Anemia 1: Fourth year Medical Students/ 16.11.2020

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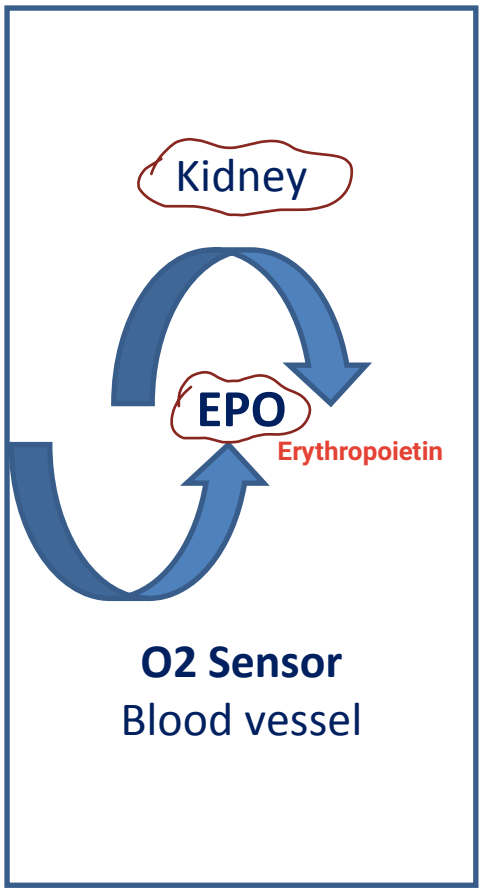
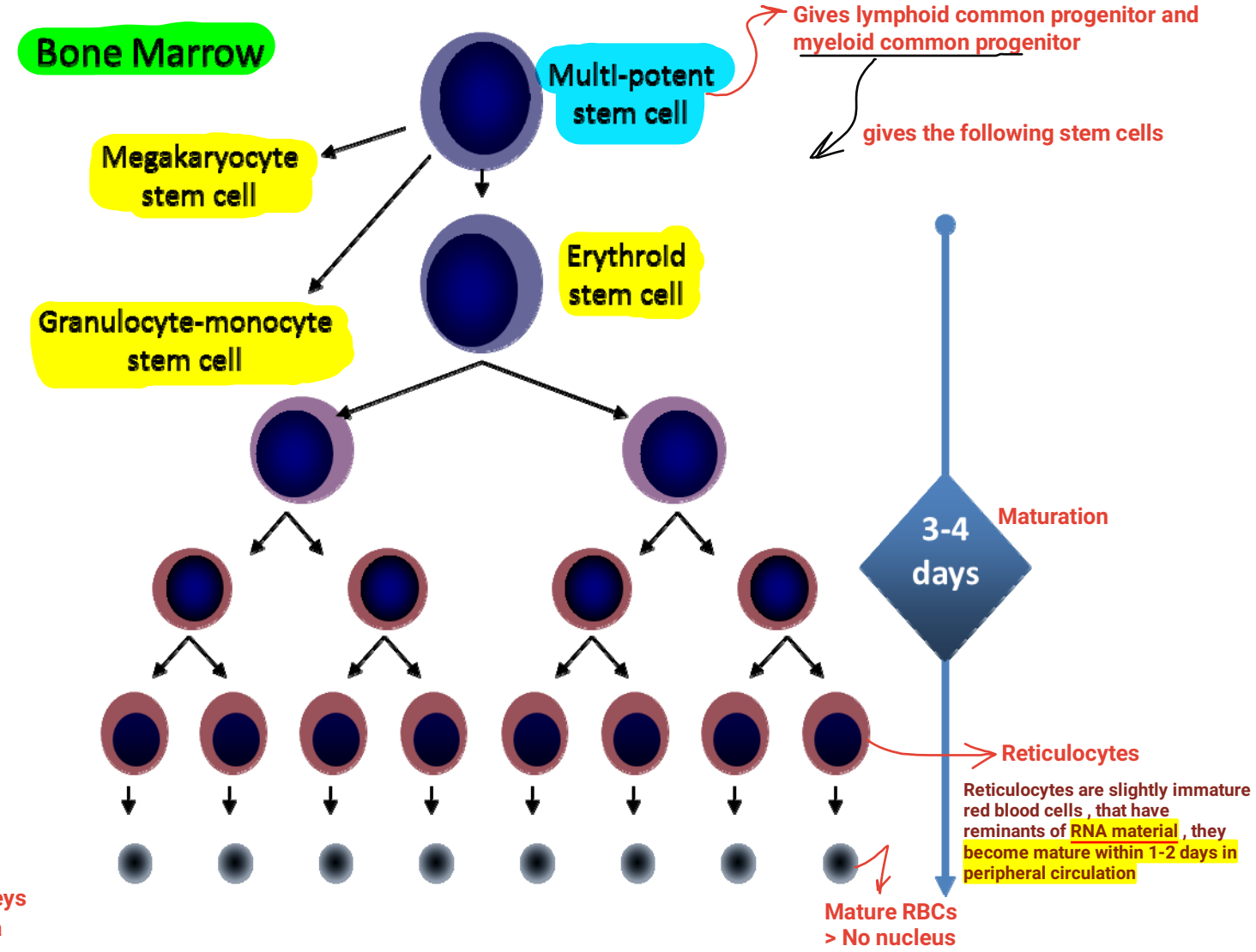


