HEMATOCRIT

Medical Editor: Dr. Sofia Suhada M. Uzir

OUTLINE

I) INTRODUCTION

- Hematocrit = **Packed Cell Volume (PCV)**
  - Volume **percentage** of **red blood cells** in blood, measured as part of a blood test
  - The value is expressed as a **percentage** or **fraction of cells** in blood
  - For example, a PCV of 40% means that there are 40 milliliters of cells in 100 milliliters of blood

Did you know?
Red blood cells account for nearly all the cells in the blood.

- The PCV rises when the number of red blood cells increases or when the total blood volume is reduced
  - Example: dehydration
- The PCV falls to less than normal, indicating **anemia** when your body decreases its production of red blood cells or increases its destruction of red blood cells.

[The Association for Clinical Biochemistry & Laboratory Medicine]

II) LAYERS IN BLOOD SAMPLE

- Example:
  - 1 mm3/ ml from brachial vein taken out and centrifuged
    - Coated with **heparin** to prevent blood clots
  - This will be separated by densities into 3 different layers:
    - Erythrocytes
    - Buffy coat
    - Plasma

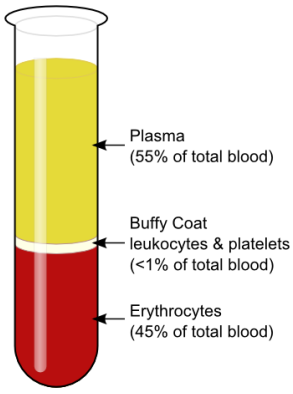

Figure 1. Layers of centrifuged blood sample [Wikipedia]

(A) ERYTHROCYTES

- It is the most dense layer
  - It constitutes about 5-6 million/ ml of blood
    - About 0.45 ml / 45% of the total blood taken
- < 45% = **anemia**
- > 45% = **polycythemia**

Classification of anemia

- Based on the mean corpuscular volume (MCV)
  - Microcytic
  - Normocytic
  - Macrocytic
- The normal MCV is 80–100 fL.
  - If more than one disorder is present, the MCV may be an average of the different populations of RBCs producing a normal MCV
  - However, in mixed disorders, the red cell distribution width (RDW) will be increased
  - Other classification schemes stratify anemias based on increased RBC loss (due to bleeding or hemolysis) or impaired production

[Oxford Medicine]

(B) BUFFY COAT

- It constitute of platelets & WBCs

(1) Platelets

- 150,00- 450,000 / ml blood
- **Function**
  - Plug up any damaged blood vessels
- <150,000 = thrombocytopenia
  - Increase chance of bleeding
- >450,000 = thrombocytosis
  - More clots formation

(2) WBC/ leukocytes

- 4800 - 11,000 / ml blood
- < 4800 = leukopenia
- >11,000 = leukocytosis
  - Leukemoid reaction
  - Leukemia
  - Infections

(C) PLASMA

- 0.55 ml = 55 % of the total blood sample taken
- 90-93% of plasma is **water**
- 8% is **protein**
- Others:
  - Oxygen, Co2, NO
  - Electrolytes
    - Sodium
    - Potassium
    - Chlorine
  - Nutrients
    - Glucose
    - Amino acids
    - Fatty acids
  - Enzymes
  - Hormones
  - Metabolic waste products
    - The plasma transports the waste product to the kidney/liver where it could be excreted in the urine/feces
      - Lactic acid
      - Uric acid
      - Creatinine

(1) Water

- 90-93% of plasma
  - Universal solvent
    - Helps transport RBCs
    - Dissolve certain types of solutes, protein, molecules within the blood vessels
    - Controls blood volume and blood pressure

(2) Plasma Protein

- 8% of plasma

(i) Albumin

- 60% of the total plasma proteins
- Regulate water balance (osmotic pressure)

(ii) Globulins

- Alpha + beta
  - Transport proteins
  - Transport substances that are not soluble within the blood plasma
  - **Examples:**
    - Transferrin
      - Iron
        - If not bounded, can cause free radicals
    - Thyroxine binding globulins (TBG)
      - Hormones T3/T4
- Gamma
  - Antibody like
  - Produced by plasma cells (differentiated B cells)
  - For fighting different types of pathogens by
    - Opsonization
    - Activating certain pathways

III) SUMMARY

- Hematocrit is also known as PCV
- There are 3 layers in centrifuged blood sample which are
  - Erythrocytes – 45%
  - Buffy coat
  - Plasma – 55%
- The buffy coat is made out of **platelets** and **WBCs**
- The plasma contains mainly water, which is a universal solvent

IV) REVIW QUESTIONS

1) **The following is true considering gamma globulins except?**
   a. It is antibody like
   b. Is produced by plasma proteins
   c. It helps in regulating blood pressure through elimination of pathogens
   d. It is involved in opsonizations of pathogens

2) **The following is true regarding hematocrit except?**
   a. It is the total amount of WBC in blood sample
   b. It is also known as packed cell volume
   c. It is expressed as a percentage
   d. It rises when the number of red blood cells increases

3) **Which of the following is true regarding blood plasma?**
   a. It constitutes 65% of the total blood sample
   b. It helps in regulating blood pressure
   c. Erythrocytes is one of the constituents
   d. It helps in the classification of anemia

4) **Why is water is known as universal solvent?**
   a. Helps transport RBCs
   b. Dissolve certain types of solutes, protein, molecules within the blood vessels
   c. Controls blood volume and blood pressure
   d. All of the above

5) **Regarding the water in plasma volume, which is true?**
   a. It doesn't transport RBCs
   b. It is 98% of the total plasma volume
   c. It is 90% of the total plasma volume
   d. It is a type of buffy coat

6) **Regarding platelets which is false?**
   a. Platelets is a component of the buffy coat
   b. Less than 150,000 is considered thrombocytopenia
   c. More than 450,000 is called thrombocytosis
   d. It always increases with RBCs

7) **Regarding the plasma, which is false?**
   a. Water is one of its components
   b. It is free of nutrients
   c. It helps in excreting metabolic waste products
   d. Oxygen is one of its components

8) **Which is true regarding the layers of a centrifuged blood sample?**
   a. There are 4 layers
   b. There are 5 layers
   c. There are 2 layers
   d. There are 3 layers

9) **Erythrocytes, which is true?**
   a. Less than 45% is called anemia
   b. More than 45% is seen in high mean corpuscular volume
   c. It constitutes about 4-5 million/ml of blood
   d. It constitutes about 5-8 million/ml of blood

10) **Regarding albumin, which is true?**
   a. Alpha and beta is a subtype of albumin
   b. Gamma is a subtype of albumin
   c. It helps in regulating water balance
   d. It helps in fighting pathogens by opsonization

CHECK YOUR ANSWERS

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ERYTHROPOIESIS: RED BLOOD CELL FORMATION

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Erythropoiesis: Red Blood Cell Formation | Part 1

Medical Editor: Dr. Sofia Suhada M. Uzir

OUTLINE

I) ERYTHROPOIESIS

- Formation of RBCs is called erythropoiesis

(A) LOCATION

(1) Sites – In order

- **Y**olk Sac
- **L**iver
- **S**pleen
- **B**one marrow (RED) (Spongy bone trabeculae)
  - Skull
  - Sternum
  - Pelvis
  - Epiphyses of long bones

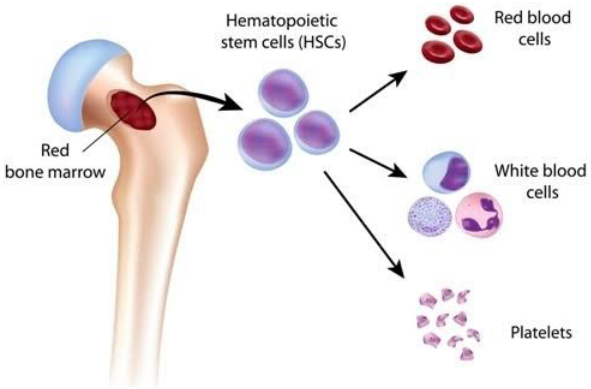

Figure 1. Hematopoiesis - bone marrow [News Medical]

(2) Mnemonic

Young **L**iver **S**ynthesizes **B**lood cells

(B) DRIVING FACTOR

- Blood loss
  - Ulceration
  - Stab wound
- Hypoxia
  - Inadequate oxygen delivery to tissue
  - Production of more RBC to supply more oxygen
- Anemia

(C) CELLS PRODUCED

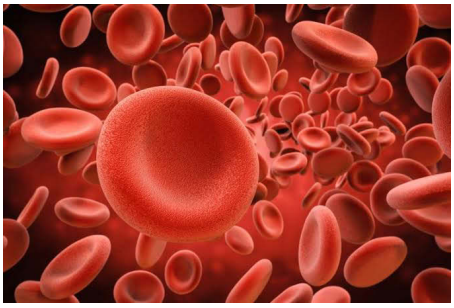

Figure 2. RBCs [European Pharmaceutical Review]

(D) GROWTH FACTORS/ MOLECULES REQUIRED

(1) Erythropoietin (EPO)

- Made by PCT cells in kidney due to hypoxia
- Hypoxia stimulus:
  - Anemia
  - Obstructive Lung disease
  - Restrictive Lung Diseases
  - Obstructive sleep apnea
  - Heart Failure
  - Circulatory Shock
  - Atherosclerosis
  - Thromboembolisms
  - Cyanide or Carbon monoxide poisoning

(2) EPO production

- Hypoxia
  - ↓ Degradation of hypoxia inducible factor (HIF)
  - ↑ HIF in kidney cells
- HIF transcription factor
  - Activates genes that become expressed and lead to synthesis of a protein called EPO
  - EPO then travels to red bone marrow where it acts on myeloid stem cells
    - This converts myeloid stem cells into RBC precursor cells

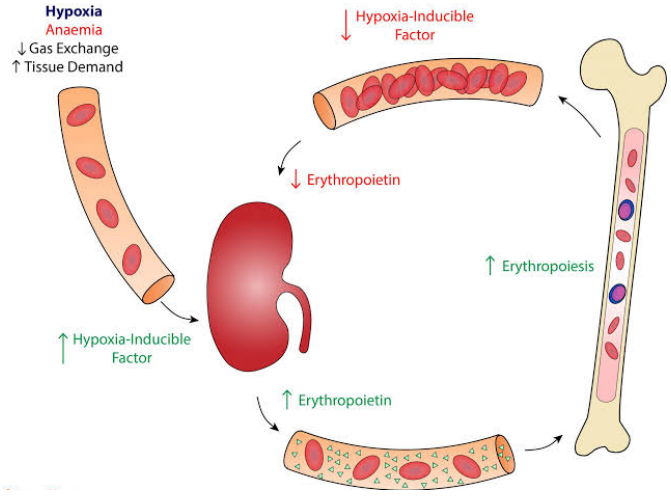

Figure 3. Erythropoiesis induced by hypoxia [Learnhaem]

(3) Requirements

- B12
- Folate
- Iron
- Carbohydrates
- Fats
- Amino acids

(4) Iron metabolism

- Iron ingested from food/supplements in Fe3+ state

(i) In duodenum – enterocytes

- A ferro-reductase enzyme known as duodenal cytochrome B converts Fe 3+ into Fe 2+
- Then Fe 2+ is brought into duodenal cell with H+ by DMT-1
- Once in duodenal cell:
  - Fe 2+ binds with apoferritin converting into ferritin
  - Ferritin can bind with multiple ferritins forming hemosiderin
  - Ferritin can release Fe 2+ on basal surface of cell where a feroportin channel transports Fe2+ from duodenal cell into blood
  - Before the Fe 2+ binds to transferrin
    - It is oxidized to Fe 3+ by hephaestin
    - Transferrin carries the Fe 3+ in the blood to various organs
      - Must bound to transferrin because it can undergo Fenton reaction producing free radicals

(ii) In the liver

- There are hepatocytes that can detect the changes in iron levels
  - It produces hepcidin
    - Hepcidin controls the activity of feroportin by blocking it
    - This is to control the amount of iron
    - Too much iron is toxic
- HFE protein
  - Controls hepcidin
  - In **hemochromatosis,** there is no production of functional HFE protein
  - Hence, iron overload occurs

(iii) In red bone marrow

- The **red bone marrow** is the organ we need it in for erythropoiesis
  - Once Fe 3+ is taken to red bone marrow
    - It is taken up into developing RBCs
    - Binds with heme pigment called protoporphyrin with the help of ferro-chelatase
    - Eventually the heme will bind with the globin chains and make hemoglobin

(5) Vitamin B12 and folic acid metabolism

- Vitamin B12 and folic acid are ingested from food such as leafy vegetables and red meat

(i) In duodenum

- Folic acid is absorbed across the gut, into the blood stream

(ii) In stomach

- Parietal cells make proteins called intrinsic factors
  - Intrinsic factors bind to vitamin B12

(iii) In the ileum

- Intrinsic factors bind with the transport protein
  - Receptor mediated endocytosis
  - Vitamin B12 is released into the circulation through the basolateral membrane
    - Binds with transcobalamin I & II

(E) SEQUENCE OF DEVELOPMENT

(1) RBC pathway

- Hemocytoblast → myeloid stem cell → proerythroblast → basophilic erythroblast → polychromatic erythroblast → orthochromatic erythroblast → reticulocyte → erythrocyte (RBC) Figure 5

(i) Basophilic erythroblasts

- Stain blue
  - RNA stains blue

(ii) Polychromatic Erythroblasts

- Stain blue & red
  - RNA is being translated into proteins which stain red

(iii) Orthochromatic Erythroblasts

- Stain red
  - RNA has been translated to proteins which stains red

(iv) Reticulocytes

- Have no nucleus or organelles after the orthochromatic erythroblast spit them out
- The reticulocytes mature into erythrocytes in **2-3 days**

- B12 and folate are needed for DNA synthesis and maturation in developing RBC's

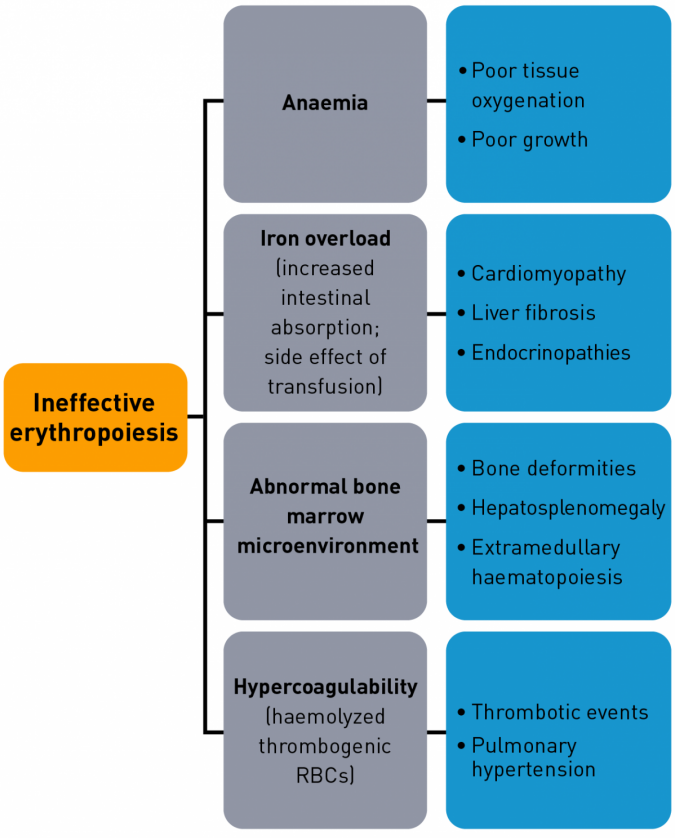

Figure 4. Causes of ineffective erythropoiesis [Keep Maturation on Track]

