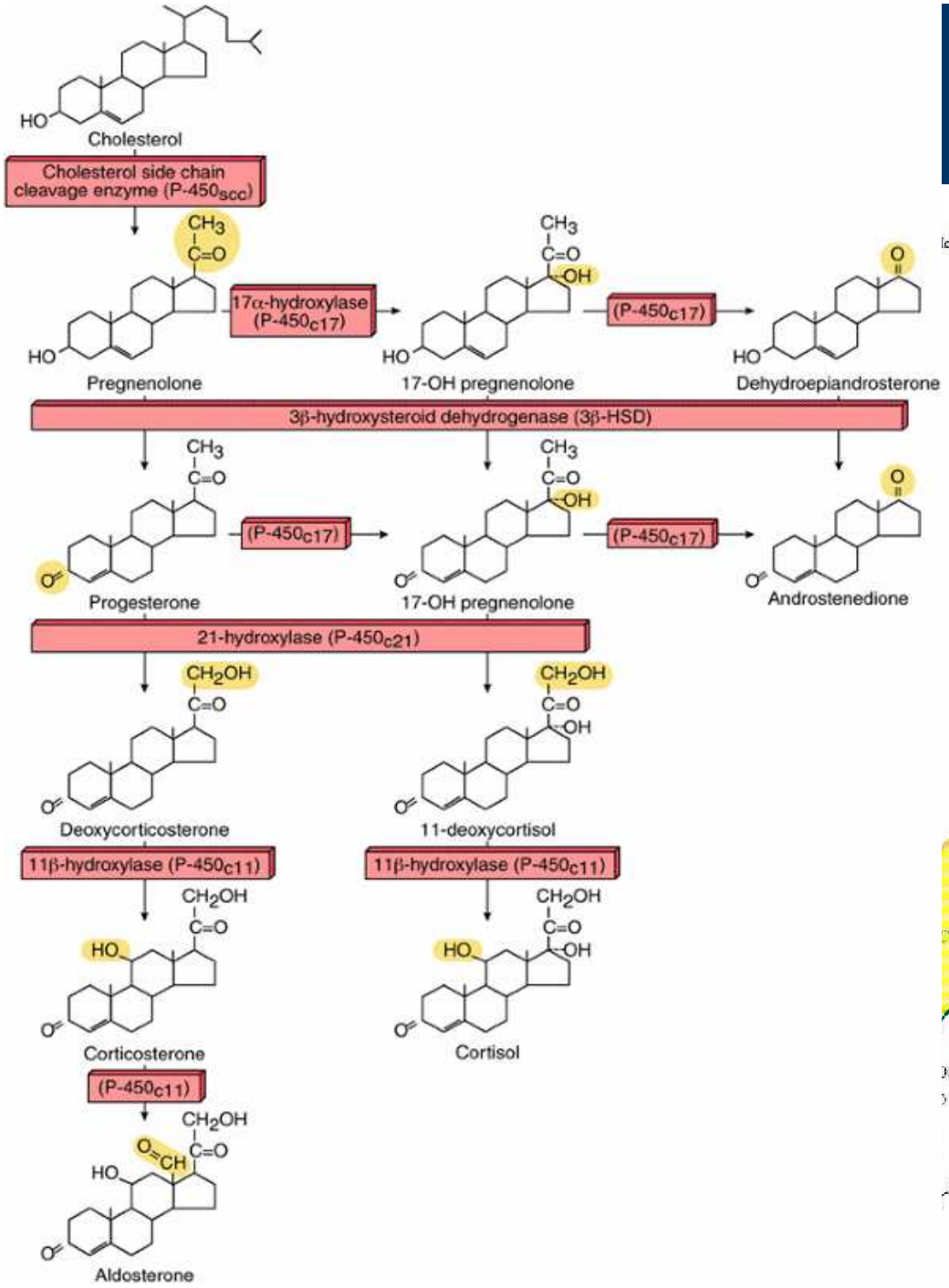
Histological overview

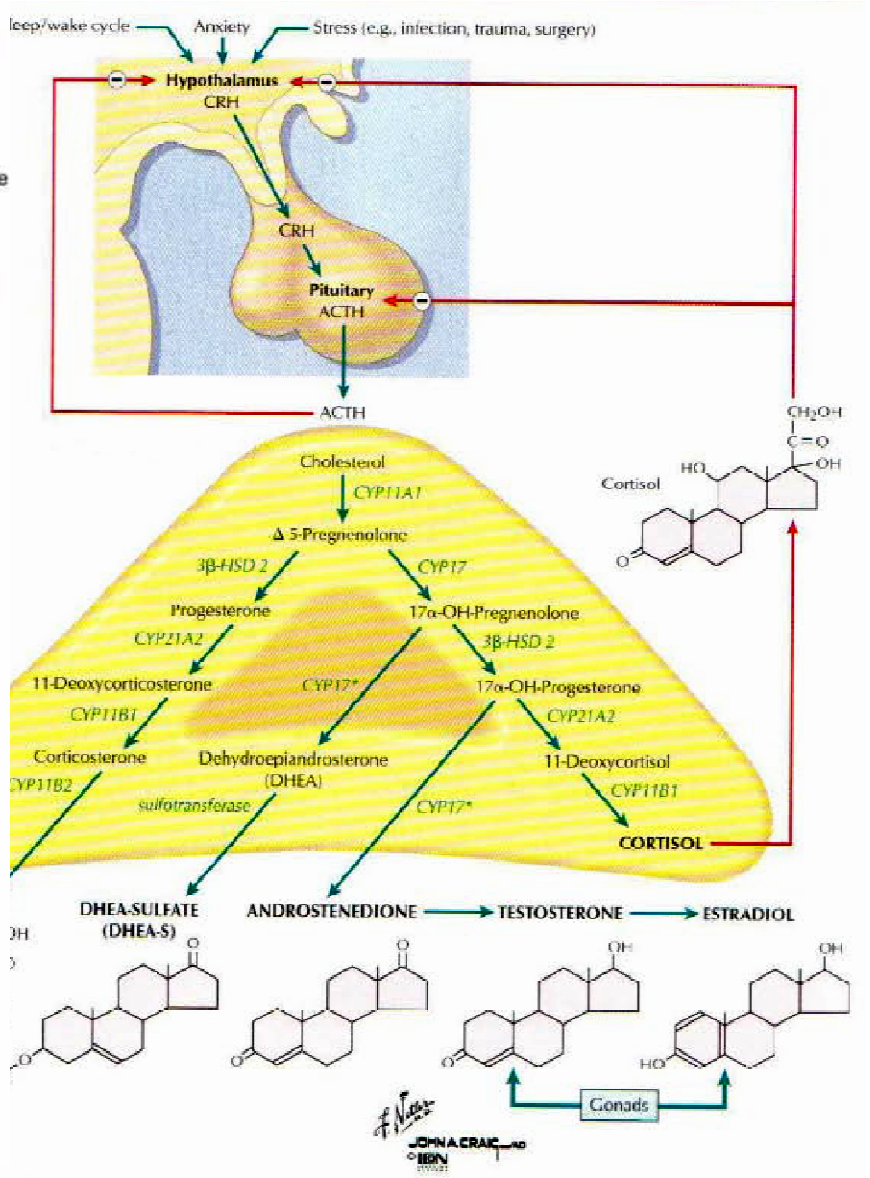
- **zona glomerulosa** - 15% of the cortex aldosterone production is stimulated by angiotensin and potassium, and inhibited by atrial natriuretic peptide and somatostatin.
- **zona fasciculata** - 75% of the cortex. glucocorticoids under the control of ACTH
- **zona reticularis** – glucocorticosteroids, weak androgen – S- DHEA

