

Physiology mind maps for midterm

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The file isn't reviewed!!

Lecture #1

Blood Functions

Transportation
- O2 by Hemoglobin
- CO2 from cells to lungs
- Nutrients
- Wastes to the liver and the kidney
- Hormones to the target organs

Regulation
- **PH**: blood contains Hemoglobin that acts as a
- **Temperature**: via dilation and constriction of blood vessels near the skin.
- **Blood Pressure**: results from force exerted by circulating blood against the walls of BV, Blood Volume is directly proportional to BP
- **Osmotic Pressure**: blood proteins, mainly albumin, exert oncotic pressure that pulls fluid back into the capillaries, helping maintain fluid balance
- **Volum**

protection
- Clotting: by coagulation mechanism.
- Immune: protection against microbes.
- Proteins: some blood proteins act as carriers.

Blood Components

Plasma 55%
Lowest density

- Water (91.5%)
- Proteins (7%)
  - Albumin (54%)
  - Globulins (38%)
  - Fibrinogen (7%)
- Other solutes (1.5%)
  - Gases, Electrolytes, Nutrients, Regulatory Substances, Waste Products.

Formed elements 45%

- Red Blood Cells 99%
  Highest density
- Buffy Coat 1%
  - Platelets-Cell fragments.
  - White Blood Cells/ Leukocytes:
    - -Neutrophils 60-70%
    - -Lymphocytes 20-25%
    - -Monocytes 3-8%
    - -Eosinophils 2-4%
    - -Basophils 0.5-1%

- If clotting occurs, some plasma components such as fibrinogen become trapped in the clot, and the remaining fluid is called serum.
* Serum = Plasma – (fibrinogen + clotting factors).

Blood Physical Characteristics

- 38°C
- Viscous sticky
- Alkaline pH (7.35-7.45)
- Color depends on O2 (bright-dark) red
- 20% of ECF, 8% by weight
- Blood volume: 5-6 Liters males, 4-5 Liters in females.
- The volume of blood is regulated **hormonally** by:

RAAS (Renin–Angiotensin–Aldosterone System): Increases blood volume and pressure by promoting sodium and water retention.

ADH (Antidiuretic Hormone): Prevents water loss by increasing water reabsorption in the kidneys.

ANP (Atrial Natriuretic Peptide): Decreases blood volume and pressure by promoting sodium and water excretion.

Blood Collection Tubes:

Venipuncture | Finger or heel stick | Arterial stick

- Tubes differ based on the additives they contain.
- Some tubes are plain (without additives), while others contain anticoagulants (such as EDTA or heparin) to prevent coagulation.

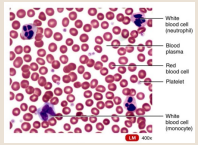
The choice of tube

depends on the type of blood test being performed

- To obtain serum, use a plain tube (no additives).
- To obtain plasma, use a tube containing an anticoagulant to prevent clotting.

Observations under the Light Microscope:

- -The most abundant cells seen are **red blood cells** (RBCs).
- - The small fragments present are **platelets**.
- - The larger cells with distinct nuclear shapes are **white blood cells** (WBCs):
  1. Monocytes: have a kidney-shaped nucleus.
  2. Neutrophils: have a multilobed (polymorphonuclear) nucleus.
  3. Lymphocytes: have a large nucleus that occupies most of the cell.





Blood as a liquid connective tissue

- extra cellular matrix is plasma
- cells are suspended in ECM

Interstitial fluid: part of ECF renewed by blood

Interstitial Fluid and Blood Interaction:

- The interstitial fluid interacts with blood through **continuous exchange** and transport processes.
- It is constantly renewed and modified by substances from **the blood plasma**.
- At the same time, a portion of the interstitial fluid returns to the bloodstream, maintaining a dynamic equilibrium between the two main components of the extracellular fluid (ECF):

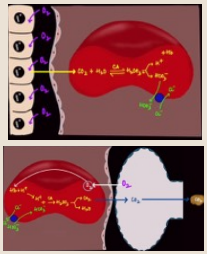
1.Blood plasma. 2.Interstitial fluid

Functions of RBCs

- Carry hemoglobin, bearing O2 to the tissues.
- Contain carbonic anhydrase, which catalyzes the reaction: $CO2 + H2O \rightarrow H2CO3$
- Allows large amounts of CO2 to be carried in solution as HCO3-
- Hemoglobin is an excellent acid-base buffer, by donating or accepting H^+.

CO_2 Transport via Bicarbonate (HCO_3^-):

1. Once produced, carbonic acid (H_2CO_3) dissociates into H^+ and bicarbonate (HCO_3^-).
2. HCO_3^- serves as the main form of CO_2 transport in the blood.
3. The conversion of CO_2 to HCO_3^- occurs inside red blood cells through the enzyme carbonic anhydrase.
4. HCO_3^- then moves out of RBCs in exchange for Cl^- ions, a process called the chloride shift.
5. In the pulmonary capillaries, HCO_3^- reenters the RBCs, recombines with H^+ to form H_2CO_3, which is then converted back into CO_2 and H_2O.
6. The CO_2 is exhaled through the lungs.



- Why is hemoglobin contained inside red blood cells (RBCs) rather than circulating freely in the plasma?

If hemoglobin were free in the plasma, it could leak into the interstitial space, causing a significant loss of hemoglobin. Moreover, free hemoglobin would be filtered out by the kidneys, leading to hemoglobin loss in urine and possible kidney damage

RBC Size and Shape

- Mean 7.8 (diameter) x 2.5 microns (thickest) or x 1 micron (center)
- **Biconcave discs** The biconcave shape results from a redundant plasma membrane and the absence of a nucleus. This unique shape, together with the flexible membrane, increases the deformability and flexibility of red blood cells.
  -It allows them to squeeze through very narrow capillaries without rupturing.
- Average volume 90-95 micrometers3

RBC Count and Indices

- Men: 5,200,000 (± 300,000)/mm3.
- Women: 4,700,000 (± 300,000)/mm3.
- RBC counts can be increased at higher altitudes because the atmosphere contains less oxygen.
- 2 million/sec production.

RBC indices

- MCV (Mean cell volume) 90 ± 9 fl = 10-15 L
- MCH (Mean Cell Hgb) 32 ± 2 pg
- MCHC (Mean cell Hgb conc) 33 ± 3%
- RDW CV 11.6-14.6%

It measures how much the sizes of red blood cells vary. Normally, the variation should be minimal.

• (SD of MCV/MCV) 39-46 fL

Lecture #2

Hemoglobin and Hematocrit

Hemoglobin

- 280 million /RBC
- Normal hemoglobin concentration is 34 g per 100 ml of packed cells
- Hemoglobin constitutes 33% of RBC weight
- Thus normal hemoglobin is 14-15 g per 100 ml of blood
- When hemoglobin is measured in 100 ml packed cells only (RBCs) it's condensed,
but if it's measured per 100 ml of whole blood then the number will be almost the half
- O2 carrying capacity is 1.34 ml / g Hgb, or 19-20 ml O2 / 100 ml blood
- transports 25% CO2

Hematocrit

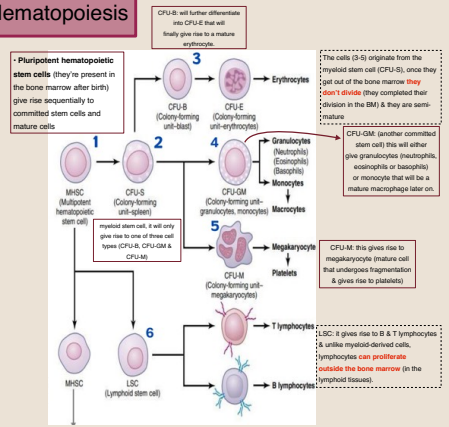
- Normal hematocrit ("packed cell volume") is 40-45% (slightly lower in women)

$$\text{Total Hemoglobin (g)} = \text{Hemoglobin Concentration} \times \text{Blood Volume}$$

$$\text{Volume of RBCs} = \text{Blood Volume} \times \frac{\text{Hematocrit}}{100}$$

$$\text{Total } O_2 = (\text{Total hemoglobin in grams}) \times (1.34\,\text{mL } O_2/\text{g Hgb})$$

