

# Biology 211

## Study Notes Exam 1

### Chapter 16: The Endocrine System

**Endocrine System:** a system of small glands scattered throughout the body that influences the metabolic activities of cells through hormones

- **Hormones:** chemical messengers released to the blood by the cells of endocrine glands that regulate the metabolic activities of other cells in the body
  - o Hormones signal target cells to perform specific chemical reactions

**Endocrine Glands:** pituitary, thyroid, parathyroid, adrenal, pineal and thymus glands.

- Organs with major functions outside the endocrine system containing endocrine tissue/cells: pancreas, gonads, hypothalamus (neuroendocrine organ)
- Tissues that produce hormones also found within: adipose cells, small intestine, stomach, kidneys, heart

#### **Hormones:**

**Amino acid-based hormones:** contain from a couple to many amino acids... vary in size from simple amino acid derivatives (amines, thyroid hormone, peptides) to proteins (polypeptides)

**Steroid hormones:** synthesized from cholesterol (includes hormones from the gonads and adrenal cortex (outer region of the adrenal gland))

**Eicosanoids:** local hormones (paracrines); biologically active lipids released from nearly all cell membranes

- effects are highly localized, different from circulating hormones
- leukotrienes: chemicals that mediate inflammation & some allergic reactions
- prostaglandins: many targets/effects... raise blood pressure, stimulate uterine contractions during birth, enhance blood clotting & inflammation

Eicosanoids are generally not considered part of the endocrine system, but will be discussed in later Chapters with the appropriate systems

#### **Mechanisms of hormone action:**

- alter plasma membrane permeability or electrical state
- stimulate synthesis of proteins within cells
- activate or deactivate enzymes
- induce secretory activity
- stimulate mitosis/cell division

#### **Amino acid-based hormones use second messenger systems**

- proteins and peptides cannot freely penetrate plasma membrane

- these hormones bind to a membrane receptor that starts a chain of reactions that activates an intracellular second messenger molecule
- **cyclic AMP signaling:**
  - o the *hormone (first messenger)* binds the membrane receptor; the receptor changes shape, which allows it to bind **G protein**
  - o G protein is activated; binds GTP & releases GDP
  - o activated G protein moves along membrane; binds to & activates (or inhibits) enzyme **adenylate cyclase** (GTP is hydrolyzed by GTPase activity of G protein)
  - o activated adenylyl cyclase converts **ATP** to **cyclic AMP (second messenger)**; if inhibited, adenylyl cyclase will not catalyze its reaction
  - o cyclic AMP is free to circulate inside the cell; triggers activation of one to several protein kinase molecules; protein kinase phosphorylates (adds a phosphate group to) many proteins
- the phosphorylated proteins may be activated or inhibited by phosphorylation
- **amplification effect:** each activated adenylyl cyclase can generate many cyclic AMP molecules; each protein kinase can catalyze hundreds of reactions
- the end effect depends on the target cell (in thyroid cells, binding of TSH to its receptor ends in the synthesis of thyroid hormone; in bone & muscle cells, growth hormone binding to its receptor ends in protein synthesis)
- *cyclic AMP* is rapidly *degraded* by the enzyme **phosphodiesterase**, but activation of protein kinase by cyclic AMP has generally already taken place
- **PIP-calcium signaling mechanism:**
  - o hormone (first messenger) binding to its receptor causes the receptor to bind inactive G protein
  - o **G protein** is activated; binds GTP & releases GDP
  - o activated G protein binds & activates a membrane-bound **phospholipase** enzyme; G protein becomes inactive
  - o phospholipase splits *phosphatidyl inositol biphosphate (PIP<sub>2</sub>)* to *diacylglycerol (DAG)* & *inositol triphosphate (IP<sub>3</sub>)*; both DAG & IP<sub>3</sub> are *second messengers*
  - o *DAG* activates protein kinases on the plasma membrane; *IP<sub>3</sub>* triggers **calcium ion** release from the ER
  - o liberated *calcium ions* (also second messengers) alter activity of some specific enzymes and ion channels or bind to the regulatory protein **calmodulin**; *calmodulin* also activates specific enzymes to amplify the cellular response
- there also appear to be other second messenger systems used by some hormones that are less understood

### **Steroid hormones & direct gene activation:**

- steroid hormones are lipid-based (synthesized from cholesterol) and can easily diffuse into target cells (no need for intracellular second messengers since the hormone can enter the cell)

- **thyroid hormone** also uses this mechanism
- hormone enters the nucleus; binds to & activates intracellular receptor
- the hormone-receptor complex binds a DNA-associated receptor protein, which turns on transcription & translation of the associated gene
- the protein synthesized in many cases is an enzyme that effects the metabolic activities of the cell to transmit the effects of the hormone

**Hormones are specific for their target cells:**

- hormones bind specific receptors; the receptor will only bind to one hormone
- the effects of the hormone depend on the blood levels of the hormone & the presence & number of receptors on the target cell
- up-regulation: increase in the # of receptors for a hormone on a target cell
- down-regulation: decrease in the # of receptors for a hormone on a target cell

The *half-life* of a hormone (persistence of a hormone in blood, a time indicating half its activity remaining) is brief (from a fraction of a minute to 30 minutes), but the effects of hormones can last for several minutes to hours

**Control of hormone release:**

**Negative feedback:** hormone secretion triggered by an external stimulus; as hormone levels rise, the hormones feed back to the metabolic pathway that produces them & inhibit their further release

**Humoral stimuli:** hormone release controlled by blood levels of specific ions and nutrients (e.g.: calcium or glucose)

**Neural stimuli:** nerve fibers stimulate hormone release (sympathetic neurons stimulate secretion of catecholamines (epinephrine & norepinephrine) from the adrenal medulla)

**Hormonal stimuli:** other hormones regulate release of a hormone (e.g.: releasing & inhibiting hormones released by hypothalamus regulate release of hormones from pituitary)

**Nervous system modulation:** the nervous system can override normal homeostatic mechanisms for hormonal control (for example, to allow more glucose for fuel to be released during excitement (“fight or flight response”))