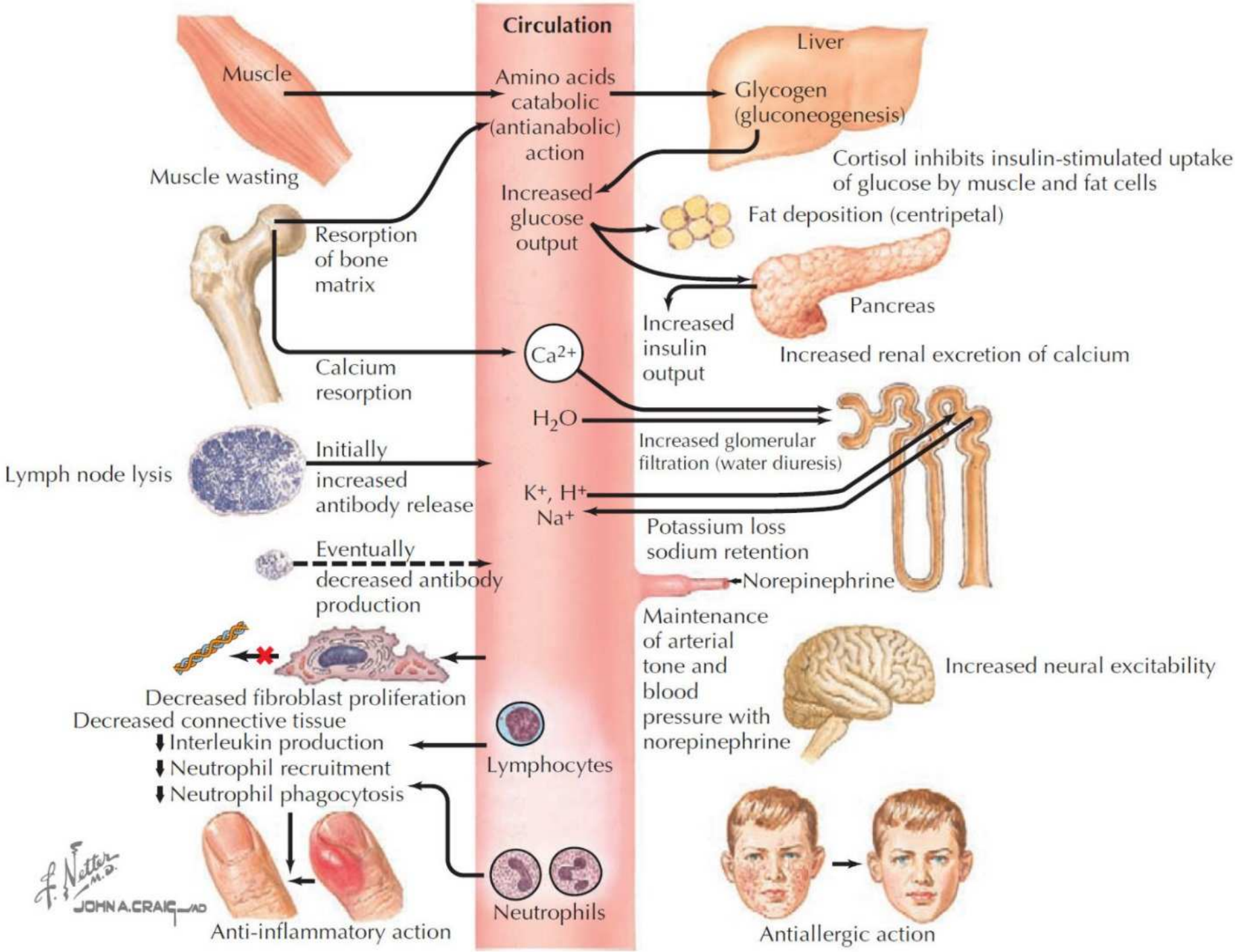
- **Ectopic adrenal tissue** - retroperitoneum, broad ligament near the ovary, near the epididymis, lung, and liver. Ectopic adrenal tissue does not contain medullary cells.


Cerebral cortex
Stress
Hypothalamus
Regulatory inhibition
CRH secretion
Portal circulation
Adenohypophysis
ACTH
Cholesterol
StAR
P450scc
△5-pregnenolone
3βHSD
Progesterone
17-Hydroxyprogesterone
P450c17
P450c21
11-Deoxycortisol
P450c11β
Cortisol
Deoxycorticosterone
Corticosterone
P450c11AS
Aldosterone
17α-Hydroxypregnenolone
Dehydroepiandrosterone
Androstenedione
17βHSD3
17βHSD2
Testosterone
P450arom
Estradiol
Adrenal cortex
Site of action of each specific enzyme on steroid nucleus is indicated in ring:
Gonads
Testosterone
Estradiol
Liver
Circulation
CBG
Cortisol
Cortisone
11β-HSD1
↑ With orally administered estrogen, pregnancy, or active hepatitis
↓ With cirrhosis, nephrotic syndrome, multiple myeloma, or hyperthyroidism
Inactivation (reduction and hydroxylation): conjugation, chiefly with glucuronic acid
Inactivation (reduction and hydroxylation): conjugation with glucuronic acid
Inactivation: conjugation, chiefly with sulfate and less with glucuronic acid
Angiotensinogen
Renin
Kidney
11β-HSD2
Cortisone 20–130 μg/24 h
Cortisol 10–50 μg/24 h
Tetra-and dihydro-cortisol and cortisone glucuronide and other C_{21} derivatives 5–10 mg/24 h
Aldosterone 1–5 μg/24 h
3-oxo derivative 5–15 μg/24 h
Tetra-and dihydro-aldosterone glucuronide 20–30 μg/24 h
17-ketosteroids: sulfates (and glucuronides) 5–15 mg/24 h