Hematopoiesis



Hematopoiesis

is driven by

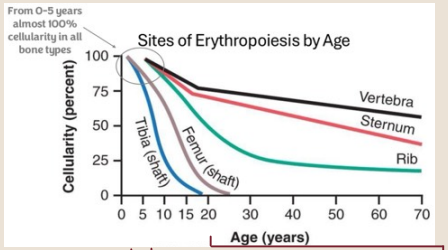
- **Growth inducers (factors; e.g. interleukin-3): they induce increase in size or number.**
- **Differentiation inducers: they induce cell differentiation to become more specific to its final mature cell**

responds to changing conditions including

- **Hypoxia (low tissue oxygen level): increases the rate of erythropoiesis**
- **Infection / inflammation: WBC production**

Sites of Erythropoiesis

- **First few weeks of gestation – RBCs production takes place in the yolk sac**
- **Mid-trimester – mainly in the Liver (+ spleen, lymph nodes)**
- **Last month of gestation through adulthood – mainly in the Bone marrow**



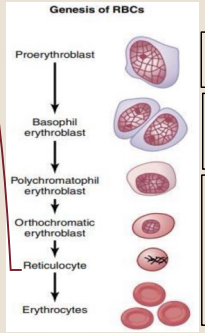
Before the age of 5
The marrow of all bones (long & short) produces RBCs .

After the age of 5
There is a decline in the production (& cellularity) of RBCs in the marrow of long bones (tibia & femur shafts with preserved cellularity in their heads) until the age of 20 .

After the age of 20
RBCs production takes place only in the marrow of short membranous bones (vertebra, sternum, ribs, ilia…) which become the main sites for erythropoiesis. While in the long bones, RBCs-producing cells are replaced by fat cells so they don't have active production of RBCs.

Erythropoiesis

from CFU-E until we reach the final mature erythrocyte.



These reticulocytes aren't considered fully mature so they require about 1-2 days until they reach the final normal shape of erythrocytes.
➢ The percentage of reticulocytes represents 1-2% of all RBCs in the blood & they reflect the newly produced
RBCs (within two days they mature), this percentage is clinically important

- if this percentage is increased this indicates that the BM is active & is responding to the stimulus
- if the percentage is low despite having anemia or haemorrhage this indicates a problem in the BM, EPO or any step of erythropoiesis

Proerythroblast is still nucleated with a basophilic cytoplasm, since it's blast it can divide & increase in number.

When it starts to have red color it's called polychromatophil erythroblast (polychromatic: more than one stain), this is the first cell where hemoglobin starts to appear.

Nucleus decrease in size (atrophy) & the cytoplasm becomes more eosinophilic (more hemoglobin) & some of the organelles will start to be reabsorbed & the nucleus will be extruded, in the reticulocyte stage we only have remnants Golgi & ER, now reticulocytes are ready to leave BM to the circulation by diapedesis through the sinusoids in the BM.

Regulation of Red Cell Production

Why important
- Maintain adequate oxygen carrying capacity
- Avoid excessive blood viscosity, if the production increases (polycythemia) , that may lead to increased resistance and impede blood flow (more sluggish blood flow)
- If the bone marrow is damaged (due to chemotherapy or radiotherapy) or if demand for erythropoiesis is extreme (due to hypoxia) , other parts of the bone marrow may become hyperplastic (increase in number in a contained space) , or extramedullary hematopoiesis may occur.

By

Erythropoietin

basal level of erythropoietin is required even if no hypoxia

- Circulating hormone, mw ~34,000 kDalton
- Necessary for erythropoiesis in response to hypoxia, when there is a hypoxia there will be increase in production of erythropoietin.
- ~90% made in the kidney mainly
- 10% of erythropoietin can arise from the liver
- Cells of origin not established.

The signaling that is responsible for stimulating erythropoietin transcription is

Renal hypoxia

Hypoxia —> HIF-1 —> binds hypoxia response element —> EPO transcription ⬆️

Extra-renal hypoxia

Extra-renal hypoxia (hypoxia outside the kidney, like certain organ) can stimulate EPO production from the kidney.

• Some factors (hormones) are activated and stimulated in that organ including, epinephrine, norepinephrine, and some prostaglandins can promote EPO production in the kidney.

Tissue O2

Response to Hypoxia

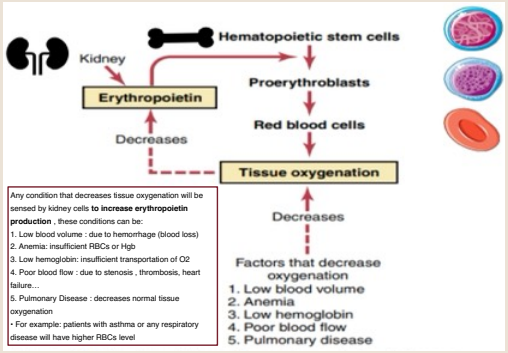
- Within Minutes to hours of hypoxia, it will lead to Erythropoietin
- New circulating reticulocyte (new RBCs) will appear from (3-5) days.

(RBCs number won't increase for at least 5 days until the final increase in number of RBCs counts appears, but erythropoietin increases from first day).

Importance of EPO

Erythropoietin remains high until normal tissue oxygenation is restored, due to negative feedback.

- drives **production** of proerythroblasts from HSCs
- accelerates their **maturation** into RBCs
- EPO can increase RBC production up to 10-fold



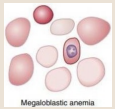
Any condition that decreases tissue oxygenation will be sensed by kidney cells **to increase erythropoietin production** , these conditions can be:
1. Low blood volume : due to hemorrhage (blood loss)
2. Anemia: insufficient RBCs or Hgb
3. Low hemoglobin: insufficient transportation of O2
4. Poor blood flow : due to stenosis , thrombosis, heart failure…
5. Pulmonary Disease : decreases normal tissue oxygenation
• For example: patients with asthma or any respiratory disease will have higher RBCs level

different forms of RBCs can indicate certain diseases

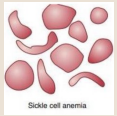
Microcytic hypochromic anemia: small & pale red RBCs can indicate low content of Hgb & this reflects low iron level.



Megaloblastic anemia: RBCs are large & they have abnormal nucleus also they're more fragile than the normal RBCs, this anemia results from vitamin B12 & folate deficiency which are important for RBCs maturation of the DNA & the nucleus (which can lead to abnormal division).



Sickle cell anemia: Malformation of hemoglobin due to a genetic disease.



Erythroblastosis fetalis



Requirements of RBCs production

Vitamin B12

- Rapid, large-scale cellular proliferation requires optimal nutrition
- Cell proliferation requires DNA replication, and requires normal level of vitamin B12 and folic acid,if there is a lack of them, this will lead to abnormal DNA replication. Any cell needs to replication, it needs to replicate its DNA to get normal proliferation and division.
- Vitamin B12 and folate both are needed to make thymidine triphosphate (thus, DNA)
- Abnormal DNA replication causes failure of nuclear maturation and cell division maturation failure large, irregular, fragile, abnormal, bizarre shaped "**macrocytes**" , but the macrocyte still has hemoglobin and it can carry oxygen but its membrane is fragile, has a short life span, thus the person will have anemia "megaloblastic anemia ".

Folic Acid

Abnormalities

Pernicious Anemia

Failure to absorb vitamin B12

- Atrophic gastric mucosa…
- Failure to produce intrinsic factor, which is secreted from gastric secretion.
- Intrinsic factor binds to vitamin B12, and facilitate its absorption.
- Protects it from digestion
- Binds to receptors in the ileum where the absorption occurs.
- Mediates transport by pinocytosis
- Vitamin B12 is ***largely stored in liver***, released as needed
- Usual stores: 1– 3 mg Daily needs: 1– 3 μg
- Thus normal stores are adequate for 3– 4 years until anemia appears

Folic Acid Deficiency

- Folic acid is present in green vegetables, some fruits, and meats like liver.
- Destroyed during cooking
- Subject to dietary deficiencies
- May also be deficient in cases of intestinal malabsorption
- Maturation failure may reflect combined B12 and folate deficiency

Lecture #3

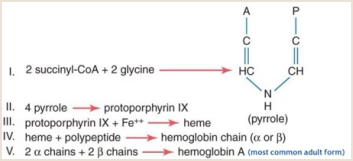
Formation of Hemoglobin

Occurs from proerythroblast

through

reticulocyte stage

• Reticulocytes retain a small amount of endoplasmic reticulum and mRNA, supporting continued hemoglobin synthesis.
• Mature RBCs do NOT produce new hemoglobin.



