



Pathology mind maps for midterm

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Lecture #1

Red Blood Cell Disorders

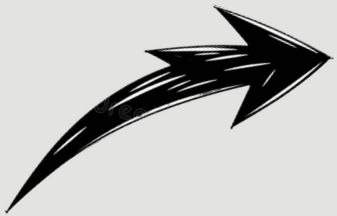
ERYTHROCYTOSIS

increased **RBCs number**.

POLYCYTHEMIA

Increase in **total RBC mass** above normal range.

Mostly, erythrocytosis is related to polycythemia



a Chronic disease

Polycythemia

Types

Absolute polycythemia

true increase in RBC mass, secondary to **increased BM (bone marrow) production**.

Relative polycythemia

secondary to decreased plasma volume (water deprivation, severe diarrhea, diuretics) .

Primary

it is mainly a neoplastic disease
"neoplasm in the bone marrow"

autonomous high bone marrow production (the problem is in the bone marrow itself produces a high amount of cells without any need) (polycythemia vera), **erythropoietin is low** (due to negative feedback as the bone marrow is producing a large number of RBCs).

Polycythemia Vera → an absolute primary polycythemia

- a type of: Myeloproliferative neoplasm . Myelo refers to the bone marrow
- Mutation in tyrosine kinase **JAK2** in bone marrow stem cells (99% of patients have this mutation)
 - JAK2 Normally acts in the signaling pathway of erythropoietin receptor and other growth factor receptors
 - Hematopoietic cells become less dependent on growth factors
 - **panmyelosis(pan=all):-** Excessive proliferation of erythroid(RBCs), myeloid cells (WBCs) and megakaryocytes.
 - Erythrocytosis is most prominent, results in polycythemia.
 - **Splenomegaly is common !!** As neoplastic cells migrate to the liver and spleen and proliferate there.

Secondary

NO splenomegaly 🚫

systemic hypoxia → **high erythropoietin** → increased erythropoiesis (synthesis of RBCs)

causes

Adaptive

- living in high altitude
- cyanotic heart disease
- chronic pulmonary diseases eg: sleep apnea

Paraneoplastic

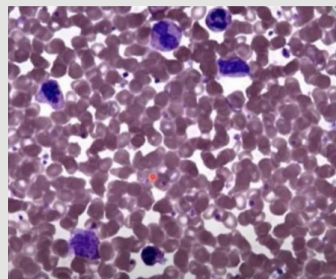
- renal cancer
- liver cancer

Surreptitious (blood doping): endurance athletes

Alcohol

- frequent urination
- depressed respiration

Smoking



Peripheral blood smear in polycythemia : packed red blood cells

Advanced stages of polycythemia

Spent phase(advanced): occurs after an interval of 10 years of symptoms, BM becomes fibrotic, hematopoiesis shifts to spleen, spleen becomes the main site for hematopoiesis leading to splenomegaly)

Blast crisis: transformation to acute myeloid leukemia (rare) by gaining more mutations.

Symptoms of polycythemia (general)

Plethora/ cyanosis

- Plethora is redness of skin especially the face.
- cyanosis is a bluish color of the skin due to the deoxygenated blood

Headache and dizziness (from hypertension) due to increased blood mass and in some cases this may lead to heart failure

Slow circulation and hyperviscosity (due to the high cellularity) cause cyanosis, blurred vision retina is involved(abnormal circulation to retina) leading to blindness, tissue ischemia

Thrombosis, or bleeding (disturbed function of vWF Von Willebrand factor is a clotting factor)

Additional Symptoms in polycythemia Vera

Pruritus (aquagenic) (as leukocytosis occurs, histamine is released in large amounts, it appears as intense itching after a hot shower that's why it is aquagenic)

Peptic ulcer (also due to histamine release)

Secondary gout (arthritis, kidney stones, tophi (solid crystals in the tissue)). due to high turnovers of RBCs which results in higher-than-normal uric acid production .
BM with hypercellularity (panmyelosis) → cells die more frequently → more DNA will be scattered → turns into purine that turns into uric acid.

Laboratory findings of polycythemia

High hemoglobin concentration (>16.5 g/dL in men, 16 in women) and high hematocrit (> 49% in men, 48% in women)

High RBCs count (erythrocytosis).

These tests might be masked if iron deficiency develops .

Additional Laboratory findings in polycythemia Vera

Leukocytosis and thrombocytosis are common.

JAK2 mutation in 99% of patients in molecular tests.

Low erythropoietin level negative feedback

Hypercellular bone marrow with panmyelosis. We take a biopsy from BM.

Lecture #2

ANEMIA

Definition

Reduction of oxygen carrying capacity of blood, secondary to decrease in red cell mass (the blood is no longer capable of delivering oxygen)



Leads to **tissue hypoxia**

In acute anemia

production can increase by **5x or more** in healthy people, Erythropoietin production can increase RBC production 5 folds in acute anemia, it's a potent hormone and in healthy patients the compensation is fast and complete, so we have good reserve and efficiency in the production of RBCs in acute anemia

In severe anemia

anemia is persistent for a long time, so erythropoietin is high for along time too

