I thought organizing this lecture would take me 30 minutes……
5 hours later, I'm questioning all my life choices!

Iron metabolism and anemia

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Anemia

Anemia is a condition characterized by a decreased oxygen-carrying capacity of the blood.

Pathophysiology:

1. Decreased oxygen (O_2) content due to a reduction in hemoglobin (Hb) concentration.
2. Arterial oxygen saturation (SaO_2) remains normal because hemoglobin is still binding oxygen efficiently.
3. Partial pressure of oxygen (PaO_2) remains normal as it reflects dissolved oxygen in plasma, which is unaffected by hemoglobin levels.
4. Decreased total red blood cell (RBC) mass, which can be measured using an RBC nuclear scan.
5. Reduction in hemoglobin (Hgb), RBC count, or hematocrit (Hct) serves as key indicators of anemia.

Signs and Symptoms:

Signs (observed by the doctor during examination):

Pallor (pale skin and mucous membranes)

Flow murmur (due to low blood viscosity and increased turbulent flow)

Symptoms (reported by the patient):

Fatigue (feeling tired)

Dizziness

Dyspnea (shortness of breath)

CAUSES OF ANEMIA

1. Production Defects
- Bone marrow or kidney damage: Reduced erythropoietin (EPO) production.
- Hypothyroidism: Hypometabolic state → low reticulocyte count ("low retic").

2. Maturation Defects
- Cytoplasmic defects: Impaired hemoglobin (Hgb) or globin synthesis.
- Nuclear defects: Vitamin B12 or folate deficiency (megaloblastic anemia).

3. Survival Defects (Hemolysis) :

A. Intrinsic RBC Defects

-Membrane disorders: Spherocytosis. → RBCs are very small / genetic

- Enzyme deficiencies:- G6PD deficiency → impaired redox (reduction) metabolism:

Glucose-6-phosphate → 6-phosphogluconate (via G6PD) → NADPH production → maintains reduced glutathione(protects against H_2O_2).

#Fenton reaction*: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+}$ + hydroxyl radical (oxidative damage).

- Glycolysis defects (e.g., pyruvate kinase deficiency):
  ~Phosphoenolpyruvate → pyruvate (yields 2 ATP + 2,3-BPG).
  ~2,3-BPG ↑ → right shift in O_2 dissociation curve.
- Hemoglobinopathies: Sickle cell disease. (next lect)

B. Extrinsic RBC Attack

- Sequestration: Hypersplenism (e.g., portal hypertension).

- Blood loss:
#Acute (e.g., peptic ulcer, hemorrhagic shock). (M/C in male)

4. **the most common cause of anemia in the US is iron deficiency anemia**

Causes and diagnosis Iron deficiency anemia

1. Iron Absorption in the Gut

A- Stomach:

-Gastric acid (HCl) and vitamin C (VC) convert dietary Fe^{3+} (non-heme iron) → Fe^{2+} (absorbable form).

- Heme iron(from animal sources) is absorbed directly.

B- Duodenum (main site of absorption):

1. Enterocytes take up Fe^{2+} via DMT1 transporter.
2. Iron is stored as ferritin (if not needed) or exported:
   - Ferroportin transports Fe^{2+} → bloodstream, where it's oxidized to Fe^{3+} and bound to transferrin.
3. Transferrin delivers iron to:
   - Bone marrow (for erythropoiesis).
   - Liver (storage as ferritin).

transferrin → inside the blood

ferritin → inside the tissue

C- Regulation by Hepcidin (liver hormone):

- ↑ Hepcidin → blocks ferroportin → reduces iron absorption (enterocytes)/recycling(macrophages).

extra
- Stimulated by: High iron stores, inflammation.
- Inhibited by: Anemia, hypoxia, erythropoiesis demand.

* Hepcidin a protein → sensitive to the ↑↑ iron

2. Causes of IDA

Blood loss (most common):

- GI: Ulcers, NSAIDs, IBD(inflammatory bowel disease), malignancy.
- Gynecologic: Menorrhagia(heavy menstrual bleeding).
- Poor absorption: Celiac disease, gastrectomy.

* iron exist in the serum but in a very small amount.

the ↑ iron in the serum cause fenton reaction!!
* slide 5 !