✓ Erythropoiesis is influenced by EPO which is a hormone secreted by the kidneys
✓ EPO secretion is stimulated by hypoxia



Definition:

Anemia is operationally defined as a reduction in one or more of the major RBC measurements:

- **Hemoglobin concentration,** → most commonly used index; g\dL
- **Hematocrit,** → Hct > the volume percentage (vol%) of red blood cells (RBC) in blood
- **RBC count** → millions\L

WHO's definition of anemia

The cut-off value defining anemia has been determined by convention as the value at -2 SD from the mean or the 2.5th percentile of the normal distribution of a healthy iron-replete population.

WHO's Hemoglobin thresholds used to define anemia in adults (g/dl)

Women, non-pregnant (>15yrs) 12. → g/dL

Women, pregnant 11.

Men (>15yrs) 13.

pregnant ladies have increased plasma volume (lower Hg concentration)

✓ There's nothing such called "anemia of elderly people" >> Hg is NOT affected by age so it's not acceptable to have an anemic old aged person and saying that this is the result of his age

✓ BUT erythropoiesis may SLIGHTLY decrease in some old men as a result of the decrease in testesterone (but not below all the previous numbers)

Severity of Anemia/g/dl/WHO Classification

	Mild	Moderate	Severe
Non-pregnant women (15 yrs and above)	11-11.9	8-10.9	< 8
Pregnant women	10-10.9	7-9.9	<7
Men (15 yrs and above)	11-12.9	8-10.9	<8