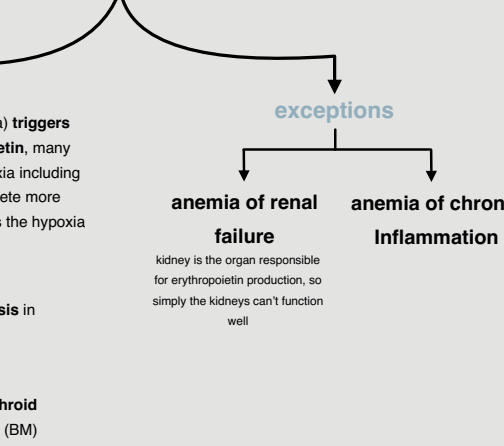
causes extramedullary hematopoiesis in **secondary hematopoietic organs** "reticuloendothelial organs" (spleen, liver, and lymph nodes), here we have production of RBCs "hematopoiesis" outside the bone marrow

RBC indices

- Can be
- directly measured
 - automated

- Slight variation is present due to
- Differences btw labs**
 - geographic areas**
high altitude, normally there is higher Hb conc.
 - Sex**
have higher Hb concentrations due to androgens, while females may have lower levels during menstruation
 - race**
African populations may have lower Hb levels compared to others due to genetic factors
 - mobility status**
less physical activity like elderly can be associated with lower Hb concentrations

Anemia and erythropoietin



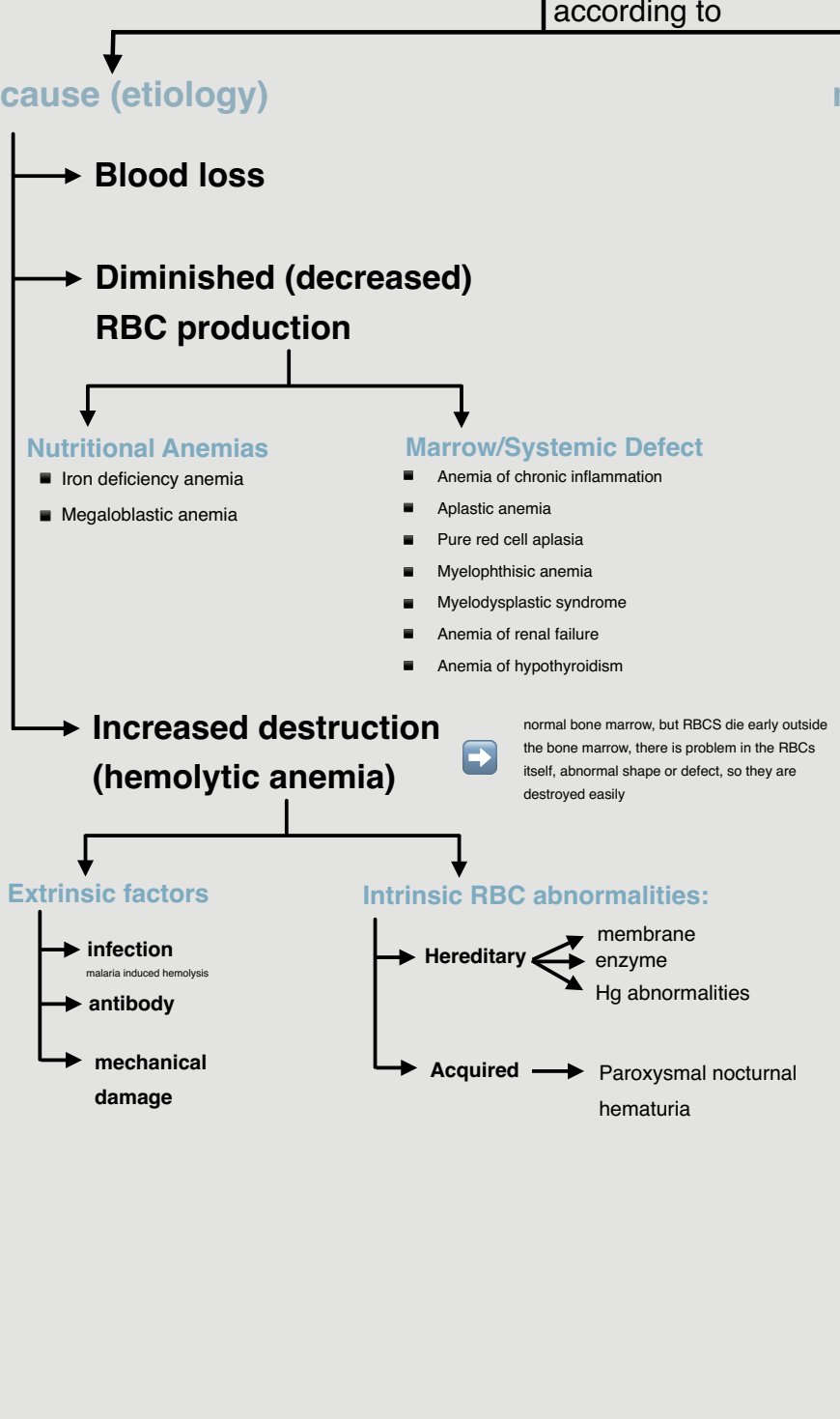
Reticulocyte count

- high reticulocyte count**
increased destruction of red blood cells, prompting the bone marrow to produce more reticulocytes (immature red blood cells that doesn't have nucleus)
In **hemolytic anemia**
- Low reticulocyte count**
bone marrow fails to produce an adequate number of red blood cells, resulting in **In aregenerative anemia**

	Units	Men	Women
Hemoglobin (Hb)	g/dL	13.2–16.7	11.9–15.0
Hematocrit (Hct)	%	38–48	35–44
Red cell count	$\times 10^6/\mu\text{L}$	4.2–5.6	3.8–5.0
Reticulocyte count	%	0.5–1.5	0.5–1.5
Mean cell volume (MCV)	fL	81–97	81–97
Mean cell Hb (MCH)	pg	28–34	28–34
Mean cell Hb concentration (MCHC)	g/dL	33–35	33–35
Red cell distribution width (RDW)		11.5–14.8	

*Reference ranges vary among laboratories. The reference ranges for the laboratory providing the result should always be used in interpreting a laboratory test.