Types of Globin Chains

α
β
γ
δ

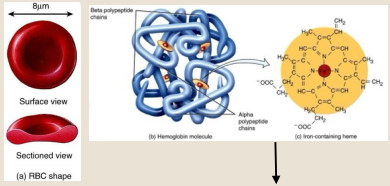
resulting from gene duplication
• Each globin chain is associated with one heme group containing one atom of iron
• Each of the four iron atoms can bind loosely with one molecule (2 atoms) of oxygen
• Thus, each hemoglobin molecule can transport 8 oxygen atoms.

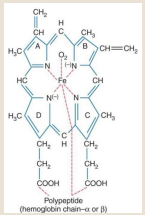
Oxygen Binding to Hemoglobin

- Must be loosely bound– binding in settings of higher O2 concentration, releasing in settings of lower concentration.
- Binds loosely with one of the coordination bonds of iron.
- Carried as molecular oxygen (not as ionic oxygen).

Shapes of RBC and Hemoglobin

each hemoglobin molecule has 4 chains, 2 alpha and 2 beta, and each chain has a heme group, which contains one iron atom, which can bind one O2, so each hemoglobin can carry 8 oxygen atoms in the form of 4 molecular oxygens (O2).





• Notice the heme group on the left.
• The bond between the oxygen (one of the oxygens of O2) and Fe is a coordinate covalent bond, not an ionic bond

Modest differences in O2 binding affinities
• Sickle hemoglobin:
Glutamic acid —> to Valine at AA 6
• Hemoglobin of homozygous individuals (“SS”) forms elongated crystals when exposed to low O2.
• The crystals makes RBCs lose their flexibility hemolysis, vascular occlusion

Hemoglobin A

Predominant form in adults
MW 64,458

2 α 2 β

Hemoglobin F

• Fetal hemoglobin is a principal oxygen carrier in blood in fetus and neonates.
• It has higher affinity to oxygen and the OHD curve is shifted to the left. (efficient extraction of oxygen from the mother’s circulation)

2 α 2 γ

Degradation of Hemoglobin

When RBCs rupture, hemoglobin is phagocytosed by macrophages, particularly in the liver and spleen

Iron is released back to transferrin in the blood to support erythropoiesis or be stored as ferritin

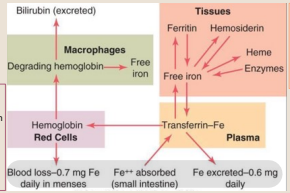
Macrophages convert the porphyrin portion, stepwise, into bilirubin, which is released into the blood and secreted by the liver into the bile

Iron

- Daily iron loss of ~ 0.6 mg/day in men (GI) or ~1.3 mg/day in women (GI and menses)
- Iron is absorbed throughout the small intestine
- Liver secretes apotransferrin into the bile, which binds with free iron and some iron compounds present in meals (e.g, myoglobin in meat) to become transferrin
- Iron binds to transferrin and the complex binds to transferrin receptors on intestinal epithelium
- Transcytosed into the blood as plasma transferrin
- Maximal absorption of a few mg per day (5-6mg), modulated over 5– 6-fold range based on body stores

- Iron is a key component of hemoglobin, myoglobin, and multiple oxidation enzymes (cytochromes, cytochrome oxidase, peroxidase, catalase)
- Thus, iron stores are critically regulated
- Total body iron ~ 4– 5 g
- 65% in hemoglobin in RBCs
- 4% in myoglobin in muscle cells
- 1% in intracellular heme compounds
- 0.1% associated with circulating transferrin
- 15– 30% stored mainly as ferritin in Reticuloendothelial system

Iron Transport and Metabolism



Breakdown of Hemoglobin
When hemoglobin is degraded from aged RBCs in the bone marrow, spleen, or liver, free iron released from it is carried in plasma to where it should be used or stored.

Forms of Iron in Tissues
Iron is present in tissues bound to the storage protein ferritin. When ferritin becomes saturated, the excess iron binds to hemosiderin (seen as clusters of iron inside cells). Iron can also be bound to heme in various cells and enzymes.

Iron in the Blood
Free iron outside cells must be bound to transferrin.
This iron is continuously renewed by hemoglobin that breaks down during the RBC life cycle.

Iron Loss and Absorption
Around 0.6 mg of iron is excreted daily through the GI system.
In females, about 0.7 mg is lost during menses.
Iron absorption from the diet occurs in the small intestine, and only the needed amount is absorbed. The rest is excreted.

Iron Absorption, Transport & Storage

- Absorbed from small intestine, combines with apotransferrin —> transferrin (transport iron)
- Iron can be released to any cell for intracellular use.
- RBC precursors have transferrin receptors and actively accumulate iron because iron is essential for erythropoiesis, especially for hemoglobin synthesis.
- Particularly in hepatocytes and reticulo-endothelial cells, iron combines with apoferritin —> ferritin (Large protein: MW 460,000)

➢ When apoferritin binds iron, it is called ferritin.

- Ferritin is variably saturated (storage iron)

➢ Sometimes it is fully saturated, other times only partially.

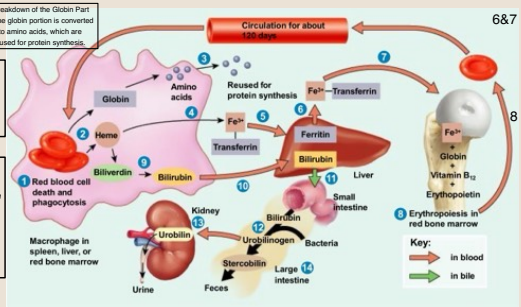
- Hemosiderin is quite insoluble excess iron over the capacity of ferritin.

➢ The clusters of iron can be apparent under LM as a pigment called hemosiderin, while ferritin can only be seen with an EM.

Iron Exchange

- When iron in the plasma is low, iron is released from ferritin and bound to transferrin for transport.
- It is delivered to the bone marrow, bound by transferrin receptors on erythroblasts, internalized, and delivered directly to the mitochondria (the place of heme production) for incorporation into heme.
- Deficiency of transferrin or apotransferrin can result in severe hypochromic anemia due to lack of iron.
- Hemoglobin released from senescent RBCs is ingested by macrophages and stored as ferritin in the liver

Formation and Destruction of RBC's



3 Breakdown of the Globin Part
The globin portion is converted into amino acids, which are reused for protein synthesis.

2 Reuse of Hemoglobin Components
After being phagocytosed, the components related to hemoglobin are reused.

1 Destruction of Aged RBCs
Aged and damaged RBCs in the spleen, liver, or bone marrow are engulfed by macrophages.
In the liver, these macrophages are known as Kupffer cells.

6&7 Iron Release and Erythropoiesis
When there is a need for new RBC or hemoglobin production,
Iron is released from ferritin and transported by transferrin to the bone marrow.
In the bone marrow, iron, amino acids, vitamin B12, folic acid, and erythropoietin (EPO) are all used for erythropoiesis (new RBC formation).

8 RBC Life Cycle
Each RBC circulates for about 120 days, then is engulfed again by macrophages, repeating the same cycle.

9. Conversion of Heme to Biliverdin and Bilirubin
After iron is removed, the remaining part of the heme is converted to biliverdin, then to bilirubin inside the macrophage.
10. Transport of Bilirubin
Bilirubin is transported through the blood to the liver.
11. Excretion of Bilirubin
In the liver, bilirubin is excreted with bile into the duodenum.
12. Conversion in the Intestine
In the small intestine, bilirubin is converted by bacteria into urobilinogen.
Urobilinogen is further converted to stercobilin, which gives feces their brown color.
13. Urobilin Formation and Urinary Excretion
Some urobilinogen is reabsorbed into the blood and excreted in urine as urobilin, giving urine its yellow color

4 Handling of the Heme Part (Iron Transport)
The iron from the heme is transported by transferrin, a protein responsible for iron transport.
Iron remains bound to transferrin in the plasma during transport.