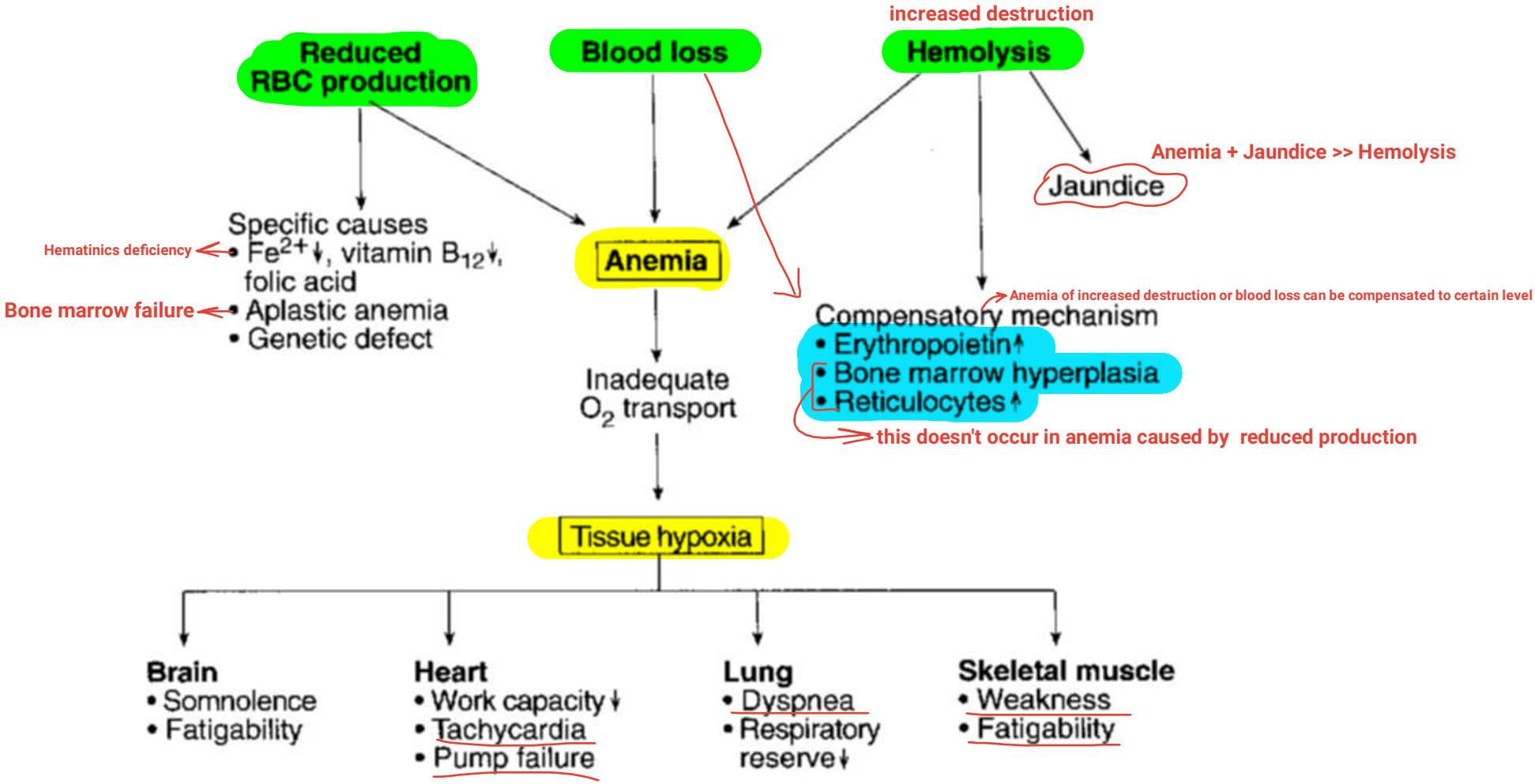
here most of patients have symptoms

Anemia

- Understanding anemia
  - Anemia is either a Disease - to be treated on its own merits
  - Or a Condition - a secondary manifestation of another disease (liver disease \ Malaria \ DIC)

- Causes (pathogenesis) (Blood loss OR imbalance btw synthesis & destruction (1&3))
  1. Decreased production
  2. Blood loss
  3. Hemolysis premature destruction (before the completion of it's lifespan) (90-120 days)

PATHOLOGY, SYMPTOMS, AND SIGNS OF ANEMIA



Symptoms at rest (as resting Tachycardia) >> sever anemia or the body fails to compensate
knowing the level of activity at which patient start having symptoms is important in assessing the severity

The symptoms evaluate the severity of the anemia and the ability of the patient's body to compensate

Clinical Evaluation of Anemia: History

- Proper History; including history of bleeding and systemic illness
- Dietary History
  - ✓ Haematinic (Iron , folate , vitB12) deficiency
  - ✓ Vegetarian
- Past History — periodic hemolysis >> as in G6PD deficiency
- Family History — hemoglobinopathies \\ RBCs disorders
- Drug history — Antifolate chemotheraputics \\ Certain drugs can cause Hemolysis
- Travel History — Malaria

The “Anemia Syndrome” due to **tissue hypoxia**

1- Dizziness

2- Fatigue

3- Shortness of breath especially on exertion

4- Headaches

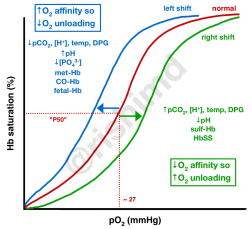
5- Chest pain/ palpitations

6-? Heart Failure

Clinical evaluation of anemia: **Physical Examination**

- **Look for signs of anemia**
  - Pallor > skin , mucosal membranes
  - Resting Tachycardia
  - Postural Hypotension → Helpful in assessing the severity
  - → in acute blood loss
- **Look for signs suggestive of type** → Later
- **Examine for splenomegaly/Hepatomegaly**
- **Look for signs suggestive of cause**
- **Examine for signs of systemic disease**
  - As in anemia of chronic disease (such as CT diseases)

Compensation in Anemic patients is done by cardiovascular system & shifting of the Hg saturation curve (to the Rt > decreasing Hg affinity to O2)



