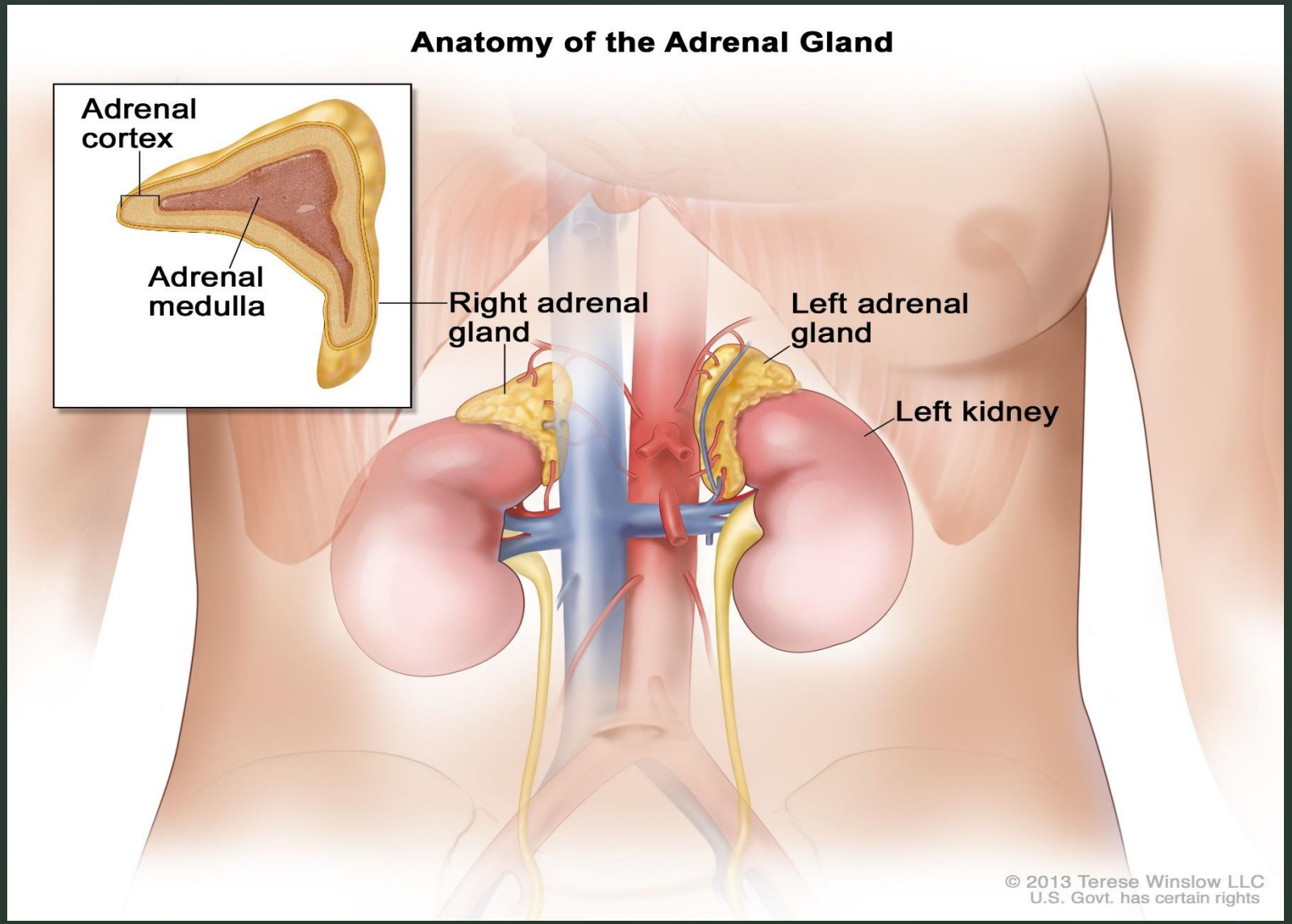