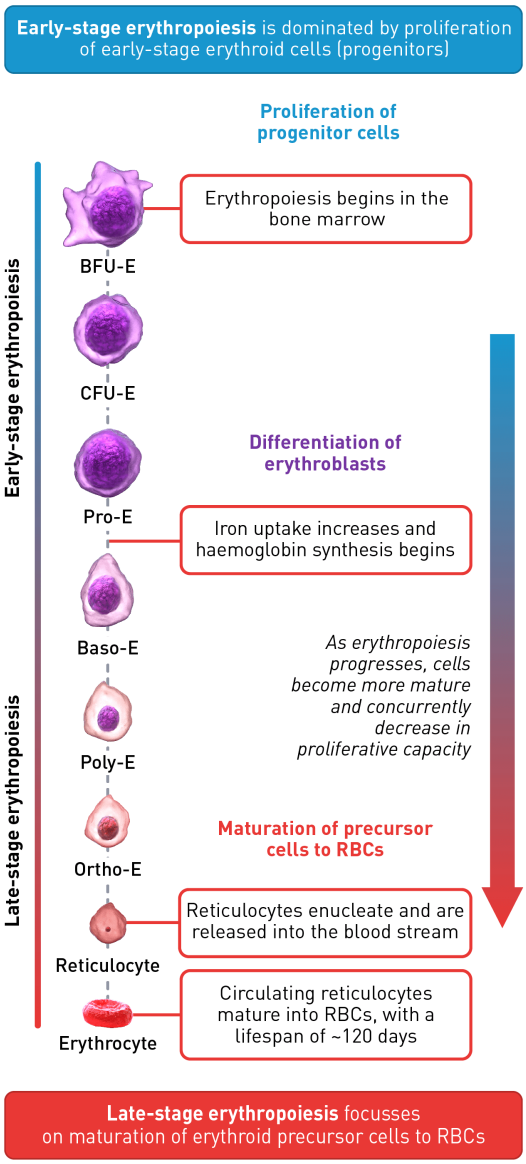

Figure 5. Stages of erythropoiesis [Keep Maturation on Track]

II) REVIEW QUESTIONS

1) **The hormone erythropoietin stimulates red blood cell production in the red bone marrow. Where in the body is erythropoietin produced?**
   a. Spleen
   b. Kidney
   c. Liver
   d. Thyroid

2) **Which of the following statements about erythrocytes is correct?**
   a. They fight infection
   b. They clot blood
   c. They lack a nucleus
   d. They are produced in the spleen

3) **Where does hematopoiesis take place?**
   a. Lungs
   b. Pancreas
   c. Liver
   d. Bone marrow

4) **Platelets are formed from what type of cell?**
   a. Melanocytes
   b. Macrophages
   c. Astrocytes
   d. Megakaryocytes

5) **The precursor of all lines of blood cells is the**
   a. Myeloblast
   b. Hemocytoblast
   c. Proerythroblast
   d. Progranulocyte

6) **Megakaryocyte give rise to**
   a. Erythrocyte
   b. Agranulocyte
   c. Granulocytes
   d. Thrombocytes

7) **The production of red blood cells in the bone marrow is regulated by**
   a. Renin
   b. Angiotensin
   c. Erythropoietin
   d. Calcium

8) **Which of the following is true regarding thrombopoiesis?**
   a. In the red bone marrow
   b. Produce RBCs
   c. Uses EPO
   d. Doesn't give rise to platelet

9) **Process of formation of blood corpuscles is called**
   a. Hemolysis
   b. Hemozoin
   c. Hemopoiesis
   d. Haemoter

10) **The blood corpuscles are of _____ kinds.**
   a. 5
   b. 4
   c. 2
   d. 3

CHECK YOUR ANSWERS

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LIFESPAN AND DESTRUCTION

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Erythropoiesis: Lifespan & Destruction | Part 2

Medical Editor: Dr. Sofia Suhada M. Uzir

OUTLINE

I) THE BASICS

- Lifespan of RBCs **100-120 days**
  - As RBCs reach this time the cytoskeleton and hemoglobin function start declining
    - → So, it's out with the old and in with the new

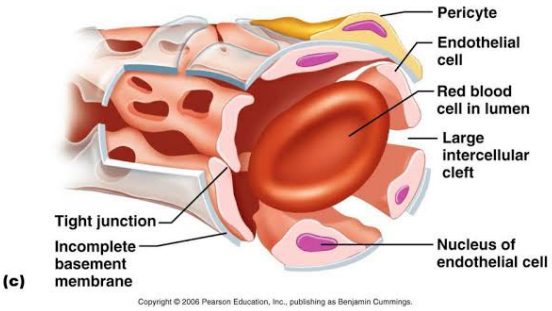
Cytoskeleton

- Proteins in the cytoskeleton help with flexibility and pliability to squeeze through small capillaries
  - Spectrin protein
    - Webbed-like protein
  - Ankyrin
    - Bind spectrin to cell membrane
  - Glycophorin
  - Band 3 protein 4.1 & 4.2
- As RBCs getting older, it becomes less flexible and more rigid.

II) SITES OF DESTRUCTION

(1) Sinusoidal capillaries

Found in:
- Spleen
- Liver
- Red Bone marrow



Have considerable permeability – found in liver, spleen, bone marrow and adrenal medulla

Figure 1. Cut section of sinusoidal capillary [Pearson Education]

III) SEQUENCES OF EVENTS

(1) Old RBCs

- Move through the sinusoids in these organs
  - RBCs gets stucked in the intercellular clefts
  - They get phagocytosed by macrophages
  - The hemoglobin in the RBC is broken down in the macrophage into:
    - Globin chains
    - Heme

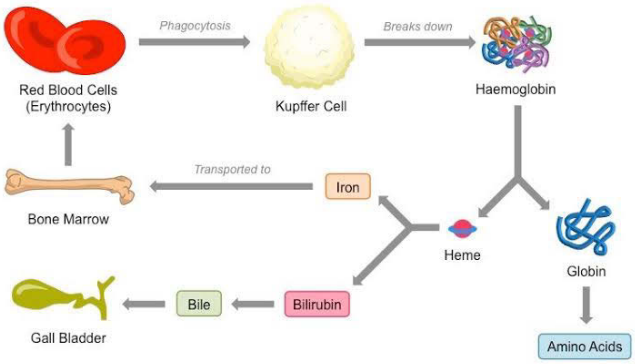


Figure 2. Recycling of RBCs [Bio Ninja]

(B) GLOBIN CHAINS

- Is one of the products of hemoglobin break down by macrophages
- The other is **heme**
- It will further break down into amino acids
  - The amino acids can be recycled to help in the erythropoietic cycle again
- Globin chains include
  - Alpha
  - Beta
  - Delta
  - Gamma

(i) Hemoglobin types

  - Adults
    - 2 alpha + 2 beta
  - Fetal hemoglobin
    - 2 alpha + 2 gamma
  - Hemoglobin A2
    - Very rare type
    - 2 alpha + 2 delta

(C) HEME

- Is one of the products of hemoglobin broken down by macrophages
- The other is **globin chains**
- It will further break down into **iron** and **biliverdin** which gets broken down into bilirubin Figure 3.

(1) Iron

- The iron that is released from heme can bind with apoferritin
  - Forming ferritin
- Ferritin molecules polymerize
  - Form **hemosiderin** that is stored in tissues like the liver and macrophages

(2) Bilirubin

- Biliverdin get broken down into bilirubin
- **Bilirubin is very toxic if it gets into the blood stream causing neurotoxicity**
- Spit out of macrophage in the unconjugated form and binds to albumin where it is transported to the liver

(i) In the liver

- Unconjugated bilirubin binds with glucuronic acid
  - Forms conjugated bilirubin
    - Soluble
  - Will be secreted into bile
    - Bile helps with fat digestion
    - Will be released in the duodenum through the hepatopancreatic ampulla

(ii) In the duodenum

- The bile is released into the duodenum
  - Helps to emulsify fat
- **Bilirubin** in the bile gets broken down to **urobilinogen** by the bacteria enzymes (such as proteases)
  - Small amounts of urobilinogen is absorbed across GIT and into blood where it is taken to kidneys and added into urine
    - This is called **urobilin**
    - Causes yellow coloration of the urine
  - Some of it can be recycled and reconjugated with glucuronic acid through the **enterohepatic circulation** Figure 4.
  - The remaining urobilinogen in the GIT gets converted into → **stercobilin** by bacteria in colon
    - This pigment gives feces its brown hue

NOTE:
- Another name for urobilinogen in the GIT is **fecal stercobilinogen**
- The colour of stool and urine is a good clinical indicator if there is an obstruction in the biliary pathway where bilirubin cannot be secreted
- Gallstone obstructed in the common bile duct can push bilirubin into the blood stream → deposits into different tissues
  - Yellowish coloration = **jaundice**

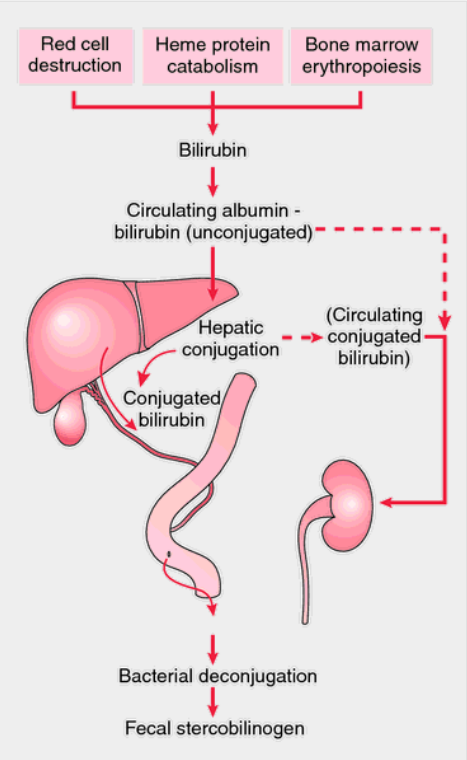


Figure 3. Bilirubin metabolism simplified [Lab Technologist Farukh]

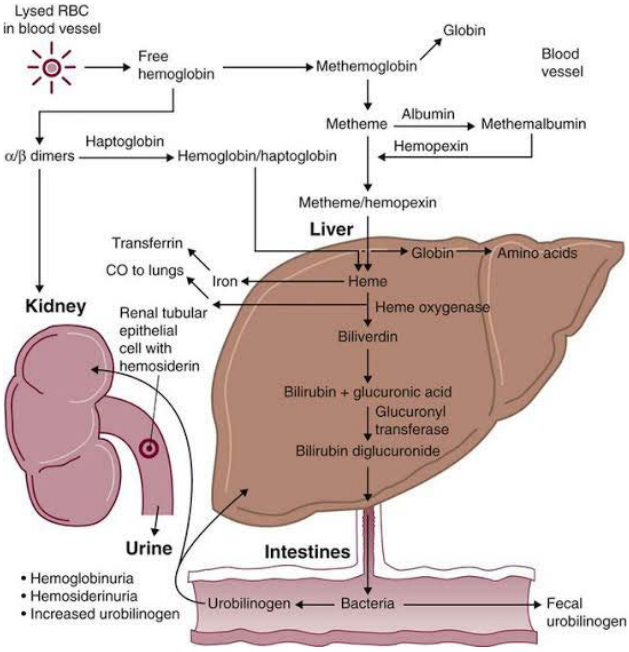


Figure 4. Detailed destruction of erythrocyte [Oncohema Key]

IV) REVIEW QUESTIONS

1) **What is the approximate formation of bilirubin in adults?**
   a. 150-220 mg
   b. 50-70mg
   c. 250-350 mg
   d. 500-700 mg

2) **Which of the following statement is NOT true?**
   a. Bilirubin is lipophilic in nature
   b. Biliverdin reductase is an ATP dependent soluble enzyme
   c. Albumin has 2 binding sites for bilirubin
   d. Heme oxygenase enzyme produces biliverdin, ferrous ion and CO

3) **Which form of energy is required for the working of complex enzyme system?**
   a. ATP
   b. ADP
   c. NAD
   d. None of the above

4) **What happens to the globin part of hemoglobin after its dissociation?**
   a. Excreted through urine
   b. Stored in liver
   c. Degraded to its amino acid
   d. None of the above

5) **What would happen to red blood cells if the heme group were removed from hemoglobin?**
   a. Red blood cells would not be able to bind oxygen
   b. Red blood cells would not be able to reproduce
   c. White blood cells would not be able to reproduce
   d. Blood clot formation would be inhibited

6) **The secretion of bilirubin from hepatocytes to canaliculi are an energy-dependent process. The transporter protein involved in this protein is**
   a. MRP2 protein
   b. Active transport coupled with Na K ATPase
   c. Bilirubin transporting protein
   d. Chylomicron

7) **In the intestine, bacterial degradation of bilirubin forms urobilinogen. Urobilinogen is a colorless bilirubin derived product that is further oxidized to form the following pigments except**
   a. Urobilin
   b. Mesobilin
   c. Stercobilin
   d. Exobilin

8) **When red blood cells are worn out, part of their components are recycled while others are disposed. Select the incorrect statement about destruction of red blood cells.**
   a. The greenish pigment, biliverdin, is recycled to the bone marrow
   b. Iron is carried to the bone marrow by a protein called transferrin
   c. Biliverdin and bilirubin impart color to bile
   d. Macrophages in the liver and spleen destroy worn out red blood cells

9) **Life span of RBC is**
   a. Around 90 days
   b. Around 50 days
   c. Around 125 days
   d. Around 115 days

10) **All of the following are the site of RBCs destruction, except**
   a. Liver
   b. Lung
   c. Spleen
   d. Bone Marrow

CHECK YOUR ANSWERS

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TYPES OF ANEMIAS

Medical Editor: Dr. Ana Guerra

OUTLINE

I) OVERVIEW

(A) DEFINITION

Anemia is defined as a low carrying capacity condition due to decrease in hemoglobin concentration.

→ The diagnostic criteria is based on low hemoglobin (Hb), low hematocrit (Hct), or decreased RBC count.

Table 1. Diagnostic criteria for anemia in males and females [LabPedia.net].