Classification of anemia



pathophysiology of red blood cell destruction

Clinical features of anemia

- All anemia cause Hypoxia (Systemic Hypoxia)
- Fatigue due to hypoxia.
- Headache due to the hypotension
- Dizziness due to hypotension
- Pallor obvious when examining the conjunctiva, nail-beds, sclera of the eye.

Adaptive changes

- (with prolonged hypoxia)
- Tachycardia.
- Tachypnea (faster respiration to bring more oxygen)
- Increased red cell 2,3-diphosphoglycerate. Facilitates the delivery of O2 (This molecule binds to hemoglobin and, in doing so, effectively displaces oxygen molecules, making it easier for hemoglobin to unload oxygen where it's needed most)
- If the patient has heart or lung diseases, symptoms will be worse

Cinical symptoms in special types of anemia

- Chronic hemolytic anemia**
 - jaundice
 - pigmented gall bladder stones
 - red urine
- Extramedullary hematopoiesis**
splenomegaly, hepatomegaly
- Thalassemia major and sickle cell anemia**
growth retardation, bone deformity (prominent cheeks and jaw), **secondary hemochromatosis** (damage to heart, endocrine glands) Due to prolonged exposure to high levels of erythropoietin

Prolonged exposure to erythropoietin can also suppress the **hormone hepcidin**, which plays a crucial role in blocking iron absorption. As a result, patients may absorb excessive amounts of iron from their diet, and since the body has limited mechanisms to excrete iron (primarily through the normal shedding of epithelial cells), it can accumulate in tissues, including the heart (leading to cardiomegaly and potentially heart failure) and endocrine glands, causing physical damage and in this phase it's usually fatal (secondary hemochromatosis). These patients do not grow normally due to hypoxia, have enlarged abdomen (enlarged spleen and liver : if you take a tissue biopsy they'll look like bone marrow and you'll see Megakaryocytes, myeloid, erythroid cells, They also have a distinctive bone shape : short structure, special skull shape)

Anemia of blood loss

Anemia of acute blood loss

- normochromic, normocytic, with reticulocytosis (bone marrow is active)**
- Symptoms are related to decreased intravascular volume (**hypovolemia and hypotension**)
- If loss is >20% of blood volume, patient might have hypovolemic shock and die We worry the most of shock so we could give fluids and depend on bone marrow to compensate the RBCs loss
- If a patient survived blood loss, the body responds by shifting fluid from interstitial to intravascular space, causing **dilutional anemia and worse hypoxia** (stays 2-3days)
- Dilutional anemia occurs when a patient experiences bleeding that is subsequently stopped. For example, if a patient initially had a hemoglobin (Hb) concentration of 14 g/dL before bleeding, and it decreased to 10 g/dL due to the bleeding, it's not uncommon to find that the Hb concentration may decrease further to 8 g/dL after a few days. This decline does not necessarily indicate ongoing bleeding but is a result of a normal physiological response – the body shifts fluids from surrounding tissues into the bloodstream to restore blood volume, leading to a dilution effect on Hb concentration.
- **Erythropoietin** secretion is stimulated, activating BM erythropoiesis (needs 5-7days)
- In internal hemorrhage, **iron** is reclaimed from extravasated RBCs and used again in erythropoiesis
- In external and GIT hemorrhage, **iron** is lost (iron deficiency), which complicates anemia

Anemia of chronic blood loss

- Results in iron deficiency, anemia appears hypochromic and microcytic, low reticulocytes (decreased production)**
- Rises from the gradual loss of blood in small amounts over an extended period
- Occurs when the rate of RBC loss exceeds regeneration
- Mostly occurs in gastrointestinal diseases (Peptic ulcers, hemorrhoids, colon cancer, small bowel inflammation), also in excessive menstruation

Lecture #3

Classification of anemia

according to

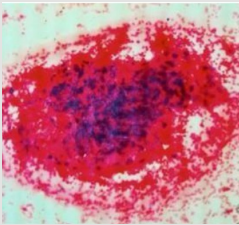
cause (etiology)

- Blood loss
- Increased destruction (hemolytic anemia)
- Diminished (decreased) RBC production

morphology blood film

- Size
- Color
- Shape

Also called anemia of chronic disease (old name)
Seen in chronic infections, cancer, chronic immune diseases
- There are chronic non-inflammatory diseases such as Alzheimer's and Parkinson's disease, those patients do not suffer from anemia, so it appears in chronic inflammatory diseases not only chronic disease.
Common in hospitalized patients
High IL-6→high hepcidin →blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages this keeps the iron inside macrophages in the BM in the form of hemosiderin). Also suppress erythropoietin secretion from kidneys. (exception! Like renal anemia)
NOTE Hepcidin is the normal antagonist for erythropoietin



o Similar to IDA: **serum iron is low**
o RBCs: normal morphology, then **hypochromic microcytic**
o Reticulocytes ↓ due to low erythropoietin
In contrast:
o Bone marrow iron stores ↑ In certain theory: The benefit of this is that iron is stored in macrophages in the BM, preventing the iron from reaching harmful bacteria as a form of protection for the body
o Serum ferritin ↑ one of the acute phase reactants

