# HEMATOLOGY REVIEWER (Lecture 1)

## I. HEMATOLOGY

### Definition

**Hematology** is the study of **blood, blood-forming organs, blood diseases, and laboratory tests** used to diagnose and monitor these disorders.

### Importance

- Diagnoses anemia and polycythemia
- Detects infections
- Evaluates bleeding and clotting disorders
- Monitors treatment

## II. BLOOD

Average Blood Volume: **5 L** in a healthy adult.

### Functions of Blood

| Function | Importance |
|---|---|
| Transport oxygen | Delivers oxygen to tissues for energy production (ATP). |
| Transport carbon dioxide | Carries $CO_2$ back to the lungs for exhalation. |
| Transport nutrients | Delivers glucose, proteins, and lipids. |
| Remove wastes | Carries wastes to the liver and kidneys. |
| Protection | WBCs fight infection. |
| Hemostasis | Platelets and clotting factors stop bleeding. |

## III. BLOOD COMPONENTS

| Component | Description | Function |
|---|---|---|
| **Plasma** | Liquid portion of blood | Contains water, proteins, nutrients, hormones, electrolytes, and **clotting factors**. |
| **RBCs** | Erythrocytes | Carry oxygen and carbon dioxide. |
| **WBCs** | Leukocytes | Defend the body against infection. |
| **Platelets** | Thrombocytes | Stop bleeding (hemostasis). |

### Why does blood clot in a red-top tube?

Because it **does not contain an anticoagulant**, so the clotting factors in plasma become activated and form a clot.

## IV. RED BLOOD CELLS (RBCs)

### Definition

RBCs (erythrocytes) are the **most abundant blood cells** responsible for transporting oxygen and carbon dioxide.

### Characteristics

| Feature | Significance |
|---|---|
| Anucleate | More space for hemoglobin. |
| Biconcave | Increases surface area and flexibility. |
| Discoid | Allows passage through small capillaries. |
| Diameter: **7–8 µm** | Normal RBC size. (7-8 mm) |
| Central pallor: **1/3** | Indicates a normal amount of hemoglobin. (1/3) |

### Function

- Carry oxygen from lungs → tissues.
- Carry carbon dioxide from tissues → lungs.

---

## V. HEMOGLOBIN (Hb)

### Definition

An **iron-containing protein** inside RBCs.

### Function

- Carries oxygen.
- Carries some carbon dioxide.

### Important Concept

**RBC → Hemoglobin → Iron → Oxygen**

- RBC = the transport vehicle.
- Hemoglobin = the oxygen-carrying protein.
- Iron = the part of hemoglobin that binds oxygen.

---

### Hypochromic RBC ← less Hgb, more pale, ↑ central pallor

**Hypo = less**
**Chromic = color**
Means the RBC contains **less hemoglobin**, making it appear paler with an increased central pallor.

---

## VI. HEMOGLOBIN MEASUREMENT

### Cyanmethemoglobin (Drabkin) Method

#### Purpose

To accurately measure hemoglobin concentration.

#### Drabkin Reagent

| Component | Function |
|---|---|
| Potassium ferricyanide | Converts Hb → Methemoglobin |
| Potassium cyanide | Converts Methemoglobin → Cyanmethemoglobin |

### Why use Drabkin reagent?

Hemoglobin exists in different forms that absorb light differently. Drabkin reagent converts them into one **stable form (cyanmethemoglobin)** for accurate measurement.

### Instrument

**Spectrophotometer**

### Wavelength

**540 nm**

### Interpretation

Higher absorbance = Higher hemoglobin concentration.

## VII. RBC COUNT

### Purpose

Measures the number of red blood cells.

| Low RBC | High RBC |
|---|---|
| **Anemia** | **Polycythemia** |
| Decreased oxygen delivery | Hyperviscosity (thick blood) |
| Fatigue, pallor, weakness | Increased risk of clotting, stroke, and heart attack |

## VIII. HEMATOCRIT (PCV)

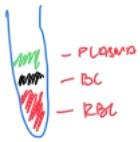
### Definition

The **percentage of blood occupied by packed red blood cells**.