**Major Endocrine Glands:**

**Pituitary Gland (Hypophysis):** connected to hypothalamus by stalk called infundibulum

- **Anterior Pituitary (Adenohypophysis):**
  - o **Growth Hormone (GH):** stimulates cell division in most cells (major targets are bone & skeletal muscle)
    - **IGFs** (insulin-like growth factors or somatomedins) mediate most effects of GH
    - **Hypersecretion:** in children, can lead to ***gigantism***; after long bones have developed, can lead to ***acromegaly***
    - **Hyposecretion:** in children, can lead to ***pituitary dwarfism***

- **Prolactin (PRL):** stimulates milk production by mammary glands of breasts
- **Follicle-stimulating hormone (FSH):** stimulates gamete production in gonads (ovaries & testes)
- **Leutinizing hormone (LH):** promotes production of gonadal hormones (testosterone, estrogen & progesterone)
- **Thyroid-stimulating hormone (TSH):** stimulates normal development of & secretion of hormones from thyroid gland
- **Adrenocorticotrophic hormone (ACTH or corticotropin):** stimulates release of corticosteroid hormones from adrenal cortex
- **Posterior pituitary (Neurohypophysis):** receives & stores hormones from hypothalamus for later release
  - **Oxytocin:** produced by paraventricular nucleus of *hypothalamus*; stimulates uterine contraction during childbirth & milk ejection during nursing
  - **Antidiuretic hormone (ADH):** produced by supraoptic nucleus of *hypothalamus*; stimulates kidney tubules to retain water
    - deficiency of ADH secretion leads to *diabetes insipidus*

**Hypothalamus:** secretes releasing & inhibiting hormones that regulate release of hormones from anterior pituitary

- **hypophyseal portal system:** network of blood vessels that delivers hormones to anterior pituitary from hypothalamus
- **Growth Hormone-Releasing Hormone (GHRH)**
- **Growth Hormone-Inhibiting Hormone (GHIH or somatostatin)**
- **Prolactin-Releasing Hormone (PRH)**
- **Prolactin-Inhibiting Hormone (PIH or dopamine)**
- **Gonadotropin-Releasing Hormone (GnRH)**
- **Thyrotropin-Releasing hormone (TRH)**
- **Corticotropin-Releasing hormone (CRH)**

### **Thyroid Gland:**

- **Thyroid Hormone:** amino acid hormones containing 2 tyrosine molecules each bound to iodine molecules; regulates metabolic activities of all cell types, especially glucose oxidation (energy & heat production)
  - **Thyroxine (T<sub>4</sub>):** major hormone released from thyroid follicles (contains 4 iodine molecules)
  - **Triiodothyronine (T<sub>3</sub>):** (contains 3 iodine molecules); generally formed from T<sub>4</sub> by cleaving an iodine molecule

- Thyroid **follicles** are sacs lined with follicular cells and containing a substance called **colloid**; colloid contains *thyroglobulin* (tyrosine molecules linked to iodines)
- Thyroid hormone formed by joining 2 tyrosine-iodine complexes
- **simple goiter**: enlargement of thyroid gland due to lack of dietary iodine (thyroid hormone precursors accumulate in gland)
- hypothyroidism in infants may be associated with **cretinism** (underdeveloped thyroid gland); symptoms are short, stocky stature & may lead to mental retardation
- **myxedema**: hypothyroidism in adults (lethargy, weight gain, hair loss, slow pulse, etc.)
- treatment for hypothyroidism is generally thyroxine therapy
- **Graves' disease**: hyperthyroidism due to enlarged & overactive thyroid gland; produces exophthalmic goiter (swelling & protrusion of eyes)
- treatment of hyperthyroidism involves thyroid gland surgery &/or radioactive iodine
  
- **Calcitonin**: produced by parafollicular cells (C cells) of thyroid gland
  - o lowers blood calcium levels by inhibiting osteoclasts & stimulating calcium uptake by bones

**Parathyroid Glands**: paired glands on posterior aspect of thyroid gland

- **Parathyroid hormone (Parathormone or PTH)**: raises blood calcium levels by stimulating osteoclasts, enhancing absorption of calcium by kidneys, & increasing absorption of calcium by cells of intestine
  - o PTH activates the inactive form of vitamin D in the kidneys; vitamin D enhances absorption of calcium by intestine

**Adrenal Glands (Suprarenal Glands)**: pyramid-shaped glands above kidneys

- **Adrenal Cortex**: releases corticosteroid hormones
  - o **Mineralocorticoids**: released primarily by cells of zona glomerulosa; regulate salt concentrations in extracellular fluids
    - **Aldosterone**: primary mineralocorticoid: enhances *sodium* (& water) reabsorption from kidney tubules
      - Sodium ion concentration in body fluids also regulated by rennin-angiotensin system, ACTH & atrial natriuretic peptide (ANP)
  - o **Glucocorticoids**: influence metabolism of body cells & help resist stressors
    - During times of stress (injury/blood loss), glucocorticoids stimulate gluconeogenesis (glucose synthesis) & mobilize fats & proteins to be used for energy to save glucose for the brain
    - **Cortisol (hydrocortisone)** is major glucocorticoid (also cortisone & corticosterone)
    - Glucocorticoids also prevent water loss from cells into tissue fluids; used as **anti-inflammatory agents**
- **Gonadocorticoids**: secondary source of sex hormones; primarily *androgens* (testosterone), but also *estrogens*
  - o may contribute to onset of puberty

- **Addison's disease:** low level of adrenal cortex hormones resulting in bronzing of skin, low blood sugar (low energy & weak immunity) & low blood sodium (low blood pressure)
- **Cushing syndrome:** high level of adrenal cortex hormones resulting in high blood sugar (& possibly diabetes mellitus), high blood sodium (hypertension), swelling & obesity & possible masculinization in women
- **Adrenal medulla:** releases *catecholamines* (norepinephrine & epinephrine)
  - Release is stimulated by *sympathetic nervous system* (“fight or flight” response)
  - **Epinephrine:** stimulates heart rate & metabolism
  - **Norepinephrine:** influences peripheral vasoconstriction & blood pressure