LABORATORY FINDINGS

BONE MARROW FAILURE

MYELOPHTHISIC ANEMIA

ANEMIA OF CHRONIC INFLAMMATION

APLASTIC ANEMIA (AA)

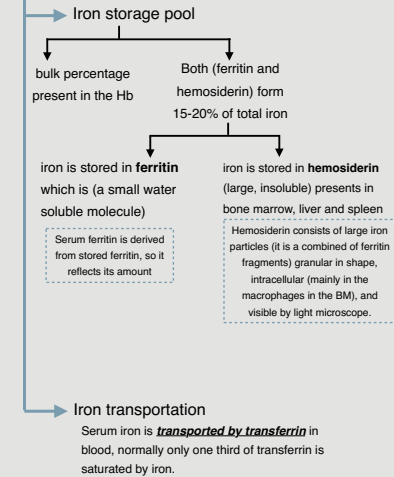
Nutritional Anemias

IRON DEFICIENCY ANEMIA (IDA)

- Most common type of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries, so it is more common in low resources countries

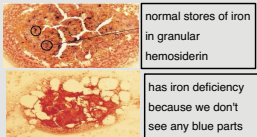
MEGALOPLASTIC ANEMIA

IRON METABOLISM

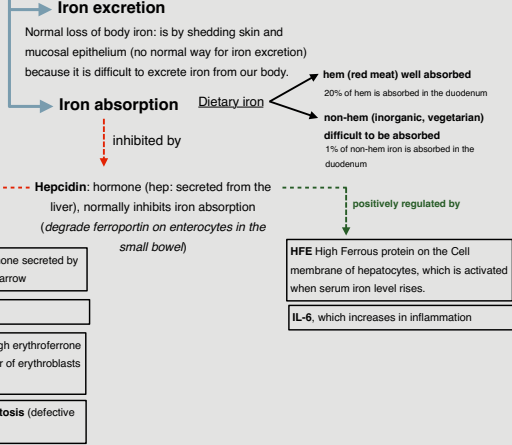


INDICATORS OF IRON STATUS

- **Bone marrow aspirate** 📷📷
(the best one and the most accurate) by inserting a needle in the bone marrow shows: earliest changes in the iron amount of BM, **invasive** procedure, painful, stained by **Perl's Prussian blue stain** special iron stain appears in form of blue granular particles (↓ in IDA iron deficiency anemia)
- **Serum ferritin level (↓ in IDA)** 📉📉
reflects **hemosiderin** in BM (low hemosiderin, low serum ferritin level)
the problem in the ferritin that is an acute phase protein increases in the inflammatory conditions that masks iron deficiency results in normal ferritin level
- **Serum iron level (↓ in IDA)** 📉📉
reflects **transferrin** and the transferrin saturation becomes lower than 1/3 which is abnormal
- **Total iron binding capacity [TIBC]** 📈📈
This is the **opposite test of transferrin saturation**. It is done by adding iron to the blood sample then if it takes a lot of iron this indicates the deficiency of iron (↑ in IDA)
- **Reticulocyte hemoglobin content (CHr): (↓ in IDA)** 📉📉
- **Mean reticulocyte volume (MRV): (↓ in IDA)** 📉📉



IRON HOMEOSTASIS

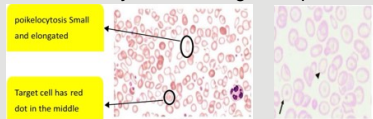


CAUSES OF IRON DEFICIENCY

- **Chronic blood loss** because iron is difficult to control by the body, and there is a high tendency to lose it with Hb.
- **Dietary:** **vegetarians**, **infants** (low iron in the Breast milk), **teenagers** (fast food, menstrual cycle in females,...)
- **Decreased absorption** due to some diseases: like **gastrectomy**, **hypochlorhydria** (low stomach acid (HCL) that is important to ferrous conversion and absorption of iron), **intestinal diseases** like **Inflammatory bowel disease** and **celiac disease** that lead to inflammation so iron level will decrease, and elderly due to physiological atrophy of the stomach which decreases iron absorption.
- **Increased demands:** growing children, pregnancy, myeloproliferative neoplasms (in this case we have a high amount of WBC that takes up the iron instead of RBC)
- **Hypotransferritinemia:** decreased synthesis of transferrin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in the urine (nephrotic syndrome)
- **Enzyme deficiency**, a congenital disease, (rare but should be considered when the deficiency develops very early in life and it is difficult to treat)