Also called: **Packed Cell Volume (PCV)**

### Blood after Centrifugation

| Layer | Contents |
|---|---|
| Plasma | Water, proteins, nutrients |
| Buffy coat | WBCs + Platelets |
| Packed RBCs | Red blood cells |




**Buffy coat is excluded** because hematocrit measures only RBCs.

## IX. MICROHEMATOCRIT EQUIPMENT

| Equipment | Purpose |
|---|---|
| Red-banded capillary tube | Heparinized; for capillary blood |
| Blue-banded capillary tube | Plain; for EDTA venous blood |
| Sealant clay | Prevents blood leakage |
| Microhematocrit centrifuge | Separates blood components |
| Locking cover | Prevents tube breakage |
| Hematocrit reader | Measures hematocrit (%) |

## X. RBC INDICES

| Index | Measures | Remember |
|---|---|---|
| **MCV** | Average RBC size | **Volume** |
| **MCH** | Average amount of Hb per RBC | **How much Hb** |
| **MCHC** | Average Hb concentration inside RBC | **How concentrated** |
| **RDW** | Variation in RBC size | **Difference in size** |

## XI. RETICULOCYTES

### Definition

Immature red blood cells.

### Characteristics

| Feature | Description |
|---|---|
| Produced in | Bone marrow |
| Mature in | Bloodstream (1–2 days) |
| Purpose | Indicates bone marrow RBC production |

### Stain

**New methylene blue (supravital/vital stain)**

**Why?** It stains the **residual RNA (reticulum)** inside immature RBCs.

## XII. WHITE BLOOD CELLS (LEUKOCYTES)

### Function

Protect the body from:

- Bacteria
- Viruses
- Fungi
- Parasites
- Foreign substances

Produced mainly in the **bone marrow**.

## XIII. WBC MOVEMENT

| Movement | Meaning |
|---|---|
| Chemotaxis | Movement toward chemicals released by infection |
| Diapedesis | WBC squeezes through blood vessel walls |
| Phagocytosis | Engulfs and destroys microorganisms |
| Phototaxis | Movement toward light ❌ (Not done by WBCs) |

## XIV. TYPES OF WBCs

| Cell | Function | Increased In |
|---|---|---|
| **Neutrophils** | Phagocytosis; kill bacteria & some fungi | Bacterial infection |
| **Band Neutrophils** | Immature neutrophils | Acute bacterial infection (left shift) |
| **Eosinophils** | Fight parasites; regulate allergies | Allergy, parasitic infection |
| **Lymphocytes** | Adaptive immunity | Viral infection |
| **Monocytes** | Become macrophages; phagocytosis | Chronic infection |

precursor of macrophage

### Neutrophils

- Most abundant WBC in **blood** (50–70%).
- Segmented nucleus (3–5 lobes). multilobed
- Granules contain bactericidal enzymes.
- First responders during bacterial infection.

### Band Neutrophils

- Immature neutrophils.
- U- or S-shaped nucleus.
- Increased bands = **Left shift**.

### Eosinophils

- Bright orange-red granules.
- Fight parasites.
- Participate in allergic reactions.

Increase = **Eosinophilia**.

### Lymphocytes

Provide **adaptive immunity**.

| Type | Function |
|---|---|
| **B cells** | Produce antibodies (**Humoral immunity**) |
| **T cells** | Kill infected cells (**Cell-mediated immunity**) |

Increase = **Lymphocytosis**, commonly seen in viral infections.

### Monocytes

precursor of macrophage

- Largest WBC.
- Become **macrophages** in tissues.

Functions:

- Phagocytosis.
- Remove dead cells.
- Present antigens to lymphocytes.

**Remember:**

- **Most abundant WBC in blood → Neutrophils.**
- **Most abundant phagocytic immune cell in tissues → Macrophages.**

---

## XV. PLATELETS (THROMBOCYTES)

### Characteristics

- Small **anucleate cell fragments**.
- Size: **2–4 µm**.

### Function

Maintain blood vessel integrity by initiating **hemostasis**.

### Hemostasis (Stopping Bleeding)

1. Platelet adhesion.
2. Platelet aggregation.
3. Activation of clotting factors.
4. Formation of a fibrin clot.

---

## XVI. BLOOD FILM EXAMINATION (Peripheral Blood Smear)

### Purpose

- Examine RBC morphology.
- Perform WBC differential count.
- Estimate platelet number and appearance.

### Procedure

1. Place a drop of blood on a glass slide.
2. Make a **wedge smear** (30–45° angle).
3. Air dry.
4. Fix with methanol.
5. Stain using **Wright** or **Wright-Giemsa** stain.
6. Examine under the microscope.