**Pancreas:** releases insulin & glucagon from *islets of Langerhans*

- **Insulin:** released by beta cells of islets; lowers blood glucose levels by stimulating glucose storage & uptake of glucose by cells for energy
  - Insulin deficiency may lead to **diabetes mellitus**
    - Insulin-dependent diabetes mellitus (IDDM): autoimmune disease where immune cells attack & destroy beta cells
    - Non-insulin-dependent diabetes mellitus (NIDDM): insulin receptors do not properly respond to insulin
- **Glucagon:** raises blood glucose levels by stimulating glucose removal from glycogen storage deposits in liver cells & gluconeogenesis

**Gonads (ovaries & testes):** produce steroidal sex hormones

- **Ovaries:** produce estrogens, progesterone, inhibin & relaxin
  - **estrogens** (estrone & estradiol) & **progesterone:** produced by ovary cells are responsible for maturation of female reproductive organs & regulation of menstrual cycle
    - also, maintain pregnancy & prepare mammary glands for lactation
  - **inhibin** inhibits FSH during ovarian cycle; **relaxin** released during pregnancy increases flexibility of pubic symphysis & helps dilate uterine cervix
- **Testes:** produce testosterone, an **androgen** (male sex hormone)
  - **testosterone:** produced by cells of testes is responsible for maturation of male reproductive organs & sperm cell production
  - **inhibin** inhibits FSH to regulate spermatogenesis

**Pineal Gland:** secretes *melatonin*

- pineal gland located in epithalamus of brain at roof of 3<sup>rd</sup> ventricle
- **melatonin** appears to be involved in maintenance or sleep/wake (day/night) cycles
  - melatonin derived from the amino acid serotonin
  - more melatonin released in darkness, less in light; norepinephrine from sympathetic fibers stimulate secretion of melatonin (may cause sleepiness)
  - during sleep, plasma levels of melatonin increase & then decrease before awakening; therapeutic use to induce sleep still under investigation

**Thymus:** secretes thymopoielins & thymosins

- thymus located behind sternum superior to heart
- **thymosin, thymic humoral factor (THF), thymic factor (TF) & thymopoielins** involved with normal development of T cells (lymphocytes); may slow aging

**Other Hormone-Producing Structures:**

**Heart:** specialized cardiac muscle cells of atria secrete atrial natriuretic peptide (ANP), which reduces blood volume, blood pressure, & blood sodium levels

**GI tract:** enteroendocrine cells secrete hormones that aid in digestion

**Placenta:** secretes steroid hormones that help during pregnancy & human chorionic gonadotropin (hCG)

**Kidney:** secretes erythropoietin that stimulates red blood cell synthesis in bone marrow

**Skin:** secretes inactive vitamin D (cholecalciferol), which is activated by PTH in kidneys

**Adipose Tissue:** secretes leptin, which binds to neurons regulating appetite control & leads to sensation of satiety

## Chapter 17: Blood

### Blood Functions:

- transport & *distribution* of oxygen & nutrients, carbon dioxide & metabolic waste, and hormones
- *regulation* of body temperature, normal pH and fluid volume in cells & tissues
- *protection* against blood loss (clotting) and infection (white blood cells)

### Blood Characteristics:

- **pH** of blood is maintained between **7.35** and **7.45** by *carbonic acid-bicarbonate ion buffer system*
- blood accounts for ~ 8% body weight
- blood volume in adults is normally 5-6 L in males and 4-5 L in females

### Blood Components:

- plasma & formed elements (erythrocytes, leukocytes & platelets)
- *hematocrit*: % of total blood volume occupied by erythrocytes (normally between 42% and 47% ± 5%)

### Blood Plasma: fluid component of blood

- mostly (~ 90%) water
- contains over 100 different dissolved solutes, including:
  - o *proteins*: albumin, globulins, clotting proteins, etc.
    - *albumin* is majority of plasma protein; albumin is carrier molecule & contributes to plasma osmotic pressure
    - *globulins* include transport proteins & *antibodies*
  - o *nutrients*: sugars, amino acids, fatty acids, cholesterol, vitamins, etc.
  - o *electrolytes*: cations (positive ions) such as sodium, potassium, calcium & magnesium; anions (negative ions) such as chloride, phosphate & bicarbonate
  - o *respiratory* gases: oxygen & carbon dioxide

### Formed Elements: *erythrocytes, leukocytes & platelets*

- **Erythrocytes: red blood cells (RBCs)**
  - o small cells; biconcave discs (flattened disc shape with thin, depressed centers – look like mini doughnuts)
  - o *anucleate* – RBCs have no nucleus
  - o *function in gas transport*
  - o most of contents of RBC (other than water) is the protein **hemoglobin**
    - *hemoglobin* is composed of 4 globin polypeptide chains each bound to a *heme* group
      - *heme* is a ringlike compound with an **iron** atom at its center
      - the iron atom in heme binds to **oxygen**
    - one hemoglobin molecule can bind to & transport up to 4 oxygen molecules
    - hemoglobin can also bind **carbon dioxide**; carbon dioxide binds to globin chain *amino acids* rather than heme
    - *oxyhemoglobin*: hemoglobin with bound oxygen