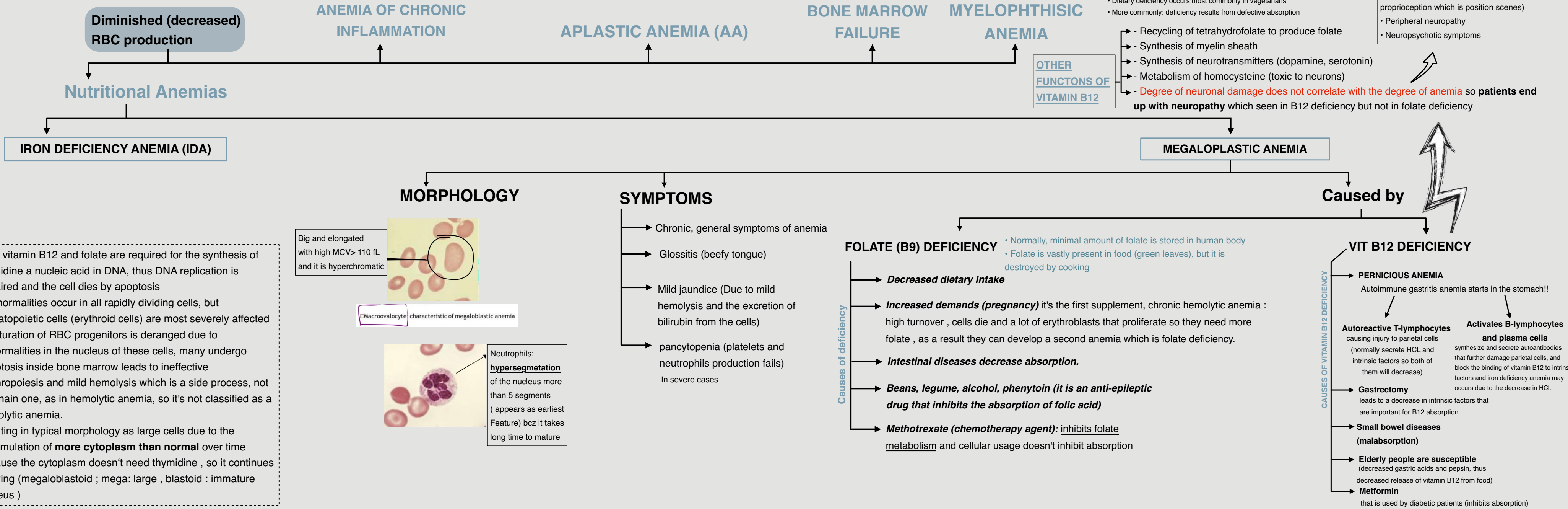
MORPHOLOGY

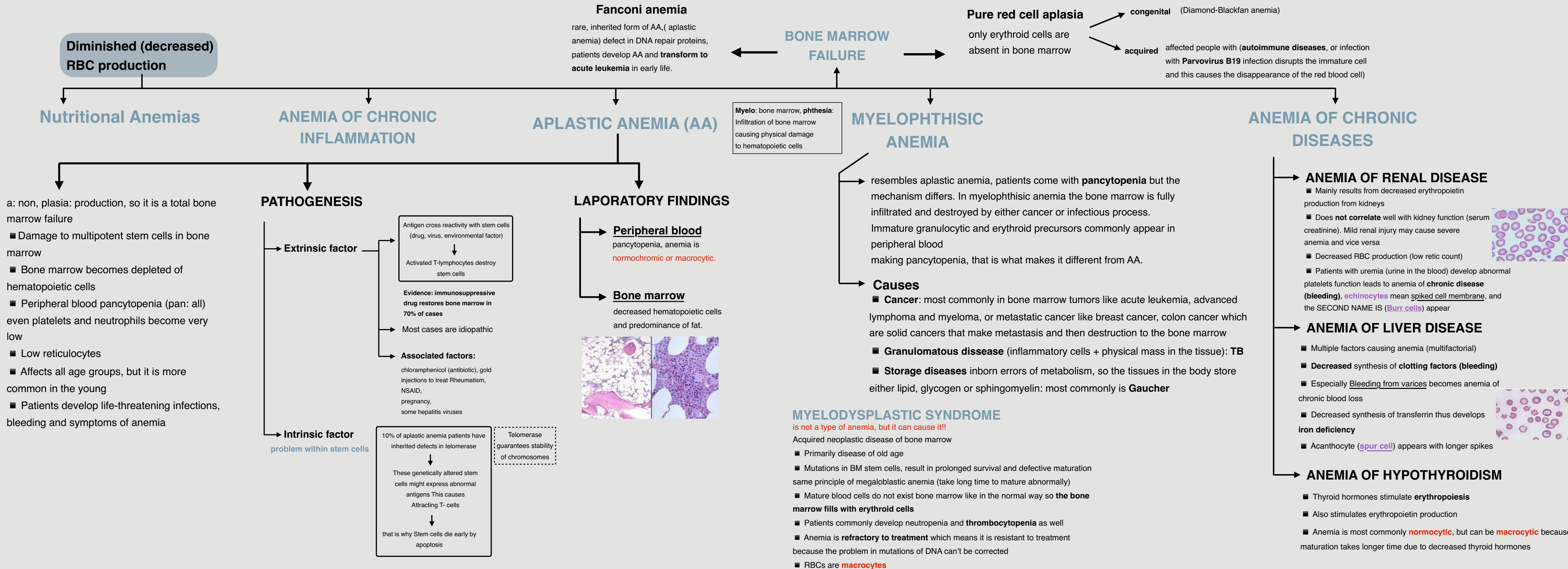
- RBCs **appear small and empty (hypochromic microcytic)**. When there's not enough hemoglobin due to iron deficiency, red blood cells become smaller and dull in color
- **Different and abnormal shapes of RBCs** appear (**poikilocytosis**) like elongated and pencil shaped RBCs because Iron is important for the integrity of the cell membrane of RBCs, so they will have abnormal shapes
- **Target cells:** RBCs with a red dot in the middle appear in iron deficiency anemia, thalassemia and sickle cell anemia (abnormal Hb = Target cells)
- **Low reticulocytes** (Erythropoietin is high, but ineffective the BM can not produce RBCs due to Iron deficiency)
- **Thrombocytosis** is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid making more platelets)