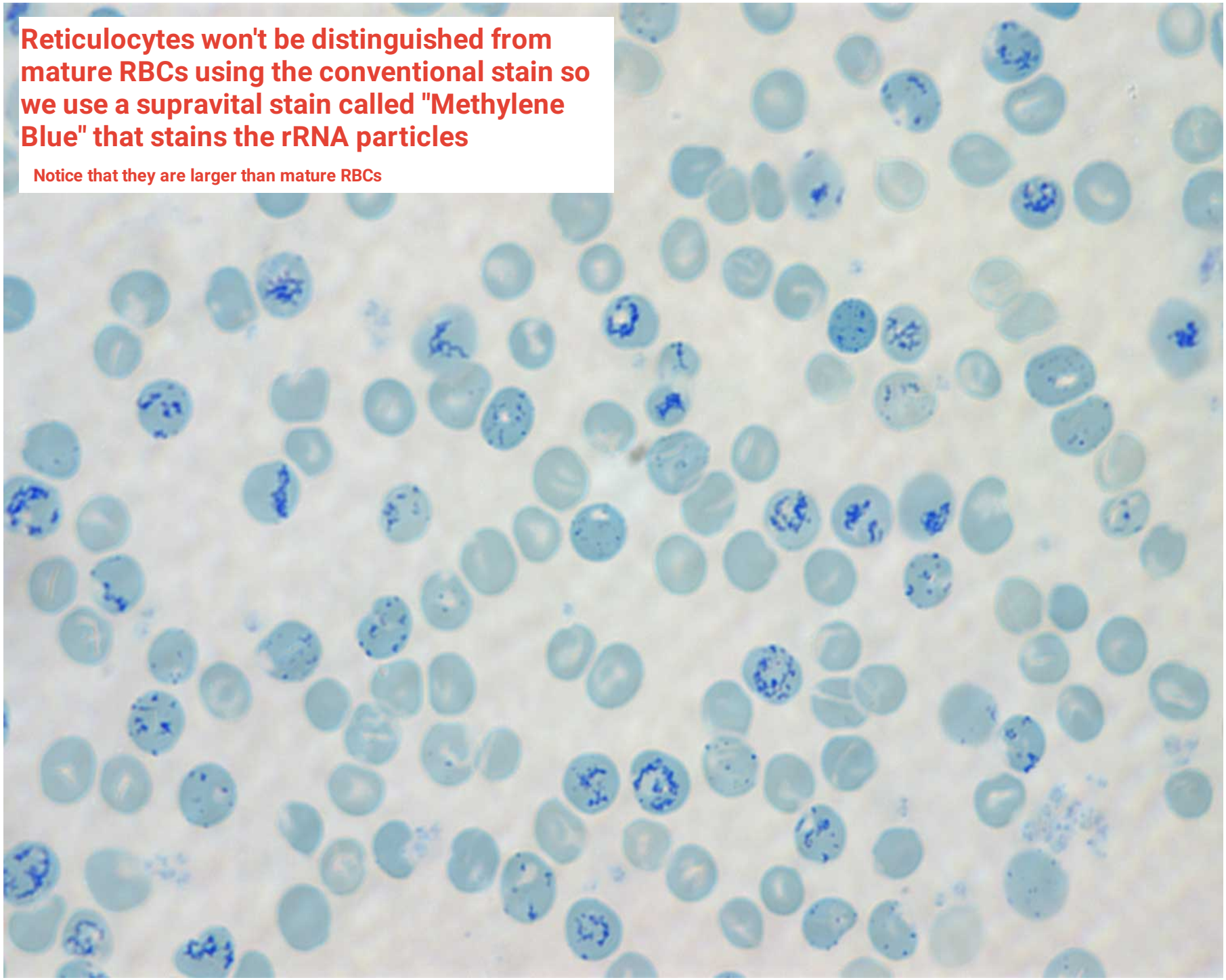
Factors that influence symptomatology and severity of symptoms btw patients

- Acute or chronic — gives the body time to compensate >> better tolerated anemia
- Cardiovascular status — CVS is needed for compensation by increasing the CO > Higher HR & SV
- Additional symptoms related to cause
- Additional symptoms related to type of anemia
- Any intravascular hemolysis

Remember : Intravascular hemolysis occurs when erythrocytes are destroyed in the blood vessel itself, whereas extravascular hemolysis occurs in the hepatic and splenic macrophages within the reticuloendothelial system.