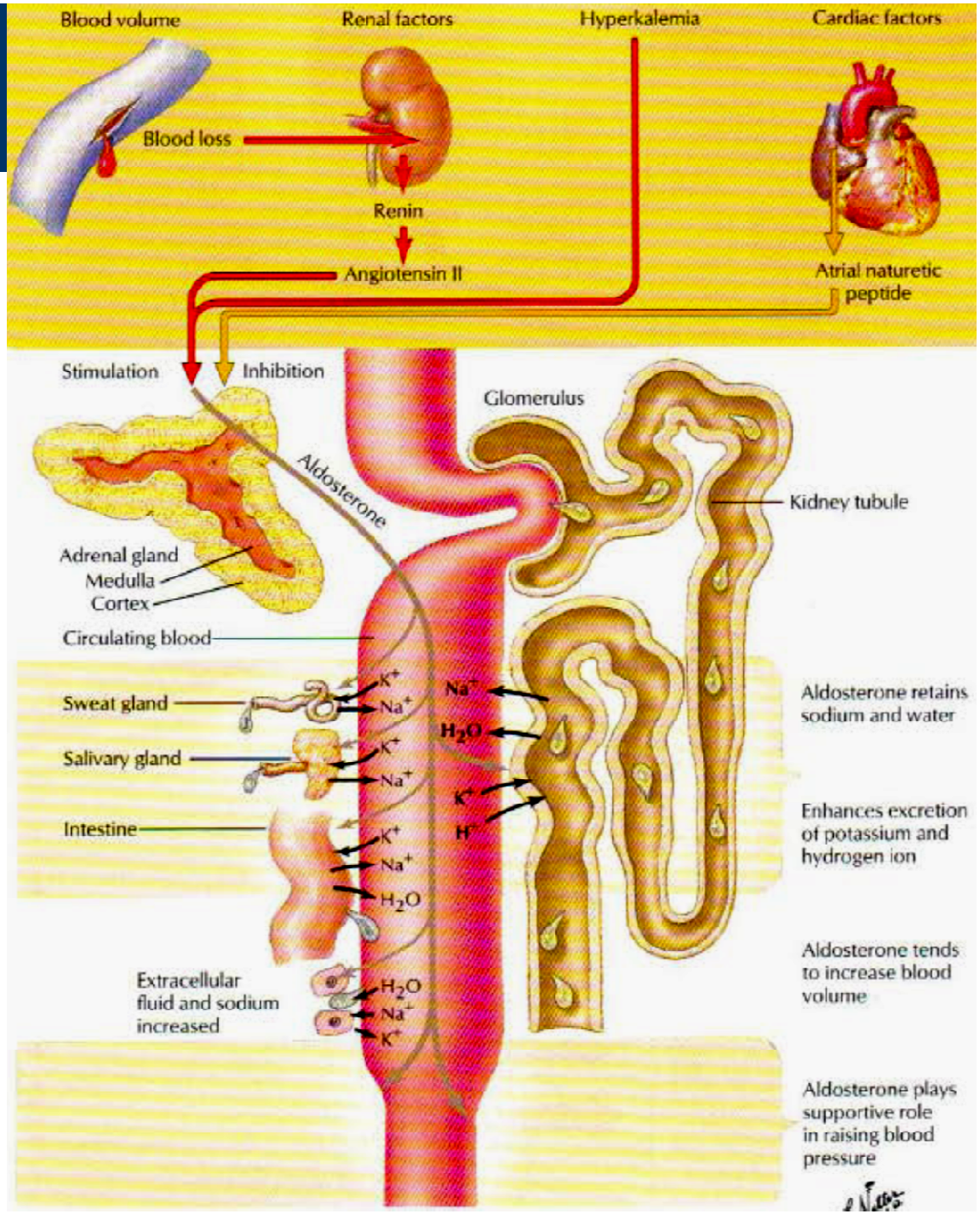
Hormone synthesis





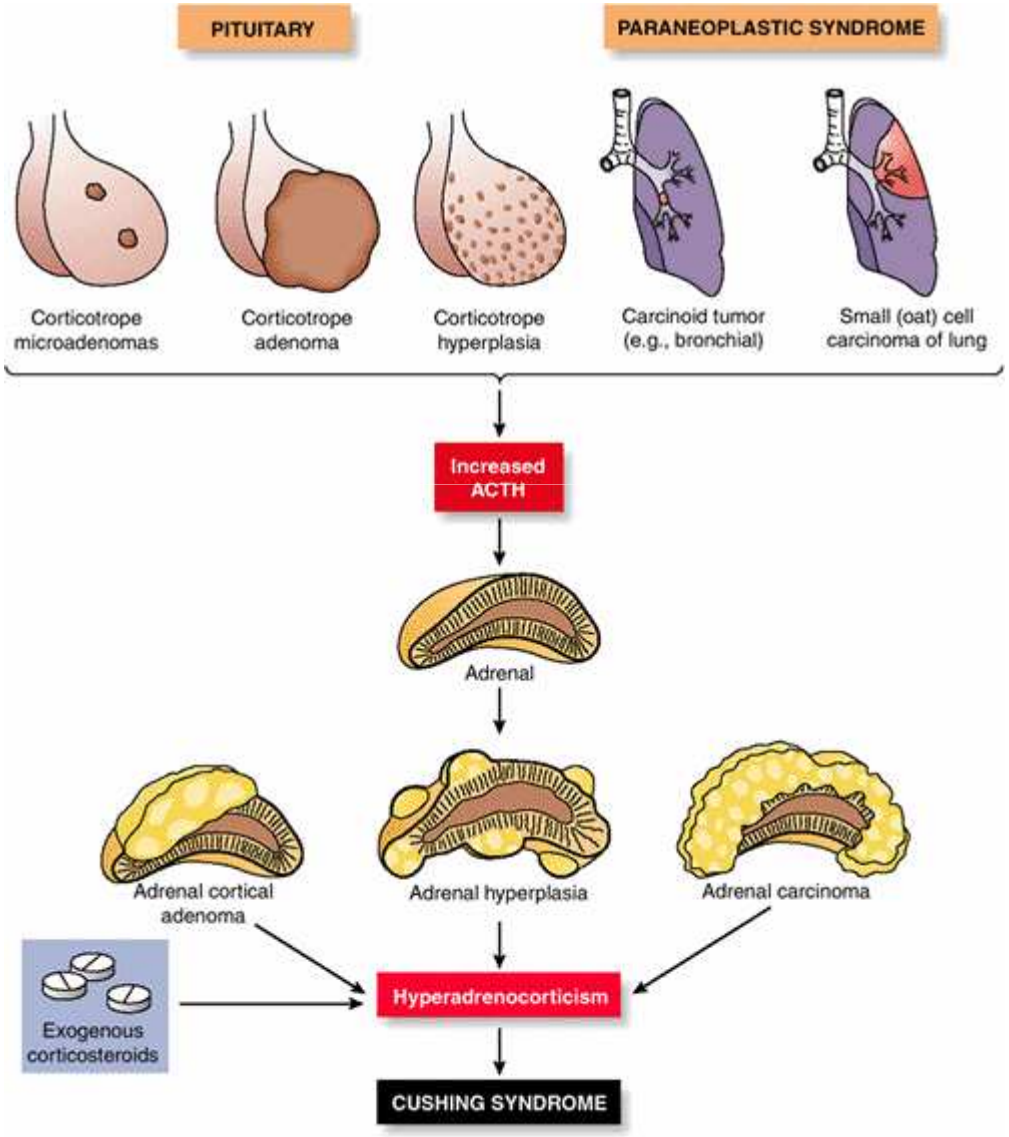

Circulation
Muscle
Muscle wasting
Amino acids
catabolic
(antianabolic)
action
Liver
Glycogen
(gluconeogenesis)
Cortisol inhibits insulin-stimulated uptake
of glucose by muscle and fat cells
Increased
glucose
output
Fat deposition (centripetal)
Resorption
of bone
matrix
Pancreas
Increased
insulin
output
Increased renal excretion of calcium
Ca2+
Calcium
resorption
H2O
Increased glomerular
filtration (water diuresis)
Lymph node lysis
Initially
increased
antibody release
K+, H+
Na+
Potassium loss
sodium retention
Eventually
decreased antibody
production
Norepinephrine
Maintenance
of arterial
tone and
blood
pressure with
norepinephrine
Increased neural excitability
Decreased fibroblast proliferation
Decreased connective tissue
Interleukin production
Neutrophil recruitment
Neutrophil phagocytosis
Lymphocytes
F. Netter M.D.
JOHN A. CRAIG M.D.
Neutrophils
Anti-inflammatory action
Antiallergic action