- **deoxyhemoglobin:** hemoglobin with **no** bound oxygen
- **carbaminohemoglobin:** hemoglobin with bound carbon dioxide
- **hematopoiesis** (*hemopoiesis*): blood cell formation; occurs in **red bone marrow** (in adults, in bones of girdles & proximal epiphyses of humerus & femur)
  - starts with **stem cell** called **hemocytoblast** (hematopoietic stem cell that is used to form all formed elements of blood)
  - **erythropoiesis** (erythrocyte production): **hemocytoblast** -> **myeloid stem cell** -> proerythroblast -> early erythroblast -> late erythroblast -> normoblast -> **reticulocyte** -> **erythrocyte**
    - cell shrinks in size; cell accumulates **hemoglobin** protein during erythroblast stages; cell **loses its nucleus** in transition from normoblast to reticulocyte
    - reticulocyte counts can be used as a rough indicator of the rate of RBC formation
    - controlled hormonally by **erythropoietin** produced by the kidneys (responding to hypoxia (low oxygen levels))
    - requires adequate supplies of **iron & amino acids** for **hemoglobin** and **B vitamins** (**vitamin B12 and folic acid**) for DNA synthesis
      - since free iron is toxic, it is always transported in **protein-iron complexes** (such as *ferritin*)
- **destruction of erythrocytes:** RBCs last ~ 100-120 days in circulation
  - aged & damaged RBCs are broken down in small channels of the spleen, liver & marrow by macrophages
  - **heme** is broken from hemoglobin; **iron** is salvaged & stored and the remainder of the group is **degraded** to **bilirubin** (yellow pigment), which is picked up by the liver, converted into bile & excreted
  - **globin** chains are metabolized are broken down into **amino acids** for protein synthesis
- **erythrocyte disorders:**
  - **anemias:** conditions that involve blood with a very low oxygen-carrying capacity
    - caused by an **insufficient number of RBCs** (hemorrhagic, hemolytic & aplastic anemias), **decreased hemoglobin content** (iron-deficiency & athlete's anemia) or **abnormal hemoglobin** (thalassemias & sickle cell anemia)
  - **polycythemia:** abnormal excess of RBCs; increases blood viscosity & can impair circulation
    - can be treated by diluting blood with saline
    - artificial polycythemia can be induced by infusing RBCs (blood doping used by some athletes to increase available oxygen... considered unfair by many games committees)
- **Leukocytes: white blood cells (WBCs)**

- only formed elements with *nucleus* & normal organelles
- involved in immune responses; protect the body from damage by bacteria, viruses, parasites, toxins & tumor cells
- **diapedesis**: white blood cells can move out of capillaries & into tissues
  - use amoeboid motion with flowing cytoplasmic extensions to move through tissue spaces
  - positive chemotaxis: follow chemical trail of other WBCs to sites of infection
- **leukocytosis**: condition of increased WBC count during infection (normal response)
  
- **Granulocytes**: WBCs with membrane-bound cytoplasmic *granules*
  - **Neutrophils**: most numerous WBCs (>50% of WBC volume)
    - ~ 2x size of RBCs
    - very fine, lightly staining granules containing enzymes or antibiotic-like proteins (defensins)
    - *nucleus* has from **3-6 lobes** (also known as **PMNs** (polymorphonuclear leukocytes))
    - **phagocytic cells** (*kill bacteria & fungi by oxidation*), chemically attracted to sites of inflammation
  
  - **Eosinophils**: ~ 1-4% of WBC population; about size of neutrophils
    - *nucleus* with **2 lobes** (like telephone receiver)
    - large, **red-staining granules** with enzymes
    - **digest** invading *parasitic flatworms & roundworms* with digestive enzymes
    - **phagocytic**; ingest immune complexes during allergic reactions
  
  - **Basophils**: ~ 0.5% of WBC population (rare); about size of neutrophils
    - large **purplish-black-staining granules** containing **histamine**
    - *histamine*: inflammatory chemical - vasodilator & chemoattractant – released by basophils
  
- **Agranulocytes**: WBCs without visible granules
  - **Lymphocytes**: small, medium & large sizes
    - large spherical nucleus occupies most of cell volume
    - most lymphocytes are in *lymphatic* organs
    - **T lymphocytes**: fight virus-infected cells & tumor cells
    - **B lymphocytes**: give rise to plasma cells that produce antibodies (immunoglobulins)
  
  - **Monocytes**: largest WBCs (2-3x size of RBCs)
    - Large U or kidney-shaped nucleus
    - differentiate into *macrophages* in tissues
    - macrophages are phagocytic cells that destroy bacteria & help in immune response against viruses

- **Leukopoiesis:** WBC production
  - Stimulated by *hormones (cytokines* such as *interleukins* & colony-stimulating factors (*CSFs*) from macrophages & lymphocytes
  - **Hemocytoblast** differentiates into either *myeloid stem cell* or *lymphoid stem cell*
    - **Myeloid stem cell** differentiates into *myeloblast* or *monoblast*
      - *Myeloblast* will form *granulocytes*
      - *Monoblast* will form *monocytes*
    - **Lymphoid stem cell** differentiates into *lymphoblast*, which will form *lymphocytes*
  
- **Leukocyte disorders:**
  - **Leukemias:** cancer of myeloid or lymphoid cell lines
    - Leukemias can be acute (rapidly advancing) or chronic (slowly advancing)
    - Treated with radiation & chemotherapy & bone marrow transplant to replace cancerous cells
  - **Infectious mononucleosis:** highly contagious viral infection
    - caused by Epstein-Barr virus (EBV)
    - symptoms (fatigue, aches, fever) last a few weeks until virus is dealt with by immune system
  
- **Platelets:** cytoplasmic fragments of *megakaryocytes* with granules containing blood-clotting enzymes
  - sometimes referred to as *thrombocytes*
  - stick together to form a plug to prevent blood loss in torn vessels
  - platelet formation regulated by hormone thrombopoietin
  - hemocytoblast differentiates into megakaryoblast, which undergoes repeated mitoses without cell division; this results in the megakaryocyte (cell with large nucleus)
  - extensions of megakaryocyte in bloodstream rupture to form platelets
  
- **Hemostasis:** stoppage of bleeding from a torn blood vessel
  - **Vascular spasms:** result in *vasoconstriction*; caused by damage to smooth muscle, chemicals & reflexes
  - **Platelet plug formation:** in response to blood vessel injury, platelets swell & form spiked processes
    - this allows them to adhere to exposed collagen fibers surrounding vessel
    - release of chemicals (serotonin, ADP) enhances vascular spasms & attracts more platelets to area (positive feedback)
    - PGI<sub>2</sub> released by endothelial cells limits platelet aggregation to area of injury
  - **Coagulation (blood clotting):** blood transformed from a liquid to a gel
    - **Prothrombin activator** converts the plasma protein *prothrombin* to *thrombin*

