M.Sc. 4th Semester
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NEUROENDOCRINE RELATED DISEASES

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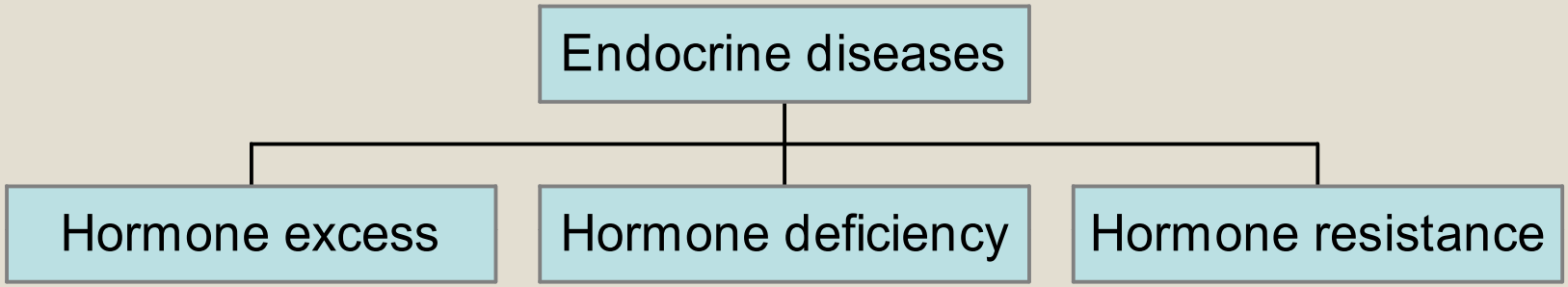

Endocrine diseases
Hormone excess
Hormone deficiency
Hormone resistance

Mechanisms of hormonal alterations

A. elevated hormones level

B. depressed hormones level

} may be caused by:

1. failure of feedback systems

2. dysfunction of endocrine gland or endocrine function of cells:

a) secretory cells are **unable to produce** or **do not obtain** an adequate quantity of required **hormone precursors**

b) secretory cells are **unable to convert the precursors** to the appropriate active form of hormone

c) secretory cells may **synthesize and release excessive amounts** of hormone

3. degradation of hormones at an altered rate or they may be inactivated by antibodies before reaching the target cell

4. ectopic sources of hormones

C. failure of the target cells to respond to hormone

May be caused by:

1. receptor-associated disorders

2. intracellular disorders

1. Receptor associated disorders

a) **decrease in the number** of receptors → ↓ hormone - receptor binding

b) **impaired receptor function** → ↓sensitivity to the hormone

c) **antibodies** against specific receptors

d) **unusual expression** of receptor function

2. Intracellular disorders

a) **inadequate** synthesis of the **second messengers**

b) **number of intracellular receptors** may be **decreased** or they may have **altered affinity** for hormones

c) **alterations in generation of new messenger RNA** or absence of substrates for new protein synthesis

Diseases of the anterior pituitary gland

Hypopituitarism is caused e.g. by infarction of the gland, removal, or destruction of the gland

Hyperpituitarism - adenoma

Hypopituitarism - insufficient secretion of one (selective form), more than one or all (panhypopituitarism) hormones of adenohypophysis

Causes: idiopathic, organic damage of adenohypophysis or hypothalamus, e.g. pituitary infarction= Sheehan syndrome, pituitary apoplexy, shock, DM, head trauma, infections, vascular malformations, tumors

Consequences - they depend on the affected hormones
- if all hormones are defficient → panhypopituitarism:

the patients suffer from:

- cortisol deficiency - because of lack of ACTH

- thyroid hormones deficiency - because of lack of TSH

- ADH defficincy - diabetes insipidus

- **defficiency of FSH and LH** - gonadal failure and loss of secondary sex characteristics

- ↓ **growth hormone** → ↓ somatomedin (they affect children growth)

- **absence of prolactin** → postpartum women are unable to lactate

- **ACTH deficiency → (within 2 weeks) symptoms of cortisol insufficiency are developed**

- nausea, vomiting, anorexia, fatigue, weakness

- **hypoglycemia** (it is caused by increased sensitivity of tissues to insulin, decreased glycogen reserves, decreased gluconeogenesis)

- **in women, loss of body hair and decreased libido →**
  → due to decreased adrenal androgen production