### Wright / Wright-Giemsa Stain

| Dye | Stains |
|---|---|
| Eosin | Pink to red structures (e.g., hemoglobin) |
| Methylene blue/Azure dyes | Blue to purple nuclei and RNA |

## XVII. HISTORY OF HEMATOLOGY

| Scientist | Contribution |
|---|---|
| **Athanasius Kircher (1657)** | Described "worms" in the blood. |
| **Anton van Leeuwenhoek (1674)** | First to describe RBCs. |
| **Giulio Bizzozero** | Described platelets ("petite plaques"). |
| **James Homer Wright (1902)** | Developed the Wright stain. |

# PATIENT SAFETY IN HEMATOLOGY AND HEMOSTASIS

## I. PATIENT SAFETY

### Definition

**Patient Safety** is the **freedom from accidental injury or harm** during healthcare.

It focuses on:

- Preventing errors
- Avoiding patient harm
- Reducing injuries if errors occur

### Simple Meaning

**Patient safety means making sure the patient receives the correct test, correct result, and correct treatment without harm.**

## II. WHY IS PATIENT SAFETY IMPORTANT IN THE LABORATORY?

Laboratory errors can lead to wrong diagnoses and treatments.

### Possible Adverse Outcomes

| Outcome | Meaning | Example |
|---|---|---|
| **False-positive** | Test result is positive even though the patient does **not** have the disease. | A healthy patient is diagnosed with HIV. |
| **False-negative** | Test result is negative even though the patient **has** the disease. | A patient with anemia is reported as normal. |
| **Missed diagnosis** | Disease is not detected. | Cancer is not identified. |
| **Delayed diagnosis** | Diagnosis is made too late. | Treatment starts late, allowing the disease to worsen. |
| **Inappropriate treatment** | Wrong treatment is given because of an incorrect result. | Patient receives unnecessary medication. |

### Clinical Significance

Laboratory errors can:

- Delay treatment.
- Cause unnecessary treatment.
- Increase healthcare costs.
- Endanger the patient's life.

## III. HEALTH CARE QUALITY

### Definition

Health care quality is the **degree to which healthcare services improve the health of individuals and populations while following current professional knowledge.**

### Simple Meaning

Healthcare should provide the **best possible outcome** using **safe and evidence-based practices**.

## IV. CHARACTERISTICS OF QUALITY HEALTH CARE

| Characteristic | Meaning | Goal |
|---|---|---|
| **Effective & Safe** | Uses the correct treatment while preventing harm. | Best patient outcome with minimal risk. |
| **People-Centred & Equitable** | Respects the patient's needs and provides fair care to everyone. | Equal and respectful healthcare. |
| **Timely & Efficient** | Delivers care without unnecessary delays or wasting resources. | Faster and more efficient service. |
| **Integrated** | Different healthcare professionals work together. | Coordinated patient care. |

## V. ESSENTIAL COMPETENCIES FOR HEALTH CARE PROFESSIONALS

### 1. Interprofessional Teamwork

#### Meaning

Healthcare professionals work together as one team.

#### Members may include:

- Physicians
- Medical Technologists
- Nurses
- Pharmacists
- Physical Therapists

#### Importance

- Improves communication.
- Reduces medical errors.
- Provides better patient care.

### 2. Evidence-Based Practice (EBP)

#### Meaning

Healthcare decisions should be based on:

- Scientific research

- Clinical experience
- Patient needs and preferences

### Importance

Ensures patients receive the most effective and updated care.

### 3. Patient-Centred Care

### Meaning

The patient is the centre of all healthcare decisions.
Healthcare providers should:

- Respect the patient's values.
- Listen to patient concerns.
- Involve patients in decision-making.

### Goal

Provide care that meets the patient's individual needs.

---

### 4. Informatics

### Meaning

The use of computers and information technology in healthcare.
Examples:

- Electronic Medical Records (EMR)
- Laboratory Information Systems (LIS)
- Hospital Information Systems (HIS)

### Importance

- Improves communication.
- Reduces documentation errors.
- Provides faster access to patient information.

---

### 5. Quality Improvement (QI)

### Meaning

A continuous effort to improve healthcare services.

### Goal

- Reduce errors.
- Improve laboratory performance.
- Increase patient safety.
- Improve patient outcomes.

---

## CELL STRUCTURE & FUNCTION

## I. CELL ORGANIZATION

### Cell

- **Structural and functional unit of life**
- Cells have specialized functions and contain components necessary to perform and maintain those functions.
- Understanding cell structure and function is fundamental to understanding **blood pathophysiology**, diagnosis, and disease processes.