RBCs values	Male	Female
Hemoglobin	13.5-17.5 g/dL	11.5-15.5 g/dL
Hct % Hematocrit **PCV** Packed cell volume	40-52%	36-48%
MCV Mean cell volume	80-95 fL	80-95 fL
MCH Mean cell hemoglobin	27-34 pg	27-34 pg
MCHC % Mean cell hemoglobin concentration	30-37%	30-37%
Reticulocytes count	0.5-1.5%	0.5-1.5%

(B) CLASSIFICATION

There are several types of classifications for anemia, but two of the widely accepted are based on:

→ The etiology
→ The morphology

(i) Classification based on etiology

1) Increased RBC's destruction (hemolysis).
2) Increased blood loss, which may be acute or chronic.
3) Defective maturation of erythropoiesis.

(ii) Morphological classification

1) Normochromic and normocytic anemia (normal MCV and MCHC).
2) Hypochromic and microcytic anemia (low MCV, MHC and MCHC).
3) Normochromic and macrocytic (high MCV, normal or increase MHC and normal MCHC).

→ MCV determines size of erythrocytes.
→ MHC and MCHC determine color.

Table 1-2. Types of anemia according to their morphology [LabPedia.net].

	Microcytic hypochromic	Normocytic normochromic	Macrocytic
MCV	<80 fl	80-95 fl	>95 fl
MCH	<27 pg	>27 pg	↑/ N
MCHC	<32%	N	N
E.g.	• Iron deficiency • Thalassemia • Sideroblastic anemia • Chronic diseases • Lead poisoning	• Hemolytic anemias • Acute blood loss • Bone marrow failure • Renal diseases	• Vit B12 deficiency • Folic acid deficiency • Aplastic anemia

(C) COMMON CLINICAL PRESENTATION

→ **Main symptoms are due to cardiovascular system adaptation**
→ Increased stroke volume, tachycardia and changes in the Hb O2 dissociation curve.
→ Weakness and fatigue.
→ Dizziness and headaches.
→ Pallor of face, tongue and conjunctives.
→ Shortness of breath.

(D) DIFFERENTIAL DIAGNOSIS STUDIES

(i) Red cell distribution width (RDW)

- Helps in the differential diagnosis of iron deficiency anemia and thalassemia.

(ii) Serum iron

- Helps differentiating between hemochromatosis and hemosiderosis.

(iii) Transferrin

- Cand help in diagnosis of anemia of chronic disease and differential diagnose with iron deficiency anemia.

(iv) Transferrin saturation

- Cand help in diagnosis of anemia of chronic disease and differential diagnose with iron deficiency anemia.

(v) Ferritin

- It correlates with total body iron stores.

(vi) Total Iron binding capacity (TIBC)

- Always done along serum iron levels.

(vii) Peripheral blood smear

- Informs abnormalities of the RBC shape, size and inclusions.

(viii) Bone marrow examination

- Helpful study when there are signs and symptoms of aplastic anemia.

(ix) Coombs test

- Very useful to differentiate between hereditary spherocytosis and autoimmune hemolytic anemia.

II) IRON DEFICIENCY ANEMA

(1) Etiology

- Excessive bleeding.
- Menorrhagia.
- Iron deficiency in diet (common in vegetarians).
- Increased demand by the body
  - Infancy, pregnancy, lactation.

→ One of the most common causes of anemia.

(2) Pathogenesis

- Absence of iron:
  - Protoporphyrin can't form heme
    - Dysfunctional hemoglobin.
      - Erythrocyte volume decrease:
        → Microcytic red blood cells.

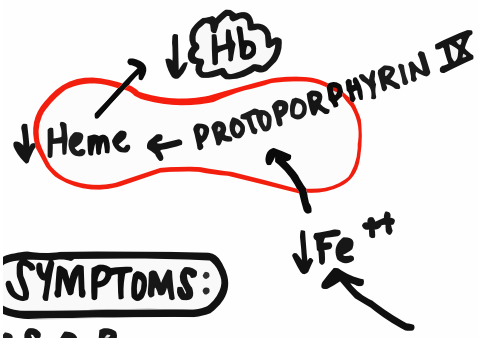


Figure 1. Pathogenesis of iron deficiency anemia.

(3) Specific symptoms

- Koilonychia: Spoon-shaped nails.
- Hair loss.
- Pica: Some patients may like to eat clay, ice and starch.
- Glossitis (smooth, red tongue).
- Stomatitis.
- Angular cheilitis.

→ Many times is asymptomatic.

(4) Diagnosis

- History of patient.
- Physical examination.
- Blood test with complete blood count (CBC).
- Levels of serum ferritin, iron, TIBC and/or transferrin.

Table 1-3. Useful tests in the diagnosis of iron deficiency anemia [Hematología. La sangre y sus enfermedades].

RBC Hg Hct	↓↓↓↓
MCV	↓
MCH	↓
MCHC	N
Reticulocytes	N / ↑
Leukocytes	N / ↓
Blood smear	Hypochromic and microcytic RBC, elliptocytes.
Platelets	N
Serum iron	↓
Ferritin	↓
TIBC	↑
RDW	↑

III) PERNICIOUS ANEMIA

(1) Etiology

- Autoimmune.
- Deficiency in diet.

(2) Pathogenesis

(i) B12 deficiency

Autoimmune condition where the body creates **antibodies against Intrinsic Factor**.

- In order to be absorbed, **B12 binds to intrinsic** factor inside the GI tract.

→ Antibodies block B12 absorption
→ Decreased B12 within the blood stream
→ Red blood cells DNA **can't mature and condense → Macrocytic RBC**
→ Abnormal function of hemoglobin, risk of hemolysis inside the capillaries.

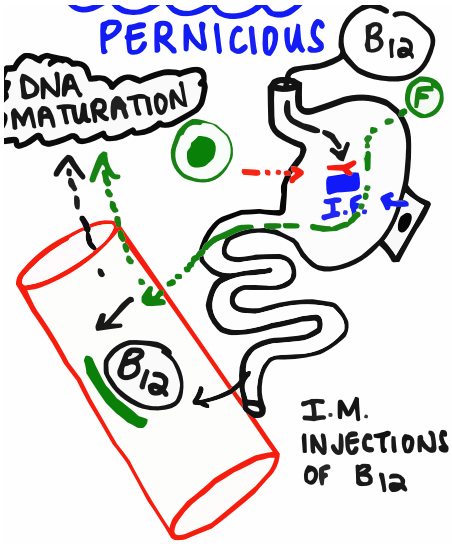


Figure 1-2. Pathogenesis of pernicious anemia.

(ii) Folic acid deficiency

Usually due to folic acid deficiency in diet.

- Folic acid is also needed for RBC to condense and mature

→ Its absence leads to macrocytic and unfunctional RBC.

(3) Diagnosis

Table 1-4. Useful tests in the diagnosis of pernicious anemia [Hematología. La sangre y sus enfermedades].

RBC Hg Hct	↓↓↓↓
MCV	↑
MCH	**N**
MCHC	N
Reticulocytes	N / ↑
Leukocytes	↓↓↓↓
Blood smear	Macrocyte RBC, teardrop cells
Platelets	↓↓↓↓

(4) Treatment

→ **IM injections of B12**

IV) HEREDITARY SPHEROCYTOSIS

(1) Etiology

- Hereditary condition with mutations in membrane proteins and erythrocyte cytoskeleton.

→ Spectrin, ankrin, band 3 or protein 4.1
→ Most common is mutation of spectrin β, ankrin or band 3.
→ Autosomal dominant inheritance.

(2) Pathogenesis

- Abnormal erythrocyte membrane due to proteins mutations.

→ Takes a spherical form
→ Poor ability to tolerate osmotic changes
→ Membrane stiffness
→ Cought in spleen → Splenomegaly → Hemolysis.

(3) Diagnosis

Table 1-5. Useful tests in the diagnosis of hereditary spherocytosis [Hematología. La sangre y sus enfermedades].

RBC **Hg** **Hct**	↓↓↓↓
MCV	↓
MCH	N / ↑
MCHC	N
Reticulocytes	↑↑↑↑
Blood smear	Microspherocytes
Platelets	N / ↑
Coombs Test	**Negative**

V) G6PDH

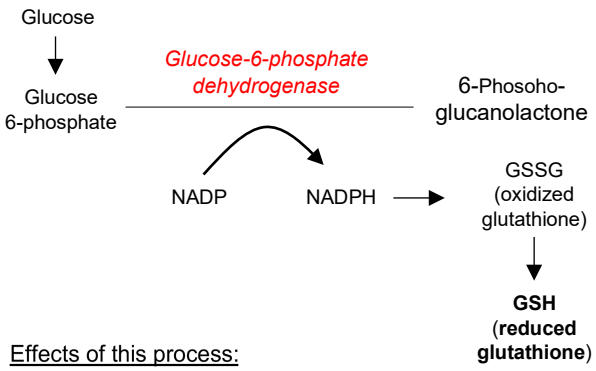
Glucose 6-phosphate Dehydrogenase deficiency

(1) Etiology

Hereditary condition

(2) Pathogenesis

- In order to obtain energy, RBC can **only** do glycolysis:



Effects of this process:

- Erythrocytes generate energy.
- The NADPH obtained thanks to the action of the G6PD enzyme, reduce glutathione allowing it to catch free radicals that are harmful for the RBC.

→ In the absence of G6PD there won't be NADPH production.
→ Glutathione won't get reduced.
→ Free radicals won't get cached by glutathione.
→ Damage to RBC membrane
→ **Heinz bodies**

(3) Diagnosis

→ **Heinz bodies on blood smear.**

VI) SICKLE CELL ANEMIA

(1) Etiology

- Hereditary condition: Missense mutation

→ Production of abnormal Hb S

(2) Pathogenesis

- Sickle cell anemia occurs due to a substitution on the position 6 of the β chain of Hb A_1
  - Glutamine is substituted by valine
    → Valine is a hydrophobic amino acid so it changes the structure of RBCs to sickle forms every time it polymerizes.
  - They only take a sickle form when they're not bound to O2 → every time they get oxygenated, RBCs go back to their normal structure.
    → This process is called **sickling.**
  - On their sickle form they can undergo hemolysis or occlude blood vessels causing a **vaso-occlusive crisis**
    - Priapism: Vessels of the penis get clogged with sickle cells, causing a painful erection.
    - Splenomegaly due to the hemolysis
      - In some cases splenectomy will be needed.

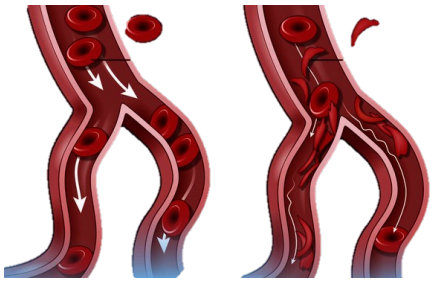


Figure 1-3. Red blood cells: Normal form and sickle form [MedlinePlus].

Nice to know
People with sickle cell anemia have been found to be resistant to malaria.

(3) Treatment

- Transfusions.
- Oxygen.
- Opioids depending on the severity of the pain.
- Fluids
- Hydroxy urea – helps producing fetal hemoglobin

VII) HEMORRAGIC ANEMIA

(1) Etiology

- Peptic ulcers due to H. pylori or aspirin
- Aneurisms
- Traumas
- Cancer
- Hemorrhoids

(2) Pathogenesis

- Excessive bleeding → ↓ RBC's
  → ↓ Oxygen → Anemia

(3) Treatment

→ It will depended on the severity of the anemia.

- Transfusions
- Fluids
- Surgery to stop bleeding

VIII) APLASTIC ANEMIA

(1) Etiology

- Idiopathic in 65%
- Drugs (e.g. chloramphenicol, benzenes, streptomycin, etc.).
- Viruses (CMV, EBV).
- Radiation.

(2) Pathogenesis

- Destruction of the myeloid stem cells

→ decreased production of RBC's, WBC's and platelets.

→ **Pancytopenia**

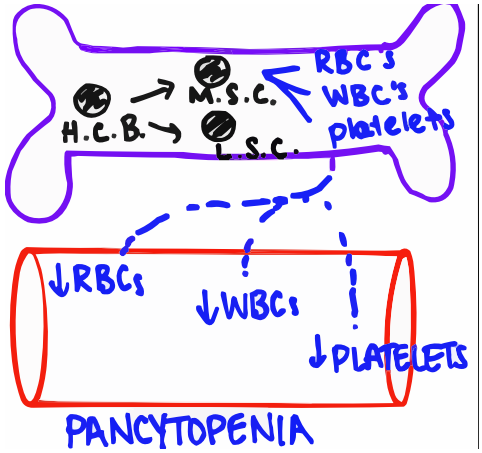


Figure 1-4. Aplastic anemia.

(3) Specific symptoms

- Current infections due to leucopenia.
- Petechiae (↑ bruising).
- Bleeding.

(4) Diagnosis

Table 1-6. Useful tests in the diagnosis of aplastic anemia [Hematología. La sangre y sus enfermedades].

RBC **Hg** **Hct**	↓↓↓↓
MCV	**N**
MCH	**N**
MCHC	N
Reticulocytes	N / ↑
Leukocytes	L: ↑ N: ↓
Platelets	↓↓↓↓
Bone marrow examination	Hypocellularity

(5) Treatment

- Bone marrow transplant.
- Transfusions.

IX) THALASSEMIA

(1) Etiology

- Hereditary condition where there is an absence of a globin chain
  - If there is an α-chain missing → α-thalassemia.
  - If there is a β-chain missing → β-thalassemia.

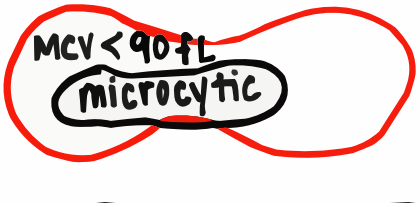
→ More common within the Mediterranean ancestry.

Nice to know

Hemoglobin is formed with two α-chains and two β-chains.

(2) Pathogenesis

- Low functional hemoglobin due to its structure mutation
  - MCV >90 ft
    - Microcytic anemia.



(3) Diagnosis

Table 1-7 Differential diagnosis of thalassemia and iron deficiency anemia [Hematologïa. La sangre y sus enfermedades].

	Thalassemia	Iron deficiency
RDW	N	↑
Serum ferritin	N / ↑	↓
Serum iron	N	↓
Transferrin saturation	N	↑

(4) Treatment

- Transfusions.
- Iron supplements.
- Oxygen.
- Bone stem cell transplant.