Laboratory Evaluation of Anemia

- Complete blood count including HB, RBC, WBC , diff WBC MCV, RDW
  - Low HB >> Low Hct
    - usually it's ~= 3.3*HB
  - ✓ A red cell distribution width (RDW)
  - ✓ If high >> your RBCs aren't not equal in size (anisocytosis)
- Reticulocyte count
  - **** A reticulocyte :
  - ✓ Normally present in peripheral circulation but not more than 1-2% of total RBC count in the peripheral circulation
  - ✓ Converted to mature RBCs within 1-2 days
  - ✓ has remnant RNA that can be stained by Methylene Blue
  - ✓ Doesn't have nucleus but has rRNA (ribosomes) so still it's capable of producing Hemoglobin (remember globin is a protein produced by ribosomes)
  - ✓ Increased in Anemia of blood loss & anemia of increased destruction
- Peripheral smear >> Blood film > to see the shape and the size of the RBCs or certain signs suggestive to certain diseases
- Other specialized tests According to your suspicion


Reticulocytes won't be distinguished from mature RBCs using the conventional stain so we use a supravital stain called "Methylene Blue" that stains the rRNA particles
Notice that they are larger than mature RBCs

Anemia Classification: Two main approaches

1- Biologic or kinetic approach

–Determined by reticulocyte count

High or Normal

2- Morphology.

mean corpuscular volume

–Determined by MCV

Normocytic , Microcytic , Macrocytic

Acute vs. chronic

–Signs and symptoms

Morphological Classification of Anemia

A- Normocytic/normochromic (normal MCV &MCH): acute blood loss, Hemolysis, ACD, BM failure

Mean corpuscular hemoglobin

B- Microcytic/hypochromic (MCV<78, MCH <26): IDA, Thalassemia

C- Macrocytic (MCV>98): megaloblastic or Non-Megaloblastic anemias.MDS.

✓ The reticulocyte count must be corrected " if the patient is Anemic" according to his Hct and HB → The calculation is necessary because the reticulocyte count is misleading in anemic patients. The problem arises because the reticulocyte count is not really a count but rather a percentage (it reports the number of reticulocytes as a percentage of the number of red blood cells). In anemia, the patient's RBCs are depleted, creating an erroneously elevated reticulocyte count.

✓ No need for correction if the patient is normal

✓ Correction is either : corrected RC or Absolute RC → number not %

✓ Normal Absolute RC is (60,000 -100,000)

✓ From the corrected RC we calculate the Reticulocyte production index

Reticulocyte production index >(2.5 is the cutoff)

More than 2.5 > Hemolysis or hemorrhage

Less than 2.5 > Anemia of decreased production

The reticulocyte count

In other words :
More than 2.5 > proper response > the bone marrow is compensating for anemia
less than 2.5 > under response (the problem in the production itself)

- **Corrected retic.** = Patients retic.(**3%**) x (Patients Hct(30)/45) : 3(%)x30/45 = 2%

  Patient Hct ← Normal Hct →

- **Retics index (RPI)** = **corrected reticulocyte count/Maturation time**

  To correct for shift reticulocytes. → Shift reticulocytes : less and less mature reticulocytes that need more time in the circulation to become mature , They are present in sever anemia