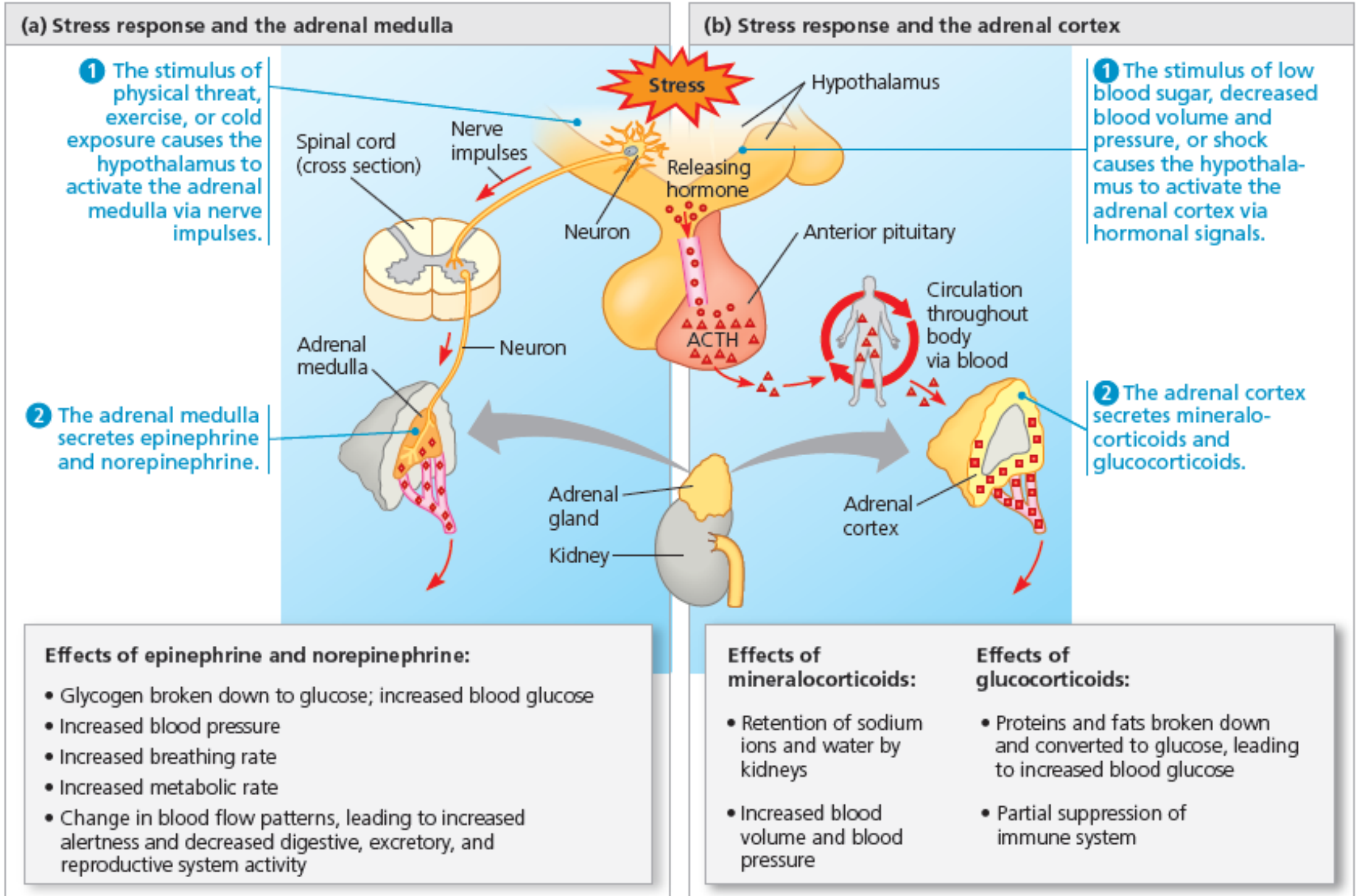
Clinical endocrinology part 2