SYMPTOMS

- IDA is a chronic anemia (never comes quickly)
- Hypotension, dizziness, fatigue** ,
- Pica** (special symptom, when patients have a strong desire to eat abnormal things like dirt, paint, and ice)
- Glossitis, stomatitis** bcz iron present in epithelial tissues
- Spooning of fingernails** wide and depressed
- Restless leg syndrome** moving the legs due to neurological condition
- Hair loss**
- Blue sclera** sclera become thin and transparent
- Weakened immunity**
- Cognitive impairment** lately and in severe cases

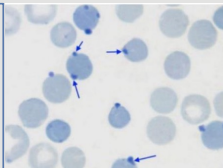




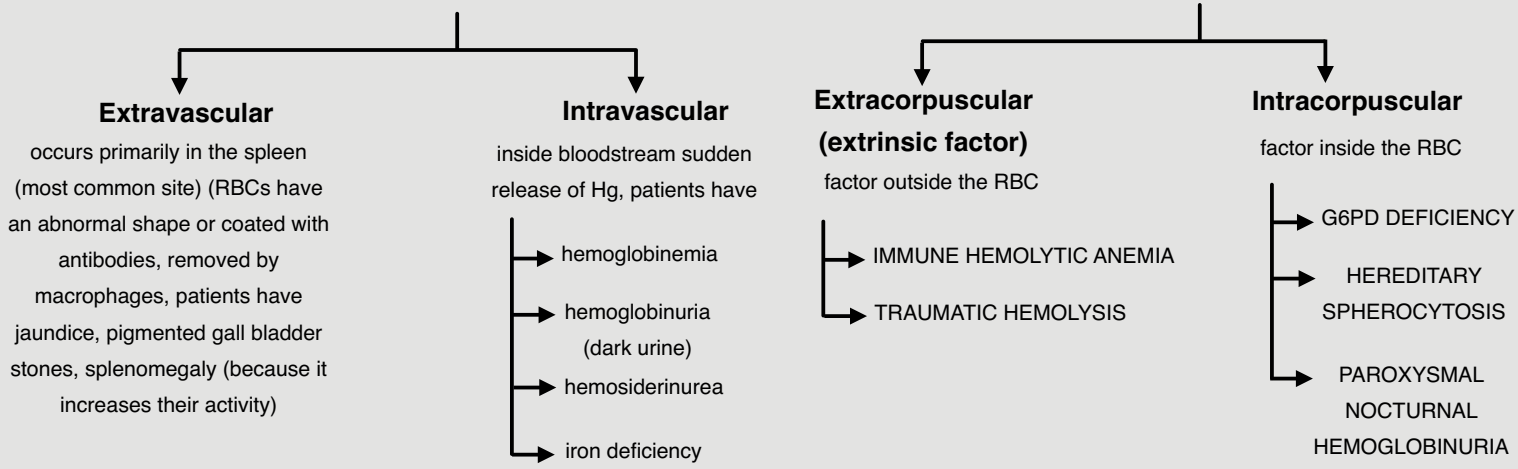
pathophysiology of Hemolytic Anemia

- ➔ **Reduced RBC life span < 120 days, which causes hypoxia.**
Hypoxia triggers the release of erythropoietin
- ➔ **Erythroid hyperplasia in bone marrow**
- ➔ **Peripheral blood reticulocytosis is in response to increased EPO and bone marrow activity**
- ➔ **Hemoglobin is released from damaged RBCs, called free hemoglobin**
- ➔ **Serum haptoglobin: decreased (binds free Hg) in both intra and extravascular hemolysis**
haptoglobin, a protein synthesized normally in the body and present in the blood, binds the free Hg molecules to neutralize it.
Low levels of haptoglobin in the serum indicate the presence of hemolysis because more haptoglobin will be bound to hemoglobin.
- ➔ **Extramedullary hematopoiesis in severe cases !!**

Supravital special stain highlights Heinz bodies as membrane-bound, dark blue spots representing condensed and denatured Hg.