---

## II. PLASMA MEMBRANE

### Plasma membrane

A **semipermeable outer boundary** separating the cell from the extracellular environment.

### Four basic functions

1. **Physical barrier**
   - Contains and protects cellular components.
2. **Transport**
   - Regulates movement of substances into and out of the cell.
   - Includes **endocytosis, exocytosis, and selective permeability**.
3. **Electrochemical gradients**
   - Establishes differences between the inside and outside of the cell.
4. **Signal transduction**
   - Receptors allow cells to respond to hormones, cytokines, and other signaling molecules.

### Fluid mosaic model

The plasma membrane consists of **proteins floating within a lipid bilayer**.

### Main membrane lipids

- **Phospholipids**
- **Cholesterol**

### Phospholipid structure

**Hydrophilic head**

- Contains phosphate
- Polar
- Water-soluble
- Faces the extracellular and cytoplasmic surfaces

**Hydrophobic tail**

- Fatty acid chains
- Nonpolar

- Water-insoluble
- Faces the center of the bilayer

### Cholesterol

- Helps maintain **membrane fluidity**
- Its hydroxyl group is hydrophilic.
- Its steroid nucleus is hydrophobic.

---

## III. MEMBRANE PROTEINS

### Transmembrane proteins

- Pass through the lipid bilayer.
- Function as:
  - Channels
  - Transporters
  - Receptors
  - Adhesion molecules

### Cytoskeletal proteins

- Located on the **cytoplasmic side** of the membrane.
- Form/support the cytoskeleton.
- Help provide structural integrity.

### Glycoprotein

Protein with carbohydrate chains covalently attached.

### Glycolipid

Lipid with carbohydrate attached.

---

## IV. GLYCOCALYX & BLOOD CELL MARKERS

### Glycocalyx

The **external protective carbohydrate coating** on the cell surface.

Made primarily from carbohydrate chains of:

- Glycoproteins
- Glycolipids

The **extracellular matrix (ECM)** also contributes to this coating.

### Functions of glycocalyx

- Cell-to-cell recognition
- Cell adhesion
- Provides a **negative surface charge**
- Helps repel adjacent circulating cells

### Surface antigens

Blood cell membranes contain **glycoproteins and glycolipids** that function as surface markers/antigens.

Different blood cells express different surface antigens at different stages of differentiation.

### CD system

**CD = Cluster of Differentiation**

A universal nomenclature for identifying blood cell antigens.

### Flow cytometry

Uses **antigen-specific monoclonal antibodies** to identify cell surface antigens.

---

## V. NUCLEUS

### Nucleus

- **Largest organelle**
- **Control center of the cell**
- Contains DNA.
- Controls cellular activities and reproduction.
- Site of:
  - **DNA replication**
  - **Transcription**

### Three components

1. Chromatin
2. Nuclear envelope
3. Nucleoli

### Wright stain

The nucleus has an affinity for **basic dyes** because of its nucleic acids.

It stains **deep purple** with Wright stain.

---

## VI. CHROMATIN

### Chromatin

Consists of:

- Double-stranded DNA
- Histone proteins
- Nonhistone proteins

DNA is tightly folded.

### Nucleosome

The **first level of DNA folding**.

Think:

**DNA → wraps around histones → nucleosomes**

### Heterochromatin

- Condensed
- Clumped
- Transcriptionally **inactive**
- Stains darker
- More abundant in mature cells

### Euchromatin

- Diffuse
- Uncondensed
- Open
- Genetically **active**
- Site where DNA is transcribed into mRNA
- Stains **pale blue** with Wright stain

### Important relationship

**More mature cell → more heterochromatin → less transcriptional activity**

---

## VII. NUCLEAR ENVELOPE

### Nuclear envelope

Consists of **two phospholipid bilayer membranes**.

### Inner nuclear membrane

Surrounds the nucleus.

### Outer nuclear membrane

Continuous with the **rough endoplasmic reticulum (RER)**.

### Perinuclear space

- Space between the two nuclear membranes
- Approximately **30–50 nm**
- Continuous with the lumen of the RER

### Nuclear pore complexes

- Penetrate the nuclear envelope.
- Allow molecules to pass between the **nucleus and cytoplasm**.

---

## VIII. NUCLEOLUS

### Nucleolus

Site of:

- **rRNA production**
- Assembly of ribosomal subunits

### Contains

- rRNA
- rDNA
- Ribosomal proteins

### rDNA

Genes coding for rRNA.