5 Iron Storage in the Liver
Iron transported by transferrin can be taken up by the liver and stored in ferritin, the main iron-storage protein

RBC Senescence & Destruction

- RBC life span is ~120 days
- Though lacking a nucleus, mitochondria, and endoplasmic reticulum, RBCs have enzymes that can metabolize glucose anaerobically and make small amounts of ATP. These enzymes…
- Maintain membrane pliability
- Support ion transport
- Keep iron in the ferrous form (rather than ferric)
- Inhibit protein oxidation
- As enzymes deplete with age, RBCs become fragile and rupture in small passages of the RES, often in the spleen

Lecture #4

Red Blood Cell Disorders

- ANEMIAS
- POLYCYTHEMIA

ANEMIAS

definition

Deficiency of Hemoglobin

can be due to

- less number of RBCs
- less hemoglobin in RBCs

- Rapid, large-scale cellular proliferation of hematopoietic stem cells in erythropoiesis requires optimal nutrition (B12, folic acid & iron)
- Cell proliferation requires DNA replication
- Vitamin B12 and folate both are needed to make thymidine triphosphate necessary for DNA (thus, DNA)
- Abnormal DNA replication due to these deficiencies causes failure of nuclear maturation and cell division…

➡ maturation failure ➡ large, irregular, fragile "macrocytes

Anemias based on cause

Blood loss

After hemorrhage, there are feedback mechanisms

Fluid volume
restored in 1– 3 days, to restore blood volume; water is added to ECF with the arterial BP regulatory mechanisms

RBC concentration
restored in 3-6 weeks, erythropoietin is released 24h after hemorrhage, thus the first increase in new RBC production will be after 5 days, however restoring to normal RBCs concentration will take 3-6 weeks

- acute
- chronic

Chronic blood loss can lead to iron deficiency with ***hypochromic, microcytic anemia*** due to continuous increase in RBCs production that needs iron for hemoglobin (the absorption of iron from the GIT will not be enough)

Diminished (decreased) RBC production

- Nutritional Anemias
- Marrow/Systemic Defect

Megaloblastic anemia

- Results from Deficiency of Vitamin B12 and / or Folic Acid, these deficiencies can result from:
  - Pernicious anemia
  - Dietary deficiency
  - Malabsorption
- Impairs DNA replication in proliferating hematopoietic cells, causing maturation failure due to the deficiency of Vitamin B12 and / or Folic Acid
- Formation of large, fragile cells with bizarre shapes (abnormal & odd shapes), which rupture easily, potentially causing profound anemia

Aplastic anemia

Bone marrow aplasia means that bone marrow fails to produce blood cells

caused by

- **Radiation** high dose of radiation sometimes in cancer therapy
- **Chemotherapy** might lead to destruction of hematopoietic stem cells which may cause anemia in few weeks.
- **Chemical toxins or drugs** such as high doses of toxins or insecticides
- **Auto-immune**: production of **Ig antibodies** for the bone marrow stem cells or RBCs; e.g., lupus erythromatosis.
- **Idiopathic** (unknown cause)

Treatment

Supported by transfusions or treated by bone marrow transplantation (transplantation of new stem cells)

Increased destruction (hemolytic anemia)

Hereditary conditions causing fragility of RBCs

- Hereditary spherocytosis
- Sickle cell anemia

Immune-mediated destruction

Erythroblastosis fetalis: when there is incompatibility between the fetus who has (Rh+) blood type & the mother who has (Rh-) blood type and she has antibodies against Rh factor, fetus RBCs will be attacked which leads to hemolytic anemia

Vitamin B12 and Folic Acid

Pernicious Anemia

- It is due to **Failure to absorb vitamin B12**
- Because of Atrophic gastric mucosa… leads to
  - Failure to produce intrinsic factor which is important for absorbing vit B12
  - Intrinsic factor binds to vitamin B12
  - Protects it from digestion by digestive enzymes
  - Binds to receptors in the ileum, after vit B12 binds to intrinsic factor they both bind to receptors in the ileum which enhances vit B12 absorption
  - Mediates transport by pinocytosis which is how B12 is absorbed
- Vitamin B12 - stored in liver, released as needed
- Usual stores: 1 – 3 mg Daily needs: 1 – 3 μg
- Thus normal stores are adequate for 3 – 4 years, so pernicious anemia may not appear until 3 or 4 yrs.

Folic Acid Deficiency

- Folic acid is present in green vegetables, some fruits, and meats.
- Destroyed during cooking
- Subject to dietary deficiencies
- May also be deficient in cases of intestinal malabsorption
- Folic acid deficiency leads to Maturation failure of RBCs may reflect combined B12 and folate deficiency if there is abnormal intestinal absorption, eg: tropical sprue

Circulatory Effects of Anemia

- **Decreased viscosity**
- **Decreased O2 - carrying capacity**
  As a result body tissues need more oxygen
- **Increased cardiac output**
  to provide more O2 (more load on heart, capillaries &local circulation. Precapillary sphincters will also dilate inducing more blood flow in the microcirculation which increases venous return thus increased cardiac output)
- **Markedly decreased exercise capacity**
  normal daily physiological activities already increase cardiac output, if anemic patients increase physical activity (heavy exercise)--> O2 insufficiency--> higher load on the heart --> serious complications due to hypoxia (the heart is unable to work harder)

Red Blood Cell Disorders

ANEMIAS

POLYCYTHEMIA

higher number of RBCs, there are 2 types

Secondary to hypoxia in tissues
(RBC ↑ ~30%; 6-7 million/mm3)

- Chronic hypoxemia due to (heart or lung disease)
- Physiologic polycythemia
  - Living at 14 - 17,000 feet (high altitudes)
  - Markedly enhanced exercise capacity at altitude

Hypoxia in tissue --> more erythropoietin stimulation, higher rate of RBC production --> higher number of RBCs (6-7 million/mm3) 30% more than normal

Polycythemia Vera

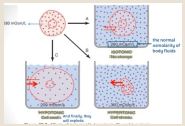
- Clonal abnormality causing excessive proliferation
- Usually all lineages (RBCs, WBCs, platelets)
- 7- 8million RBCs / mm3; Hematocrit 60-70%, instead of 45-50%
- Blood volume increased almost two-fold
- Hyperviscosity, up to 3-fold than normal which is (10xwater)

It is a genetic form of the disease resulting in continuous proliferation in all blood cell types even when there is enough number of RBCs

Polycythemia & Circulation

- Increased viscosity ➡ decreases venous return
- Increased blood volume ➡ increases venous return
- 2/3 normotensive, 1/3 hypertensive
- The subpapillary venous plexus under the skin becomes engorged with slow-moving, de-saturated blood, producing a ruddy complexion to the skin

زيادة اللزوجة (بسبب الـ Polycythemia) تقلل من قدرة الدم على العودة إلى القلب.
زيادة حجم الدم تعوض جزئيًا هذا التأثير، مما يساعد على زيادة عودة الدم الوريدي.
نتيجة لذلك، معدل الضخ القلبي (cardiac output) قد يظل طبيعيًا تقريبًا رغم زيادة اللزوجة، بسبب التوازن بين مقاومة الأوعية وزيادة حجم الدم.



RBCs

in a hypotonic medium

a net **influx** of water occurs so the cells swell, when the swelling overcomes the membranes' integrity, the integrity of their membranes is disrupted and cell explode resulting in hemolysis

in an isotonic medium

the intracellular and extracellular fluids are in **osmotic equilibrium** across the cell membrane, and there is **no net influx or efflux** of water.

in a hypertonic media

a net **efflux** of water occurs so the cells lose their normal biconcave shape, undergoing collapse and they will shrink

LAB TESTS

Packed Red Blood Cell Volume PCV

- PCV is the ratio of the volume of packed red cells to the total blood volume.
- Adult males: 40-54% (avg = 47%).
- Adult females: 38-46% (avg = 42%)
- How to measure PCV?