- limited maximum aldosterone secretion

- **TSH deficiency → (within 4-8 weeks) symptoms of TSH deficiency are developed:**
  - **cold intolerance**
  - **dryness of skin**
  - **decreased metabolic rate**
  - **mild myxedema**
  - **lethargy**
- **FSH and LH deficiences → in female of reproductive age:**
  - **amenorrhea**
  - **atrophic changes of vagina, uterus and breasts**

→ in postpubertal men:

- **atrophy of the testicles**
- **decreased beard growth**

Hyperpituitarism - excessive production of adenohypophyseal hormones

Causes: - adenoma of adenohypophysis
- hypothalamic form of hyperpituitarism

Consequences:

a) excessive secretion of prolactin → ↓ secretion of GnRH → → ↓gonadotrophins

In men: impotency, decreased libido

In women: amenorrhea, galactorrhea

b) excessive secretion of somatotrophine (growth hormone)

→ acromegaly (in adults)

→ gigantism (in adolescents whose epiphyseal plates have not yet closed)

Pathomechanisms involved:

-The usual GH baseline secretion pattern is lost (as are sleep – related GH peaks)

- A totally unpredictable secretory pattern of GH occurs

- GH secretion is slightly elevated → ↑somatomedin → stimulation of growth (in adolescent)

In adults:

- Connective tissue proliferation

- Bony proliferation → characteristic appearance of acromegaly

- ↑Phosphate reabsorbtion in renal tubules → hyperphosphatemia

- Impairement of carbohydrate tolerance

- ↑ Metabolic rate

- Hyperglycemia - it is a result of GH inhibition of peripheral glucose uptake and increase hepatic glucose production → compensatory hyperinsulinism → → insulin resistance → diabetes mellitus

c) excessive secretion of corticotrophin (ACTH) → central form of Cushing syndrome (Cushing disease)

Causes: micro- or macroadenomas of adenohypophysis, hypothalamic disorders

Pathophysiology:

Chronic hypercortisolism is the main disturbance of ↑ ACTH

Symptoms and signs:

- **weight gain:** - accumulation of adipose tissue in the trunk, facial, and cervical areas (truncal obesity, moon face, buffalo hump)
  - weight gain from Na and water retention
- **glucose intolerance** → DM type 2
- **polyuria:** osmotic polyuria due to glycosuria

- **protein wasting**: due to catabolic effects of cortisol on peripheral tissue (muscle wasting → muscle atrophy and weakness → thin lower extremities)

→ **in bone:** - loss of protein matrix → osteoporosis
- ↑blood calcium concentration → renal stones

→ **in skin:** - loss of collagen → thin, weakened integumentary tissues → purple striae; rupture of small vesels

- thin, atrophic skin is easily damaged, leading to skin breaks and ulceration

- **hyperpigmentation:** due to very high levels of ACTH - manifestation in: mucous membranes, hair, and skin

- **hypertension:** results from permissive effect of cortisol on the actions of the catecholamines (KA) → ↑ vascular sensitivity to KA → → vasoconstriction → hypertension

- **suppression of the immune system** → ↑ susceptibility to infections

- **alteration of mental status** - from irritability and depression up to schizophrenia

- **symptoms and signs of ↑adrenal androgens level in women:**

  - ↑ hair growth (especially facial hair)
  - acne
  - oligomenorrhea
  - changes of the voice

- **hyperglycemia, glycosuria, hypokalemia, metabolic alkalosis**

- **excessive secretion of thyrotrophin and gonadotrophins** is rare

Alterations of thyroid function

Hyperthyroidism is a condition in which thyroid hormones (TH) exert greater-than-normal response

Causes:

- Graves disease
- exogenous hyperthyroidism (iatrogenic, iodine induced)
- thyroiditis
- toxic nodular goiter
- thyroid cancer

- All forms of hyperthyroidism share some **common characteristic:**
- **metabolic effect of increased circulating levels of thyroid hormones** → ↑ metabolic rate with heat intolerance and increased tissue sensitivity to stimulation by sympathetic division of the autonomic nervous system;

The major manifestations of hyperthyroidism and mechanisms of their onset

a) endocrine:

- enlarged thyroid gland (TG) with systolic or continous bruit over thyroid due to ↑blood flow
- ↑ cortisol degradation – due to ↑metabolic rate
- hypercalcemia and decreased PTH secretion - due to excess bone resorption
- diminished sensitivity to exogenous insulin- due to ↑hyperglycemia (↑glycogenolysis and gluco-neogenesis)

b) reproductive:

- oligomenorrhea or amenorrhe due to hypothalamic or pituitary disturbances
- impotence and decreased libido in men

c) gastrointestinal:

- weight loss and associated increase in appetite due to increased catabolism
- increased peristalsis → less formed and more frequent stools - due to malabsorption of fat
- nausea, vomiting, anorexia, abdominal pain
- increased use of hepatic glycogen stores and adipose and protein stores
- decrease of tissue stores of vitamins
- hyperlipid – acidemia (due to ↑lipolysis)

d) integumentary:

- excessive sweating, flushing, and warm skin
- heat loss
- hair faint, soft, and straight, temporary hair loss
- nails that grow away nail beds

All these signs and symptoms are due to metabolic effect of TH

Hypothyroidism - **deficient production of TH by the thyroid gland and/or ↓ their action to the tissue**

A. Primary hypothyroidism is caused by:

1. **congenital defects or loss of thyroid tissue**
2. **defective hormone synthesis - due to: autoimmune thyroiditis, endemic iodine deficiency, antithyroid drugs**

B. Secondary hypothyroidism is caused by:

1. **insufficient stimulation of the normal gland**
2. **peripheral resistance to TH**

The major manifestations of hypothyroidism and mechanism of their onset

- Hypothyroidism generally affects all body systems with the extent of the symptoms closely related to the degree of TH deficiency.

- The individual develops a low basal metabolic rate, cold intolerance, slightly lowered basal body temperature

- A decrease in TH → ↑ production of TSH → goiter

- Characteristic sign of hypothyroidism is mixedema →

increased amount of protein and mucopolysaccharides in dermis → ↑ water binding → nonpitting edema, thickening of the tongue, and the laryngeal and pharyngeal mucous membranes → thick slurred speech and hoarseness

Other manifestations:

a) neurologic:
- confusion, syncope, slowed thinking, memory loss, lethargy, hearing loss, slow movements
- cerebellar ataxia

Mechanisms involved:
- decreased cerebral blood flow → cerebral hypoxia
- decreased number of beta-adrenergic receptors

b) endocrine:
- ↑ TSH production (in primary hypothyroidism)
- ↑ serum prolactin levels with galactorrhea
- ↓ rate of cortisol turnover, but normal cortisol levels

Mechanisms involved:
- ↓ TH → ↑ TSH
- stimulation of lactotropes by TRH → ↑ prolactin
- decreased deactivation of cortisol

c) reproductive: - ↓ androgen secretion in men

- ↑ estriol formation in women due to altered metabolism of estrogens and androgens

- anovulation, decreased libido

- spontaneous abortion

d) hematologic: - ↓ RBC mass → normocytic, normochromic anemia

- macrocytic anemia due to vitamin B_{12} deficiency and inadequate folate absorption

Mechanisms involved:

- ↓ basal metabolic rate → ↓ oxygen requirement → → ↓ erythropoietin production

e) cardiovascular:

- ↓ heart rate and stroke volume →↓ CO
- ↑ peripheral vascular resistance → cool skin
- enlarged heart - due to ↑ amount of protein-muco-polysacharides
- ↓ intensity of heart sounds due to fluid in the pericardial sac
- ECG changes - low amplitude QRS, flattened or inverted T, depressed P, prolonged PR, sinus bradycardia

Mechanisms involved:

- ↓ metabolic demands and loss of regulatory and rate - setting effects of TH
- pericardial effusions

f) pulmonary: - dyspnoea - due to pleural effusions

- myxedematous changes of respiratory muscles→ → hypoventilation

g) renal: -↓ renal blood flow → ↓ GFR → ↓renal excretion of water→ →↑total body fluid → dilutional hyponatremia

- ↓ production of EPO

Mechanisms involved: - hemodynamic alteration

- mucinous deposits in tissue

h) gastrointestinal: ↓ appetite, constipation, weight gain

↓ absorption of most nutrients

↓ protein metabolism, ↓ glucose uptake

↑ sensitivity to exogenous insulin

↑ concentration of serum lipids

i) **musculosceletal**:

- muscle aching and stiffness
- slow movement and slow tendon jerk reflexes
- decreased bone formation and resorption → ↑ bone density
- aching and stiffness in joints

Mechanisms involved:

- decreased rate of muscle contraction and relaxation

j) **integumentary**:

- dry flaky skin
- dry, brittle head and body hair
- reduced growth of nails and hair