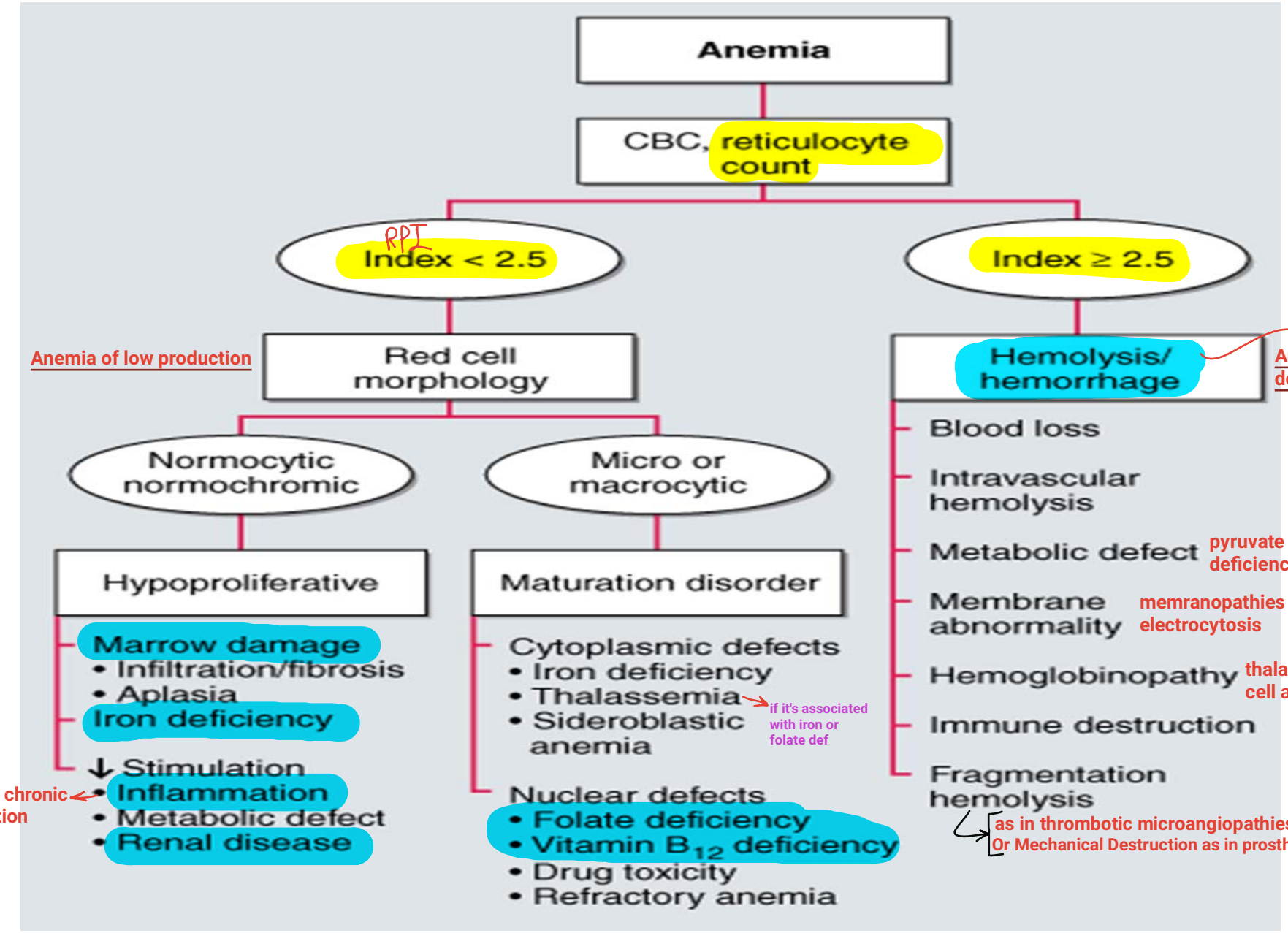
  (Maturation time = 1 for Hct=45%, 1.5 for 35%, 2 for 25%, and 2.5 for 15%.) example above: 2/1.75= **1.14**

- Absolute reticulocyte count = retics % x RBC number.