Withdraw blood, **place** it in a tube, **centrifuge** it, then measure the volume of the red bottom layer and compare it to the total blood volume : PCV is also called hematocrit

decreases in cases of anemia

increases in polycythemia and dehydration

Erythrocyte Sedimentation Rate (ESR)

It's increase reflects the tendency of red blood cells to settle more rapidly in the presence of inflammatory conditions, usually because of increases in plasma fibrinogen, immunoglobulins, and other acute-phase reaction proteins,
More inflammation = faster sedimentation

- The rate at which red blood cells settle out when anticoagulated whole blood is allowed to stand for a period of one hour.
- The ESR is a simple, **sensitive but non-specific** screening test that indirectly measures the presence of inflammation in the body, It is non-specific as it indicates the presence of inflammation without indicating its reason or the site.
- Changes in red cell shape or numbers may also affect the ESR, e.g. in anemia.
- The RBCs sediment even without centrifuging because their density is greater than that of plasma. The sedimentation increases if stacking of RBCs (rouleaux formation) happens.
- Rouleaux formation is possible because of the discoid shape of RBCs
- Normally, RBCs have negative charges on the outside of the cells, which cause them to repel each other and decreases or prevents rouleaux formation.
- Many plasma proteins have positive charges and can neutralize the negative charges of the RBCs, which allows for the formation of the rouleaux.
- Therefore, an increase in plasma proteins (present in inflammatory conditions) will increase the rouleaux formations, which settle more readily than single red blood cells leading to increased ESR during inflammation

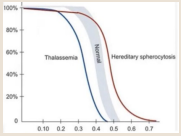
- High ESR
  - ➢ Inflammation
  - ➢ Anemia
  - ➢ Old age
  - ➢ Pregnancy
  - ➢ Technical factors: tilted ESR tube, **high** room temperature

- Some interferences which decrease ESR:
- Abnormally shaped RBC (sickle cells and spherocytosis)
- Polycythemia
- Technical factors: low room temperature, delay in test performance (>2 hours), clotted blood sample

Normal ESR values
- **Adult males < 15mm/hr**
- **Adult females < 20mm/hr**

Osmotic fragility

- A test designed to measures red blood cell's resistance to hemolysis when exposed to a series of increasingly dilute saline solutions.
- The susceptibility of RBCs to hemolysis is determined by:
  - ➢ Surface area to volume ratio.
  - ➢ Cell membrane composition and integrity
- This test is mainly used to diagnose **hereditary spherocytosis**



Increased red cell fragility (increased susceptibility to hemolysis) is seen in
- ➢ Hereditary spherocytosis
- ➢ Autoimmune hemolytic anemia
- ➢ Toxic chemicals, poisons, infections, and some drugs.
- ➢ Severe burns

cells have a low (surface area: volume) ratio

Decreased red cell fragility (increased resistance to hemolysis) is seen in
- ➢ Thalassemia.
- ➢ Iron deficiency anemia

cells have a high (surface area: volume) ratio

Normally:(numbers indicates saline concentrations)
- ➢ Form 0.7% to 0.5% there is no hemolysis
- ➢ At the concentration of 0.48% hemolysis starts, and the solution becomes red in color (Due to the explosion of some cells), but there are some settled RBCs in the tube.
- ➢ The concentration of 0.36% the solution is bright red and there are no settled RBCs (complete hemolysis)
- When does spherocytosis hemolysis at the concentration of 0.68% which means RBCs can't resist hemolysis as they normally do (They are more fragile)

Lecture #5

leukocytes

Phagocytes

ways to defend our body against microorganisms

- recognize, ingest, and destroy invading organisms
- participate in tissue reactions that "wall off" infection

Other white cells

lymphocytes

get activated to mediate responses that destroy or neutralize specific microorganisms.

ways to defend our body against microorganisms

These methods are called acquired immunity

- release antibodies which are molecules that can bind to the microorganism making it recognizable to the surrounding tissues or destroy it. (plasma cells)
- The cells can directly kill the microorganism. (cytotoxic cd8+ cells)

leukopoiesis

Myeloid lineage

Bone marrow only

Lymphoid lineage

Mainly in lymphogenous tissues, lymph glands, thumus…..

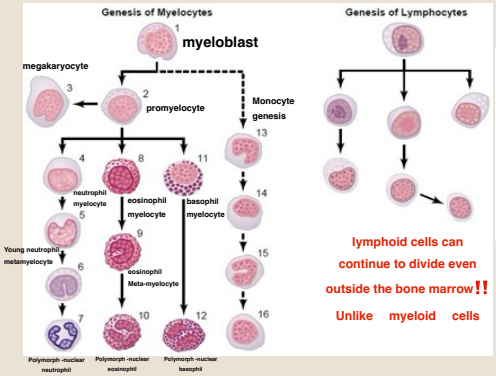


Figure 33–1

Genesis of white blood cells. The different cells of the myelocyte series are 1, myeloblast; 2, promyelocyte; 3, megakaryocyte; 4, neutrophil myelocyte; 5, young neutrophil metamyelocyte; 6, "band" neutrophil metamyelocyte; 7, polymorphonuclear neutrophil; 8, eosinophil myelocyte; 9, eosinophil metamyelocyte; 10, polymorphonuclear eosinophil; 11, basophil myelocyte; 12, polymorphonuclear basophil; 13–16, stages of monocyte formation.

lymphoid cells can continue to divide even outside the bone marrow!!

Unlike myeloid cells

White Blood Cells

Granulocytes

- Polymorphonuclear **neutrophils**
- Polymorphonuclear **eosinophils**
- Polymorphonuclear **basophils**

Agranulocytes

Monocytes

- Macrophages
- Dendritic cells

Lymphocytes

- B cells
- T cells

Platelets

(from megakaryocytes)

They are considered leukocytes because they share the same cellular origin, but their primary function is hemostasis (blood coagulation).

Genesis of white Blood Cells

Granulocytes

develop in the bone marrow, and most remain there as spare until needed peripherally (number in marrow ~3x blood; 6-day supply)

Agranulocytes

Monocytes

Lymphocytes

develop mostly in the peripheral lymphoid organs (thymus, spleen, tonsils, lymph nodes, Peyer's patches), less found in blood

Platelets

(from megakaryocytes)

Megakaryocytes develop and reside in the marrow, fragment to release platelets

White Blood Cells Counts

Total WBC ~ 7,000 / mm3 in blood (almost 1,000-fold fewer than RBCs)

Never **L**et **M**onkeys **E**at **B**ananas

Neutrophils 62% Lymphocytes 30% Monocytes 5.3% Eosinophils 2.3% Basophils 0.4%

Life Span of white Blood Cells

Granulocytes

- **Circulating** 4 – 8 hours
- **In the tissues** 4 – 5 days

Agranulocytes

Monocytes / Macrophages

- **Circulating** 10– 20 hours
- **In the tissues** Need 8 hours to mature in tissues • As tissue macrophages, months or longer

Lymphocytes

Continuously re-circulate from site of origin through diapedesis



Variable: Long-lived… weeks, months, longer (memory cells stay for years)

Platelets

Replaced every ten days~ 30K each day

Phagocytes perform their function by engulfing and digesting foreign or necrotic particles

Neutrophils
mature cells that can respond immediately to infection

Macrophages
Monocytes mature in the tissues for ~8 hours to become macrophages (monocytes in blood little ability)

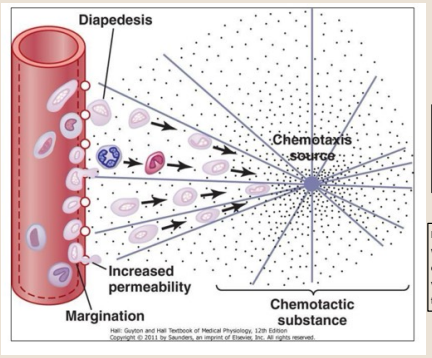
Both exhibit motility to the infection site

steps in the process of leukocyte extravasation

Diapedesis
↓
Ameboid motion
↓
Chemotaxis
that act to attract the PMNs or macrophages to the site of infection.

Chemoattractants

- bacterial products
- tissue degradation products
- complement fragments
- other chemical mediators



The source of infection releases *chemoattractants* to **recruit PMNs and macrophages.**

↓

Signaling occurs between WBC plasma membrane proteins and endothelial cells, leading to **migration (diapedesis)** of these cells

↓

Margination is the process by which WBCs adhere to the endothelial wall. Increased vascular permeability allows them to extravasate into the tissue.