Adrenal gland



- The adrenal glands play a major role in the response to *stress*, a state of threatened homeostasis. Located atop the kidneys (the *renal* organs), each **adrenal gland** is actually made up of two glands with different cell types, functions, and embryonic origins: the adrenal *cortex*, the outer portion, and the adrenal *medulla*, the central portion

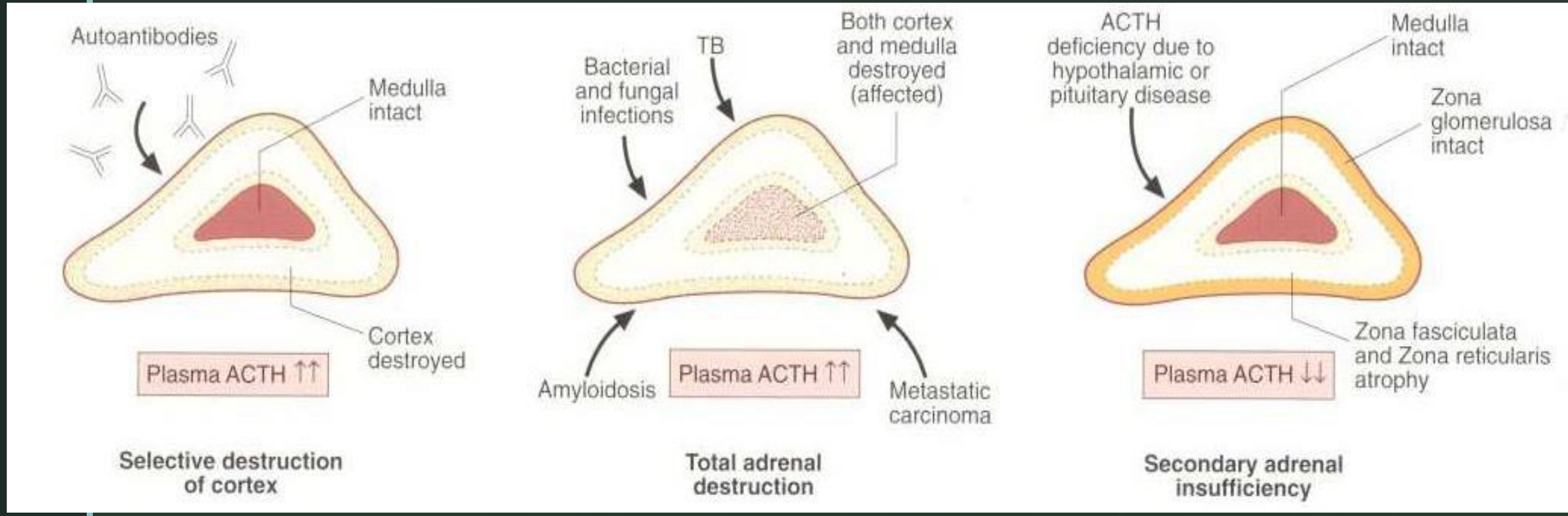

(a) Stress response and the adrenal medulla
(b) Stress response and the adrenal cortex
1 The stimulus of physical threat, exercise, or cold exposure causes the hypothalamus to activate the adrenal medulla via nerve impulses.
Stress
Spinal cord (cross section)
Nerve impulses
Neuron
Hypothalamus
Releasing hormone
Anterior pituitary
ACTH
Circulation throughout body via blood
Adrenal medulla
Neuron
2 The adrenal medulla secretes epinephrine and norepinephrine.
Adrenal gland
Kidney
Adrenal cortex
1 The stimulus of low blood sugar, decreased blood volume and pressure, or shock causes the hypothalamus to activate the adrenal cortex via hormonal signals.
2 The adrenal cortex secretes mineralocorticoids and glucocorticoids.
Effects of epinephrine and norepinephrine:
• Glycogen broken down to glucose; increased blood glucose
• Increased blood pressure
• Increased breathing rate
• Increased metabolic rate
• Change in blood flow patterns, leading to increased alertness and decreased digestive, excretory, and reproductive system activity
Effects of mineralocorticoids:
• Retention of sodium ions and water by kidneys
• Increased blood volume and blood pressure
Effects of glucocorticoids:
• Proteins and fats broken down and converted to glucose, leading to increased blood glucose
• Partial suppression of immune system

Gland & region/ cells	Hormones	Regulation of secretion	Functions
Adrenal cortex Zona glomerulosa	Mineralcorticoids, e.g. aldosterone	Stimulated by angiotensin II	Regulates salt & water balance in blood by increasing Na^+ & H_2O absorption and K^+ secretion by the distal convoluted tubules in the kidney
Adrenal cortex Zona fasciculata	Glucocorticoids, e.g. cortisol & weak androgens	Stimulated by adrenal corticotrophic hormone	Suppresses immune response and regulates carbohydrate metabolism
Adrenal cortex Zona reticularis	Weak androgens, e.g. dehydroepiandrosterone	Stimulated by adrenal corticotrophic hormone	Precursor for testosterone production
Adrenal medulla Chromaffin cells	Catecholamines, e.g. Epinephrine & norepinephrine	Preganglionic sympathetic neurons	Increases heart rate, respiration, and blood pressure Constricts vessels to reduce blood flow to GI tract

❑ Adrenal gland dysfunctions

- **1) Adrenal insufficiency (Addison's):**
- **-** It is a rare condition that if unrecognized is potentially fatal. It is relatively simple to treat once it is diagnosed.
- **-** It is characterized by decrease in glucocorticoids, mineralocorticoids and androgens leading to hypoglycaemia, hyperkalaemia, hyponatremia, postural hypotension, decreased androgen and hyper-pigmentation (due to Increase in ACTH).