Anemia of chronic inflammation

- Cytokines

  Bone Marrow: insensitive to erthropotein and Suppression

  Erythrocyte: Autolysis and Apoptosis

  Spleen and liver : Storage of iron into ferritin

.All of these are strategies to prevent bacteria from growth

Anemia of chronic inflammation (ACI), occurs when long-term infections, autoimmune disorders, or cancers disrupt normal iron metabolism and red blood cell (RBC) production. The body's immune response, while fighting disease, inadvertently causes anemia through three key mechanisms

explanation

1. Cytokine-Driven Suppression of Erythropoiesis

-Pro-inflammatory cytokines(e.g., IL-6, TNF-α, IFN-γ):
- Bone marrow: Make RBC precursors insensitive to erythropoietin (EPO), reducing new RBC production.

- Erythrocytes:Trigger autolysis (self-destruction)and apoptosis (programmed death) of mature RBCs, shortening their lifespan.

2. Iron Sequestration (Locked Away in Storage)

- Spleen and liver: Cytokines (especially IL-6) stimulate hepcidin release from the liver → traps iron inside ferritin in macrophages and hepatocytes.
- Result: Iron is not released for RBC production, even if body stores are normal.

3. Evolutionary Defense Strategy

- These responses starve pathogens of iron, which is critical for bacterial growth.
- Trade-off: Temporary anemia helps the body fight infection but becomes harmful if chronic.

IRON STUDIES

1. Ferritin (Iron Stores)
- Normal range: 1–8 mg (bone marrow reserves)
- Low: Iron deficiency anemia (depleted stores)
- High: Chronic inflammation

2. Serum Iron (Circulating Iron)
- Low: Iron deficiency anemia, chronic inflammation
- High: Hemochromatosis, sideroblastic anemia

- Heme is composed of → protoporphyrin, Iron (Fe^{+2})
- in sideroblastic anemia, protophyrin synthesis is defective, so iron can't bind to form heme!
- as a result, iron accumulates forming ringed sideroblast and iron overload

3. Total Iron-Binding Capacity (TIBC)
- Reflects transferrin levels (liver-produced iron transporter).
- High: Iron deficiency (↑ transferrin to compensate)
- Low: Chronic inflammation (↓ transferrin due to hepcidin)

4. Transferrin Saturation (%) (Iron saturation percentage)
- Formula: (Serum Iron / TIBC) × 100
- Normal: ~33%
- Low: Iron deficiency
- High: Iron overload (e.g., hemochromatosis) + (Sideroblastic)

5. Soluble Transferrin Receptors (STFR)
- High: Iron deficiency (↑ erythropoietic demand)
- Normal: Chronic inflammation (iron trapped in macrophages)

Explained in slide 10, don't worry 😇

Features of Hemolysis

Extravascular	BOTH	Intravascular

acute

- Reticulocytosis
- Hyperbilirubinemia (indirect)
- ↑ LDH
- ↓ haptoglobin

- Free hemoglobin in plasma
- Hemoglobinuria
- Hemosiderinuria

chronic

- BM erythroid hyperplasia
- ↑ folate requirement
- gall stones (bilirubin)

- Fe deficiency

In detail :-

① RBC lifespan ≈ 120 days

② fate :→ aged, abnormal or damaged RBCs are broken down by the spleen (key site for macrophages activity)