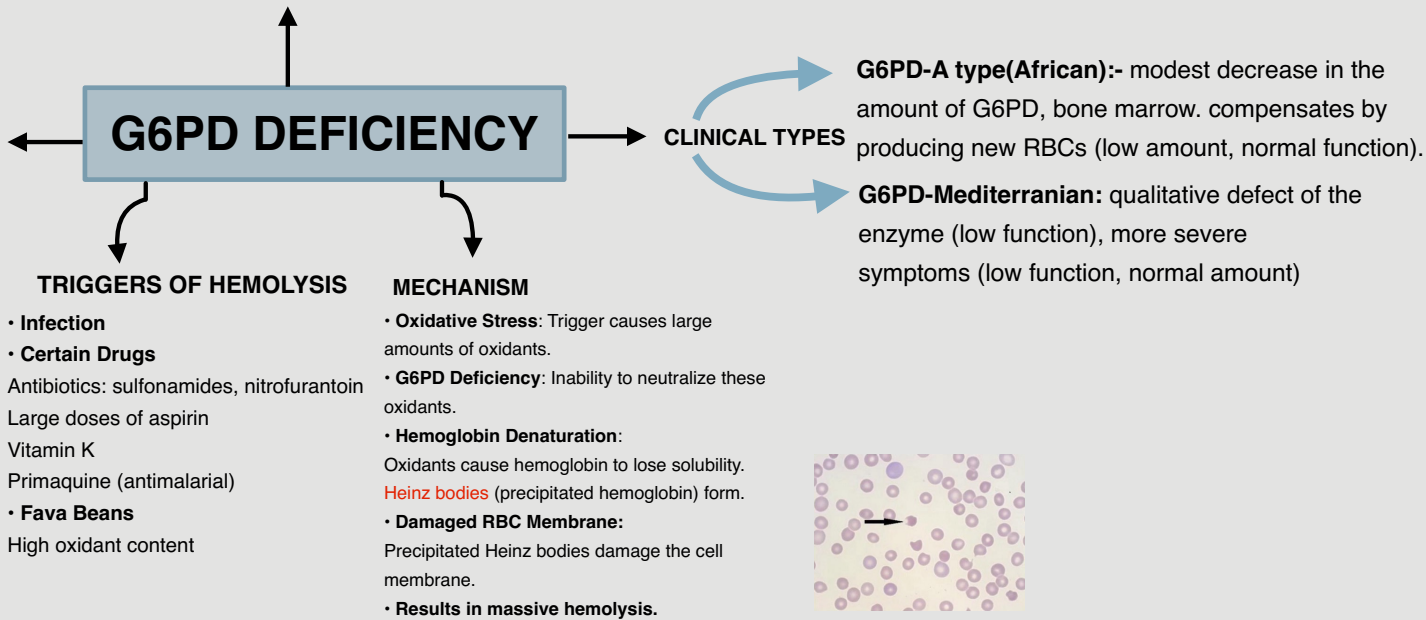
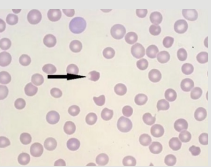


Classification of hemolytic anemia according to Main site of hemolysis the cause of hemolysis



CONSEQUENCES OF HEMOLYSIS

- 2-3 Days After Trigger: Hemolysis occurs.
- Loss of RBC Deformability: Due to Heinz bodies.
- Formation of Bite Cells:
- Macrophages in the spleen target Heinz bodies.
- Partially phagocytosed RBCs result in bite cells.

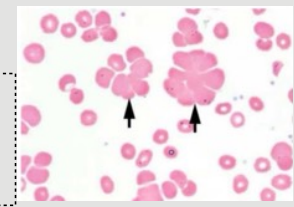
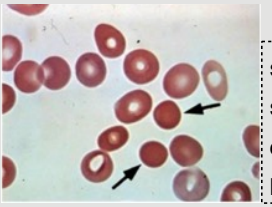


Direct Coombs test: RBCs of the patient are incubated with synthesized antibodies that target normal human antibodies (specifically target the Fc portion of the autoantibodies coating the RBCs) (if the test is positive the antibodies combined that means of the RBCs combined together, so RBCs will agglutinate), if it's negative then the sample will remain fluid.

Indirect Coombs test: Patient serum is added to “test RBCs (synthesized RBCs)” that have certain surface proteins (identify the type of antigen)
Here we do the opposite, instead of taking the RBCs of the patient we take their serum and incubate it with RBCs containing targeted antigens, to test if the serum of the patient contains antibodies for it. The advantage of this test is that we can target the antigen specifically, like in Rh tests.

An acquired autoimmune disease.
■ The presence of auto antibody against RBC membrane protein in the serum, and some are already coating the RBCs.

agglutination: RBC clumps in different directions



spherocytes appear as small, round (there's no central pallor) hyperchromatic RBC

IMMUNE HEMOLYTIC ANEMIA

CLINICAL TYPES

- WARM TYPE (More common) Coombs test +**
 - High-affinity auto-antibody (mostly **IgG type**, sometimes **IgA**)
 - Binding occurs in core circulation (37° C), the temperature at which binding occurs at its best.
 - Removed by macrophages in the spleen
 - Spherocytes develop, then destroyed by the spleen (extravascular hemolysis)
 - Severity of anemia is variable, most patients have mild chronic anemia and splenomegaly
- 60% are idiopathic
- 25% are associated with other autoimmune diseases such as systemic lupus erythematosus which targets all body tissues
- 15% by drugs in certain individuals only (α-methyl dopa : anti hypertensive, penicillin attaches to antigens of RBCs that get targeted)

- COLD TYPE**
 - Low-affinity autoantibody (IgM)
 - Binding occurs in peripheral areas of body and tips of nose and ears (areas where the temperature is (<30oC) IGM perfectly works at cold temperature .
 - After IgM binding to RBC, few C3b and C3d (which they are part of complement system proteins) molecules bind RBCs. IgM doesn't bind to the RBC alone, proteins from the complement system bind to it too, they normally circulate the blood but when they get activated they bind to cell membranes and cause their lysis.
 - When RBCs return to core circulation where the temperature is

37°C, IgM dissociates (remember it binds with low affinity which makes it easy to detach), but C3b stays, identified by splenic macrophages and removed. The same concept happens here, macrophages recognize complement proteins and phagocytose them, pinching off pieces of the membrane as they do so, turning the RBCs into spherocytes. The RBCs leave the spleen as spherocytes and get destroyed in the spleen in second circulation.
• IgM binds 5 RBCs because it's big, thus creating in vivo agglutination (RBC clumps formation, acts like a thrombus), might block small capillaries (ischemia) in fingers and toes causing **Raynaud phenomenon**.