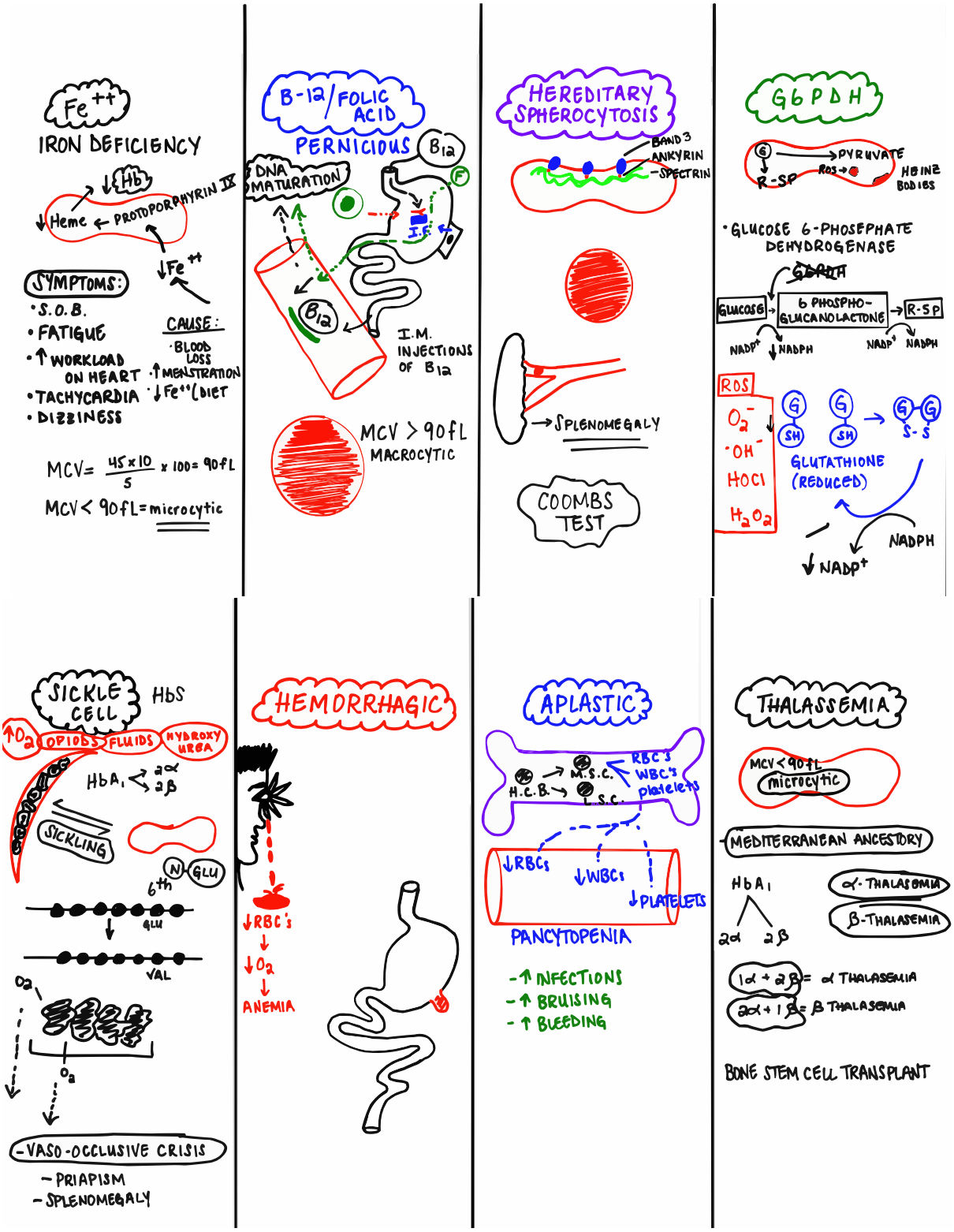


Figure 5. Summary of types of anemias.

XI) REVIEW QUESTIONS

1) A 31 year old woman is presented with history of fatigue, dizziness and headaches since three months ago.

A blood test was performed and results showed Hb 10 g/dL; Hct 40%; MCV 78 fl; MHC 25 pg and MCHC 30%.

According to laboratory findings, how would you morphologically classify this type of anemia?

a) Microcytic normochromic.
b) Macrocytic hypochromic.
c) Microcytic hypochromic.
d) Normochromic normocytic.

2) The following test comes to be very useful in the differential diagnosis of hereditary spherocytosis and autoimmune hemolytic anemia:

a) RDW
b) Peripheral blood smear
c) TIBC
d) Coombs test

3) G6PDH deficiency is a condition where glucose can't turn into 6-phospho-glucanolactone due to lacking of G6PDH, which leads damage to RBC's membranes.

What is exactly the mechanism of this damage?

a) NADP can't turn into NADPH so glutathione can't be oxidized, leading to increased free radicals.
b) NADP can't turn into NADPH so glutathione can't be reduced, leading to increased free radicals.
c) NADPH can't turn into NADP so glutathione can't be reduced, leading to increased free radicals.
d) NADPH can't turn into NADP so glutathione can't be oxidized, leading to increased free radicals.

4) If you're suspecting of pernicious anemia on your patient, which finding on a blood smear test would support your diagnosis?

a) Teardrop cells.
b) Elliptocytes.
c) Heinz bodies.
d) Microspherocytes.

5) The followings are specific symptoms of iron deficiency anemia EXCEPT for:

a) Pica.
b) Tachycardia.
c) Koilonychia.
d) Angular cheilitis.

CHECK YOUR ANSWERS

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POLYCYTHEMIA

Last edited: 8/21/2021

Medical Editor: Dr. Sofia Suhada M.Uzir

OUTLINE

I) INTRODUCTION

- Polycythemia is an abnormally increased concentration of RBCs in the blood, either through reduction of plasma volume or increase in red cell numbers. [Oxford Languages]
- There are two types:
  - Polycythemia vera (primary)
  - Secondary polycythemia

II) ERYTHROPOIETIN (EPO)

- EPO is made by the kidneys at the distal convoluted tubules
  - It stimulates myeloid stem cells and proerythroblasts into erythropoietic process Figure 1
  - EPO increases RBCs through JAK STAT pathway
- In the proximal convoluted tubules, there are also cells that are constantly secreting EPO

Note:

- JAK STAT
  - Janus Kinase and Signal Transducer and Activator of Transcription

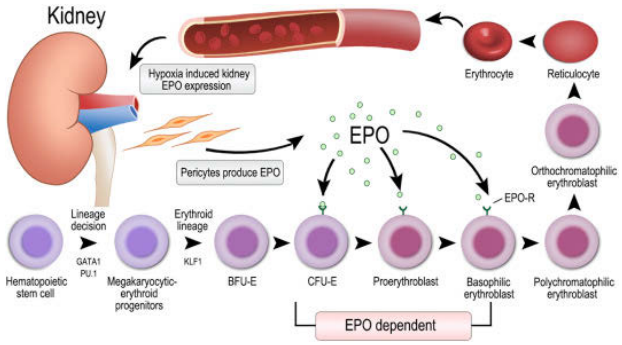

Figure 1. EPO stimulating proerythroblast in erythropoiesis [Science Direct]

III) POLYCYTHEMIA VERA

- Increase in RBC production primarily due to hyper functional JAK STAT pathway in the bone marrow
- There is a problem in the receptor in which EPO binds to
  - Causes increased in functions of JAK STAT pathway
    - Signal nucleus for proliferations
    - Activating genes to undergo transcription and translations
  - Hyperfunctioning → amplified effects → increase in erythropoiesis = increase in the RBCs

  Remember:
    - Polycythemia = abnormal increase in production of RBCs

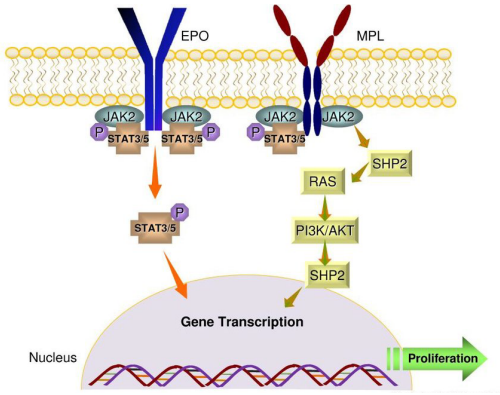

Figure 2. JAK STAT pathway [ResearchGate]

(A) EFFECTS OF POLYCYTHEMIA

- Polycythemia causes:
  - Increase RBC to water ratio
    - Viscosity of blood will increase → **thicker blood**
    - Increase incidence of clot formations (thrombi/emboli)
      - In veins → deep vein thrombosis (DVT) may develop
      - In coronary artery → myocardial infarction
      - In pulmonary arteries → pulmonary embolism
      - In cerebrum → stroke
  - Increase bleeding → longer prothrombin time

IV) BLOOD DOPING

- Causes transient polycythemia
- For example, in the Olympics (non-ethical!)
  - Athletes take their blood out and store it to be reinserted into the circulatory system a day before their event

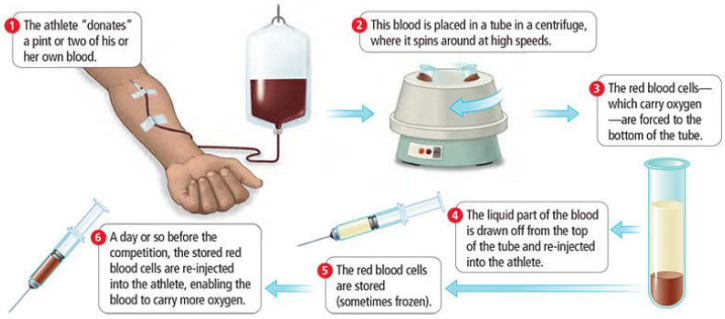

Figure 3. Summary blood doping [Sports247]

(1) Why blood doping?

- Blood doping helps to increase in the number of RBCs in the body
  - Increases oxygen carrying capacity
    - More blood oxygen supply to the muscle
    - More endurance

(2) Drawbacks

- Increase in viscosity
  - Thicker blood → increase incidence clot formation, thrombi/emboli especially if not properly hydrated
  - Increase peripheral resistance → increase in the blood pressure (may cause hypertension)
    - Dizziness
    - Headaches

V) SECONDARY POLYCYTHEMIA

- Due to the enhance of EPO production
- Causes:
  - Hypoxia/low amount of oxygen
    - High altitudes
    - Cardiovascular diseases
      - Decrease oxygen carrying capacity
    - Renal cancer
      - Enhance production of EPO
- Increase EPO → increase JAK STAT pathway → increase erythropoiesis → increase in RBCs

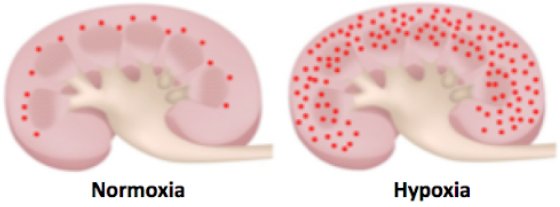

Figure 4. Number of cells producing erythropoietin [Vivo Pathophysiology]

VI) SUMMARY

- Polycythemia is primarily due to hyper functional JAK STAT pathway in the bone marrow.
  - This triggers more erythropoiesis hence, more RBCs formation.
- Secondary polycythemia is caused by the increase in production of EPO → Increases the JAK STAT pathway and RBCs

VII) REVIEW QUESTIONS

1) **Regarding polycythemia, which is correct?**
   a. There are 2 types
   b. There are 3 types
   c. There are 4 types
   d. There are 5 types

2) **In polycythemia vera, which is true?**
   a. There is hyper functionality of erythropoiesis in the liver
   b. There is hyper functionality of JAK STAT pathway in the liver
   c. There is hyper functionality of erythroblasts in the bone marrow
   d. There is hyper functionality of JAK STAT pathway in the bone marrow

3) **In secondary polycythemia, which is false?**
   a. It is due to enhance of EPO production
   b. It can be seen in certain renal cancers
   c. It decreases the oxygen carrying capacity
   d. Hypoxia is one of the main causes

4) **Thrombosis in polycythemia vera is due to**
   a. Erythrocytosis
   b. Leukocytosis
   c. Thrombocytosis
   d. all of the above

5) **True regarding pathogenesis of polycythemia vera**
   a. erythropoietin independent erythroid colony formation
   b. hypersensitivity of polycythemia vera erythroid progenitor cells to EPO
   c. resistance of polycythemia vera progenitor cells to apoptosis
   d. all of the above

6) **The following may be caused by polycythemia except**
   a. Thrombi formation
   b. Decrease in functioning RBCs
   c. Stroke
   d. DVT

7) **What causes secondary polycythemia?**
   a. Low oxygen levels
   b. Renal cancer
   c. Heart diseases
   d. All of the above

8) **The following typically distinguishes polycythemia vera from other causes of erythrocytosis**
   a. Massive splenomegaly
   b. Aquagenic pruritis
   c. High hematocrit
   d. High hemoglobin

9) **The following cause microcytic erythrocytosis**
   a. Beta thalassemia trait
   b. Hypoxic erythrocytosis
   c. Polycythemia vera
   d. All of the above

10) **Regarding polycythemia vera all are true except**
   a. Erythroid progenitor cells are resistant to apoptosis
   b. Autonomous clonal form of erythrocytosis
   c. Elevated plasma erythropoietin level excludes polycythemia vera as the cause for erythrocytosis
   d. Abundant bone marrow iron

CHECK YOUR ANSWERS

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LEUKOPOIESIS (WHITE BLOOD CELL FORMATION)

Last edited: 8/22/2021

Leukopoiesis: White blood cell formation

Medical Editor: Dr. Sofia Suhada M. Uzir

OUTLINE

I) LEUKOCYTES

- Normal range
  - 4,000-11,000 WBCs/mm3

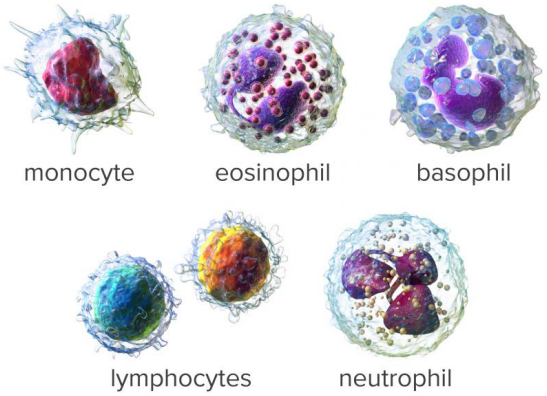

Figure 1. Different types of WBCs [Medical News Today]

(A) GRANULOCYTES

- **Visibly** stained granules after **wright's stain**
  Figure 2
  - Neutrophils
  - Eosinophils
  - Basophils

(B) AGRANULOCYTES

- **No visibly** stained granules after **wright's stain**
  - Monocytes
  - B-lymphocytes
  - T-lymphocytes

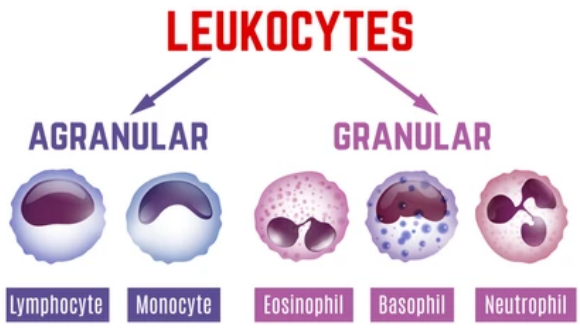

Figure 2. Agranular vs granular lymphocytes [Shutterstock]