Ameboid movement helps them reach the site.

Phagocytosis the ingestion of particles

Appropriate phagocytic targets

- **May have rough surfaces**
- **Lack protective protein coats**
- **May be immunologically marked for phagocytosis** by antibodies or complement components after activation like C3 that are recognized by receptors on the phagocytes … this immunologic marking is called "opsonization"

Phagocytes

Neutrophils
can ingest 3-20 bacteria
have short life span

Macrophages
- After being activated in the tissues, are extremely effective phagocytes (up to ~100 bacteria)
- can extrude digestion products and survive and function for many months

↓

can ingest larger particles…
- Damaged RBCs
- Malarial parasites

Digestion of Ingested Particles

In both neutrophils and macrophages, phagosomes fuse with lysosomes and other granules to form phagolysosomes (digestive vesicles)

phagolysosomes contain
- lipases *in macrophages* (important in killing tuberculosis bacillus and some other bacteria that have lipid coats)
- proteolytic enzymes

Bactericidal Agents Bacteria may be killed even if they are not digested

- Superoxide (O2-)
- Hydrogen peroxide (H2O2)
- Hydroxyl ions (OH-)

The enzyme Myeloperoxidase

$H_2O_2 + 2\ Cl^- \longrightarrow 2\ H^+ + 2\ ClO^-$

hypochlorous acid (HOCl), a highly reactive antimicrobial compound.

bactericidal reactive oxygen species generated in in the phagosome or in **peroxisomes**

The Reticuloendothelial System

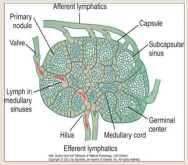
The monocyte-macrophage system

- Circulating monocytes
- mobile macrophages
- fixed tissue macrophages
- some specialized endothelial cells

After entering the tissues, **macrophages** become fixed and may be resident for years

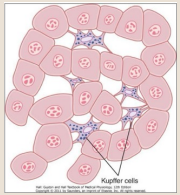
Specialized Macrophages
- **(histiocytes)** Skin, subcutaneous
- **Lymph nodes** Ingest / sample particles arriving through the lymph
- **Alveolar macrophages** Digest or entrap inhaled particles and microorganisms like silica, tuberculosis bacilli.
- **Kupffer cells** Lining sinusoids, Surveillance of the portal circulation.
- **Macrophages in the spleen and bone marrow** Surveillance of the general circulation

Structure of a Lymph Node

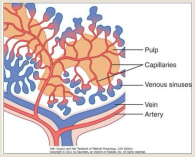


It is a meshwork that acts as a filter, with macrophages preventing microorganisms from entering the blood circulation.

Kupffer Cells in the Liver Sinusoids



Structure of the Spleen



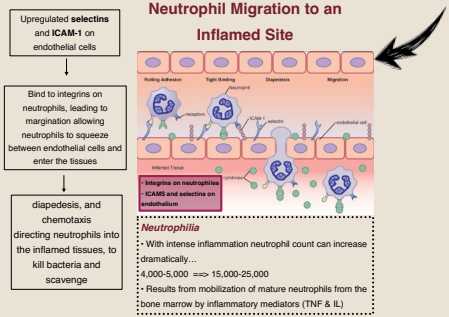
Resembles the structure of lymph nodes: the red pulp and venous sinuses contain macrophages that line them to capture microorganisms.

Inflammation

a cascade of events driven by chemical mediators and characterized by heat, redness, swelling, and pain

Physiologically, it involves

- **Vasodilatation and increased blood flow**
- **Increased capillary permeability increasing the swelling**
- **Coagulation of interstitial fluids**
  when fibrinogen leaks from blood into the interstitial space, forming a gel that walls off the infection and helps prevent its spread.
- **Accumulation of granulocytes and monocytes**
- **Swelling of tissue cells**



Eosinophils

- Eosinophils are weak phagocytes, they have granules and exhibit chemotaxis
- Particularly important in defense against ***parasites***, Ex: schistosomiases and trichinosis
- Can adhere to parasites and release substances that kill them (hydrolases, reactive oxygen species, major basic protein (larvacidal).
- Also accumulate in tissues affected by allergies, perhaps in response to eosinophil chemotactic factor from basophils (eosinophils may detoxify some products of basophils)

Basophils

- Similar to mast cells adjacent to Capillaries, both cell types **release heparin**
- Basophils and mast cells both release **histamine, bradykinin, and serotonin** which are involved in aggravating the inflammatory reaction.
- When **IgE** bound to receptors on their surfaces is cross-linked by its specific antigen, mast cells and basophils degranulate, releasing…
- histamine, bradykinin, serotonin, heparin, leukotrienes, and several lysosomal enzymes

Lines of defenses

first line of defense (min)

Tissue macrophages that encounter foreign particles enlarge and become mobile

2nd line of defense

Within an hour ***neutrophils*** migrate to the area in response to inflammatory cytokines (TNF, IL-1) released from the macrophages

3rd line of defense

Secondary Macrophage Invasion

- In response to chemoattractants, ***monocytes*** gradually accumulate (slowly) and become macrophages (after ~ 8 hours mature)
- In part due to increased bone marrow production (store is low), ***macrophages*** become the dominant inflammatory cell over several weeks, cleaning up remaining bacteria, necrotic tissue, and directing tissue remodeling

4th line of defense

Bone Marrow Response to Inflammation

- First mature cells released after 3– 4 days after stimulation of the BM.
- The bone marrow can increase production of granulocytes and monocytes by 20– 50- fold and maintain this for months or years

"Walling Off" Sites of Inflammation

- ***Fibrinogen*** clots and other mediators *minimize fluid flow in and out of the inflamed area*

- **Staphylococci**
  cause intense inflammation being more toxic are effectively "**walled off**"
- **Streptococci**
  induce less intense inflammation and may be more likely to spread than staphylococci, and cause death

Mediators

- histamine
- bradykinin
- serotonin
- prostaglandins
- complement products
- clotting components
- lymphokines

Formation of Pus

composed of

- dead bacteria
- neutrophils
- many dead macrophages
- necrotic tissue

Formed by

proteases, and tissue fluid, often in a cavity formed at the inflammatory site

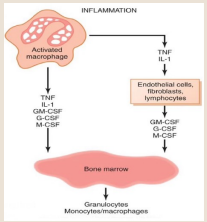
Absorption

Over days and weeks it is absorbed into the surrounding tissue and lymph and disappears (monocytes in blood little ability)

Two ways to stimulate bone marrow:

Cytokines such as TNF, IL-1, GM-CSF, G-CSF, and M-CSF are released into the blood to stimulate the bone marrow to produce more granulocytes and monocytes.

Growth factors produced in response to infection and inflammation drive proliferation and differentiation of leukocyte precursors in the marrow



the contribution from activated macrophages is more significant.

TNF and IL-1 may a activate other cells– such as endothelial cells, fibroblasts, an lymphocytes—to produce these cytokines

Lecture #6

Immunity

Innate Immunity
general immunity

- inborn ability to resist damaging organisms and toxins **non specifically**.
- Skin, gastric ascids, tissue neutrophils and macrophages, complement system; sometimes it requires binding of antibodies to antigens.
- microbicidal and lytic chemicals (digestive chemical found in lysosomes) in blood and blood cells.

Acquired Immunity
specific/ adaptive immunity

- Humoral (B cells) Secretes antibodies
- Cellular (T cells) activate cells that specifically target and destroy invading organisms and toxins

Powerful: can neutralize 100,000 x lethal dose of some toxins.
It means if the body doesn't have acquired immunity a very simple dose of toxins will be lethal.. Our acquired immunity give us a powerful protection against toxins

Antigen

antibody generator

- A substance that can elicit an immune response.
- we have two types of Antigens, self and foreign.
- Unique to each invading organism.
- Usually proteins or large polysaccharides expressed on plasma membrane.
- Most are large (MW > 8,000) and have recurring molecular groups on their surfaces (specific sequences for the certain molecular groups act as a **barcode** for these type of microorganisms).
- The molecular structures that are specifically recognized in acquired immunity are called "**epitopes**"

Lymphocytes

- It has **two types**: 1. **T** Lympocytes 2. **B** Lymphocytes.
- Mediate acquired immunity.
- Develop in **lymphoid tissues** (they start in the liver in the mid fetal life, Then bone marrow and complete their development and lodge in the lymphoid tissues **such as:** tonsils, adenoids, Peyer's patches (GI), lymph nodes, spleen, thymus, marrow.
- Are strategically positioned so they can sense and recognize the pathogens since they enter the body.