- *Thrombin* catalyzes joining of **fibrinogen** molecules in plasma to form a **fibrin** mesh that seals vessel
  - **Clotting factors** enhance clot formation (several require **vitamin K** for formation)
  - *Anticoagulants* inhibit clotting
- **Clot retraction & repair:** within 30-60 minutes after injury, platelets contract, pulling on fibrin strands to pull ends of torn vessel closer together
    - **Platelet-derived growth factor (PDGF)** released by platelets to stimulate division of smooth muscle cells & fibroblasts to rebuild vessel wall
  - **Fibrinolysis:** removes unneeded clots after healing has occurred
    - **Tissue plasminogen activator (tPA)** activates plasma **plasminogen**, which is converted to **plasmin**
    - **Plasmin** is an enzyme that digests fibrin, breaking down clot
  - **Factors limiting clot growth/formation:**
    - *Anticoagulants* antithrombin III, protein C & heparin work to inhibit procoagulants & thrombin
  - **Disorders of Hemostasis:**
    - **Thromboembolytic disorders:** a **thrombus** (clot) forms in an unbroken blood vessel; if it detaches from the vessel wall, the resulting **embolus** can travel through the blood & block blood vessels
      - Free blood clots can be treated by anticoagulants aspirin, heparin & warfarin
  - **Bleeding disorders:**
    - thrombocytopenia
    - impaired liver function
    - hemophilia

### Transfusion & Blood Replacement:

- whole blood transfusions are used to treat conditions involving massive blood loss
- packed red cells can be used to treat anemias
- **Human Blood Groups:** red blood cells have many (perhaps > 100) cell surface antigens – glycoproteins known as agglutinogens
  - antigens determining ABO and Rh blood groups cause transfusion reactions
  - **ABO blood groups:**
    - **type A blood** individuals have *surface antigen A*
    - **type B blood** individuals have *surface antigen B*
    - **type AB blood** individuals have *both A & B* surface antigens
    - **type O blood** individuals have *neither A nor B* surface antigens

- individuals make **antibodies** (*agglutinins*) against the antigen(s) not present on their red blood cells (e.g.: type A blood individuals will make anti-B agglutinins); this does not require previous exposure to the antigen(s)
- **Rh blood groups:**
  - Humans may also have one of several *Rh factors* present on the surface of their red blood cells
  - An individual without Rh factor will make antibodies against Rh factor, but only after exposure to the antigen

#### **Transfusion reactions: agglutination & hemolysis**

- following infusion of mismatched blood, agglutination occurs as antibodies complex with the foreign blood group antigens
- this blocks blood vessels & hinders blood flow; reduces oxygen availability to tissues, as the RBCs are lysed, hemoglobin escapes & may precipitate in kidney tubules leading to renal failure
- treatment involves diluting agents & diuretics
- *type O blood is the universal donor*
- *type AB<sup>+</sup> blood is the universal recipient*

#### **Plasma & Blood Volume Expanders:**

- plasma can be temporarily used to replace some blood volume when properly typed blood is not immediately available
- also, blood volume expanders such as albumin & dextran, which draw fluid into blood, can be used temporarily

#### **Diagnostic Blood Tests:**

- differential white blood cell count: to assess infection
- platelet count: used to assess thrombocytopenia
- complete blood count (CBC) used routinely to provide counts for all formed elements & tests for clotting factors

## Chapter 20: The Lymphatic System

### Functions of Lymphatic System:

- *Draining excess interstitial fluid:* lymphatic vessels drain excess fluid from tissue spaces & return it to the blood
- *Transporting dietary lipids:* lymphatic vessels transport lipids & lipid-soluble vitamins (A,D,E & K) absorbed by GI tract to the blood
- *Carrying out immune responses:* lymphatic tissue initiates specific immune responses to microbes or abnormal cells

**Lymphatic Vessels (Lymphatics):** system of drainage vessels that collects excess protein-containing interstitial fluid (fluid between cells) & returns it to blood

- used to return fluid escaped from blood into tissue spaces back to blood
- **lymph** is interstitial fluid that has entered lymphatic vessels
- form one-way system; blood flows toward heart
  
- **Lymph capillaries:** occur almost everywhere blood capillaries occur (except bones & teeth, bone marrow, & central nervous system (uses CSF to collect fluid))
  - o the edges of endothelial cells in walls of lymph capillaries loosely overlap forming minivalves to prevent backflow
  - o collagen filaments anchor the endothelial cells to connective tissue outside, allow the flaps to open when interstitial fluid volume increases such that fluid enters the lymphatic capillaries
  - o lymphatic capillaries (unlike blood capillaries) can easily take up proteins, foreign cells & debris... fortunately lymph is circulated through lymphoid organs with immune cells to examine the fluid for undesirables
  - o lacteals are specialized lymphatic capillaries in the intestinal mucosa that carry a thick white fatty lymph (chyle) to the blood
  - o lymph flows from lymphatic capillaries to collecting vessels, trunks, and ducts
  - o **lymphangitis:** inflammation of lymphatics
  - o lymphatic ducts: right lymphatic duct drains lymph from right upper arm, right side of head & thorax; thoracic duct arising from the sac-like cisterna chyli drains the rest of the body
  
- **Lymph transport:** slow transport; lymph is not pumped, but flows by smooth muscle contraction in the walls of the vessels, pressure changes in the thorax during breathing & valves to prevent backflow
  - o Also, bundling with blood vessels helps along with movements in adjacent tissues

### Lymphoid Cells:

- **Lymphocytes:** *T cells & B cells*
  - o **T cells** direct the immune response against virally-infected cells & cancer cells
  - o **B cells** produce plasma cells that synthesize antibodies
- **Macrophages:** phagocytize foreign substances & help activate T cells (along with *dendritic cells*)
- **Reticular cells:** provide stroma to nourish cells of lymphoid organs

**Lymphoid Tissue:**

- reticular connective tissue: forms a network around macrophages & lymphocytes in lymphoid organs
- diffuse lymphatic tissue: scattered reticular tissue elements
- **lymphatic nodules:** tightly packed reticular elements & cells
  - o **germinal centers:** actively dividing B cells & T cells

**Lymphoid Organs:** lymph nodes, spleen & thymus**Thymus:** bilobed organ in inferior neck extending into mediastinum

- functions in maturation of T cells; mostly in childhood
- size decreases with age as most tissue replaced by connective tissue
- thymic lobules each contain a cortex and medulla with lymphocytes (T cells); medulla contains Hassal's corpuscles (appear red)
- thymocytes (epithelial cells in stroma) secrete hormones (thymosins) for development of T cells