(C) NEUTROPHILS

- Relative abundance (%)
  - 50-70% relative abundance in differential

(1) Structure

- Multi-lobulated nucleus also referred to as polymorphonuclear leukocytes (PMNs)
- Granules stains pink
  - Absorbs red (eosin) acid
  - Absorbs blue (methylene) base

(2) Function

- Phagocytosis of pathogens
- Contain granules with leukocyte alkaline phosphatase (LAP)
- Performs respiratory burst
  - Uses hydrogen peroxide to kill bacteria
  - This process causes neutrophil to die as well and release its DNA which creates a net on pathogen tagging them to be destroyed

(3) Clinical significance

- ↑ Neutrophils → neutrophilia
  - Bacterial infections
    - Most common: Strep Pneumoniae, S. Aureus
  - Inflammation
  - Drugs
    - Corticosteroids
- ↓ Neutrophils → neutropenia
  - Bone marrow failure
    - Aplastic anemia
    - Chemotherapy
    - Radiation therapy
  - Drugs
    - Clozapine

(D) EOSINOPHILS

- Relative abundance (%)
  - 2-4% relative abundance in differential

(1) Structure

- Granules stain red
  - Absorbs red (eosin) acid
- Contains Bilobed (Telephone shaped) Nucleus

(2) Function

- Kills parasitic worms with major basic proteins and cationic peptides
- Involved in allergic reactions
- Involved in asthma

(3) Clinical significance

- ↑ Eosinophils → eosinophilia
  - Atopic dermatitis
  - Asthma
  - Parasitic Infections
  - Acute Interstitial Nephritis
    - Caused by drugs like macrolides and allopurinol
  - Churg Strauss Syndrome
  - Adrenal Insufficiency
- ↓ Eosinophils → eosinopenia
  - Cushing's Syndrome
  - Drugs:
    - Corticosteroids

(E) BASOPHILS

- Relative abundance (%)
  - 0.5-1% relative abundance in differential

(1) Structure

- Contain S-shaped nucleus
- Granules stains blue
  - Absorbs blue (methylene) base

(2) Function

- Release histamines, leukotrienes and serotonin during inflammation and allergic reactions to cause vasodilation of capillaries and cause chemotaxis of WBC's
- Contain heparin granules which are important for preventing blood clots

(3) Clinical significance

- ↑ Basophils → basophilia
  - Allergic reactions
  - Chronic myelocytic leukemia (CML)
- ↓ Basophils → basopenia
  - Rare

(F) MONOCYTES

- Relative abundance (%)
  - 3-8% relative abundance in differential

(1) Structure

- Kidney bean shaped nucleus
- Largest WBC

(2) Function

- Become macrophages when they leave blood and enter tissues
- Types of macrophages:
  - Kupffer cells in liver
  - Microglia in brain
  - Alveolar macrophages in lungs
  - Osteoclasts in bone
  - Langerhans cells in skin
- Phagocytosis of pathogens
- Antigen presenting cell
  - Presents antigens to T-cells on its MHC-II complex

(3) Clinical significance

- ↑ Monocytes → monocytosis
  - Tuberculosis
  - Hodgkin's lymphoma
  - Chronic Myelocytic leukemia
- ↓ Monocytes → monocytopenia
  - HIV
  - EBV
  - Acute Myelocytic Leukemia
  - Chemo-Radiation

(G) LYMPHOCYTES

- Relative abundance (%)
  - 20-30% relative abundance in differential

(1) Structure

- Spherical nucleus takes up most of cell volume
- Small amount of cytoplasm

(2) Function

- T-lymphocytes
  - T-helper (CD4+ cells)
    - Activate B cells and turn them into plasma cells to make antibodies
  - Cytotoxic T cells (CD8+ cells)
    - Kills viral infected cells and cancer cells
- B-lymphocytes
  - Become plasma cells and release antibodies

(3) Clinical significance

- ↑ Lymphocytes → lymphocytosis
  - Viral Infections
    - EBV
    - Mumps
  - Lymphoma
  - Tuberculosis
- ↓ Lymphocytes → lymphopenia
  - Immunosuppression
    - HIV/AIDS
    - DiGeorge Syndrome
    - Drugs: Chemo-radiation
  - Lymphoma

II) LEUKOPOIESIS

- Leukopoiesis is the formation of white blood cells
- The stem cell associated with the process is **hemocytoblast**

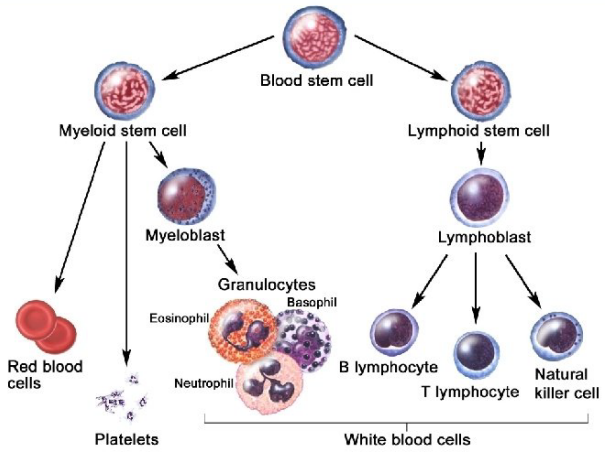

Figure 3. Summary of WBCs formations [Teresa Winslow]

(A) LOCATION

- Site of leukopoiesis:
  - Red bone marrow
    - Has sinusoidal capillaries
  - Skull
  - Sternum
  - Pelvis
  - Epiphyses of long bones (trabeculae/spongy bone)

(B) CELLS PRODUCED

- White blood cells

(C) GROWTH FACTORS / MOLECULES REQUIRED

- Granulocyte growth factors
  - Neutrophils
    - IL-3, IL-6 and G-CSF
  - Eosinophils
    - IL-4 and IL-5
  - Basophils
    - IL-3 and IL-4
- Agranulocytes
  - B-Lymphocytes
    - Made in red bone marrow
    - IL-6
  - T-Lymphocytes
    - Made in red bone marrow
    - Go to thymus to mature into:
      - T helper
      - T regulatory
      - Cytotoxic
    - IL-2, IL-4, IL-6, IL-7
- Monocytes
  - M-CSF

III) SEQUENCE OF DEVELOPMENT

- Pathways:
  - Granulocyte pathways
  - Agranulocyte pathway
  - Monocyte pathway

(A) GRANULOCYTE PATHWAY

- Hemocytoblast → myeloid stem cell → myeloblast
- Myeloblast will divide into 3 different promyelocyte Figure 3
  - Neutrophilic
  - Eosinophilic
  - Basophilic
- These will continue to their corresponding myelocyte
  - beginning to form U-shaped nucleus constriction with granules
- → metamyelocyte
- → band cell
  - perfectly constricted U-shaped nucleus
- → granulocyte
  - Nuclei segmented
    - Basophil
      - U-shaped / S-shaped
      - Stain blue with methylene blue based
    - Eosinophil
      - Bilobed nucleus
      - Granules stain red with red (eosin) acid
    - Neutrophilic
      - Polymorphonuclear leukocytes
      - Granules stains pink
        - Absorbs red (eosin) acid
        - Absorbs blue (methylene) base
- **GM-CSF** is needed for myeloid cell formation
- **IL-3, IL-5, G-CSF** is needed for myeloblast formation

Remember:
- Myeloid stem cell can divide into 3 cell lineages forming:
  - Red blood cells – **EPO** dependent
  - Platelets – **TPO** dependent
  - Granulocytic white blood cells and monocytes

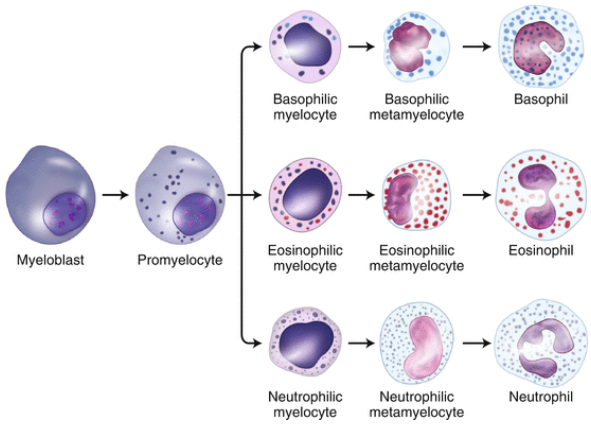

Figure 4. Granulocyte pathway [SpringerLink]

(B) AGRANULOCYTE PATHWAY

- Hemocytoblast → lymphoid stem cell → lymphoblast → prolymphocyte
- → Lymphocyte
  - → B-lymphocyte (mature)
  - → T-lymphocyte
- **IL-3, IL-5, AG-CSF** are needed for lymphoblast formation

(i) B-lymphocyte

- Functional
- Settles in lymphatic tissue
  - Spleen
  - Lymph nodes
  - MALT

(ii) T-lymphocyte

- Non-functional
- Goes to thymus gland (primary lymphoid organ) and matures into
  - Cytotoxic, T-helper or T-regulatory cells → then settles in lymphatic tissue
    - Spleen
    - Lymph nodes
    - MALT

(C) MONOCYTE PATHWAY

- Hemocytoblast → myeloid stem cell → monoblast → promonocyte → monocyte → leaves blood enters tissues → becomes macrophage
- **GM-CSF** is needed for monoblast pathway
- **IL-3, IL-5, AG-CSF** are needed for monoblast formation

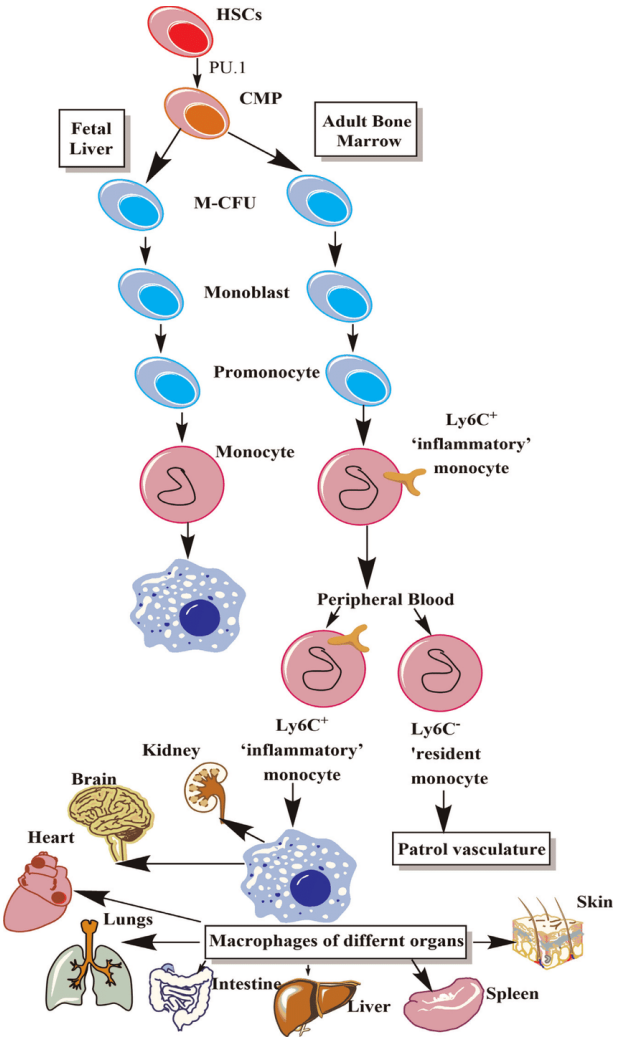

Figure 5. Monocyte pathway [ResearchGate]

IV) THROMBOPOIESIS

- Formation of platelets is called thrombopoiesis Figure 6

(A) LOCATION

(1) Sites

- Bone marrow (RED)
  - Skull
  - Sternum
  - Pelvis
  - Epiphyses of long bones

(B) CELLS PRODUCED

- Platelets

(C) GROWTH FACTORS/MOLECULES REQUIRED

(1) Thrombopoietin (TPO)

- Made by PCT cells of kidney and liver
- Goes to red bone marrow and stimulates platelet pathway Figure 7

(D) SEQUENCE OF DEVELOPMENT

- Platelet pathway
- Hemocytoblast → myeloid stem cell → megakaryoblast → promegakaryocyte → megakaryocyte → platelets

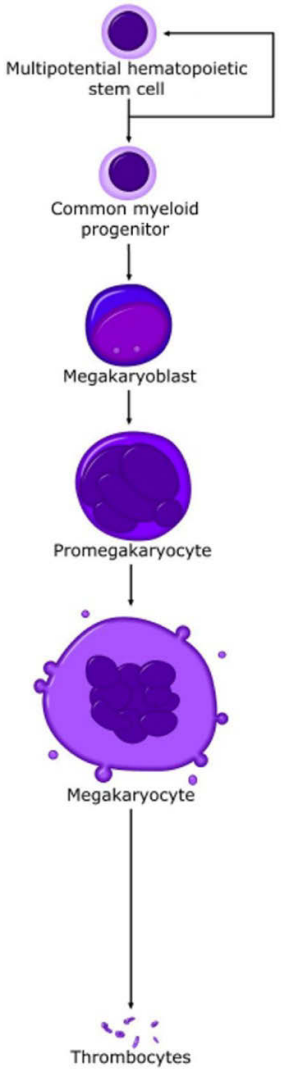

Figure 6. Stages of thrombopoiesis [Wikivet]

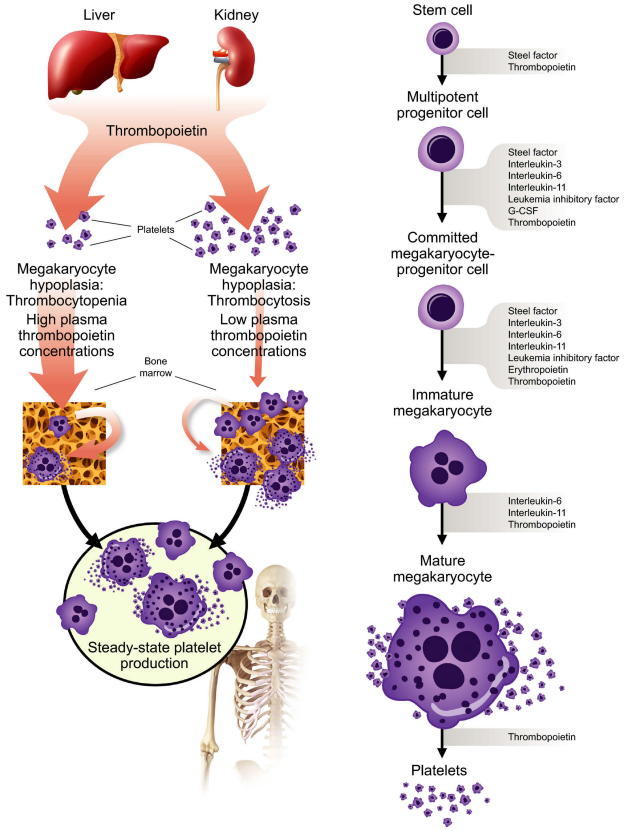

Figure 7. The actions of TPO [Wiley Online Library]