### Ribosome production

**rDNA → rRNA precursor → processed rRNA → combines with ribosomal proteins → small + large ribosomal subunits**

The subunits leave through the **nuclear pores**.

### Metabolically active cells

Have more prominent nucleoli because they require greater amounts of **protein synthesis**.

### Maturing blood cells

Protein synthesis decreases, so nucleoli eventually **disassemble**.

---

## IX. CYTOPLASM

### Cytosol

The **homogeneous, continuous aqueous solution** of the cytoplasm.

It is the environment where organelles exist and function.

---

## X. RIBOSOMES

### Ribosomes

Macromolecular complexes consisting of:

- Small subunit
- Large subunit
- rRNA
- Ribosomal proteins

### Main function

**Site of protein synthesis**

### mRNA

Provides the genetic code for the amino acid sequence.

### tRNA

Carries amino acids to the ribosome.

### Free ribosomes

Found in the cytoplasm.

Generally synthesize proteins used **within the cell**.

### RER-bound ribosomes

Attached to the rough endoplasmic reticulum.

Synthesize proteins destined for:

- Secretion
- Membranes
- Certain organelles

### Polyribosomes

Ribosomes arranged in chains.

### Basophilia

Cells actively producing proteins contain many ribosomes and therefore stain **dark blue** with Wright stain.

Particularly prominent in **erythroid precursor cells**.

---

## XI. ENDOPLASMIC RETICULUM

### Endoplasmic reticulum

A membrane-bound interconnected network of:

- Flattened sacs
- Tubes

### Cisternae

Channels within the ER.

---

### Rough ER (RER)

Has **ribosomes** attached to its outer surface.

### Functions

- Synthesizes membrane-bound proteins
- Synthesizes proteins destined for secretion
- Processes proteins

### Key clue:

**"Stubbled/studded appearance due to ribosomes" → RER**

---

### Smooth ER (SER)

Has **no ribosomes**.

### Functions

- Phospholipid synthesis
- Steroid synthesis
- Detoxification/inactivation of harmful compounds and drugs
- Calcium storage and release

### Easy comparison

**RER → proteins**

**SER → lipids + detoxification + calcium**

---

## XII. GOLGI APPARATUS

### Structure

Stacked, flattened membrane-bound sacs called **cisternae**.

### Functions

**Modifies → sorts → packages** macromolecules.

Especially proteins coming from the RER.

### Cis face

Receives vesicles from the **RER**.

### Trans face

Vesicles leave the Golgi.

They may become:

- Lysosomes
- Secretory vesicles
- Vesicles destined for the plasma membrane

### Protein modifications

- Glycosylation
- Sulfation
- Phosphorylation

---

## XIII. MITOCHONDRIA

### Structure

- Outer membrane
- Inner membrane
- Intermembrane space
- Matrix

### Cristae

Folds of the inner mitochondrial membrane.

### Function

Produces most of the cell's **ATP through aerobic respiration**.

### Simplified pathway

**Glucose → pyruvate → acetyl-CoA → citric acid cycle → NADH + $FADH_2$ → electron transport chain → ATP**

### Why are cristae important?

They greatly increase the surface area of the inner membrane, increasing ATP-producing capability.

### Matrix contains

- Mitochondrial DNA
- Ribosomes
- Enzymes
- Proteins

### Special characteristics

Mitochondria:

- Have their own circular DNA
- Have RNA
- Can self-replicate

### Hematology connection

A component of **heme biosynthesis** occurs in the mitochondrial matrix.

---

## XIV. LYSOSOMES

### Lysosomes

Membrane-bound organelles containing **acid hydrolases**.

### Main function

**Intracellular digestion**

They digest cellular materials and material brought into the cell.

### Acid hydrolases

Work best at approximately **pH 5.0**.

### Why membrane-bound?

The membrane:

- Keeps digestive enzymes contained.

- Prevents them from digesting the cell.
- Helps maintain the acidic environment.

### Proton pumps

Pump $H^+$ into the lysosome to maintain its acidic pH.

### Hematology

With Wright stain, lysosomes appear as **granules in WBCs and platelets**.