**Lymph Nodes:** hundreds of small organs that cluster along lymphatic vessels

- filter lymph: macrophages in lymph nodes remove debris & destroy microorganisms
- activate immune system: lymphocytes within follicles monitor lymph for foreign antigens & mount responses against them
- T cells circulate between blood, lymph nodes & lymphatic vessels for continuous exposure to foreign substances
- Lymph sinuses: large capillaries surrounded by reticular fibers with macrophages
- Structure:
  - o Capsule: dense connective tissue surrounding lymph node with trabeculae that extend inward to divide the node into compartments
  - o Cortex: outer region of lymph node (just inside capsule) containing follicles; germinal centers of follicles contain dividing B cells
  - o Medulla: medullary cords from cortical tissue contain lymphocytes & plasma cells
- circulation: afferent lymphatic vessel -> subcapsular sinus -> cortical & medullary sinuses -> efferent lymphatic vessel at hilus
- lymph nodes can become inflamed when overwhelmed with foreign substances & can become secondary cancer sites

**Spleen:** largest lymphoid organ; located in left side of abdominal cavity just below diaphragm

- blood flows through sinuses; spleen removes aged & defective blood cells from circulation & contains macrophages to cleanse blood of foreign matter
- stores breakdown products of red blood cells for later use
- in fetus, produces erythrocytes
- stores blood platelets
- red pulp: most of mass of spleen; concerned with blood-cleansing & removal of old RBCs

- white pulp: contains lymphocytes (B cells)
- direct spleen injury can cause it to rupture; treatment = removal (splenectomy)

**Tonsils:** small organs around the entrance to the pharynx

- contain follicles with germinal centers with dividing B cells
- palatine tonsils: paired at posterior end of oral cavity; most likely to be infected
- lingual tonsils: at base of tongue
- tubal tonsils: at openings of auditory tubes into pharynx

**Lymphoid Follicle Aggregates:**

- Mucosa-associated Lymphatic tissue (MALT)
  - o Peyer's Patches in intestine (ileum)
  - o Appendix

## Chapter 21: The Immune System: Innate & Adaptive Body Defenses

**The Immune System:** a *functional* system consisting of trillions of immune cells & molecules that inhabit lymphatic tissues & circulation providing resistance to disease (*immunity*).

**Innate (Nonspecific) Defenses:** cells & molecules *present from birth* in skin & circulation that protect against invading pathogens

- **Surface Barriers (Skin & Mucosae)**
  - keratinized epithelial cells of skin & epithelial mucosae provide a physical barrier to infection
  - protective chemicals secreted by cells of skin & mucosae:
    - acidic (pH 3-5) secretions of skin inhibit bacterial growth & chemicals in sebum are toxic to bacteria
    - stomach mucosa secretes concentrated HCl solution (pH 0.5-2.5) & proteases that kill microorganisms
    - saliva in oral cavity & lacrimal fluid in eyes contain lysozyme protein that kills bacteria
    - mucus of respiratory & digestive mucosae traps microorganisms
  
- **Internal Defenses: Cells & Chemicals**
  - **Phagocytes:** cells that ingest large particles & bacteria and break them down
    - **macrophages:** develop from *monocytes* that enter tissues; most dominant phagocytes
      - Free macrophages: alveolar macrophages of lungs, dendritic cells of epidermis (Langerhans' cells)
      - Fixed macrophages: Kupffer cells of liver, microglia of brain
    - also: neutrophils, eosinophils & mast cells have phagocytic activity
    - **mechanism of phagocytosis:**
      - microbe or foreign particle adheres to phagocyte
        - adhesion is dependent on recognition of carbohydrates on surface of microbe (some bacteria with complex carbohydrate capsules do not adhere well)
        - adhesion is enhanced by **opsonization** (foreign **antigen** is coated with complement & antibodies)
      - phagocyte forms pseudopods that engulf particle
      - particle taken into phagocyte in phagosome (phagocytic vesicle)
      - phagosome fuses with lysosome, & lysosomal enzymes within phagolysosome digest particle
        - respiratory burst: free radicals released to complete killing
      - residual body (remaining material in phagolysosome) released from cell by exocytosis
  
  - **Natural Killer (NK) Cells:** large granular lymphocytes present in blood & lymph that kill cancer cells & virus-infected cells

- unlike T cells, NK cells are not specific for a specific virus or cancer cell type
- like T cells, use *perforins* to kill target cell
- **Inflammation:** response to tissue injury (caused by trauma, heat, chemicals or infection)
  - prevents spread of damage
  - disposes of cell debris & pathogens
  - begins repair processes
  - 4 signs of inflammation: redness, heat, swelling & pain
  - **vasodilation & increased vascular permeability:** mediated by histamine, kinins, prostaglandins, complement & cytokines
    - vasodilation leads to hyperemia (blood congestion) – redness & heat
    - increased permeability of capillaries allows exudates (fluid with protein factors) to flow into tissue spaces causing edema (swelling) & pain (from adjacent nerves)
    - swelling dilutes toxic chemicals from pathogens & speeds delivery of repair materials
    - **phagocytes migrate to the area:**
      - *leukocytosis* – chemicals released by injured cells draw neutrophils
      - *margination* – neutrophils cling to walls of capillaries
      - *diapedesis* – neutrophils move through capillary walls into tissue spaces
      - *chemotaxis* – inflammatory chemicals draw more WBCs to the area, especially monocytes
      - monocytes enter tissue spaces & develop into *macrophages*, which finish the disposal of microbes
      - pus: mix of dead or dying WBCs & pathogens
- **Antimicrobial proteins**
  - **Interferon (IFN):** proteins released by virus-infected cells that prevent viral replication in neighboring cells
    - Interferons also mobilize macrophages to area & activate NK cells
  - **Complement:** group of plasma proteins that, when activated, release chemical mediators that amplify inflammatory response, enhance phagocytosis (*opsonization*) & lyse cells
    - activated by complement factors binding to antibody-antigen complex or cell wall polysaccharides of microorganisms
    - **membrane attack complex (MAC):** group of complement proteins that inserts into cell membrane to cause cell lysis (death)
- **Fever:** abnormally high body temperature in response to chemicals called *pyrogens* secreted by leukocytes & macrophages exposed to bacteria & antigens