- Acute**
follows infection: Transient(which is can be recovered without treatment) forms of cold-IHA occur in recovery of infections by:
(1) **mycoplasma pneumonia** (2) **Epstein Barr virus (EBV)**: causes infectious mononucleosis which is a systemic disease. Both cases are mild, self-limited
- Chronic**
persistent form occur in B-cell lymphoma (it's a cancer in which neoplastic cells produce different types of antibodies) or idiopathic

pathophysiology

When the proteins are abnormal or absent → RBC loses part of cytoskeleton → cell membrane becomes unstable → keeps losing parts of it as the RBCs age (as it is circulating).

- little amount of the cytoplasm is lost (hemoglobin stays inside)
- With decreasing surface area, the RBC loses its normal biconcave morphology and becomes a smaller sphere

Spherocytes are non-deformable (take a longer time when they pass through capillaries) → Entrapped in small vessels in the spleen, engulfed by histiocytes and destroyed (extravascular hemolysis).

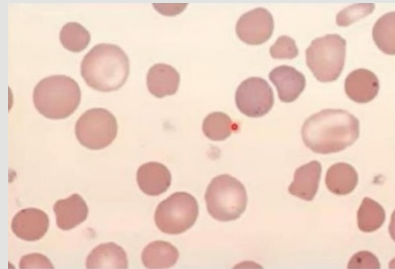
HEREDITARY SPHEROCYTOSIS

Treatment

Patients are treated by a splenectomy. If the spleen is removed, spherocytes persist in peripheral blood, thus, anemia is corrected, and the cells continue their movement in the circulation to deliver oxygen normally even though the cell defect persists.

LABORATORY FINDINGS

In the blood film, we are obviously going to see the appearance of spherocytes in peripheral blood with no central pallor (morphology similar to warm type hemolytic anemia, except Coombs test is negative, and there is family history)



Changes in RBC indices:

- Large number of spherocytes causes a change in the mean cell volume (spherocytes have a smaller size → low MCV)
- volume of the cell is constant, little cytoplasm is lost, normal amount of Hg (normal MCH). Hence, MCHC is increased (we divide MCH which stays the same by MCV which is decreased). Spherocytes show increased fragility when put in hypotonic solution (increased osmotic fragility)

$$\uparrow \text{MCHC} = \frac{\text{MCH}}{\text{MCV} \uparrow}$$

autosomal dominant trait
results in mild hemolysis

autosomal recessive
results in severe hemolysis

DIAGNOSIS

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

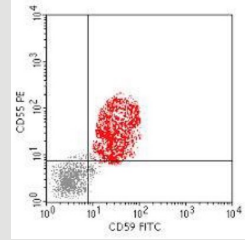
Paroxysmal: sudden hemolytic attack.
Nocturnal: more active at night.
Hemoglobinuria: intravascular hemolysis

In PNH: RBCs (most prominent), and to a lesser degree WBCs and platelets, are spontaneously lysed inside blood (so sometimes it could also lead to **pancytopenia not just anemia**)

PATHOGENESIS

Complement system: circulating proteins that are part of the immune system. They are activated (C5b-C9) and attack cell membrane to create pores, causing lysis. Blood cells protect themselves by membrane proteins CD55 and CD59, that are normally attached to PIG (and since the PIG is deficient in this disease, the RBCs cannot negatively regulate the complement effect and get lysed through pore-forming complexes)

- Having relative hypercapnia ($\uparrow \text{CO}_2$), leading to relative acidosis ($\downarrow$ blood pH), more active complement system, more hemolysis.
- Thrombosis is common, which can be life-threatening and even the main symptom that the patient presents with, and upon further investigation we find out it's PNH.



So basically, the red population have moved diagonally, meaning they have the antigens as normal, while the gray population hasn't moved, meaning the antigens were not detected, so they lack PIG (remember only stem cells which acquired mutations are producing abnormal colonies, so you can find normal colonies in a PNH patient)

a Rare, acquired disease, in which a Mutation in **PIGA gene** results in deficiency in phosphatidylinositol glycan (PIG), a structural protein on cell membrane that anchors many other proteins, and carries the normal antigens on RBCs. Mutation occurs in bone marrow stem cell, leukocytes, RBCs and platelets are all affected.

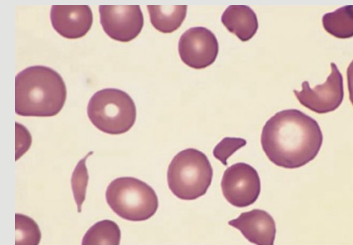
Disseminated thrombi (microangiopathic hemolytic anemia):

these are an entity of medical disease in which hemolysis happens in small blood vessels + thrombosis in multiple distributed vessels of the body

TRAUMATIC HEMOLYSIS

Hallmark of traumatic hemolysis:

schistocytes (broken, torn, fragmented RBCs and different shapes of RBCs)



Direct physical force, or turbulence causing lysis of RBCs (**intravascular hemolysis**)

Patients who have Prosthetic heart valves

for example stenosis which restricts the RBCs causing their lysis. And also in those who have prosthetic valves

Repetitive physical pounding (marathon, boxing, marching)