③ Macrophages → phagocytize RBCs

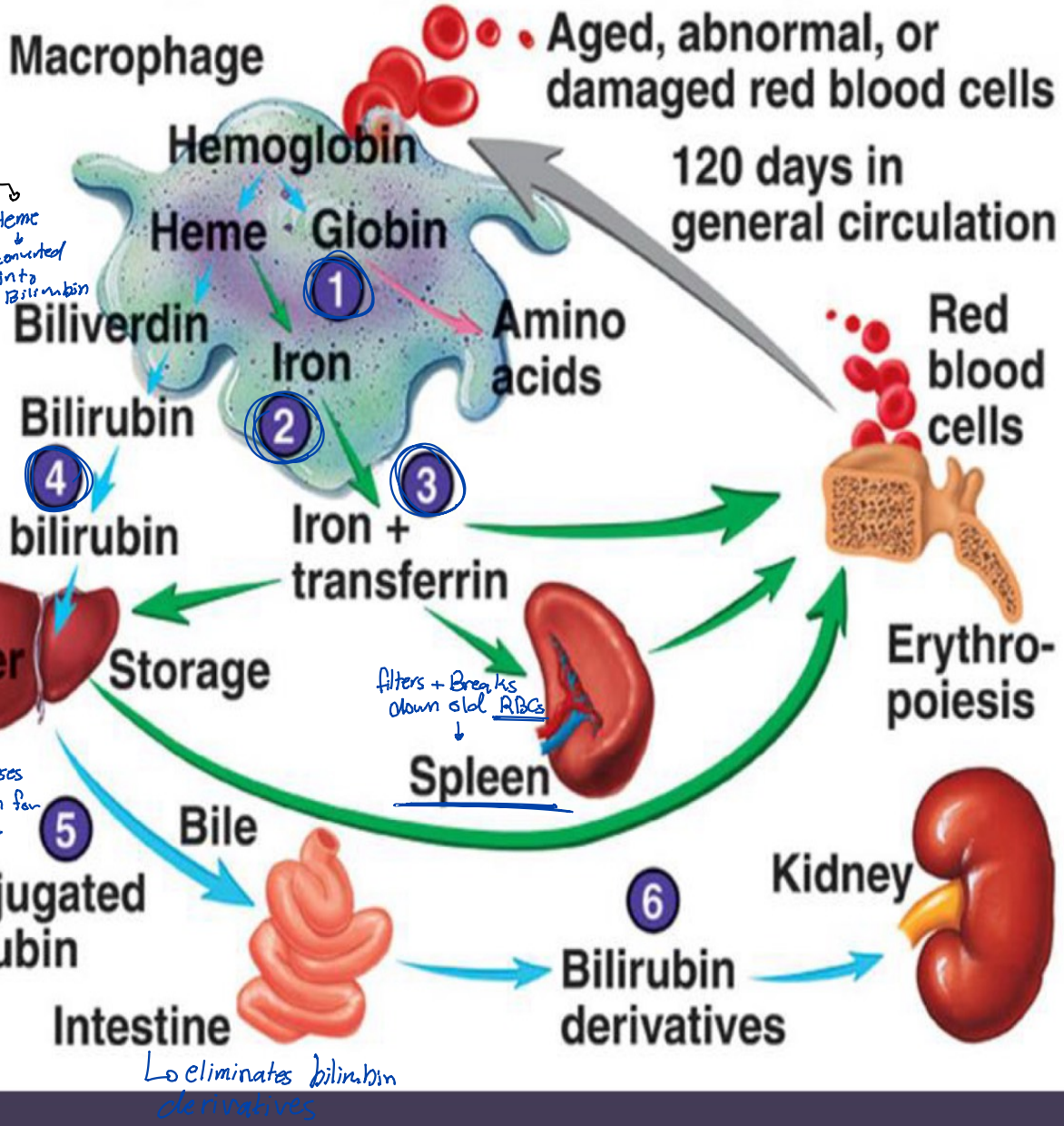
④ The Hgb from the RBCs is broken into

- ① globin → degraded into amino acid → for protein synthesis
- ② Iron → bound to transferin (transporter protein) then recycled for new RBC production (erythropoiesis)
- ③ Heme → converted into Bilirubin

⑤ free (unconjugated) bilirubin released into the bloodstream → taken by the Liver → convert it into conjugated form → excreted into bile → enters the intestine

⑥ Intestinal fate → converted into bilirubin derivatives → excreted by (feces/urine)

[Normally]



In short :-

① RBCs (120 days)
↓
spleen (Macrophages)
↓
Hemoglobin
- Globin (amino acid)
- Iron (transferin)
- Bilirubin

② Bilirubin → Liver (conjugation)
→ Intestine → excretion

Slide 8 explanation 🙂

Hemolysis = Premature destruction of red blood cells (RBCs).
It happens in 2 main places, each with unique features:

1. Extravascular Hemolysis

(RBCs destroyed in spleen/liver by macrophages)

Key Signs: Shared by both Extra+Intravascular

- **Reticulocytosis: Bone marrow makes more young RBCs (reticulocytes) to compensate.**
- **Indirect hyperbilirubinemia: Hemoglobin breaks down → unconjugated (indirect) bilirubin ↑ (yellowish skin/eyes).**
- **High LDH: Enzyme leaks from damaged RBCs.**
- **Low haptoglobin: This protein "mops up" free hemoglobin → levels drop as it gets used up.**