**Adaptive (Specific) Defenses:** B cells & T cells that recognize specific foreign substances & act to immobilize, neutralize & destroy them

- adaptive defenses are: antigen-specific, systemic (immune cells present throughout body), & have memory (memory cells enhance response to previously encountered antigens)
- **humoral immunity (antibody-mediated immunity):** mediated by **antibodies** in the body's "humors" or fluids (blood, lymph, etc.)
  - o *B cells* produce plasma cells that release antibodies that bind antigens
- **cellular immunity (cell-mediated immunity):** mediated directly by **T cells**
  - o T cell receptors recognize & bind to antigens on virus-infected cells & cancer cells
  
- **antigens:** substances that can provoke an immune response
  - o most antigens are molecules that are not normally present in the body (nonself)
  - o **immunogenicity:** the ability of an antigen to stimulate proliferation of lymphocytes & antibody production
  - o **reactivity:** the ability of an antigen to react with the lymphocytes & antibodies
  - o **haptens:** small molecules that are reactive but not immunogenic unless attached to a protein carrier
  - o **antigenic determinants:** immunogenic regions of antigen
  - o **self antigens:** antigens that are not immunogenic to an individual but strongly immunogenic to others
    - **MHC (major histocompatibility complex) proteins:** self antigens involved in cellular immunity
      - In humans, called **HLA (human leukocyte antigen)** molecules
      - Class I MHC proteins: on surface of nearly all cells
      - Class II MHC proteins: only on surface of professional **antigen-presenting cells (APCs)**
  
- **Lymphocytes:** produced from lymphoid stem cells in bone marrow
  - o must become immunocompetent (able to bind antigen); where cell becomes immunocompetent determines whether it is a T cell or B cell
  - o **B cells** become immunocompetent in *bone marrow*
  - o **T cells** become immunocompetent in *thymus*
    - **Self-tolerance:** T cells that strongly bind self-antigens or are not immunocompetent are weeded out & destroyed (negative selection), while T cells that weakly bind self antigens continue to develop (positive selection)
  
- **antigen-presenting cells:** one of several cell types that engulfs & digests antigens & presents part of them on its plasma membrane bound to MHC molecules for recognition by *T cell receptors*
  - o *antigen presentation* by APCs is essential for the cellular immune response
  - o *professional APCs* include *dendritic cells, macrophages & activated B cells*, but most cell types can function as APCs

**Humoral Immune Response:** *B cells* stimulated by antigen; leads to production of *antibodies* by plasma cells

- **Clonal selection of B cells:** immunocompetent but naïve B cell is activated by antigen binding its receptor, & forms a *clone* (population of identical cells)
  - most cells of clone *differentiate* into **plasma cells**, which secrete *antibodies*
  - some cells become **memory B cells** that can mount an immediate response to another encounter with the same antigen
  
- **Immunological memory:**
  - **Primary immune response:** clonal selection & differentiation outlined above
    - takes approximately 3-6 days to start antibody production
  - **Secondary immune response:** rapid response to subsequent exposure to same antigen
    - within 2-3 days, a much higher level of antibody is produced than is generated during primary response
  
- **Active & Passive Humoral immunity:**
  - **Active immunity:** response by our own B cells to antigen(s)
    - **naturally acquired:** antigens from bacteria & viral infections
    - **artificially acquired:** antigens from vaccines
  - **Passive immunity:** antibodies harvested or delivered from immune serum (from human or other animal)
    - **naturally acquired:** antibodies pass from mother to child via placenta
    - **artificially acquired:** antibodies acquired from injection of immune serum
  
- **Antibodies (immunoglobulins or Igs):** gamma globulin component of blood serum
  - Y-shaped proteins produced by activated B cells & plasma cells in response to antigen
    - composed of 2 identical **heavy (H) chains** & 2 identical **light (L) chains**
    - each chain has a **variable (V) region** & **constant (C) region**
    - variable regions of 1 H chain & 1 L chain make up **antigen-binding site**; each antibody has 2 antigen-binding sites
    - constant region of H chains make up **complement binding site** & **macrophage binding site**
  - **5 classes of antibodies:**
    - **IgD:** B cell antigen receptor
    - **IgM:** monomer & pentamer forms
      - *monomer* – B cell antigen receptor
      - *pentamer* – circulates in blood plasma; first Ig class secreted; potent agglutinating agent
    - **IgG:** most abundant circulating antibody; protects against bacteria, viruses & toxins; fixes complement; primary antibody of primary & secondary responses; confers naturally acquired passive immunity
    - **IgA:** monomer & dimer forms
      - *monomer:* small amounts in plasma

- *dimer*: found in secretions (mucus, saliva, sweat intestinal juice, milk), helps to prevent pathogens from entering body
  - **IgE**: normally rarely in plasma (levels rise during allergic reaction), secreted by plasma cells in skin, mucosae of digestive & respiratory tracts, & tonsils; when activated by antigen, binds to mast cells & basophils & causes release of histamine & other mediators of inflammation
- **antibody diversity**: genes for H & L chain proteins contain segments of DNA that are “shuffled” by somatic recombination, & V regions are hot spots for mutation; the result is an enormous variation in the antigen specificity of the antibodies produced
  - also, plasma cells can produce more than 1 class of antibody (“switch” from producing IgM to IgG)
- **Antibody functions**: antibodies bind to antigens to form antigen-antibody complexes that inactivate antigens or target them for destruction
  - **Precipitation**: large antigen-antibody complexes formed that settle out of solution; makes easier targets for macrophages
  - **Lysis**: antibodies bind to antigens on surface of bacteria & mismatched red blood cells; complement binding site of antibody binds complement, which triggers complement fixation & cell death
  - **Agglutination**: IgM binds to antigens on surface of mismatched red blood cells & forms large complexes (clumping)
  - **Neutralization**: antibody binds to active site of toxin (from virus or bacteria) & inactivates it
  - **Monoclonal antibodies**: pure antibody preparations produced from a B cell clone used in clinical applications