T Lymphocytes

- Some of these T lymphocytes can recognize self antigens so they will start attacking host cells, so in thymus **apoptosis** will happen to all cell clones that are reactive against our own tissues (another important process in the thymus which is called Development of tolerance/preprocessing against host cells (immune cells will not develop reactivity against our own cells), the T lymphocyte may be mixed with our self antigens, any reactive T cell will go apoptosis.
  The only T cells that will release in to the blood or go to lymph nodes are the ones that will recognize **foreign antigens**
- Maturation of T cells in the Thymus:
  -Rapid expansion.
  - Each clone is specific for a single antigen
  - Self-reactive clones are deleted (up to 90%) (Destroyed or apoptosis)
  - Migrate to peripheral lymphoid organs
  - Much of the above occurs just before and shortly after birth
- If the thymus is removed before birth what will happen to acquired immunity?
  Acquired immunity rely on the function of **T helper** cells to a very high extent and even on **B cells**, So if all these processes didn't happen, T cells will not be functional, this will affect the whole acquired immunity.
- if a child who lacks acquired immunity (he has no thymus) and doctors want to transplant an organ for him , will he have rejection?
  No, as rejection is a function of T cells.
- if the thymus is removed after 6 months or a year of age what will happened to the acquired immunity?
  There will be a lot of T lymphocytes that were processed before, although the immunity will be diminished but we will not loose the whole acquired immunity.

Development of Lymphocytes

Production starts from bone marrow just just before they birth and after it.

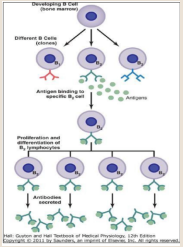
Hematopoietic stem cells

- **Myeloid stem cells**
- **Lymphoid progenitor cells**
  - **T cells**: Will leave BM to the thymus, where they increase in their numbers make thousands of clones in it, a each clone will recognizes specific antigen and becomes activated if that antigen is released in the blood.
  - **B cells**: They will be released to the blood and Lymph nodes or lymph tissues, once B lymphocyte recognize or interface the antigen that it is raised against, it will be activated, proliferate and secrete a lot of antibodies

B Lymphocytes

- Initial growth and differentiation in the liver (fetal) and bone marrow (after birth). Migrate to the peripheral lymphoid organs.
- Each clone is specific for a single antigen; There will be limitless antibody specificity, they are specific and millions of antigens can be recognized, each clone is specific to one Ag.
- Clonal development provides almost limitless antibody specificity
- After being activated by specific antigens, the secreted antibodies destroy or neutralize molecules or organisms bearing their cognate antigen
- **B cell proliferation in response to antigen:**

-This figure shows how different clones of B lymphocytes are produced during the processing, when one of these clones binds to its respective antigen, it will get activated then proliferate to increase in number and secrete a high amount of antibodies in order to fight microorganisms.
- This process usually occurs in lymph nodes (or lymphoid tissues in general) where B cells recognize pathogens and get activated.
-They are all a clone of the same lymphocyte that is reactive to an antigen.



Immunologic Specificity

- Each B or T cell clone is specific for a single epitope of a single antigen.
- The genes for B cell receptors (immuno-globulins) and T cell receptors have hundreds of "gene segments" that are used in varying combinations.
- Permutations (arrangements) of these cassettes allow specificity for millions of distinct epitopes
- Each B or T cell has **specific receptors** for each single epitope of various antigens.
- The variability of receptors are created from the **rearrangement of hundreds of gene segments** not from a whole gene, allowing millions of unique specificities and ability to recognize different antigens.

Lymphocyte Activation

T helper cells get activated once T lymphocytes are activated by certain antigens. T helper cells then release lymphokines that are important for the function of both B and T cells.
T cells in order to become activated need antigen presenting cells (APCs), (as T lymphocytes can't recognize antigens alone without help) like macrophages, B lymphocytes, or dendritic cells that destroy microorganisms and digest their antigens to expose them into the surface using major histocompatibility (MHC) proteins so that T cells are able to recognize the pathogen's antigens

A. **Macrophages** in lymphoid organs:
1.ingest antigen and present antigenic peptides to helper T cells
2. Secrete IL-1, other cytokines that promote lymphocyte growth and differentiation
B. **Helper T cells** produce additional cytokines that stimulate **B** and **T cells** proliferation and differentiation.
C. Both B and Tcells **require** antigenic stimulation to proliferate.

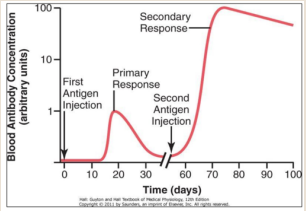
Memory B cells and Secondary responses

- After the **first** Ag injection, the increased of antibody titer will be delayed from **ten days to two weeks** and the potency will be **low** and **won't last for longer** than 20 days.
- After the **second** exposure the titer will robust (a hundred times more than the first response) with **a very fast** increase that will **remain high** for much **longer** and more potent
- This concept is used in **immunization** where we give newborns vaccines at different time intervals to strengthen their immunity against pathogens

Antibody production

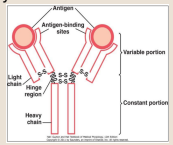
A function of B Lymphocytes

- B cells bind intact antigen, (B cells interact with an antigen for the first time, but are able to recognize them by the huge amount of receptors on their surface).
- T cells bind presented antigenic peptides
- B cells proliferate (with T cell help), developing lymphoblasts and plasmablasts (Some of B lymphocytes when get activated will be kept as **latent memory** cells until the next exposure of the same antigen in the future, and the activation process will be faster).
- Up to 500 antigen-specific progeny in 4 days by each activated lymphoblast, each producing as many as 2,000 Ig molecules/sec (Antigenic stimulation differs between primary or secondary responses).
- Can persist for many weeks (short lived), if antigenic stimulation persists (Some are long lived and continue the production of antibodies for years and for the rest of a person's life)



Structure of Immunoglobulins

- The simplest form has 2 light chains and 2 heavy chains with 2 **binding sites.**
- Each binding site is composed of one light and one heavy chain.
- The antigen binding site is **the variable part**, because of the high variabilities of chemical composition of segments to recognize different antigens.
- The **constant part** is important for different characteristics, such as diffusibility in tissues, attachment to tissues, and activation of the compliment system.
- A **Bivalent Ig** has two binding sites.



Antibody Classes (isotypes)

- **IgM** (earliest produced and primary response, five pairs of heavy chains and light chains)
- **IgG** (75% of all immunoglobulins)
- **IgA**
- **IgD**
- **IgE** (Critically involved in allergic ractions)

Immunoglobulins make up about 20% of all plasma proteins

Antibodies mechanisms of action

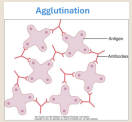
Agglutination
reaction involves binding of the antigen by several antibodies and each antibody can bind to several antigens in order to make a clump of toxins and microorganisms to isolate them from other body tissue.

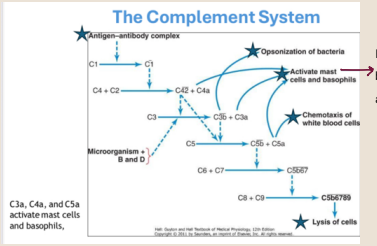
Precipitation
happens when an antigen is soluble and when it clumps it becomes insoluble which will also help isolate it.

Neutralization
is covering up the active site on the pathogen to prevent its harmful effects.

Lysis
is when the antibodies poke holes into the pathogen that will result in swelling of the pathogen and lysis.

The **binding** between the antigen and the antibody (the constant portion) will result in activation of certain members of the complement system, then cascade of activation of proenzymes present in the blood of different functions.





Release of histamine, bradykinin and serotonin aggravating the inflammation

T cell Activation

Binds to antigen presented by antigen-presenting cell.

Rapid expansion of T helper (CD4) cells.