Example: $1.1\% \times 4.96 \times 10^6 = 55{,}000/\mu l$

$12.2\% \times 2.05 \times 10^6 = 250{,}000/\mu l$

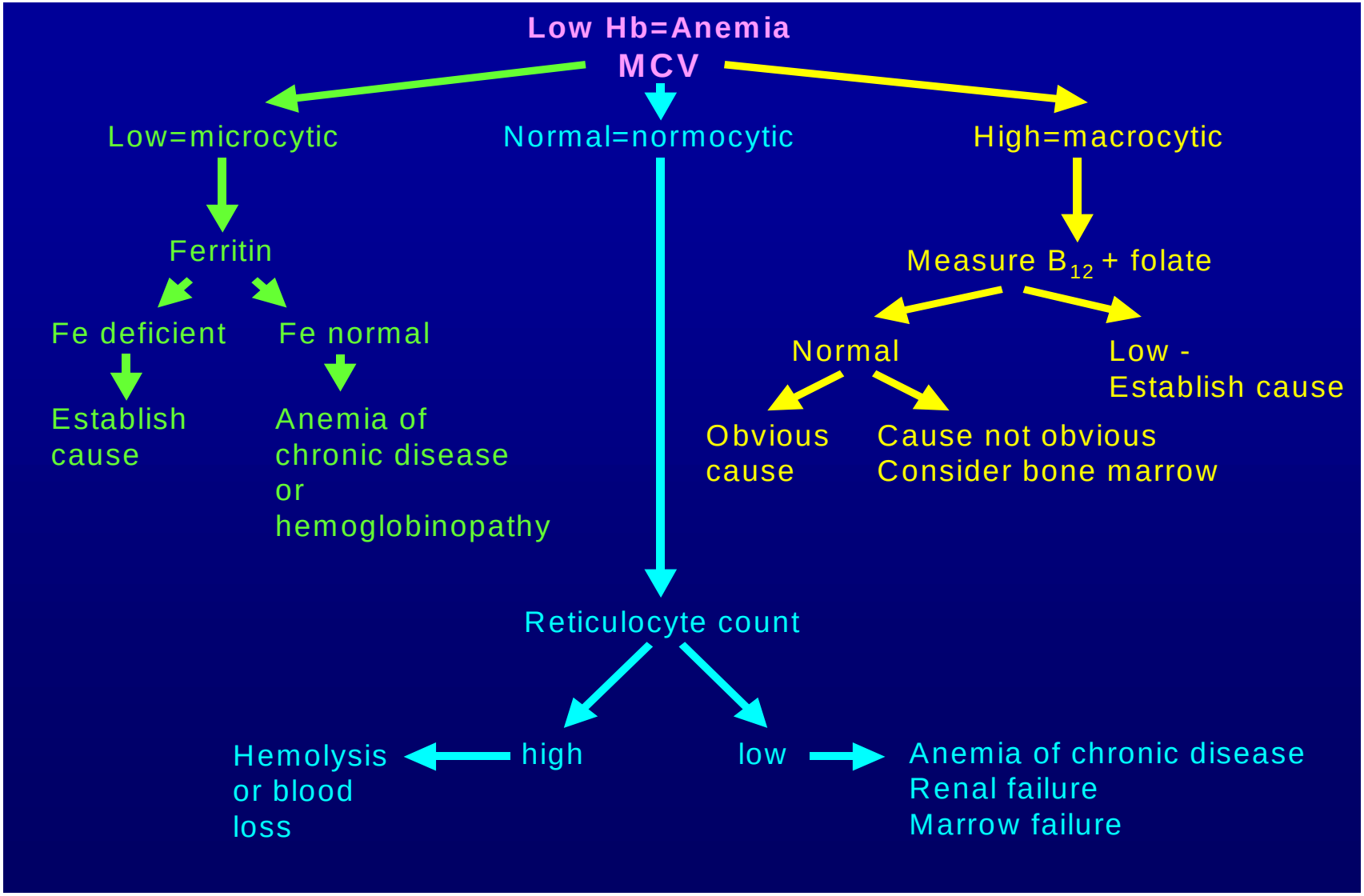
More than 100,000 >> The bone marrow is compensating
Less than 60,000 >> the problem is in the production itself



** Combined etiologies of anemia :

✓ Blood loss > if chronic may cause IDA (combined)

✓ Thalassemia > Hemolysis later may be combined with iron or folate def


Low Hb=Anemia
MCV
Low=microcytic
Normal=normocytic
High=macrocytic
Ferritin
Fe deficient
Fe normal
Establish cause
Anemia of chronic disease or hemoglobinopathy
Measure B_{12} + folate
Normal
Low - Establish cause
Obvious cause
Cause not obvious Consider bone marrow
Reticulocyte count
high
low
Hemolysis or blood loss
Anemia of chronic disease
Renal failure
Marrow failure

Iron Deficiency Anemia (IDA)

Remember : Normal MCV is between 80 and 100 fL.

Microcytic Hypochromic Anemia:

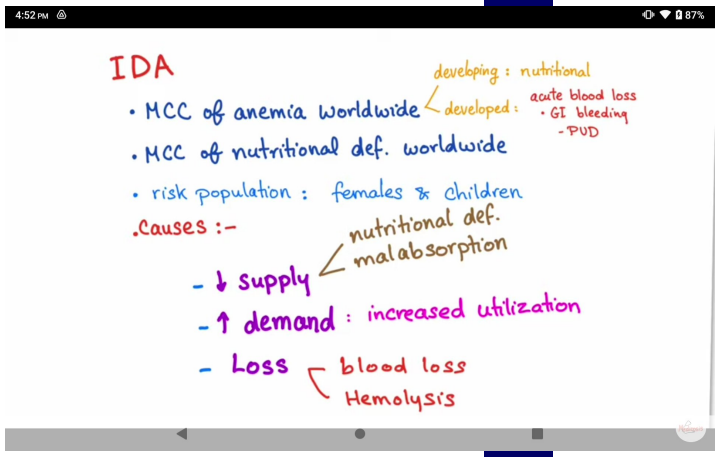
Low MCV Low MCH

Diagnosis

- ✓ Low MCV
- ✓ Low MCH
- ✓ RPI < 2.5 %

- Mild (MCV > 70 fl)
  - Iron deficiency Most common
  - Thalassemia
  - Lead toxicity
  - Sideroblastic anemia
  - Anemia of chronic disease

other DDx for Microcytic hypochromic anemia



- Severe (MCV < 70 fl)
  - Iron deficiency
  - Thalassemia

Evolution of Iron Deficiency Anemia

2 Steps

- **Depletion of body Iron stores only but No anemia**
- **Iron Deficiency with anemia**
- **Ferritin: The Best Marker for Iron Deficiency in “adults”**