V) SUMMARY OF CELL FUNCTIONS

(1) Monocyte

(i) Functions in the tissue

- Phagocytosis
- Antigen presenting cells (APCs)

(ii) Types of macrophages

- Can be free in the lymphatic system or reside at several places Figure 6
  - Central nervous system
    - Microglia
  - Liver
    - Kupffer cells
  - Alveoli
    - Alveolar macrophages
  - Bones
    - Osteoclasts

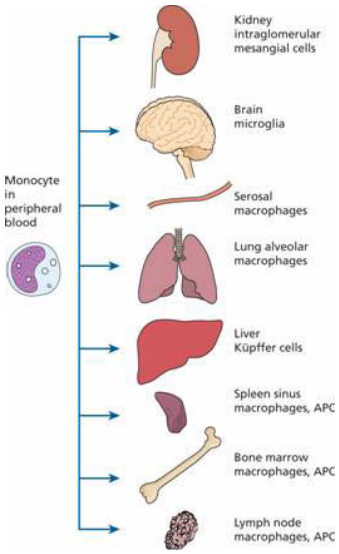

Figure 8. Macrophages in different organs [OncohemaKey]

(2) Basophil

- Granules can secrete
  - Heparin
    - natural anticoagulant
  - Histamines
    - regulate inflammation by vasodilation
      → increase blood flow

(3) Eosinophil

- Secrete very toxic proteins killing parasites/worms
  - Cationic peptide
  - Major basic protein
- Plays a role in type 1 hypersensitivity reaction

(4) Neutrophil

- Phagocytosis
- Oxidative/respiratory burst
  - Release free radicals
  - Take oxygen → superoxide → hydrogen peroxide
    - Hydroxide radical
    - Hypochlorous acid
  - Damage DNA, proteins and cell membrane

(5) Platelets

- Play a role in blood clots
  - Plug the blood vessel to prevent blood loss

(6) B-lymphocyte

- Plays a role in humoral immunity
  - Turns into plasma cells secreting antibodies

(7) T-lymphocyte

- Divide into lineages
  - T-helper cells
    - Help B-lymphocytes turn into plasma cells
    - React with APCs
  - Cytotoxic T-cells
    - Induce apoptosis of infected cells
      - Viral
      - Cancer cells

(B) MNEMONIC

- Differentiated white cell count (DWC)
  - Percentage of each when taking 1 mm^3 blood sample
- **N**ever **L**et **M**onkeys **E**at **B**ananas
  - **N**eutrophils – 50%-70%
  - **L**eukocytes – 20%-30%
  - **M**onocytes – 3%-8%
  - **E**osinophils – 2%-4%
  - **B**asophils – 0.5%-1%

VI) REVIEW QUESTIONS

1) **The common progenitor cell for granulocytes and monocytes which gives rise to the myeloblast**
   a. GM-CSF
   b. Eo-CSF
   c. GM-CFC
   d. A and C
   e. None of the above

2) **They proliferate in response to immunologic stimulation (e.g. allergic reactions)**
   a. Neutrophils
   b. Eosinophils//
   c. Basophils
   d. Monocytes
   e. Lymphocytes

3) **Stage when cell may be recognized specifically as a neutrophil, eosinophil, or basophil.**
   a. Myeloblast
   b. Promyelocyte
   c. Myelocyte//
   d. Metamyelocyte
   e. Stab Form

4) **Has a ground-glass appearance**
   a. Metamyelocyte
   b. Megakaryocyte
   c. Promyelocyte
   d. Myeloblast
   e. Promonocyte//

5) **Has a pale clear blue cytoplasm**
   a. Metamyelocyte
   b. Megakaryocyte
   c. Promyelocyte
   d. Myeloblast //
   e. Promonocyte

6) **Has an indented kidney shaped nucleus**
   a. Myeloblast
   b. Promyelocyte
   c. Myelocyte
   d. Metamyelocyte//
   e. Stab form

7) **Also called a "juvenile cell"**
   a. Myeloblast
   b. Promyelocyte
   c. Myelocyte
   d. Metamyelocyte//
   e. Megakaryoblast

8) **Has a partially constricted nucleus**
   a. Segmented form
   b. Band form//
   c. Metamyelocyte
   d. Myelocyte
   e. Promyelocyte

9) **Has a streaked chromatin pattern**
   a. Monocyte//
   b. Megakaryocyte
   c. Neutrophilic Myelocyte
   d. Mast cells
   e. Plasma cells

10) **Contain heparin, peroxidase, and histamine**
   a. Neutrophil
   b. Basophil
   c. Eosinophil
   d. Mast cells
   e. B and D//

CHECK YOUR ANSWERS

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HEMOSTASIS: COAGULATION CASCADE

Last edited: 10/24/2021

Hemostasis: Coagulation Cascade

Medical Editor: Mariel Antoinette L. Perez

OUTLINE

I) INTRODUCTION

(1) HEMOSTASIS

- Word Etiology
  - "hemo" – blood; "stasis" – stop
- Localized blood stopper
- Usually occurs when there's damage to blood vessels
  - E.g., ruptured, lacerated, leaking out
- A sequence of five steps

(2) NATURAL ANTI-COAGULATION OF BLOOD

- Before studying the process of hemostasis, it's important to understand what keeps the blood *naturally thin*
  - Prevents blood from becoming **thrombotic,** *coagulating on its own*, and *forming a **clot***
- There are three general layers to take note of:
  - *Endothelial cells*
    - secrete chemicals
      - **Nitric Oxide (NO)**
      - **Prostacyclin (PGI_2)**
  - *Subendothelial cells*
    - underneath the endothelial layer
    - made up of connective tissue, specifically collagen
    - collagen-rich layer
  - *Smooth muscle cells* with specific types of receptors
    - nociceptors = pain receptors

(1) Platelet Inactivation

- There are two things in the blood: plasma and cells
  - Cells (or *formed elements*) such as White Blood Cells (WBCs), Red Blood Cells (RBCs), and platelets
  - **Platelets**
    - Microscopic (tiny), cytoplasmic fragments
    - Derived from megakaryocytes
    - Naturally **inhibited by NO and PGI2**
      - keeps **platelet inactive** to prevent it from binding onto the surface of the endothelial cell

(2) Heparin Sulfate

- Glycosaminoglycan present on the membrane
- **Natural anti-coagulant**
- Binds and activates protein **Anti-Thrombin III (ATIII)**
  - Degrades and inactivates clotting factors **II, IX, X**
    - Clotting factors are naturally just circulating in the bloodstream

(3) Thrombomodulin

- Binds with protein called **Thrombin (Factor II/ FII)**
  - **Activates Protein C**
    - Degrades and *inactivates factors **V** and **VIII***

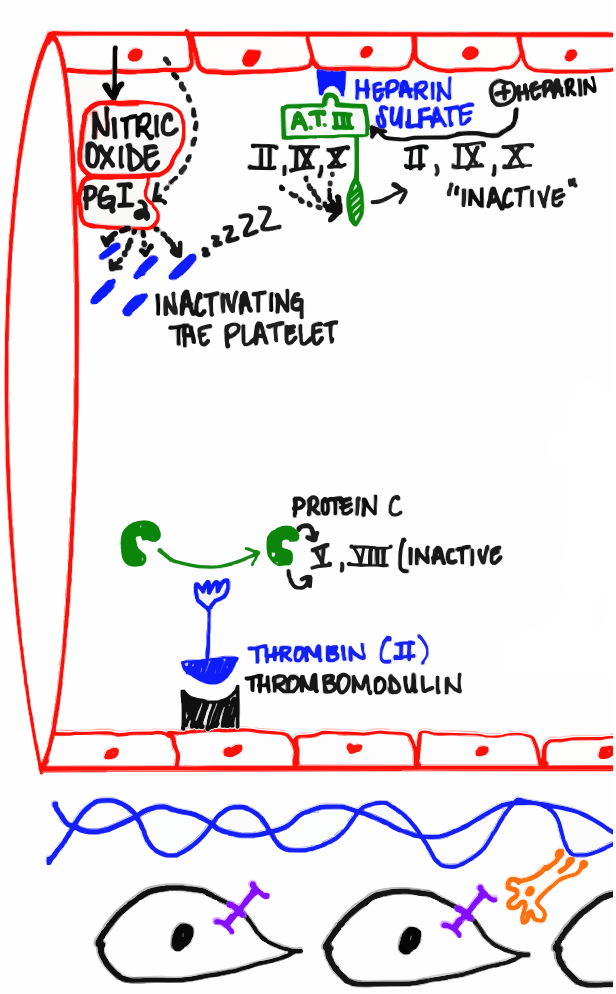
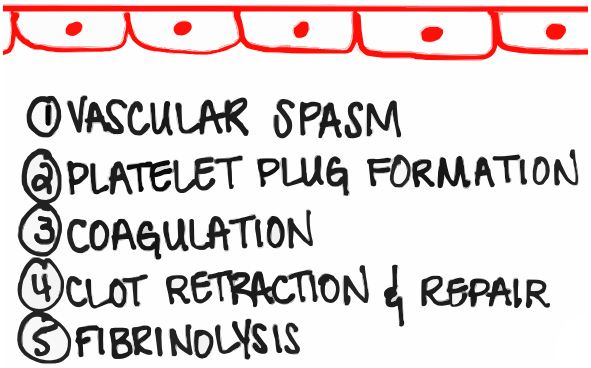


Figure 1 Natural Nanti coagualtion mechanisms

II) FIVE STEPS OF HEMOSTASIS



(1) VASCULAR SPASM

(1) Trigger

- injured blood vessel → endothelial damage
  - May also cause damage to the underlying tissue
  - Blood may leak out and decrease blood volume

(2) Purpose

- Prevent blood loss from occurring by contracting or constricting blood vessels

(3) Mechanism

(i) Endothelin

- Secreted by injured endothelial cells
- binds on to receptor on **smooth muscle**
- activates intracellular PIP2-Calcium mechanism
- smooth muscle contracts → triggers vessel vasoconstriction → decreases blood vessel diameter → prevents blood loss

(ii) Myogenic Mechanism

- Direct contact or injury to smooth muscle causes smooth muscle contraction

(iii) Nociceptor Activation

- Inflammatory chemicals are released when there's inflammation
  - E.g., histamine, leukotrienes, prostaglandins,
- These chemicals stimulate the nociceptors
- Nociceptors (pain receptors) will initiate pain
- Pain reflex induces vasoconstriction

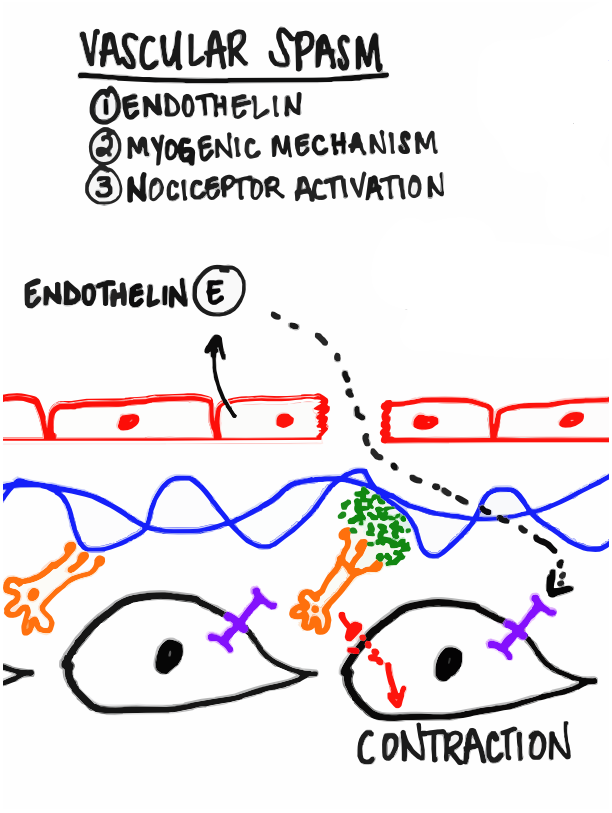


Figure 2 Vascular Spasm

(2) PLATELET PLUG FORMATION

- With the endothelial cells damaged,
  - There will be a **decreased release of NO and PGI_2**
    - Platelets will not be inactivated
    - Allow platelets to attach to endothelium
  - Damaged heparin sulfate will not be able to keep clotting factors inactivated
  - Damaged thrombomodulin will not be able to activate protein C → cannot keep FV and FVIII inactivated

(1) Platelet Activation

- Platelets are activated when *GP1b binds with vWF*
  - **GP1b (glycoprotein-1b)**
    - Platelet receptor that specifically binds to vWF
  - **von Willebrand Factor (vWF)**
    - secreted by injured endothelial cells

(2) Platelet chemical release

- Once activated, will release the following
  - Adenosine Diphosphate (ADP)
  - Thromboxane A2 (TXA2)
  - Serotonin (5-hydroxytryptamine or 5-HT)

(3) Platelet Aggregation

- Platelets have receptors on their membrane that specifically bind with ADP and TXA2
- ADP & TXA2 stimulates platelets to come and aggregate at area of injured vessel
- Platelets bind with other platelets via their **GP2b/3a**, with **fibrinogen** bridging them together

(4) Vascular Spasm Effect Enhancement

- TXA2 and serotonin bind to the smooth muscle
  - Cause contraction
  - Triggers ↑vasoconstriction of injured blood vessels
  - Enhances the vascular spasm effect

(5) Clinical Significance

- Aspirin: ↓TXA2 release
- Clopidogrel, Prasugrel, Ticagrelor: ↓ADP release
- Abciximab: inhibits GP2b/3a inhibitors
- Von Willebrand Disease: ↓VWF production

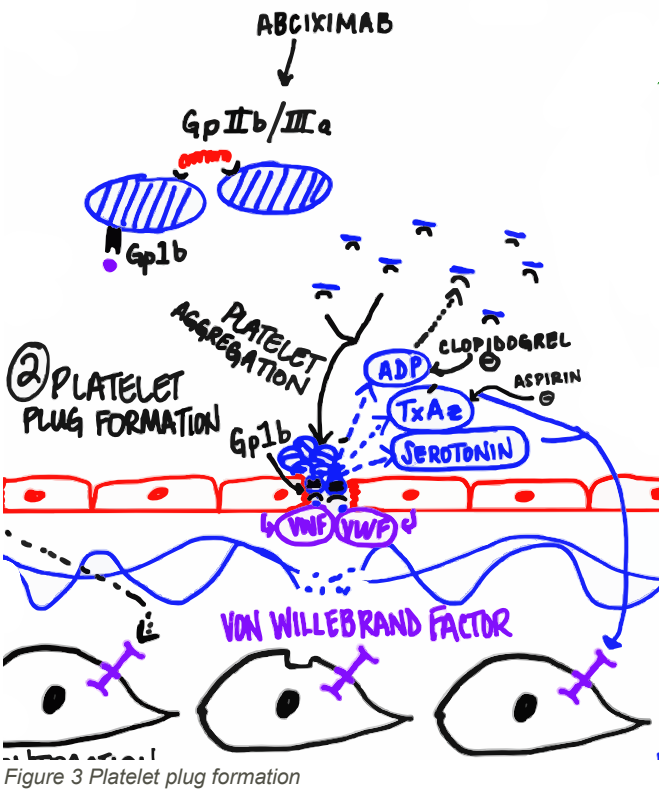


Figure 3 Platelet plug formation

(3) COAGULATION CASCADE

- **Intrinsic pathway**
  - **Independent** of the extrinsic pathway
    - For example, someone's blood in a test tube is not heparinized (no heparin coating)
      - Glass has rough, charged surface → hence, XIIa from the intrinsic pathway gets activated
    - This shows that the intrinsic pathway can occur in a test tube independent of the extrinsic pathway.
  - Takes 4-6 minutes
- **Extrinsic pathway**
  - **Dependent** on some of the factors and proteins within the intrinsic pathway
  - Takes 30 seconds

Note: An "a" after the roman numeral indicates an activated factor.