Mechanisms involved:

- reduced sweat and sebaceous gland secretion

Alterations of parathyroid function

- **Hyperparathyroidism is characterized by greater than normal secretion of parathormone (PTH)**

Three types do exist:

primary - PTH secretion is autonomous and not under the usual feedback control mechanism

secondary - compensatory response of parathyroid glands to chronic hypocalcemia

tertiary - loss of sensitivity of hyperplastic parathyroid gland $\rightarrow\uparrow$ level of autonomous secretion of PTH

The main manifestations of hyperparathyroidism and mechanisms of their onset

a) renal colic, nephrolithiasis, recurrent urinary tract infections, renal failure:

- they result from hypercalcemia, calciuria, hyperphosphaturia, proximal tubular bicarbonate leak, urine pH > 6

Mechanisms: - calcium phosphate salts precipitate in alkaline urine in renal pelvis, and in collecting ducts

b) abdominal pain, peptic ulcer disease

- result from hypercalcemia → stimulated hypergastrinemia → → elevated HCl secretion

c) pancreatitis - due to hypercalcemia

d) bone disease - osteitis fibrosa and cystica; osteoporosis results from PTH hypersecretion →stimulated bone resorption and metabolic acidosis

e) muscle weakness, myalgia

- probably due to PTH excess and its direct effect on striated muscle and on nerves → myopathic changes, suppressed nerve conduction