Physiological effects of mineralocorticoids



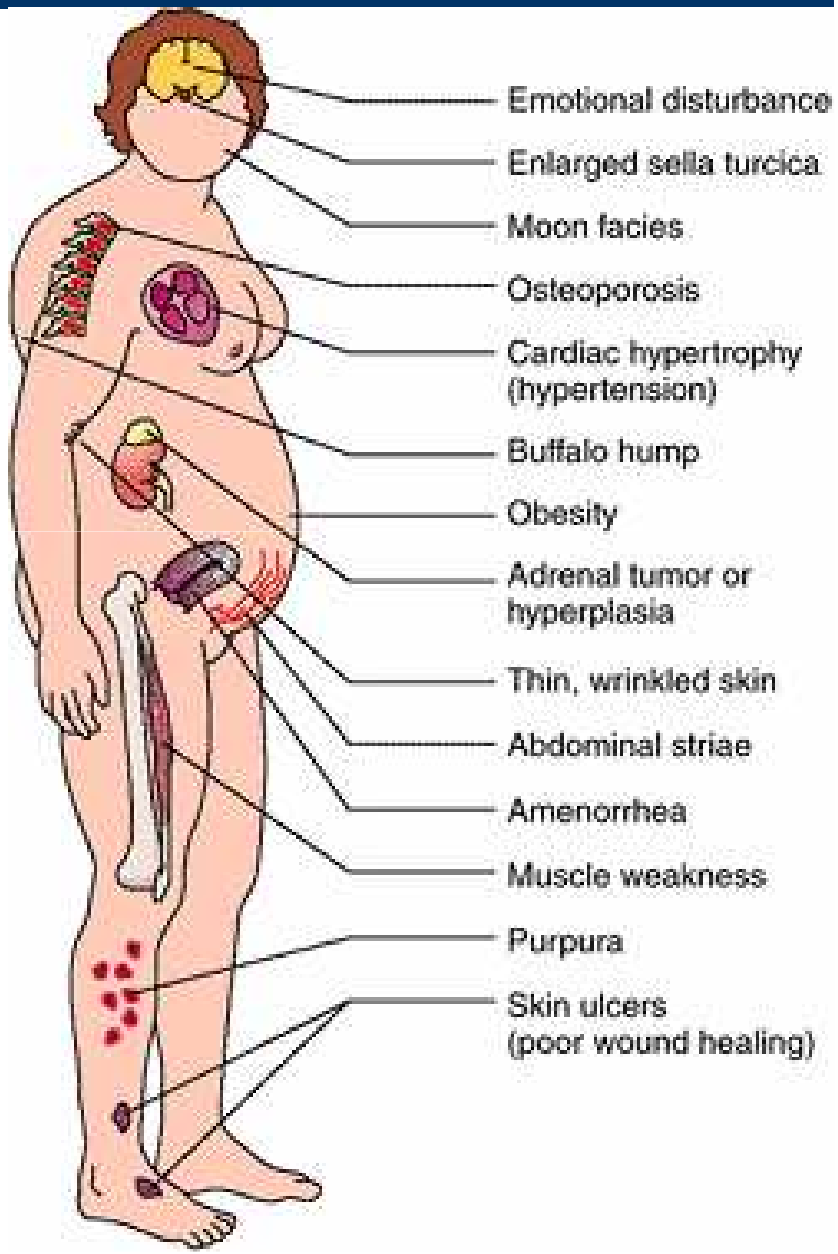
Hypercortisolism

Hypercorticism - Cushing syndrome

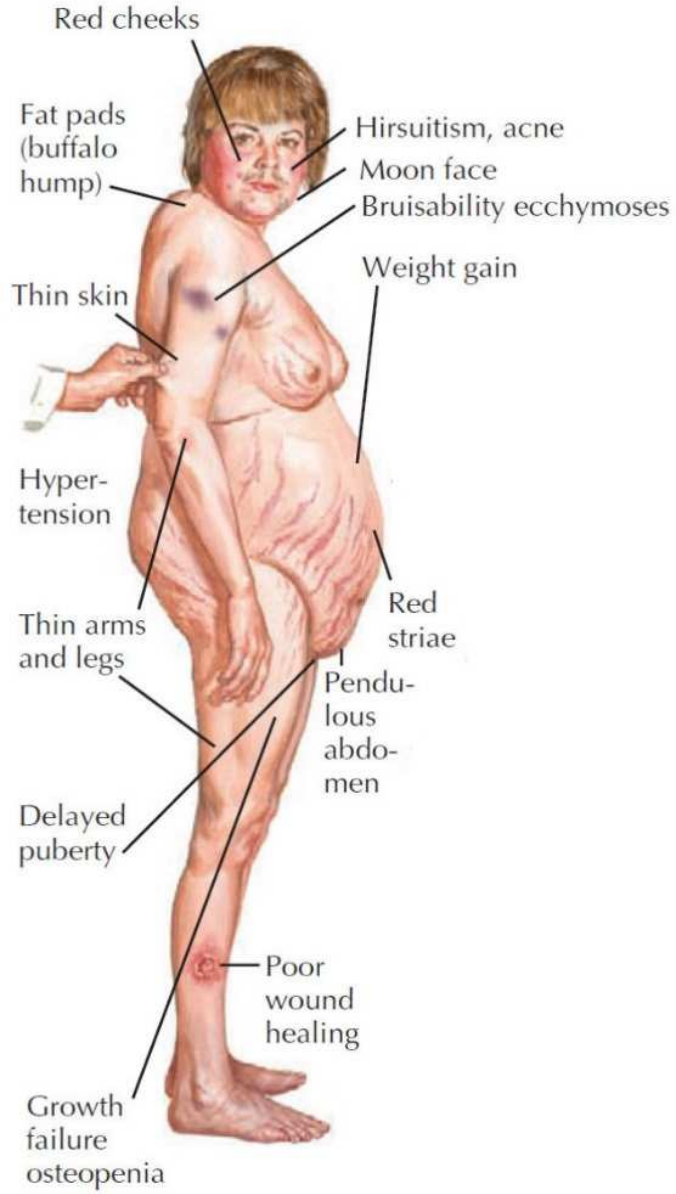


Cushing syndrome - symptoms

- **Obesity** of the face (moon face), neck (buffalo hump), trunk, and abdomen; extremities are even wasted (spider)***;*** skin is atrophic; fat decreased.
- Enlargement of the abdomen fat deposition stretches the thin skin and produces **purplish striae**,
- **Skin** - atrophic; hyperpigmentation (POMC). Acanthosis nigricans
- **Bone resorption** – osteoporosis, fractures of ribs, occ. long bones, vertebral fractures + back pain.
- Proximal muscle wasting (***steroid myopathy***) - weakness (severe)
- **Hypertension** (excessive mineralocorticoid activity), congestive heart failureincreased intraocular pressure (1/4)
- **Sex:** women (virilism) - increased facial hair, thinning of scalp hair, acne, and oligomenorrhea. men - erectile dysfunction, decreased libido.
- **Hyperglycaemia** + hyperinsulinemia. (**steroid diabetes** in 15% of patients)
- **Personality changes** (irritability, emotional lability, depression, and paranoia, suicide.