(1) Intrinsic Pathway

- Liver constantly creates clotting proteins that are normally inactivated while circulating in the blood
- Activated platelets express phosphatidyl serine groups on their membrane, causing a **negative charge**
- Negative charge will interact with and activate Factor XII (Hageman Factor)
  - XII → XIIa
- XIIa activates XI → FXIa
- XIa activates IX → IXa
- IXa forms a complex with VIIIa
  - Complexation requires PF3 and Ca^{2+}
- VIIIa-IXa activates X → Xa

(2) Common Pathway

- X → Xa is the start of the common pathway
- Xa, Va, and Ca^{2+} will activate **prothrombin activator**
  - converts prothrombin (II) to thrombin (IIa)
- Thrombin reacts in two ways:
  - Links together Fibrinogen (I) into Fibrin (Ia)
    - Fibrinogen is soluble
    - Fibrin is *insoluble* in the plasma
      - Helps turn liquid blood into a jelly-like substance to slows down blood flow in the area and prevent loss of RBCs
  - Activates XIII → XIIIa
    - Requires Ca^{2+}
- **Factor XIIIa**
  - Also known as *Fibrin Stabilizing Factor*
  - Crosslinks fibrin stands together
- **Crosslinked fibrin**
  - Creates a **fibrin mesh**
    - Mesh will hold down the platelet plug in place
    - Mesh prevents platelets from dislodging and going to different areas to cause an embolism
  - Thickens the blood passing through the area to slow down the blood flow and prevent blood loss

(3) Extrinsic Pathway

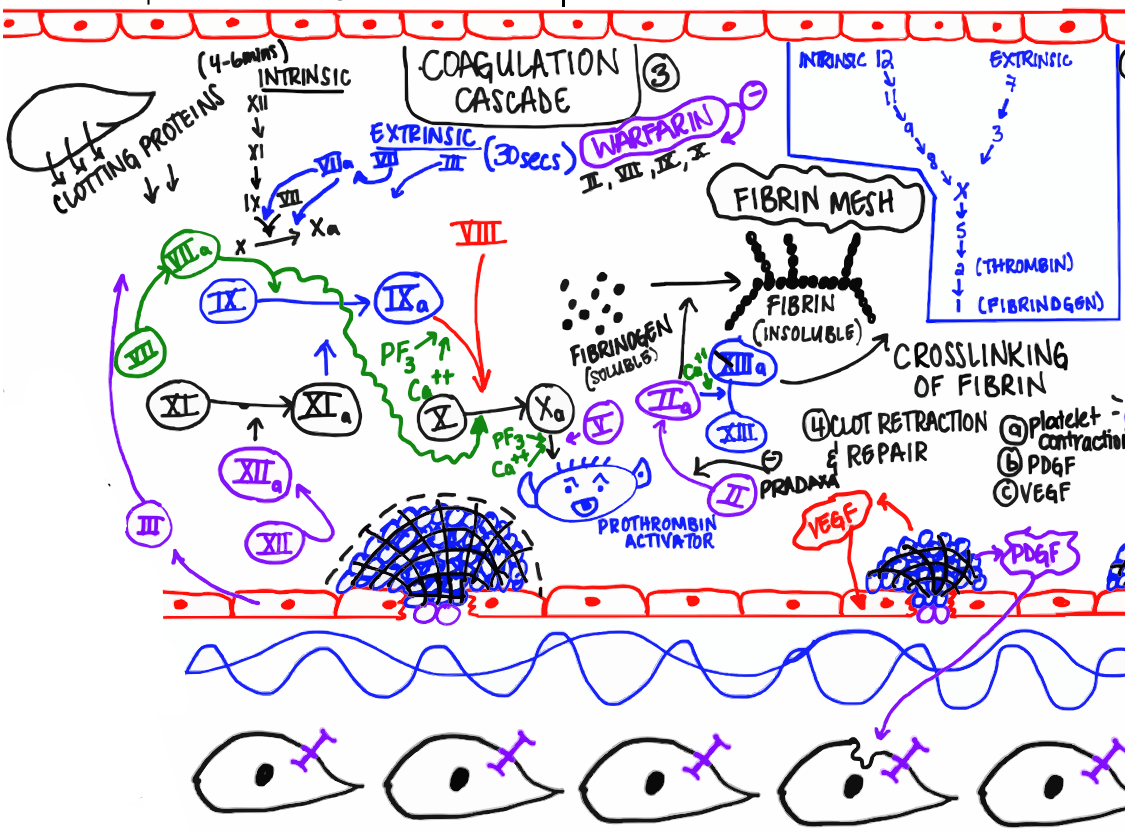
- Blood vessel injury triggers release of **Tissue factor (Factor III)**
- Factor III activates Factor VII → VIIa
  - requires Ca^{2+} and PF4
- VIIa can activate IX → IXa
- VIIa can converge into or stimulate the common pathway
  - Requires Ca^{2+} and PF4

Note: ***Tip for Remembering the Coagulation Cascade***

- X marks the spot in the middle = Factor X
- Left (intrinsic pathway) count downwards
  - 12 → 8 (skip 10)
- Right (extrinsic pathway)
  - 3 + 7 = 10
- Common Pathway
  - 5 x 2 x 1 = 10

(4) Clinical Significance

- Hemophilia A⟶↓in factor VIII
- Hemophilia B⟶↓in factor IX
- Hemophilia C⟶↓in factor XI
- Heparin, Factor X inhibitors (Rivaroxaban)⟶↓factor X
- Heparin, Factor II Inhibitors (Dabigatran)⟶↓thrombin or also known as Factor II
- Warfarin⟶↓ formation of Thrombin, Factor VII, Factor IX, Factor X



(4) CLOT RETRACTION & REPAIR

(1) Platelet Contraction

- Platelet contraction is stimulated once the platelet plug is anchored to injured vessel wall by fibrin mesh
- Platelets contains contractile proteins
  - Actin and myosin7
- When platelets contract, they pull the damaged edges of the injured blood vessel close to each other
- This squeezes some serum out of the injured vessel

(2) Platelet-Derived Growth Factor (PDGF) Secretion

- If smooth muscle cells are damaged, PDGF triggers mitosis or proliferation of smooth muscle cells
- Damage to connective tissue, PDGF forms connective tissue patches to regenerate collagen fibers

(3) Vascular Endothelial Growth Factor (VEGF) Secretion

- Regenerates the new endothelial lining
- The blood vessel then starts to go through healing & remodeling

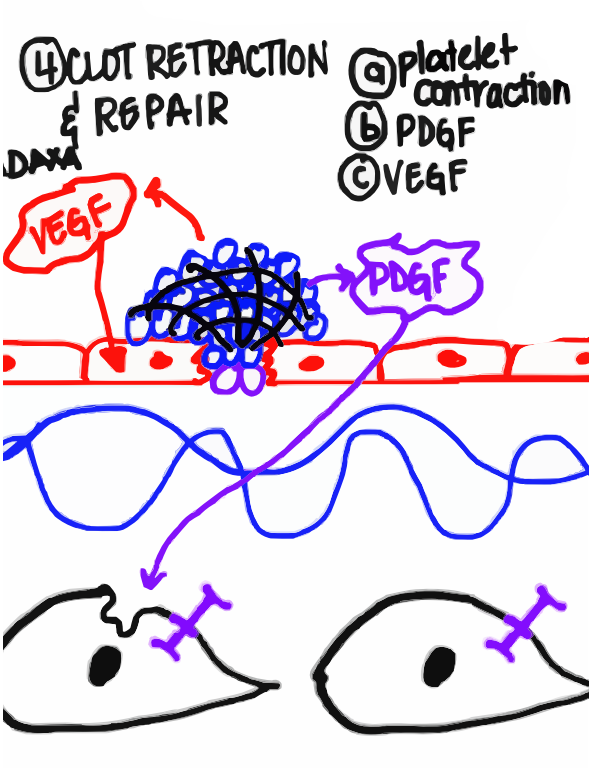


Figure 4 Clot Retraction

(5) FIBRINOLYSIS

(1) Breaking Down Fibrin Mesh

- There's a need to get rid of the clot
  - The clot may be big enough that it could occlude blood flow and possibly cause ischemia
- Endothelium expresses protein **Tissue Plasminogen Activator (TPA)**
- TPA converts **Plasminogen into Plasmin**
  - Plasminogen is naturally occurring in the bloodstream
- Plasmin breaks down **Fibrin mesh** into *Fibrinogen* and *Fibrin degradation products* like D-Dimer
  - This process recanalizes the clotted vessel

(2) Clinical Significance

- TPA Drugs
  - ↑Plasminogen to Plasmin
    - Increased rate of blood clot breakdown
  - Given to patient who have stroke or some type of ischemic attack within hours
- Elevated D-Dimers can be indicative of blood clots and inflammation
  - Specific blood tests can be done to determine if patient has had some type of clot formation
- Antifibrinolytics (TXA)→↓Plasminogen to plasmin→↓break down of blood clot and stabilizes clot

Figure 5 Fibrinolysis

III) APPENDIX

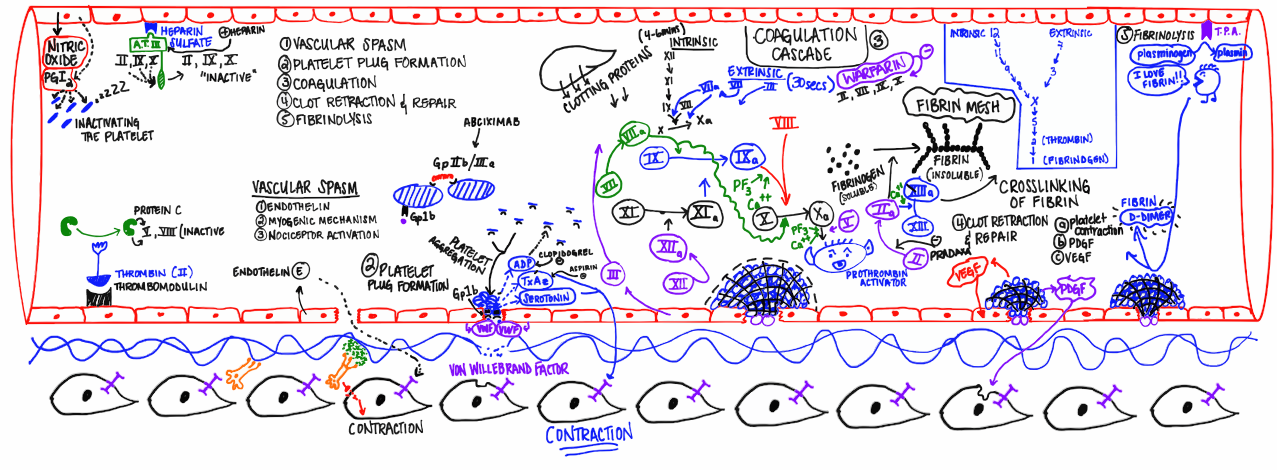


Figure 6. Summary of Hemostasis

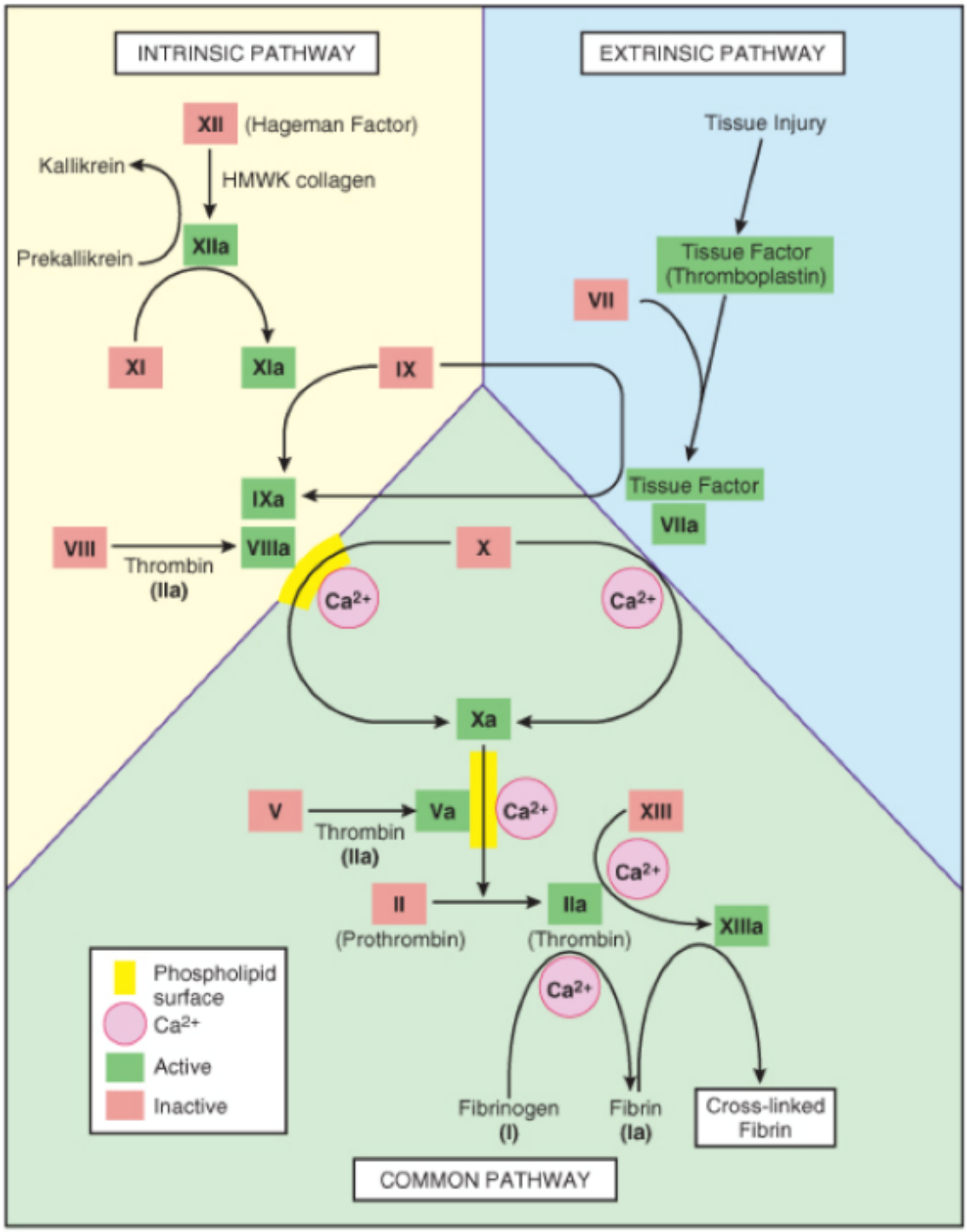


Figure 7. Coagulation Cascade

IV) REVIEW QUESTIONS

1) Which is not a natural way of the body to prevent blood from becoming thrombotic?