### Lysosomal storage diseases

Examples:

- Gaucher disease
- Niemann-Pick disease

---

## XV. CYTOSKELETON

Three major filament systems:

| Structure | Approx. diameter | Major function |
|---|---|---|
| Microfilaments | 5–7 nm | Movement, contraction, intracellular transport |
| Intermediate filaments | 8–10 nm | Structural stability |
| Microtubules | ~25 nm | Cell shape, movement, organelle transport, mitotic spindle |

---

### Microfilaments

Made primarily of **actin**.

- Double-stranded
- Intertwined
- Work with myosin
- Cell motility
- Contraction
- Intracellular transport
- Cell division
- Cytoskeletal support near plasma membrane

---

### Intermediate filaments

- Approximately **8–10 nm**
- Most durable cytoskeletal element
- Provide structural stability
- Important in cells exposed to physical stress

Examples:

- Keratins
- Lamins

---

### Microtubules

- Hollow cylindrical structures
- Approximately **25 nm**
- Made of **α- and β-tubulin**
- 13 protofilaments form one microtubule

### Functions

- Maintain cell shape
- Cell motility
- Intracellular organelle movement
- Form mitotic spindle fibers
- Major component of centrioles

---

## XVI. CENTROSOMES & CENTRIOLES

### Centrosome

Contains **two centrioles**, usually positioned at right angles.

### Centriole

Contains: **9 bundles × 3 microtubules**

### Function

Serves as an insertion/organizing point for **mitotic spindle fibers**.

---

## XVII. MEMBRANE TRANSPORT

Two major mechanisms:

### Passive transport

- Does **not require energy**

- Moves **along concentration gradient**
- High → low

Types:

1. Simple diffusion
2. Facilitated diffusion
3. Osmosis

### Active transport

- Requires energy
- Moves **against concentration gradient**
- Low → high

Types:

1. Primary active transport
2. Secondary active transport
3. Vesicular transport

---

## XVIII. SIMPLE DIFFUSION

Small **nonpolar/hydrophobic molecules** cross the membrane.

Examples:

- $O_2$
- $CO_2$

**No ATP.**

---

## XIX. FACILITATED DIFFUSION

Uses **transmembrane proteins**.

Moves substances down their concentration gradient.

Examples:

- $Na^+$
- $K^+$
- $Ca^{2+}$
- Glucose

### Channels

Create pathways through the membrane.

### Carriers

**Change conformation** during transport.

### Aquaporins

Special membrane channels that transport **water** rapidly.

---

## XX. OSMOSIS

Movement of **water** across a selectively permeable membrane.

Water moves:

**Low solute concentration → High solute concentration**

Until equilibrium is reached.

### Hematology connection

Demonstrated by the **osmotic fragility test** in RBCs.

---

## XXI. PRIMARY ACTIVE TRANSPORT

Uses **ATP directly**.

Transmembrane pumps move substances against their concentration gradient.

Important ions:

- $Na^+$
- $K^+$
- $Ca^{2+}$
- $Mg^{2+}$

### RBC example

**Sodium-potassium ATPase**

Na+/K+ ATPase

Maintains:

- High intracellular $K^+$
- Low intracellular $Na^+$

Helps maintain RBC:

- Volume
- Shape

---

## XXII. SECONDARY ACTIVE TRANSPORT

Does not directly use ATP at the transporter.

Uses energy stored in an **electrochemical gradient**.

### Symport

Two substances move in the **same direction**.

### Antiport

Two substances move in **opposite directions**.

---

## XXIII. VESICULAR TRANSPORT

Uses membrane-bound vesicles.

### Exocytosis

Moves substances **out** of the cell.

Vesicle fuses with plasma membrane and releases contents.

### Endocytosis

Moves substances **into** the cell.

Three types:

1. Pinocytosis
2. Phagocytosis
3. Receptor-mediated endocytosis

---

### Pinocytosis

**"Cell drinking."**

- Membrane folds inward
- Small pit forms.
- Pit pinches off.
- Fluid-filled vesicle enters cell.

Also helps recycle membrane components.

---

### Phagocytosis

**"Cell eating."**

- Plasma membrane forms **pseudopods**.
- Engulfs particles.
- Forms a **phagosome**.

Phagocytes:

- Neutrophils
- Monocytes/macrophages

Can engulf:

- Bacteria
- Foreign antigens
- Senescent RBCs

---

### Receptor-mediated endocytosis

Highly **specific**.

#### Sequence:

**Ligand binds receptor → receptors cluster → membrane invaginates → clathrin-coated pit → endosome**

Example:

**Transferrin + iron → transferrin receptor → cell uptake**

---

## XXIV. CELL COMMUNICATION

### Gap junctions

Directly connect adjacent cells.