Causes of Addison's disease



Lab. Diagnosis:

- 1) Hyponatraemia: low in aldosterone → increased Na and H2O loss → hypovolaemia and hypotension → stimulation of ADH → H2O retention
- 2) Hyperkalaemia
- 3) Elevated serum urea
- 4) Hyperpigmentation: In primary hypofunction, ACTH increased due to feed-back stimulation of anterior pituitary. ACTH has melanocyte-stimulating activity

5) Serum cortisol and ACTH levels

Plasma cortisol	Plasma ACTH	Disorder	Affected gland
low	high	Primary Addison	Adrenal gland
low	low	Secondary Addison	Pituitary gland

- 6) Synacthen tests:
- Synacthen is a synthetic analogue of ACTH
- a) **Short synacthen test (SST):** IV administration of 25 □g of synacthen, cortisol is measured at 0, 30, and 60’
- b) **Long synacthen test (LST):** equivocal response to SST may require LST. IM 1 mg of depot synacthen is administered daily for 3 days

2) Adrenal Hyperfunction:

- **- Cortisol excess (Cushing's Syndrome):** Prolonged exposure of the body tissues to cortisol or other glucocorticoids leads to clinical feature known as **Cushing's Syndrome**
- ▪ Causes: 1. Excessive production of ACTH from pituitary tumour (**secondary**).
- 2. Adrenal gland tumours (**primary**).
- 3. Exogenous administration of glucocorticoids or ACTH (**iatrogenic**).
- 4. Ectopic ACTH-secreting tumours.

- ▪ **Symptoms:** Moon face, obesity , hirsutism, Hypertension, menstrual disturbance, osteoporosis, emotional disorders muscle weakness and capillary fragility.

Lab. diagnosis:

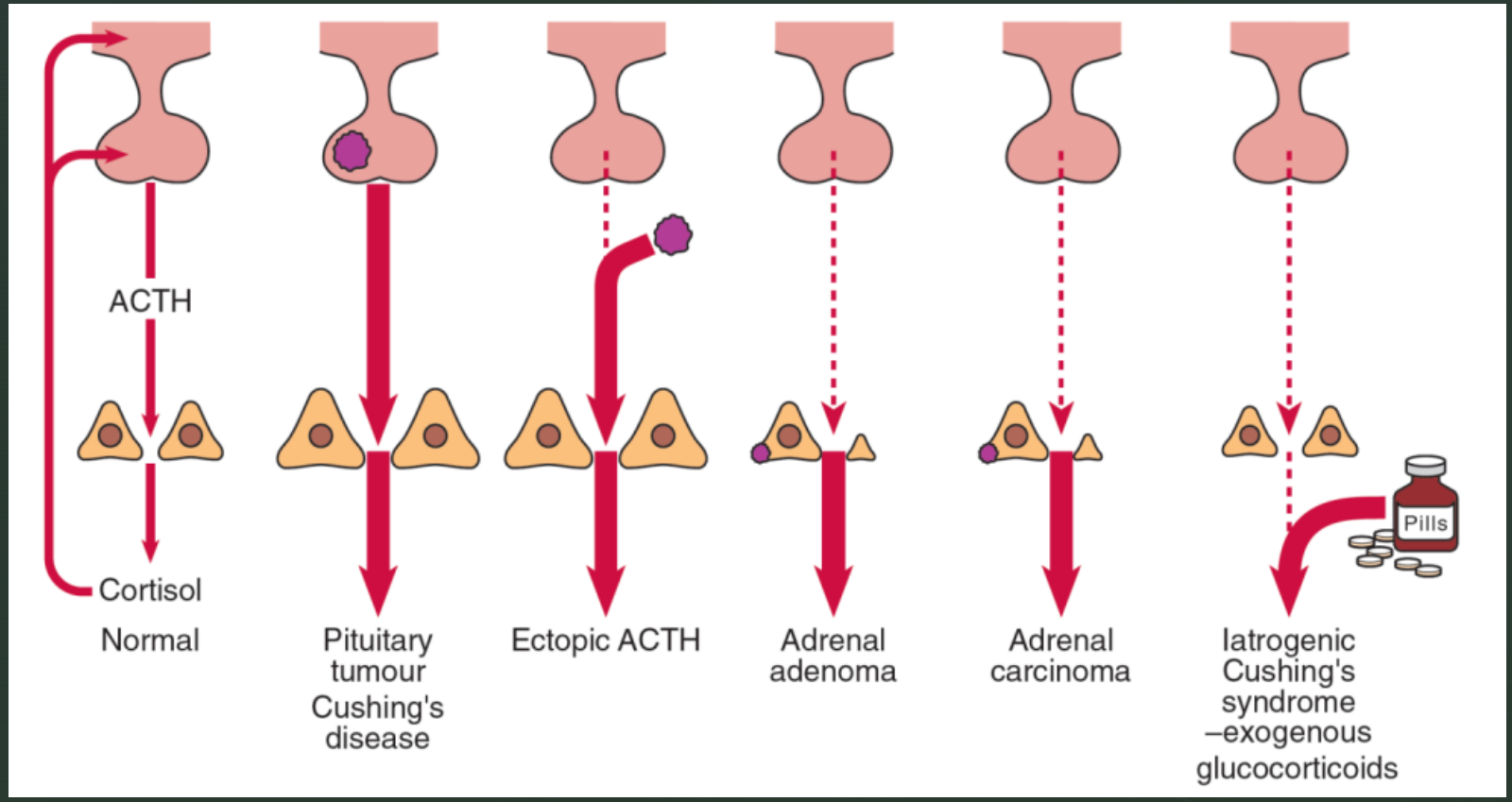
- 1. **Urinary free cortisol:** The excess amounts of cortisol will exceed the available capacity of plasma binding protein and the free cortisol is filtered readily into the urine. Free cortisol is measured in 24-hrs urine sample or assessed as cortisol:cratinine ratio in an early morning urine sample. Cortisol:cratinine ratio can be made on a small aliquot of urine, if the test is negative on three occasions, Cushing's syndrome may be excluded.
- 2. **Serum cortisol level:** Cortisol is measured at 8:00 and 22:00 (morning sample having higher value than the evening). This difference is not apparent in Cushing's syndrome.
- 3. Dexamethasone suppression test
- Low dose DST: (1 mg Dexamethason orally at 23:00 and cortisol measured at 9:00, if < 50 nmol/L ® normal
- High dose DST: (8 mg of Dexamethason is used if failure to response to Low dose DST due to overproduction of ACTH (Cushing or ectopic malignant or adrenal production of cortisol)