Cushing syndrome

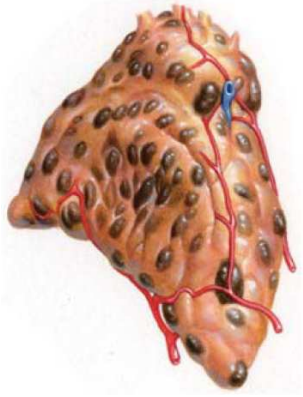


The Carney complex is characterized by spotty skin pigmentation. Pigmented lentigines and blue nevi can be seen on the face—including the eyelids, vermilion borders of the lips, the conjunctivae, the sclera—and the labia and scrotum.

Additional features of the Carney complex can include:

- Myxomas: cardiac atrium, cutaneous (e.g., eyelid), and mammary
- Testicular large-cell calcifying Sertoli cell tumors
- Growth hormone–secreting pituitary adenomas
- Psammomatous melanotic schwannomas

PRIMARY PIGMENTED NODULAR ADRENOCORTICAL DISEASE



PPNAD adrenal glands are usually of normal size, and most are studded with black, brown, or red nodules. Most of the pigmented nodules are less than 4 mm in diameter and interspersed in the adjacent atrophic cortex.

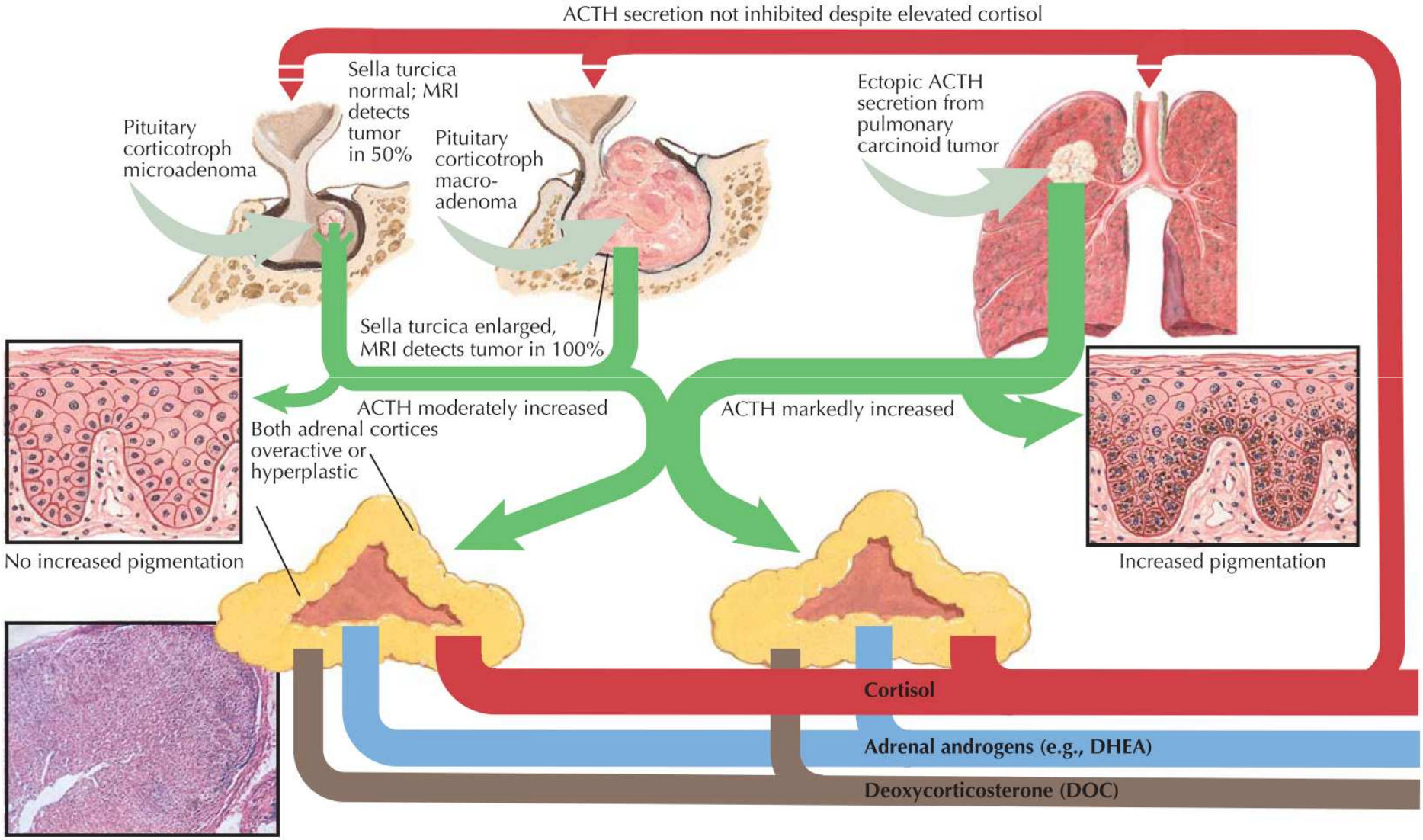
Hypercortisolism

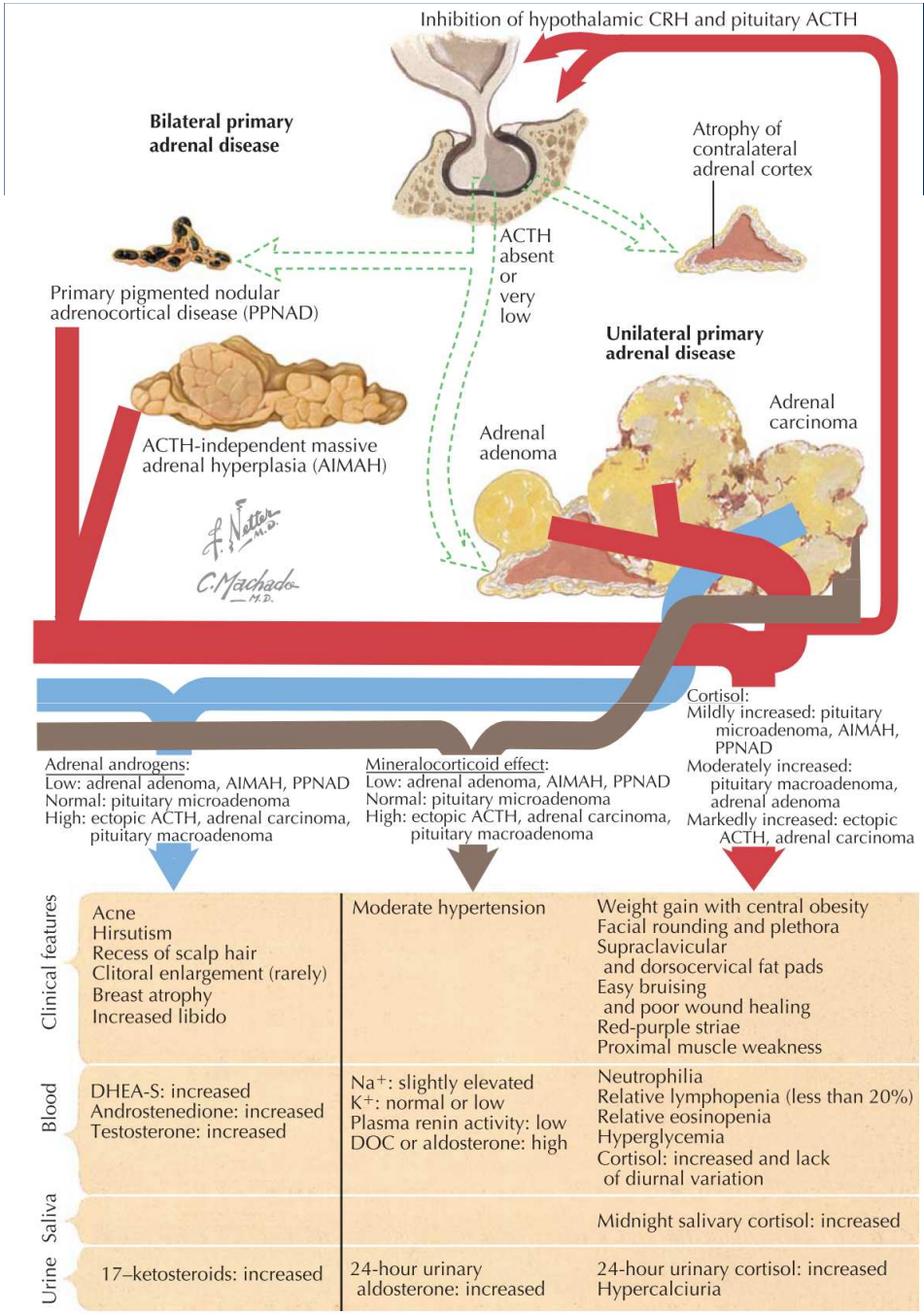
- **Laboratory -** lymphopenia (2/3), low eosinophils (1/3). Hypercalciuria. Normocallcxuria; cholesterol and triglyceride levels are frequently elevated.
- Increased glucocorticoid levels + **dexamethasone suppression test** distinguishes ACTH-dependent and ACTH-independent forms of Cushing sy.
- Dexamethasone suppresses pituitary ACTH secretion

Woman with ACTH - adenoma

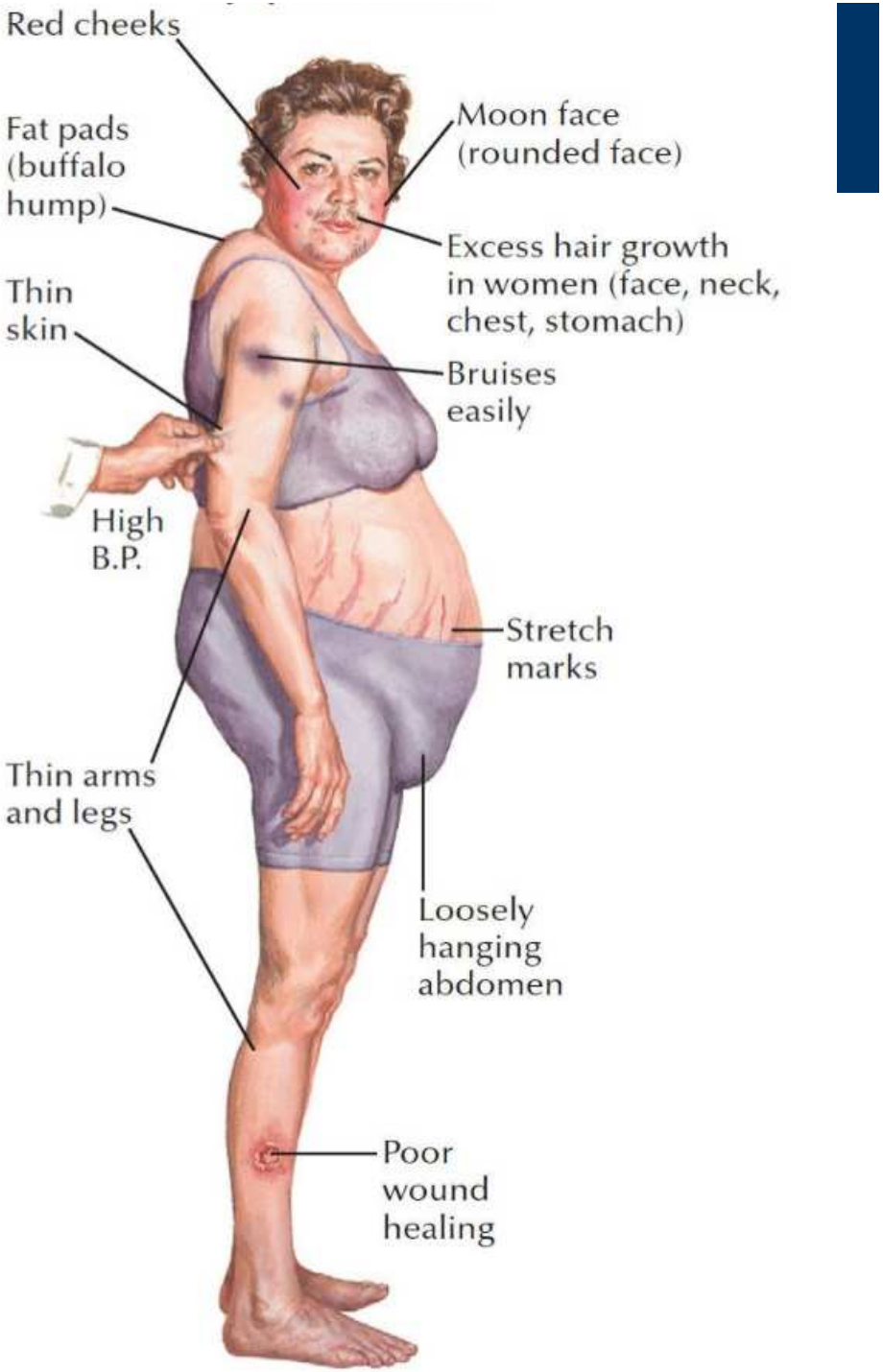
Note the wide (> 1 cm) purplish abdominal striae in Cushing's syndrome