2. Intravascular Hemolysis

(RBCs burst inside blood vessels)

Key Signs: only with intravascular

- **Free hemoglobin in plasma: RBCs rupture → hemoglobin spills into blood.**
- **Hemoglobinuria: Hemoglobin leaks into urine → pink/cola-colored pee.**
- **Hemosiderinuria: Iron from hemoglobin stains urine (later sign).**

Chronic Hemolysis Complications

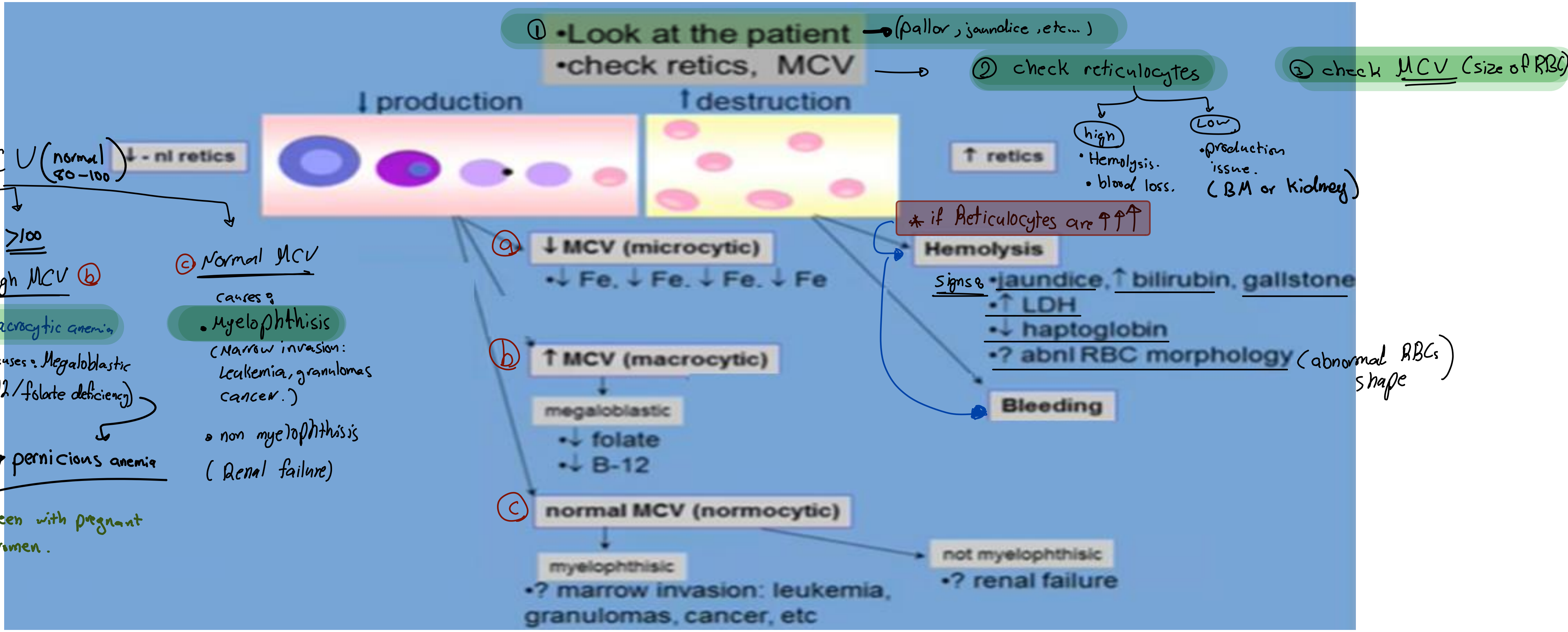
ما حكت عنهم بس موجودين بالوسعة فوق

If hemolysis lasts months/years:

- Bone marrow erythroid hyperplasia: Marrow works overtime → expands (can cause bone pain).
- Folate deficiency: Rapid RBC production uses up folate.
- Gallstones: Excess bilirubin forms pigment stones.
- Iron deficiency: Loss of hemoglobin iron in urine (if intravascular).