- 4. **Insulin-induced hypoglycaemia:** In normal, a hypoglycaemia (< 2.2 mmol/L) leads to rise in serum cortisol more than 200 mmol/L. Failure of the serum cortisol to rise after insulin-induced hypoglycaemia is diagnostic for Cushing’s syndrome

- **5. Differential diagnosis:**

Cortisol	ACTH	Disorder	Affected gland
High	low	Primary Cushing	Adrenal gland
high	High or normal	Secondary Cushing	Pituitary gland
high	High	Ectopic ACTH production	Ectopic foci

Causes of Cushing's syndrome



3) Aldosterone excess:

- - Primary hyperaldosteronism (Conn’s Syndrome) is rare disease, in most cases is due to a single adrenocortical adenoma. Secondary hyperaldosteronism is common and associated with renal, heart or liver diseases
- - Symptoms: polydipsia and polyuria, tetany, hypertension.
- - Lab. Diagnosis: Hypernatremia, hypokalaemia with increased urinary potassium. Plasma levels of aldosterone and renin. Hypokalaemia with increased aldosterone level is diagnostic to Conn’s.

Sex hormones

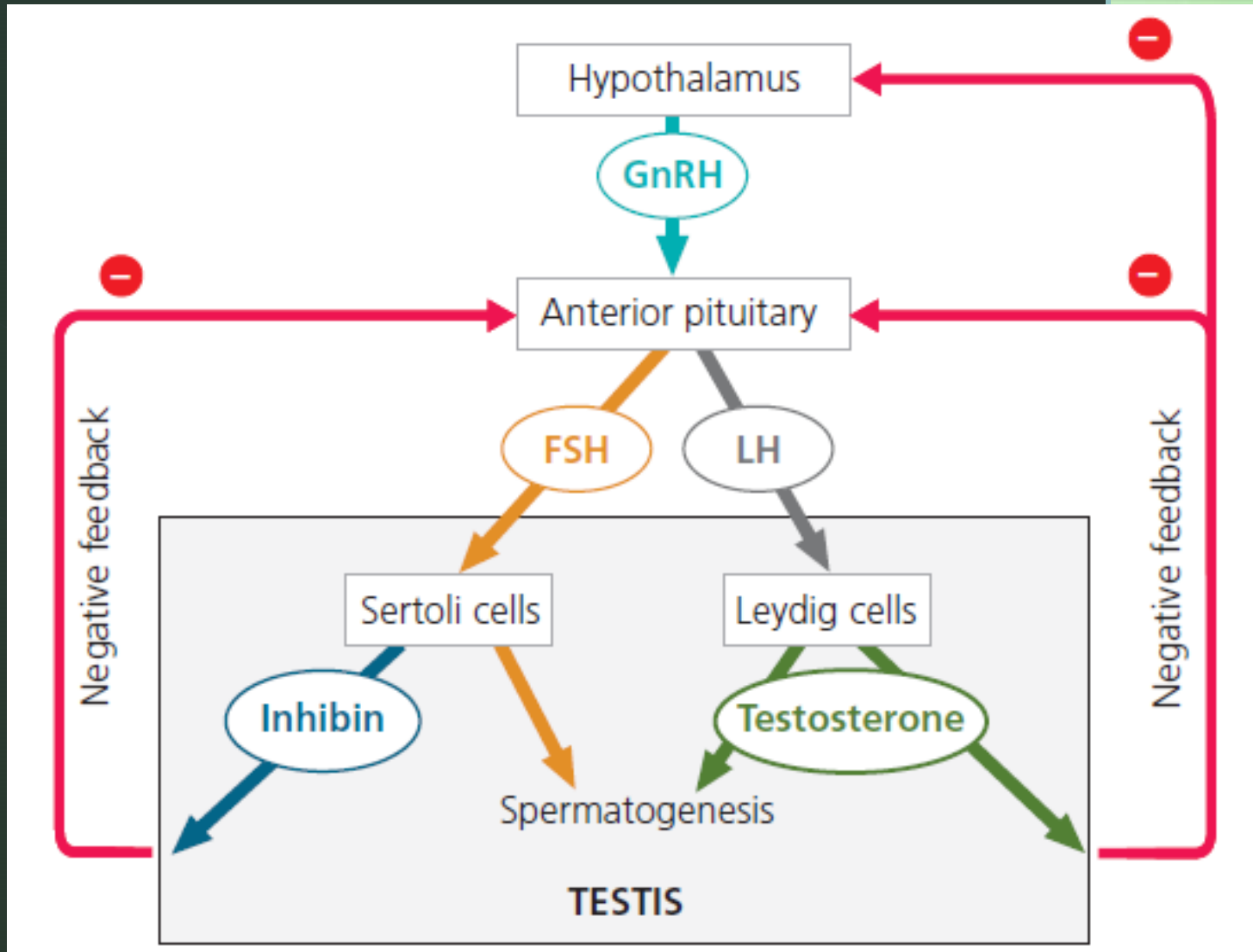
- The gonads produce and secrete three major types of steroid sex hormones: *androgens*, principally **testosterone**; *estrogens*, principally **estradiol**; and **progesterone**. All three hormones are found in both males and females, but at quite different concentrations. Testosterone levels in the blood are roughly ten times higher in males than in females. In contrast, estradiol levels are about ten times higher in females than in males; peak progesterone levels are also much higher in females.

- During sexual maturation, sex hormones in human males and females induce formation of secondary sex characteristics, the physical and behavioral differences between males and females that are not directly related to the reproductive system. Secondary sex characteristics often lead to the difference in appearance between the male and female adults.