Cushing syndrome - pathophysiology

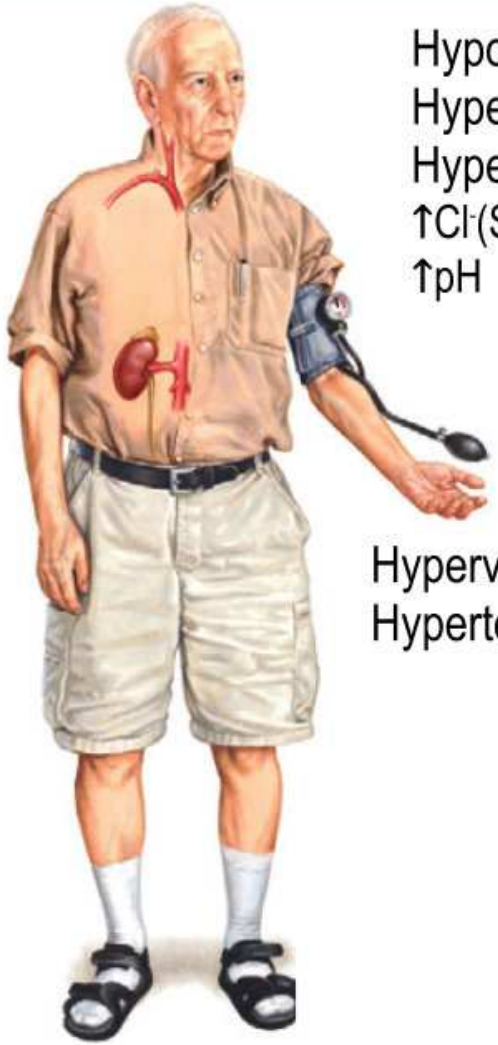




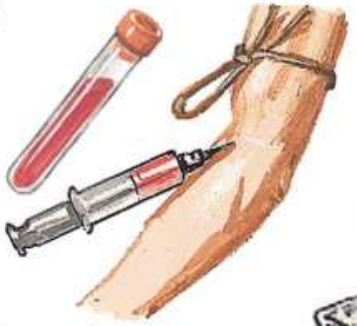
Clinical features	Acne Hirsutism Recess of scalp hair Clitoral enlargement (rarely) Breast atrophy Increased libido	Moderate hypertension	Weight gain with central obesity Facial rounding and plethora Supraclavicular and dorsocervical fat pads Easy bruising and poor wound healing Red-purple striae Proximal muscle weakness
Blood	DHEA-S: increased Androstenedione: increased Testosterone: increased	Na^+: slightly elevated K^+: normal or low Plasma renin activity: low DOC or aldosterone: high	Neutrophilia Relative lymphopenia (less than 20%) Relative eosinopenia Hyperglycemia Cortisol: increased and lack of diurnal variation
Saliva			Midnight salivary cortisol: increased
Urine	17–ketosteroids: increased	24-hour urinary aldosterone: increased	24-hour urinary cortisol: increased Hypercalciuria



Hyperaldosteronism



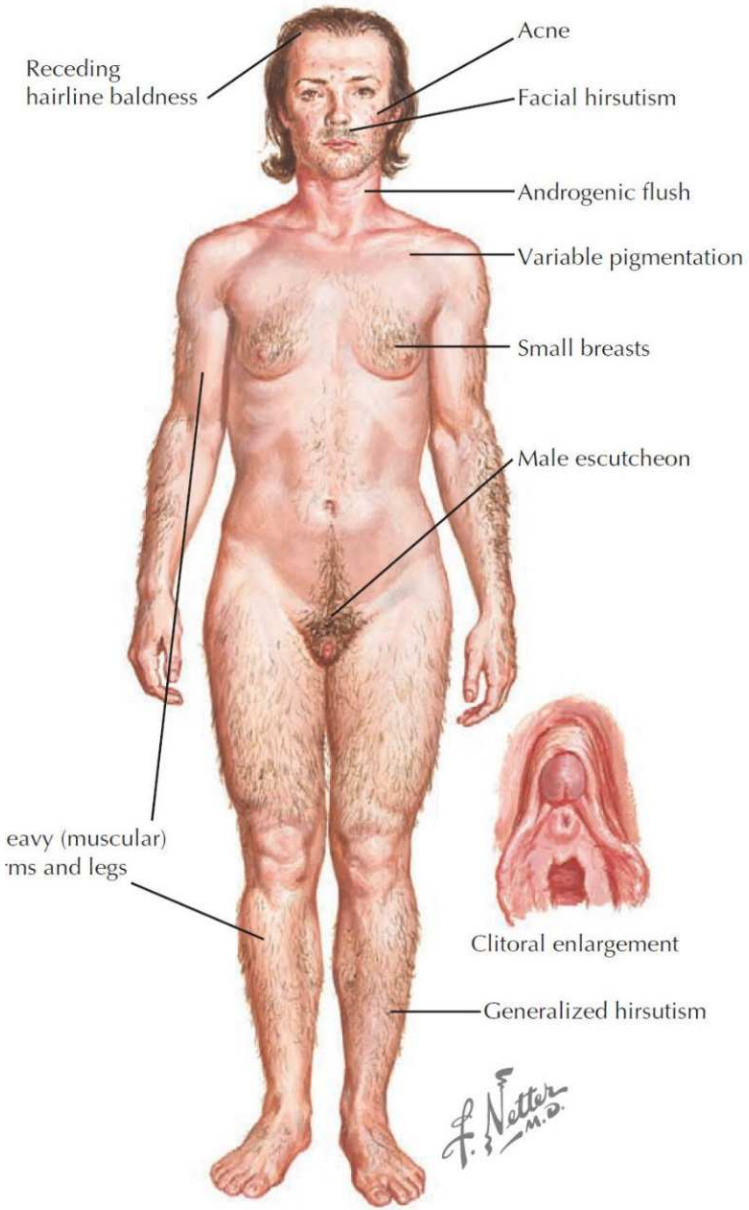
Hypokalemia ↓K^+(S)
Hypernatremia ↑Na^+(S)
Hyperchloremic alkalosis
↑Cl^-(S)
↑pH