**Cell-mediated immune response**: *T cells* stimulated by antigen; leads to lysis of virus-infected cells or cancer cells &/or elevation of immune response

- **Clonal selection of T cells**: immunocompetent but naïve T cell is activated by binding of its T cell receptor (TCR) to **antigen-MHC protein complex** on cell surface of **antigen-presenting cell**, & forms a *clone* (population of identical cells)
  - most cells of clone **differentiate** into mature T cells
    - **cytotoxic T cells (CD8 cells or T<sub>C</sub> cells)** lyse target cells
    - **helper T cells (CD4 cells or T<sub>H</sub> cells)** release chemicals called **cytokines** that amplify immune response (stimulate production of more B cells & T cells, mobilize phagocytes & attract more WBCs to area)
    - some cells become memory T cells that can mount an immediate response to another encounter with the same antigen
- **T cell activation**:
  - **Antigen recognition & MHC restriction**: T cell receptors recognize & bind to antigen-MHC protein complex on cell surface of APC
  - T cell receptors must recognize both self (MHC) & foreign (antigen) molecules in complex on the surface of APC

- **T<sub>C</sub> cell** receptors bind to short peptides from *endogenous antigens* (foreign/viral proteins inside cell) in complex with **MHC Class I molecule**
  - **T<sub>H</sub> cell** receptors bind to longer peptides from exogenous antigens (foreign/bacterial proteins/allergens phagocytized from outside cell in blood/plasma) in complex with **MHC Class II molecule**
  - **Costimulation:** T cell must be exposed to *costimulatory signal* to continue activation
    - signal can be binding to additional receptor on APC surface (B7 on macrophages binds CD28 on T cell) or cytokine stimulation
    - if no signal, T cell will halt activation & may become tolerant to antigen (*anergy*)
- **Cytokines:** hormone-like glycoproteins released by activated T cells & macrophages
- **interleukins (*IL-1 & IL-2*)** act as costimulators of T cells & T cell proliferation
  - include cell toxins (perforin), inflammatory factors
- **Specific T cell roles:**
- **helper T cells (T<sub>H</sub> cells):** in most cases, required for adaptive immune responses
    - release *cytokines* that:
      - activate B cells bound to certain antigens (T cell-dependent antigens)
      - mobilize immune cells & macrophages
      - attract more WBCs to area (chemotaxis) & enhance nonspecific defenses
  - **cytotoxic T cells (T<sub>C</sub> cells):** also called killer T cells, directly attack & kill APCs with recognized foreign antigen/MHC complex on cell surface
    - mainly target virus-infected cells, but also target some bacteria, parasites, cancer cells & foreign RBCs
    - once bound to target cell & activated by helper T cells, release perforin (or lymphotoxin) to lyse target APC (similar to complement lysis)
  - **other T cells:**
    - **suppressor T cells (T<sub>S</sub> cells):** release cytokines that suppress activity of T & B cells; may be involved in ending/cleaning up response
    - **delayed-type hypersensitivity cells (T<sub>DH</sub> cells):** release cytokines to activate macrophages in delayed hypersensitivity reactions
    - **gamma-delta T cells:** small intestinal population of T cells

**Organ Transplants & Prevention of Rejection:** cytotoxic T cells will normally target & kill foreign tissue

- both ABO blood group antigens & MHC antigens are typed to match (slight mismatches in MHC antigens are often tolerable)
- *immunosuppressive therapy* kills activated & circulating immune cells (as well as other rapidly dividing cells)

**Immunodeficiencies:** conditions where the production or function of immune cells, phagocytes or complement is impaired or abnormal

- **severe combined immunodeficiency syndrome (SCID):** congenital (present from birth) condition resulting from deficits in both T and B cells
  - can be caused by nonfunctional interleukin receptors, defective adenosine deaminase (toxic to T cells)
  - fatal if untreated (due to any infection), but can be treated with bone marrow transplant
- **acquired immunodeficiency syndrome (AIDS):** infection with *human immunodeficiency virus (HIV)* destroys *helper T cells*
  - viral surface proteins target/bind to CD4 protein on helper T cells
  - if untreated, over time helper T cell populations diminish & the condition can be fatal due to any type of infection
  - treatments are available that inhibit viral replication/synthesis, but must be continuous as the virus is not eliminated by the treatment
  - since these treatments only prevent new viral production, new research is aimed at treatments to prevent viral binding to/entry into helper T cells & specific removal of infected T cells

**Autoimmune diseases:** condition in which the body produces antibodies & activated cytotoxic T cells that target & destroy (self) body tissues

- causes include improper negative selection of self-directed lymphocytes in bone marrow & thymus during development, appearance of new antigens on cells, or foreign antigens that resemble self antigens
- examples are systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) & multiple sclerosis (MS)
- treatments include anti-inflammatories to control symptoms & antibodies/chemicals to suppress lymphocyte activity

### **Hypersensitivities:**

- **Immediate hypersensitivities:**
  - **Type I (anaphylaxis):** contact with allergen sensitizes individual; second contact results in immediate symptoms (swelling caused by **IgE** binding to allergen & causing release of histamine from mast cells & basophils)
    - Produces symptoms of asthma - treated with antihistamines
    - In rare cases, may cause anaphylactic shock due to loss of blood plasma (hypotensive shock); can be fatal - treated with epinephrine
    - *Atopy:* rarely symptoms may appear without initial sensitization
- **Subacute hypersensitivities:** mediated by **IgG & IgM**
  - **Type II (cytotoxic) reactions:** antibodies bind to antigens on cell surfaces (bacteria or foreign red blood cells) & stimulate phagocytes & complement-mediated lysis (example: transfusion reactions)
  - **Type III (immune complex) reactions:** insoluble antigen-antibody complexes form resulting in intense inflammatory reaction (example: autoimmune diseases)
- **Delayed hypersensitivities:**

- ***Type IV reactions:*** slower to appear (1-3 days); mediated by ***T cells*** (cytotoxic & delayed hypersensitivity) (example: allergic contact dermatitis)