- When human males enter puberty, androgens cause the voice to deepen, facial and pubic hair to develop, and muscles to grow (by stimulating protein synthesis). Androgens also promote specific sexual behaviors and sex drive, as well as an increase in general aggressiveness. Estrogens similarly have multiple effects in females. At puberty, estradiol stimulates breast and pubic hair development. Estradiol also influences female sexual behavior, induces fat deposition in the breasts and hips and increases water retention.

❑ Gonadal Disorders

- ▪ Male sex hormones
- 1) **Testosterone** is the principal androgen and is synthesized by the testes. It is most important androgen, both in terms of potency and the amount secreted.
- 2) **Androstenedione and DHEA:** these are weaker androgens that secreted by **testes**. Also secreted by the **adrenal glands** but adrenal androgen secretion does not appear to be physiologically important in the male
- 3) **Estradiol:** very little amounts are present due to the peripheral conversion of **testosterone** and **androstenedione** in the liver and adipose tissue by the action of **aromatase** enzyme

FSH stimulates *Sertoli cells*, located within the seminiferous tubules, to nourish developing Sperm.LH causes *Leydig cells*, scattered in connective tissue between the tubules, to produce testosterone
and other androgens, which promote spermatogenesis in the tubules.



Plasma androgens:

- - Testosterone in the plasma is very low before puberty, but then rise rapidly to reach normal adult values.
- - In the circulation, 97% of testosterone is protein bound, principally to **SHBG**
- - Testosterone is a powerful anabolic hormone. It is essential both to the development of secondary sexual characteristics in the male and for spermatogenesis.
- - The biological activity of testosterone is mainly due to dihydrotestosterone (DHT). This is formed from testosterone target tissues by **5 α-reductase**.
- - In a rare condition in which there is deficiency of this enzyme, DHT cannot be formed; male internal genitalia develop normally but masculinization, which requires DHT, is incomplete.
- - In states of androgen insensitivity, defects of the receptors for either testosterone or DHT, or both, can cause a spectrum of clinical abnormalities ranging from gynecomastia to disorders of sex development.