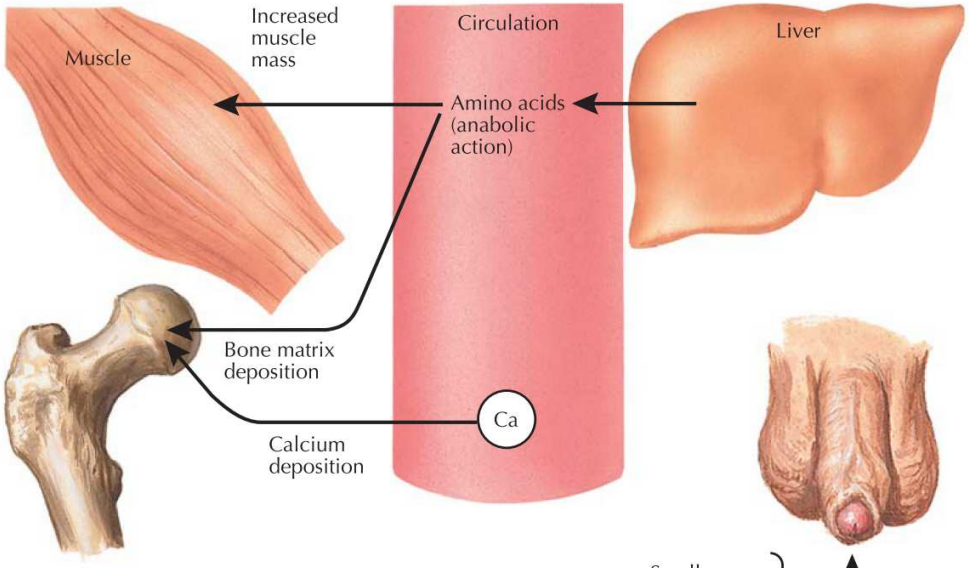


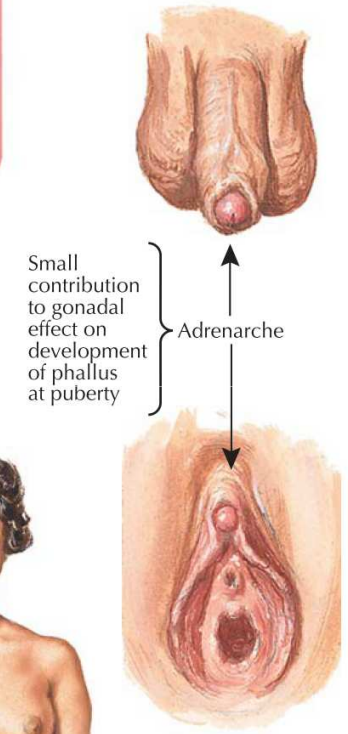
Hypervolaemia
Hypertension

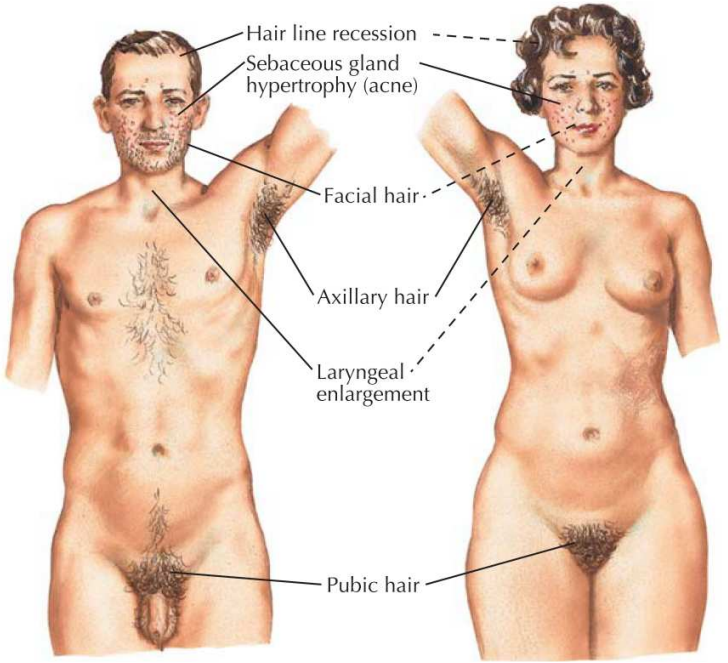
Testing of urine or blood samples can confirm the diagnosis. The plasma renin activity (PRA) blood test can tell whether primary (low PRA) or secondary (high PRA) aldosteronism is present.

Adrenogenital syndrome









Hypocorticism

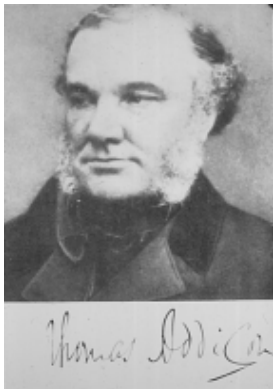
Addison disease

SECONDARY ADRENAL INSUFFICIENCY

30% of cases
a) hypothalamic insufficiency - low CRH
b) pituitary insufficiency (radiation) - low ACTH
c) therapy by cortisol or prednisone

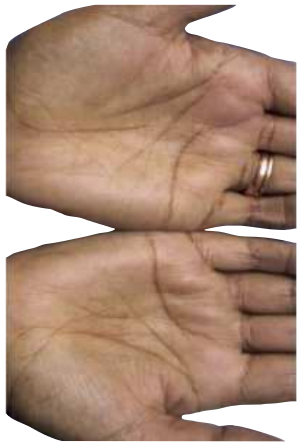
PRIMARY ADRENAL INSUFFICIENCY

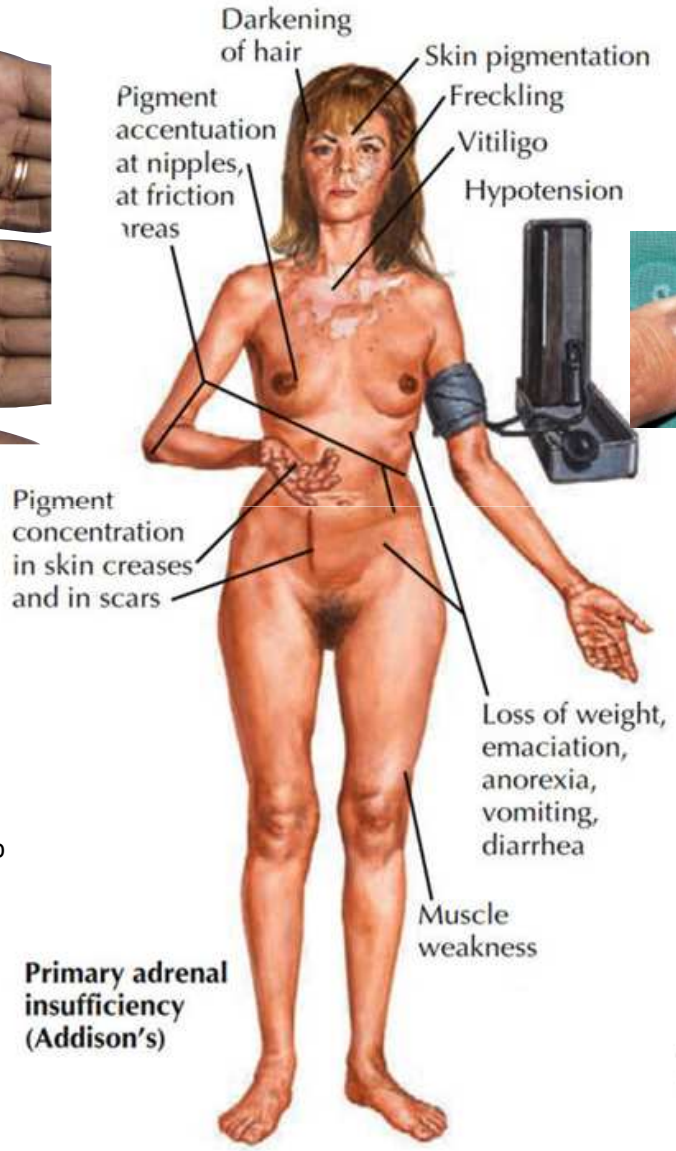
70% of cases
a) auto-immune (adrenal cortex atrophy
~ 90% of gland must bedestroyed)
- mostly (80% of cases) both glucocorticoids and mineralocarticoids are deficient
b) long term chronic systemic inflammations (TBC in 20% of cases)
c) metastasis to
d) amyloidosis



Thomas Addison (1793 - 1860)
University of Edinburgh & Guy's Hospital (1837)
english physician after whom Addison's disease, a metabolic dysfunction caused by atrophy of the adrenal cortex, and Addison's (pernicious) anaemia were named.
Elements of the Practice of Medicine (1839).
Doctor
The founder of endocrinology
Fellow of the Royal College of Physicians

Addison disaease





Nausea, Vomiting

Hyperpigmentation 92 - 96 %
Weakness & fatigue 74 - 100 %
Weight loss & lack of appetite 56 - 100 %
Hyponatriemia 88 - 96%
Hypotension, dehydration 58 - 88 %
Hyperkalemia 52 - 64 %
GIT symptoms - nausea, vomiting, diarrhea 56 %
Postural dizziness 12 %
Adrenal calcifications 9-33 %
Hypercalcaemia 6 - 41 %
Muscle and joint aches 6 %
Intolerance to cold 5 %
Vitiligo 4 %