T helper cells produce cytokines (Cytokines regulate the functions of the whole immune system such as cytotoxic T cells, B lymphocytes, and macrophages).

Drives expansion of both T helper (CD4) and cytotoxic (CD8) T cells (CD8 plays an important role in the destruction of the pathogen).

Both types of cells also generate clonal memory T cells, which are retained for future exposure to the same antigen. This enables a fasterand more robust response in the future.

Antibody Specificity

- Each antibody has a steric configuration specific to its antigen (in the **variable part**)
- Multiple prosthetic groups of each antigen interact with complementary structures of the antibody, through…

1. hydrophobic bonding
2. hydrogen bonding
3. ionic interactions
4. van der Waals forces

The more bonds that we have, the more specific and tighter binding which affects the quality of activation of antibodies.

- Antibodies are at least **bivalent**

Certain antibodies could have up to ten binding sites depending on the number of light and heavy chains. For example, IgM has 5 binding sites (5 pairs of light and heavy chains).

You should recognize the functions of each.

Lecture #7

MHC proteins

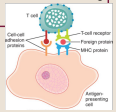
During antigen presentation and T cell activation, MHC proteins play a major role, as T cells do not recognize free antigens. Instead, T cells only recognize antigen fragments that are presented by MHC molecules of antigen presenting cells:

1.macrophages
2.B lymphocytes
3.dendritic cells

B cells and secreted antibodies recognize intact antigen.

Antigen presentation

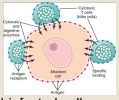
As shown in the figure, the MHC protein is an integral plasma membrane protein on the antigen- presenting cell, that binds to the foreign antigen. This binding allows recognition by T cell receptors (TCRs), which specifically interact with the presented antigen. In addition, cell-to-cell adhesion proteins help strengthen and prolong this contact, facilitating effective T cell activation.



MHC Molecules

- MHC I — Present to cytotoxic T cells (CD8)
- MHC II — Present to helper T cells (CD4)

Killing by cytotoxic T cells



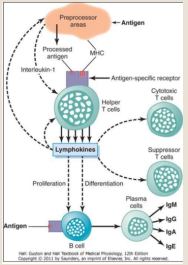
- Virus-infected cells.
  - They directly interact with viral-infected cells, creating pores in the plasma membrane and infusing digestive and destructive substances that lead to the destruction of the infected cell.
  Cancer cells.
- Transplanted organs and tissues.
- This is the underlying cause of **graft vs host** disease.

Helper T cells (CD4)

- ~ 75% of all T cells.
- Regulate functions of other immunologic cells by producing cytokines (Interleukin (IL-) 2, 3, 4, 5, 6, GM-CSF, Interferon-gamma).
- There are different subsets of T helper cells each of these subsets has major lymphokines that are produced that are involved in different immune reactions:

	T_H1	T_H2	T_H17
Lymphokines that induce subset	IFN-γ, IL-12	Il-4	TGF-β, Il-1, Il-6, IL-23
Major lymphokines/ factors produced	IFN-γ, Il-2 TNF-α, GM-CSF	IL-4, IL-5, Il-6, IL-10, Il-13	Il-17, IL-22
Major immune reactions	Macrophage activation, Stimulate IgG antibody production	Stimulate IgE production, Activation of mast cells and eosinophils	Recruitment of neutrophils and monocytes

- T helper cells play a crucial role in several **positive feedback** mechanisms for cytotoxic T cells, suppressor T cells, macrophages, and their own self-regulation.
  - Positive feedback for helper T cells (IL-2).
  - Stimulation of cytotoxic T cells (IL-2, other cytokines).
  - Stimulation of B cells (IL- 4, 5, 6 (BCGFs)).
  - Macrophage accumulation, since T helper cells promote their attachment and slow their movement, leading to their accumulation at the site of infection, activation, enhanced killing, and phagocytosis functions.



The Clinical perspective of Leukocytes and immunity

- Leukopenia
- Leukemias
- Immunologic Tolerance
- Immunization
- Allergy and hypersensitivity
- Mast cell / basophil degranulation

Leukopenia

- Leukopenia, or low white blood cell count, is usually the result of reduced production of cells by the bone marrow.
- It can allow clinically severe infections with organisms that are not usually pathogenic.
- Within two days of bone marrow shutdown mucous membrane ulcers or respiratory infection may occur.
- Causes of leukopenia: radiation, chemical toxins, some medicines; due to damage of the bone marrow cells and having an aplastic effects
  In most cases marrow precursors can reconstitute normal blood cell counts with proper support after the acute phase.

Leukemias

- Uncontrolled production of abnormal immature white blood cells due to a genetic mutation.
- It is characterized by having Clonal proliferation, lineage-specific tumors, often immature cells.
- Leukemias are:
  - **Lymphocytic vs. myelogenous** (depending on the origin of those tumor cells).
  - **Acute vs. chronic** (sometimes up to 10-20 years).
- Leukemias with partially differentiated cells may be classified as the type that is more similar to neutrophilic, eosinophilic, basophilic, or monocytic leukemias.
- **Clinical Effects of Leukemias:**
  Resulting from the overgrowth of leukemic cells in **abnormal** sites.
  1. **Invasion** of bone from the marrow, with pathologic fractures.
  2. Eventually **spreads** to vascular and lymphatic “filters”…spleen, lymph nodes, liver, other organs.
  3. **Replacement** of normal bone marrow, resulting in infection, and bleeding. (due to the decrease in the number of WBCs and platelets).
  4. **Wasting** because of metabolic demands

Immunologic Tolerance

- Host defense employs powerful destructive mechanisms.
- These must be directed at pathogens while protecting host tissues from damage. (and that is the function of the Tolerance Mechanism).
- "**Tolerance**" in acquired immunity is achieved mainly by clonal selection of T cells in the thymus and B cells in the bone marrow
  - clones that bind host antigens with high affinity are induced to undergo apoptosis, and are deleted.
  - The immune system selects only the clones that are reactive against foreign antigens, and that's how it works as a kind of protection for our body's tissues.
- **Failure of tolerance produces autoimmuny, such as:**
  1. Rheumatic fever (cross-reactivity with streptococcal antigens).
  2. Post-streptococcal glomerulonephritis.
  3. Myasthenia gravis (antibodies to acetylcholine receptors).
  4. Systemic lupus erythematosis (auto-immunity to multiple tissues).

Immunization is a method used to strengthen our immune response by injecting either killed or attenuated organisms at short or long intervals, several times.

Immunization

- Injecting **killed** organisms or their — typhoid, whooping cough (pertussis), diphtheria, tetanus toxoid
- **Passive** immunity — Infusing antibody or activated T cells from an individual (antibodies last 2-3 weeks),
- Infection with **attenuated** organisms — Smallpox, yellow fever, polio, measles, herpes zoster, other viral diseases

Allergy and hypersensitivity

T cell meadiated (delayed)

- poison ivy , nickel allergies.
- usually cutaneous; can occur in lungs with airborne antigens.

IgE mediated (immediate)

IgE-mediated allergic reactions occur when IgE binds to an antigen, **activating basophils or mast cells**. This causes an **immediate** response and is seen in allergies like eczema and hay fever. Activated cells can bind millions of IgE molecules and release histamine, triggering inflammation.

- typical allergies.
- a single mast cell / basophil can bind 500,000 IgE Molecules

Allergic manifestation

Anaphylaxis

- systemic, potentially fatal
- widespread vasodilatation
- ↑ ↑ capillary permeability, volume loss
- leukotrienes → bronchospasm and wheezing
- **Treatment**: epinephrine and antihistamines

Urticaria

- Localized vasodilatation and red flare
- Increased permeability and swelling ("hives")
- **Treatment**: antihistamines

Hay fever

- histamine mediated
- vascular dilatation in the nasal passages and sinuses (and eyes)
- leakage of fluid
- sneezing
- **Treatment:** Anti-histamines, local corticosteroids

Asthma

- mediated largely by leukotrienes
- sustained bronchospasm
- **Treatment**: β agonists (bronchodilator), inhaled steroids, leukotriene receptor blockers; treat upper airway component

Mast cell/ Basophil degranulation release

- Histamine
- Proteases
- Leukotrienes
- Eosinophil and neutrophil chemotactic factors
- Heparin
- Platelet activating factor