Allow rapid exchange of very small molecules such as:

- cAMP
- $Ca^{2+}$

---

## XXV. TYPES OF SIGNALING

### Juxtacrine/contact-dependent

Signaling requires direct cell-to-cell contact.

### Autocrine

Cell signals **itself**.

### Paracrine

Signal acts on **nearby cells**.

### Endocrine

Hormone travels through the **bloodstream** to distant target cells.

---

## XXVI. SIGNAL TRANSDUCTION

### Basic sequence

**Ligand → receptor → signaling cascade → second messengers → target proteins → cellular response**

### First messenger

The **ligand**.

### Second messengers

Examples:

- $Ca^{2+}$
- cAMP
- cGMP
- DAG
- $IP_3$

### Possible cellular effects

- Ion transport
- Metabolism
- Gene expression
- Cell shape
- Cell movement
- Cell growth
- Cell division

---

## XXVII. THREE MAJOR PLASMA MEMBRANE RECEPTORS

### 1. Ion channel-linked receptors

Ligand binding opens an ion channel.

Converts:

**Chemical signal → electrical signal**

Important in:

- Neurons
- Muscle cells

---

### 2. G-protein-coupled receptors

**Multipass transmembrane proteins**

Have **7 transmembrane repeats**.

Associated with G-protein.

Inactive: **GDP-bound**

Activated: **GDP → GTP**

---

### 3. Enzyme-linked receptors

**Single-pass transmembrane proteins**

Have:

- Extracellular ligand-binding domain
- Transmembrane domain
- Cytoplasmic component

Ligand binding causes: **Dimerization → conformational change → kinase/enzyme activation → phosphorylation → downstream signaling**

Example: **FLT3 receptor**

Another hematologic example: **Erythropoietin receptor + JAK2**

---

## XXVIII. CELL ADHESION MOLECULES

### CAMs

Cell adhesion molecules.

Functions:

- Cell-to-cell signaling
- Cell adhesion
- Binding to ECM

Examples:

- Integrins
- Selectins
- Mucins
- Immunoglobulin-type CAMs
- Leucine-rich CAMs

### Integrins

- CAMs
- α and β chains
- Cell adhesion
- Motility
- Growth
- Survival

Can signal:

**Outside-in**

or

**Inside-out**

---

## XXIX. CELL CYCLE

Purpose:

**Replicate DNA once and distribute identical chromosome copies to two daughter cells.**

### Four main stages

**$G_1 \rightarrow S \rightarrow G_2 \rightarrow M$**

### $G_1$

- Cell growth
- Synthesizes components needed for replication

### S

- DNA replication
- Sister chromatids produced
- Centrosome duplicated

### $G_2$

- Checks DNA replication
- Checks for damage

### M

Mitosis + cytokinesis.

### $G_0$

Quiescence.

Cell is **not actively participating in the cell cycle**.

---

## XXX. MITOSIS

### Prophase

- Chromosomes condense.
- Centrosomes separate.
- Spindle fibers appear.

### Prometaphase

- Nuclear envelope disassembles.
- Centrosomes move toward opposite poles.
- Sister chromatids attach to spindle fibers.

### Metaphase

- Sister chromatids align at the middle/equidistant position.

### Anaphase

- Sister chromatids separate.
- Move toward opposite poles.

### Telophase

- Nuclear membrane reassembles.
- Spindle fibers disappear.

### Cytokinesis

Cell divides into **two identical daughter cells**.

### Interphase

**$G_1$ + S + $G_2$**

---

## XXXI. CELL CYCLE CHECKPOINTS

### Restriction point

Late $G_1$.

Checks:

- Nutrients
- Cell volume

### $G_1$ checkpoint

Checks DNA damage.

Possible outcomes:

- DNA repair
- Apoptosis

### S checkpoint

Checks:

- DNA damage
- Completion of replication

### $G_2$ checkpoint

Checks:

- Proper DNA replication
- DNA damage

### Metaphase checkpoint

Checks:

- Chromosome attachment
- Chromosome alignment
- Spindle integrity

Defects can block **anaphase**.

---

## XXXII. CYCLINS & CDKs

### Cyclin

Activates a specific **cyclin-dependent kinase (CDK)**.

Cyclin/CDK complexes phosphorylate substrates and drive cell-cycle progression.