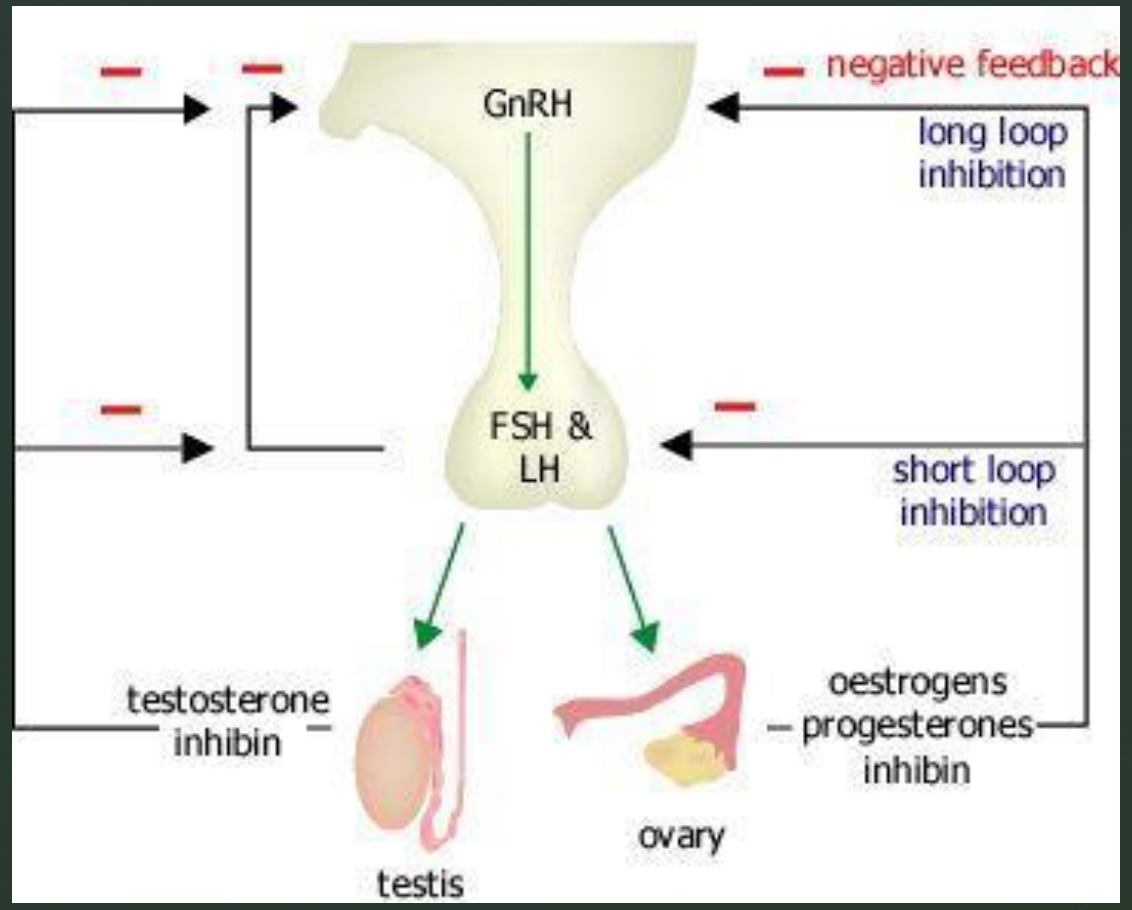
Female sex hormones

- 1) **Estradiol:** secreted by **ovaries** and widely varied in plasma throughout the female menstrual cycle.
- 2) **Progesterone:** secreted by **ovaries** and **corpus luteum** after ovulation
- 3) **Testosterone:** very little amounts, about half of which comes from **ovaries** and half from peripheral conversion of androstenedione and DHEA

Plasma estradiol

- Plasma oestrogens are low before puberty. During puberty, oestrogen synthesis increases and cyclical changes until the menopause. After the menopause, the sole source of oestrogens is from the metabolism of adrenal androgens; plasma concentrations fall to very low values
- - In the plasma, oestrogens are transported bound to protein, 60% to albumin and the remainder to SHBG.
- - Oestrogens are responsible for the development of many female secondary sexual characteristics. They also stimulate the growth of ovarian follicles and the proliferation of uterine endometrium.
- - Progesterone has many important effects on the uterus, including preparation of the endometrium for implantation of the conceptus. It is pyrogenic and mediates the increase in basal body temperature that occurs with ovulation.
- - SHBG binds both testosterone and oestradiol in the plasma, although it has greater affinity for testosterone. The plasma concentration of SHBG in males is about half that in females.
- - If SHBG concentration decreases, the ratio of free testosterone to free estradiol increases, although there is an absolute increase in the concentrations of both hormones. If SHBG concentration increases, the ratio decreases.