a) Heparin Sulfate
b) Nitric Oxide
c) Thromboxane
d) Prostacyclin

2) Which of the following is more stable?

a) Fibrinogen
b) Fibrin
c) They are equally stable

3) What is the third step of hemostasis?

a) Platelet Plug Formation
b) Coagulation Cascade
c) Vascular Spasm
d) Fibrinolysis

CHECK YOUR ANSWERS

V) REFRENCES

- Le T, Bhushan V, Sochat M, Chavda Y, Zureick A. First Aid for the USMLE Step 1 2018. New York, NY: McGraw-Hill Medical; 2017
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BLOOD TYPING

Last edited: 12/9/2021

Blood Typing

Medical Editor: Mariel Antoinette L. Perez

OUTLINE

I) BLOOD TYPE DONATION

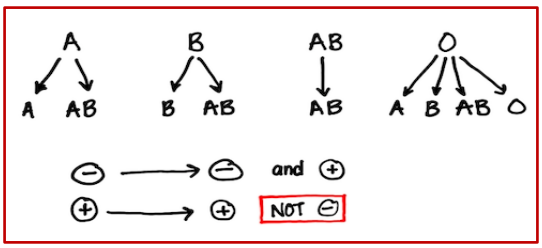

Figure 1. Blood Type Compatible Donation

- In Figure 1, the arrow denotes "can donate to"
- ABO Typing
  - Type A can donate to A and AB
  - Type B can donate to B and AB
  - Type AB can only donate to AB
  - Type O can donate to all blood types A, B, AB, and O
- Rh Typing
  - Rh negative
    - can donate to both positive and negative
  - Rh positive
    - can only donate to Rh positive
    - can't donate to Rh negative

II) ANTIGENS AND ANTIBODIES

	Group A	Group B	Group AB	Group O
Red blood cell type	A	B	AB	O
Antibodies in plasma	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens in red blood cell	A antigen	B antigen	A and B antigens	None

Figure 2. ABO Blood Types and Their Corresponding Antigens and Antibodies

(A) ANTIGENS

- Surface markers on red blood cells that let the immune system know what your blood type is
- All other blood types that's not yours is considered foreign
- As seen in **Figure 2**
  - **Type A** blood has A antigen
  - **Type B** blood has B antigen
  - **Type AB** blood has both A and B antigens
  - **Type O** blood has neither A nor B antigens

Note: To make it easier to remember, the "O" in Type O is empty because there neither antigen is present!

(B) ANTIBODIES

- Found in the plasma or circulation
- Made by our immune system
- Protects blood from incompatible blood
- As seen in **Figure 2**
  - **Type A** blood has Anti-B antibodies
  - **Type B** blood has Anti-A antibodies
  - **Type AB** blood has neither antibodies
  - **Type O** blood **has both** Anti-A and Anti-B antibodies

(C) ANTIGEN-ANTIBODY REACTION

- Three different dishes per plate or scenario
- Each dish is coated with antibodies
  - 1st dish is coated with Anti-A antibodies
  - 2nd dish is coated with Anti-B antibodies
  - 3rd dish is coated with Anti-Rh antibodies
- **Agglutination**
  - Clumping of red blood cells
  - Produced when blood with a specific antigen interacts with its respective anti-antibody
    - A-antigen reacts with Anti-A antibodies
    - B-antigen reacts with Anti-B antibodies
    - Rh-antigen reacts with Anti-Rh antibodies

Note: Anti-Rh is the same as Anti-D.

III) BLOOD TYPING COMPATIBILITY

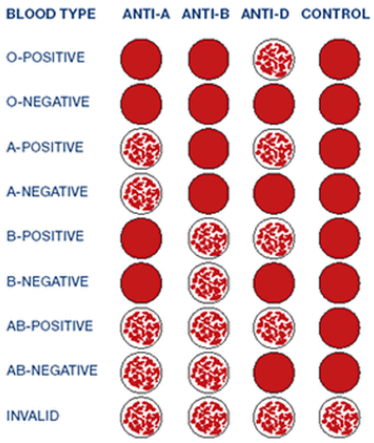

Figure 3. How to Read Blood Typing Results

- Figure 3 shows a summary of agglutination reactions for the different blood types
- **Blood Type O** can be donated to all ABO blood types.
  - **Type O^-** is the **universal donor**.
    - They have all the antibodies in their plasma
      - Other blood types can benefit/receive.
      - All the antibodies in their plasma will attack other blood types
    - Great donor, terrible recipient.
  - **Type O^+** can ***donate to all positive*** blood types
    - *Remember: Rh^+ can't donate to Rh^-*
- **Blood Type AB** can receive all ABO blood types.
  - **Type AB^-** can ***receive from all negative*** blood types
    - *Remember: Rh^+ can't donate to Rh^-*
  - **Type AB^+** is the **universal recipient.**
    - can receive from ALL blood types
    - Blood Type or Rh typing does not matter

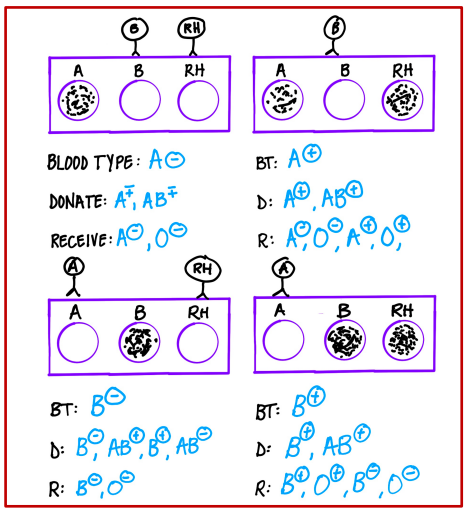

Figure 4. Blood Typing 1

- In Figure 4,
  - Top-Left
    - **Blood Type A⁻**
      - Can donate to A (+/-), AB (+/-)
      - Can receive A⁻, O⁻
  - Top-Right
    - **Blood Type A⁺**
      - Can donate to A⁺, AB⁺
      - Can receive A (+/-), O (+/-)
  - Bottom-Left
    - **Blood Type B⁻**
      - Can donate to B (+/-), AB (+/-)
      - Can receive B⁻, O⁻
  - Bottom-Right
    - **Blood Type A⁺**
      - Can donate to A⁺, AB⁺
      - Can receive B (+/-), O (+/-)

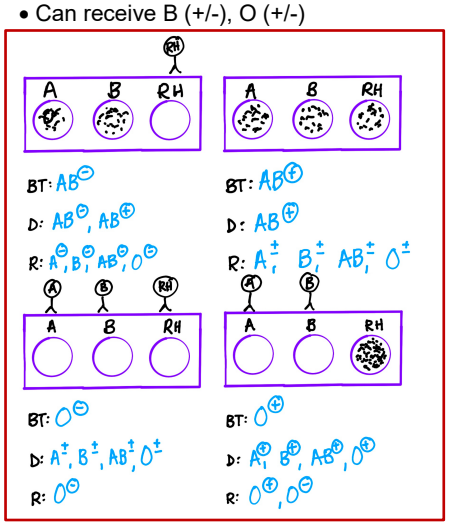

Figure 5. Blood Typing 2

- In Figure 5. Blood Typing 2,
  - Top-Left
    - **Blood Type AB⁻**
      - Can donate to AB (+/-)
      - Can receive A⁻, B⁻, AB⁻, O⁻
  - Top-Right
    - **Blood Type AB⁺**
      - Can donate to AB⁺
      - Can receive A (+/-), B (+/-), AB (+/-), O (+/-)
  - Bottom-Left
    - **Blood Type O⁻**
      - Can donate to A (+/-), B (+/-), AB (+/-), O (+/-)
      - Can receive O⁻ only
  - Bottom-Right
    - **Blood Type O⁺**
      - Can donate to A⁺, B⁺, AB⁺, O⁺
      - Can receive O (+/-)

IV) CLINICAL SIGNIFICANCE

(A) HEMOLYTIC DISEASE OF THE NEWBORN

(1) Definition

- Also called **Erythroblastosis fetalis**
- One of the dangerous mismatched transfusions
- Endogenous: happens within the person's body
- Usually not a problem for the first birth
  - But first birth triggers it
  - Sometimes not a problem for the second birth; but generally, the risk increases with every birth.

(2) First Fetus/Birth

- **Mother: Rh⁻**
  - Has no Rh antibodies
    - Unless she has had some type of mismatched transfusion in the past
- **Fetus: Rh⁺**
  - It has an Rh antigen on its membrane
- In the first birth, when the placenta breaks away from the uterus, some of the blood of the fetus leaks away and mixes with the mother's blood
  - **Fetal RBCs in mother's circulation triggers immune system to make Anti-Rh antibodies**

(3) Following Birth/s

- Rh⁻ mother has another fetus with Rh⁺ RBCs
- The Anti-Rh antibodies that the mother's immune system produced during the 1st birth can cross placenta and attack fetus RBCs
- Fetal RBCs undergo agglutination and hemolysis

(4) Effect on Affected Baby

- Baby will have hemolytic anemia
- Decreases baby's RBCs
- Increases bilirubin levels to the maximum
- May cause kernicterus and mental retardation

(5) Treatment

- This can be recognized during pregnancy
- Diseases can be prevented by giving **Rhogam**
  - Anti-Rh antibody drug
  - Binds to the Anti-RH antibodies and renders them ineffective

V) APPENDIX

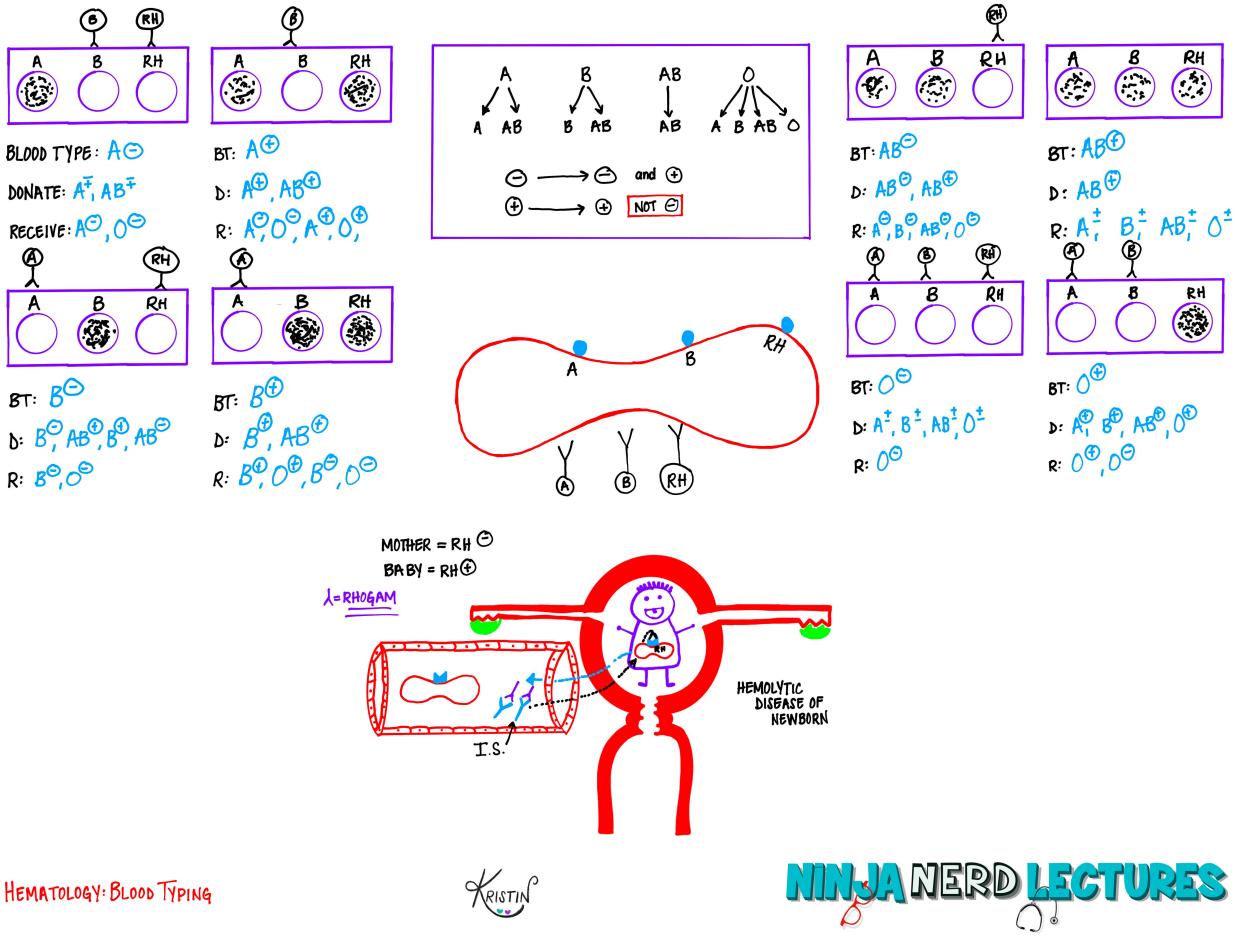

Figure 6. Summary of Blood Typing Lecture

VI) REVIEW QUESTIONS

1) Which of the following is considered a universal donor?

a) Type AB^+
b) Type AB^-
c) Type O^+
d) Type O^-

2) Which of the following is considered a universal receiver?

a) Type AB^+
b) Type AB^-
c) Type O^+
d) Type O^-

3) Assuming that the following are valid results, identify the blood type:

a)
b)
c)
d)

CHECK YOUR ANSWERS

VII) REFRENCES

- Le T, Bhushan V, Sochat M, Chavda Y, Zureick A. First Aid for the USMLE Step 1 2018. New York, NY: McGraw-Hill Medical; 2017
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