Important:

- **Cyclin D + CDK4/6 → $G_1$**
- **Cyclin E + CDK2 → $G_1$ → S**
- **Cyclin A + CDK2 → S**
- **Cyclin A + CDK1 → S completion/$G_2$ → M**
- **Cyclin B + CDK1 → Mitosis**

### TP53

Tumor suppressor gene.

TP53 protein:

- Detects DNA damage during $G_1$.
- Can trigger apoptosis.

Loss/mutation of TP53 allows abnormal cells to continue dividing.

---

## XXXIII. CELL DEATH

Two major mechanisms:

### Necrosis

**Pathologic cell death caused by external injury.**

Causes:

- Ischemia
- Infection
- Trauma
- Toxins

Morphology:

- Cell **swelling**
- Membrane disruption
- Cell lysis

- Contents leak out

Result: **Inflammation**

---

### Apoptosis

**Programmed/self-inflicted cell death.**

Cell:

- Shrinks
- Nuclear chromatin condenses
- DNA fragments
- Forms membrane-bound apoptotic bodies

Plasma membrane remains intact.

Phosphatidylserine flips from: **inner leaflet → outer leaflet**

Macrophages recognize and engulf apoptotic bodies.

Result:

**No significant inflammation.**

---

## XXXIV. APOPTOSIS PATHWAYS

### Extrinsic pathway

Also called:

**Death receptor pathway**

Ligand binds death receptor.

Examples:

- Fas + Fas ligand
- TNFR1 + TNF

Activates:

**Caspase-8 / sometimes caspase-10**

---

### Intrinsic pathway

Triggered by intracellular stress:

- Hypoxia
- DNA damage
- Membrane disruption

Mitochondria release:

**Cytochrome c**

Cytochrome c + APAF-1 + caspase-9 →

**Apoptosome**

Activates **caspase-9**.

---

### Execution phase

Initiator caspases:

**8, 9, 10**

activate executioner caspases:

**3, 6, 7**

→ apoptosis.

---

## XXXV. APOPTOSIS REGULATORS

### Antiapoptotic

- Bcl-2
- Bcl-XL
- Growth factors such as erythropoietin

### Proapoptotic

- BAX
- BAK

The balance between pro- and antiapoptotic proteins regulates apoptosis.

---

## XXXVI. HEMATOPOIETIC MICROENVIRONMENT

### Hematopoiesis

Occurs predominantly in the **bone marrow** from the third trimester of fetal life through adulthood.

### Bone marrow microenvironment supports:

- Stem cell self-renewal
- Proliferation
- Differentiation
- Apoptosis
- Development of progenitor and precursor cells

### Stromal cells

Include:

- Endothelial cells
- Fibroblasts
- Adventitial reticular cells
- Adipocytes
- Chondrocytes
- Osteoblasts
- Osteoclasts

---

## XXXVII. EXTRACELLULAR MATRIX

Stromal cells produce ECM components such as:

- Collagen
- Fibronectin
- Thrombospondin
- Laminins
- Tenascin
- Proteoglycans

Examples of proteoglycans:

- Hyaluronate
- Chondroitin sulfate
- Heparan sulfate

### ECM functions

- Supports cell growth
- Anchors developing blood cells
- Provides environment for hematopoiesis

---

## XXXVIII. GROWTH FACTORS

Growth factors regulate:

- Proliferation
- Differentiation
- Survival

They must bind to **specific receptors** on target cells.

### Synergism

Several different growth factors work together to produce a stronger/more effective response.

### Important example

**Erythropoietin**

Produced in the **kidney**.

Acts on erythroid progenitors in the **bone marrow**.

---

## XXXIX. HIGH-YIELD HEMATOLOGY CONNECTIONS

### RBC + membrane

Membrane maintains:

- Shape
- Volume
- Ion balance

### RBC + mitochondria

Mature RBCs **lack mitochondria**, so they cannot perform oxidative phosphorylation.

### RBC + cytoskeleton

Cytoskeletal abnormalities can alter RBC morphology.

Example:

**Hereditary spherocytosis → spherical RBCs → hemolytic anemia**

### Leukocyte + lysosome

Lysosomal acid hydrolases help digest engulfed microorganisms.

### Hematopoiesis + mitochondria

ATP is needed for proliferation and cellular activity, while mitochondria also participate in heme biosynthesis.

### Hematopoiesis + apoptosis

Apoptosis removes unnecessary or potentially harmful blood cells and helps maintain appropriate blood-cell numbers.

---