f) neurologic and psychiatric alterations

- result from hypercalcemia → neuropathy develops

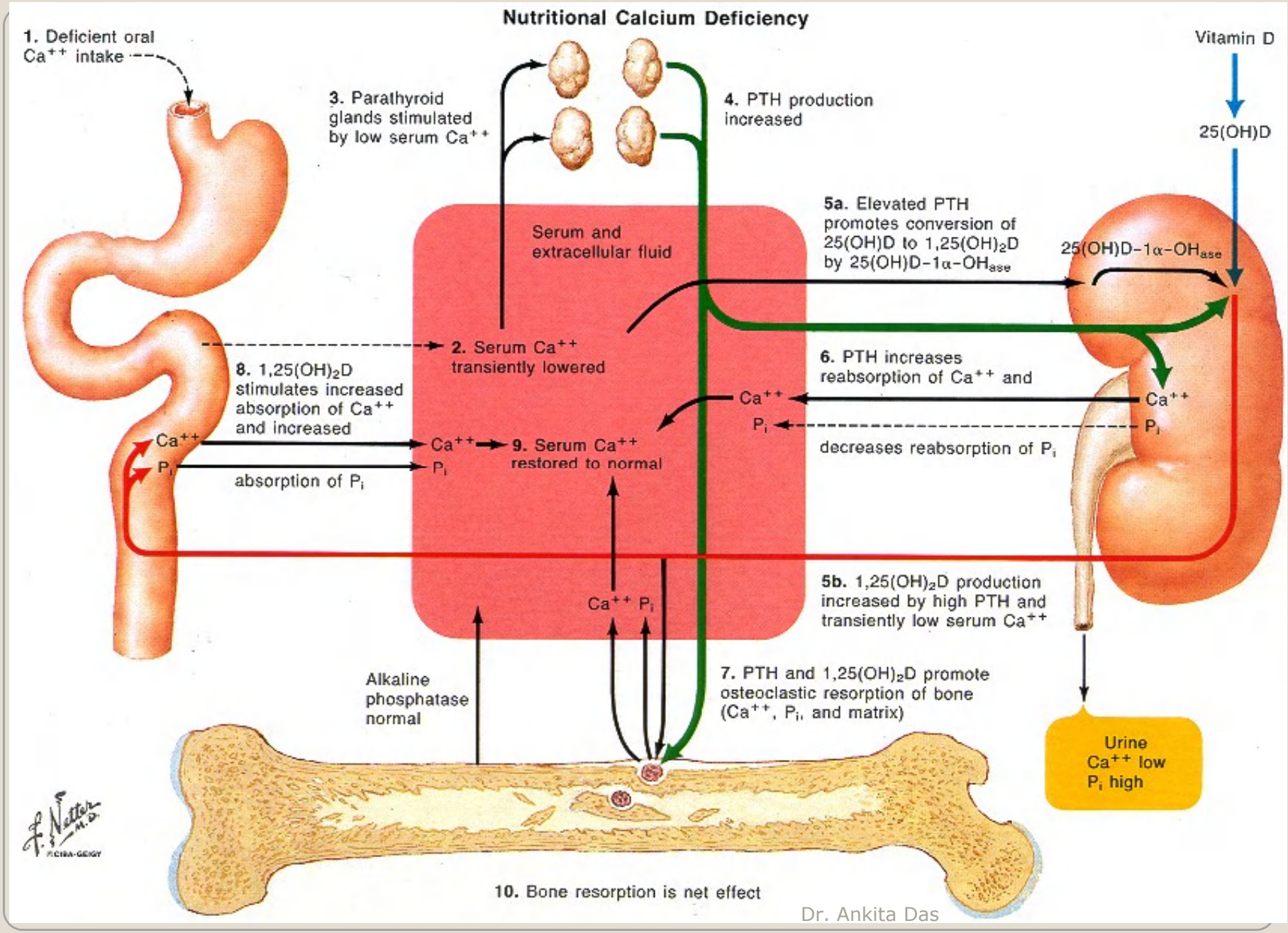
g) polyuria, polydipsia

- they result from direct effect of hypercalcemia on renal tubule $\rightarrow \downarrow$ responsiveness to ADH

h) constipation - is due to decreased peristalsis induced by hypercalcemia (smooth muscle weakness)

i) anorexia, nausea, vomiting - due to stimulation of vomiting center by hypercalcemia

j) hypertension - due to secondary renal disease



Hypoparathyroidism is characteristic by abnormally low PTH levels

Causes: - damage to the parathyroid gland due to thyroid surgery

Consequences:

a) depressed serum calcium level and increased serum phosphate level

Mechanisms involved:

- ↓ resorption of Ca from GIT, from bone and from renal tubules

-↑ reabsorption of phosphates by the renal tubules

b) lowering of the threshold for nerve and muscle excitation

- muscle spasms, hyperreflexia, clonic - tonic convulsions, laryngeal spasms - **tetany**

c) dry skin, loss of body and scalp hair, hypoplasia of developing teeth, horizontal ridges on the nails, cataracts, basal ganglia calcifications (Parkinsonian sy.)

Mechanisms involved: unknown up to now

d) hyperphosphatemia → inhibition of renal enzyme necessary for the conversion of vitamin D to its most active form →further depression of serum calcium level by reducing GIT absorption of calcium.

Diseases of the posterior pituitary gland

Syndrome of inappropriate ADH secretion (SIADH):

It is characterised by **high levels of ADH** in the **absence** of normal physiologic stimuli for its release

1. **Elevated levels of ADH** is caused by ectopically produced ADH (cancer of the lung, leukemia, response to surgery, inflammation of lung tissue, psychiatric disease, drugs-barbiturates, general anaesthesia, diuretics...)

→ water retention → ↑ total body H_2O →↓ aldosteron production

→ solute loss (Na^+) → hyponatremia → hypoosmolality

→ ADH is released continually

→ dilutional hyponatremia → suppression of renin production →
→ ↓aldosterone production→ ↓Na^+ reabsorbtion in kidney

→ even if **hyponatremia** develops slowly, serum sodium levels below 110 to 115 mmol/l are likely to cause **severe** and sometimes **irreversible neurologic damage**

→ rapid decrease of serum Na^+ from 140 to 130 mmol/l →thirst, anorexia, dyspnea on exertion, fatigue occur

2. **Diabetes insipidus (DI)** - is related to an **insufficiency of ADH** leading to **polyuria and polydipsia**

Three forms of DI do exist:

a) neurogenic or central form - ↓ amount of ADH production

b) nephrogenic form - inadequate response to ADH

c) psychogenic form - extremely large volumes of fluid intake → → inhibition of ADH production

Pathophysiology:

DI - partial to total inability to concentrate urine due to chronic polyuria →
→ washout of renal medullary concentration gradient

- increase in plasma osmolality → thirst → polydipsia (looking for cold drinks)

- ↑ urine output, ↓ urine specific gravity (1.00-1.005)

- dehydratation (if not adequate fluid intake)

Books to refer:

1. Medical Physiology, Guyton and Hall
2. Medical Physiology, Ganong
3. General Physiology, A.K. Jain

Practice Questions:

1. Mention the ways in which the hormone level can be altered in the body.
2. Discuss the pathophysiology of hypercortisolism.
3. Describe the symptoms of hyperthyroidism.
4. What is goiter and myxedema?