Feature	Extravascular	Intravascular
Reticulocytosis	✓	✓
↑ LDH	✓	✓
↓ Haptoglobin	✓	✓
Hemoglobinuria	✗	✓
Hemosiderinuria	✗	✓

How to approach Differential diagnosis of anemia



① •Look at the patient → (pallor, jaundice, etc...)
•check retics, MCV → ② check reticulocytes
③ check MCV (size of RBC)
high: • Hemolysis. • blood loss.
Low: • production issue. (BM or Kidney)
↓ production
↑ destruction
↓ - nl retics
↑ retics
* if Reticulocytes are ↑↑↑
Hemolysis
Signs: •jaundice, ↑ bilirubin, gallstone
•↑ LDH
•↓ haptoglobin
•? abnl RBC morphology (abnormal RBCs shape)
Bleeding
ⓐ ↓ MCV (microcytic)
•↓ Fe, ↓ Fe, ↓ Fe, ↓ Fe
ⓑ ↑ MCV (macrocytic)
megaloblastic
•↓ folate
•↓ B-12
ⓒ normal MCV (normocytic)
myelophthisic
•? marrow invasion: leukemia, granulomas, cancer, etc
not myelophthisic
•? renal failure

MCV (normal 80–100)

- <80 — Low MCV ⓐ
  - Microcytic anemia
  - key: iron studies (Fe, ferritin)
  - causes (Iron deficiency)
- >100 — High MCV ⓑ
  - Macrocytic anemia
  - causes: Megaloblastic (B12/folate deficiency)
  - * pernicious anemia
  - * seen with pregnant women.
- ⓒ Normal MCV
  - causes:
  - • Myelophthisis (Marrow invasion: Leukemia, granulomas cancer.)
  - • non myelophthisis (Renal failure)

* بشوفه اكثر بال folate
لانه ال storage
اله جدًا قليل اقل من
B12
only 3-4 mounths → bcz it is soluble.

65 yr old woman with fatigue, wt loss, and night sweats.

Test ordered	Result	Units	Ref range
Hemoglobin	6.8L	g/dL	13-18
Hematocrit	22L	%	37-55
Reticulocytes	0.3L	%	0.4-1.5
MCV	93	fL	78-93
Bilirubin, total	1.2	mg/dL	0.2-1.2
Bilirubin, dir.	0.1	mg/dL	0.1-0.3
LDH	230	U/L	100-230
Haptoglobin	200	mg/dL	30-200

① → severe anemia (↓ Hgb + ↓ Hematocrit)
so reduced O_2 carrying capacity.

② → Reticulocytes (Low) → so this suggests a production problem rather than blood loss / hemolysis.

③ → MCV (normal range) ⇒ Normocytic anemia
* Rules out microcytic (Iron deficiency) + Macrocytic (B12/folate).

④ LDH + Haptoglobin + bilirubin ≈ normal, No evidence of Hemolysis

⑤ Fatigue + weight loss + night sweats in 65 y → concerning for
ⓐ Malignancy (Leukemia. ✓)
ⓑ granulomas (TB) ✓
ⓒ renal failure) ✓
} may be

⇒ [* BM biopsy / or before that we do another test to know if BM is functioning properly, and producing RBCs ✓
→ Index 2-3 → then BM is ok ✓

→ > 2-3 → BM is suppressed
so then we take biopsy

5 Year old boy noted by his new pediatrician to be mildly icteric. Mom says: "he's got his father's coloring."

↑ Reticulocytes → destruction ✓

[↑ bilirubin, ↑ LDH, ↓ Haptoglobin]

↓

Hemolytic pattern !!

Test ordered	Result	Units	Ref range
Hemoglobin	11.5L	g/dL	13-18
Hematocrit	35L	%	37-55
Reticulocytes	5H	%	0.4-1.5
MCV	89	fL	78-93
Bilirubin, total	1.6H	mg/dL	0.2-1.2
Bilirubin, dir.	0.3	mg/dL	0.1-0.3
LDH	380H	U/L	100-230
Haptoglobin	10L	mg/dL	30-200

something hereditary (genetic)

- spherocytosis → this is the most common genetic in young babies.
- G6PD less likely
- Thalassemia less likely