Hypothalamic pituitary gonadal axis



- **Disorders of male gonadal function**
- **1) Hypogonadism:** The term hypogonadism implies defective spermatogenesis or testosterone production or both. It can be primary (i.e. due to testicular disease) or occur secondarily to pituitary or hypothalamic disease.
- ▪ **Primary hypogonadism** is sometimes referred to as **‘hypergonadotrophic hypogonadism’** and **secondary hypogonadism** as ‘hypogonadotrophic hypogonadism’

Primary (FSH and LH are high)	Secondary (FSH and LH are low)
Congenital: Testicular agenesis 5α-reductase deficiency Klinefelter's syndrome **Acquired:** Testicular torsion Cytotoxic drugs Irradiation Mumps infection	Pituitary tumor specially if causing hyperprolactinemia Hypothalamic disorders such as Kallman's syndrome

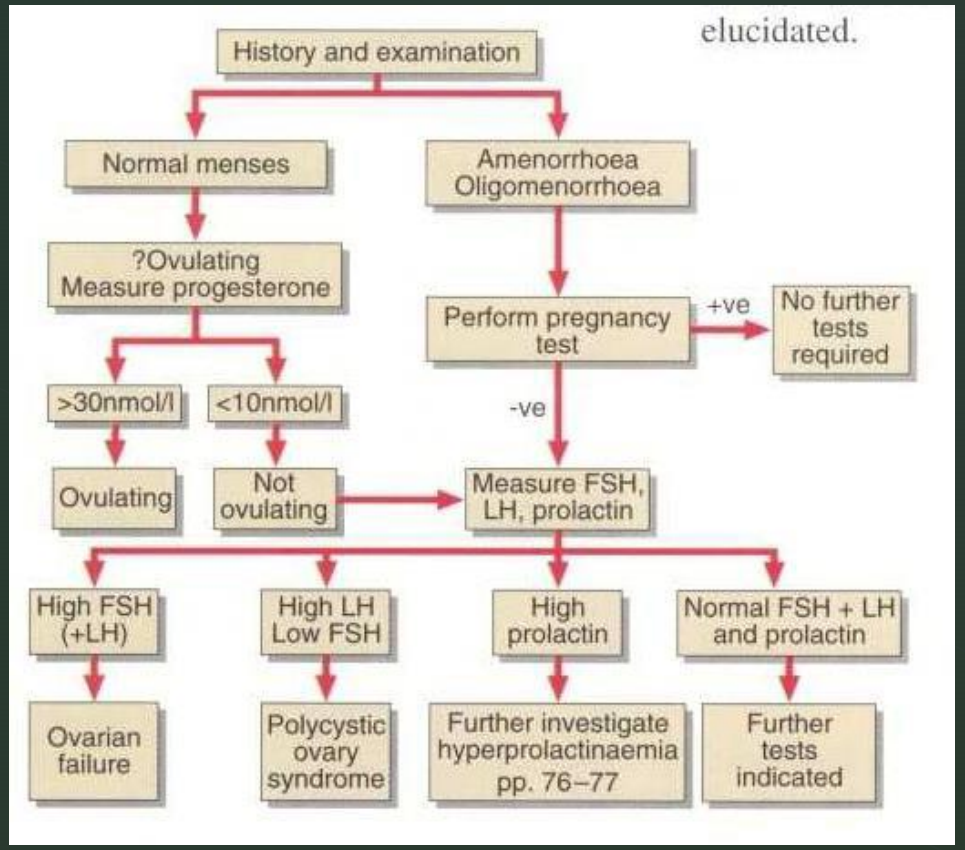
- **2) Gynecomastia:** Breast development in males may be caused by**:**
- a) Physiological: imbalance between oestrogens to androgens 1) Neonatal: as a result of exposure to maternal oestrogens.
- 2) Pubertal, approximately 50% of normal boys develop gynecomastia owing to temporarily increased secretion of oestrogens relative to androgens. In both instances, the gynecomastia resolves spontaneously.
- 3) Elderly, as a result of a decrease in testosterone secretion.

- b) Pathological: increased estrogens, decreased androgens or androgens insensitivity
- c) Pharmacological: estrogens, digoxin (binds to estrogen receptors), anti-androgen drugs, or cytotoxic drugs (testicular damage)

Disorders of female gonadal function

- **1) Hypogonadism:** Girls with delayed puberty usually present because of absence of breast development or amenorrhoea. Girls with no breast development by the age of 13 or with primary amenorrhoea after the age of 15 should be investigated further
- **2) Hirsutism:** it is an increase in body hair with male pattern distribution. It may be idiopathic but the commonest pathological cause is obesity
- **3) Virilism:** it is uncommon but serious disease. Characterized by marked elevation in testosterone leading to clitoromegaly, male-pattern hair growth, deepening of the voice and breast atrophy.

Infertility tests in female



Infertility tests in male