✓ Low ferritin and low HB is diagnostic for IDA

✓ Remember : ferritin is an "acute-phase reactant" that becomes elevated in response to inflammation , So the patient may have Crohn's disease that caused IDA but ferritin still high due to the inflammation

✓ Iron content in the body : 3-4 g \\ most of it used by RBCs in HB synthesis
✓ Normal loss everyday is very little ~1-2 mg , should be easily met by Normal diet
✓ There's no method for Iron excretion from the body
✓ Iron def >> decrease intake \ increase loss \ increase demand → pregnancy

Nutritional or malabsorption

blood loss

Major Categories of the cause of IDA

Heme iron (ferrous +2) found in red meet is more easily absorbed than non-heme iron (ferric +3) found in vegetables which needs high acidity to get reduced to ferrous in order to be absorbed

1- Nutritional: poor or absent red meat consumption

most common in females after menopause and in men

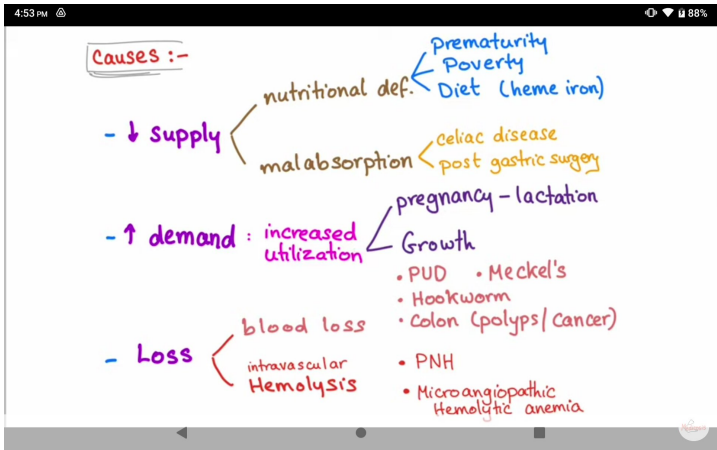
most common cause in females in their reproductive age

2- Blood loss: GI/GU/: benign or malignant lesions. Hemosiderinuria

celiac Disease

3- Malabsorption: Gluten enteropathy , diseases affecting stomach acidity , bariatric surgery

4- Repeated pregnancies >> increased demand

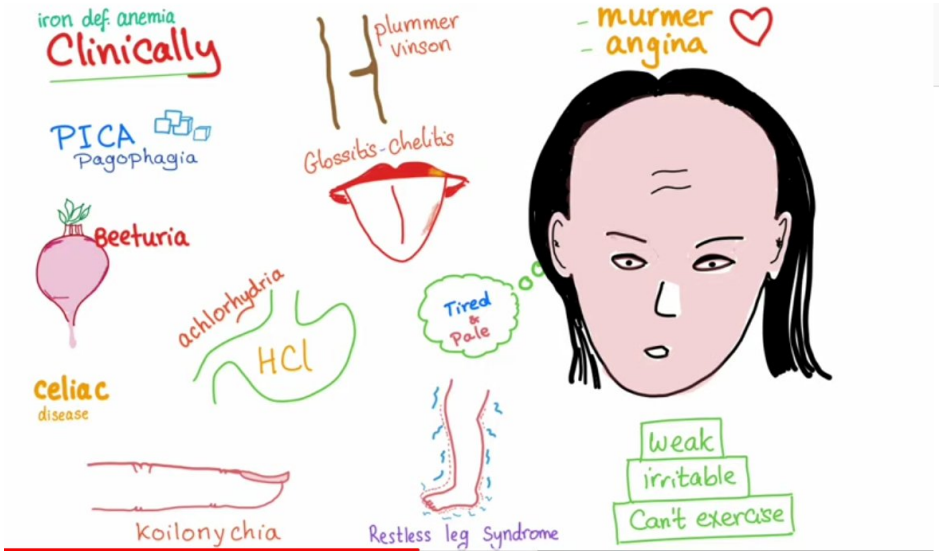


** IDA isn't a final Dx u have to establish the cause and try to treat it

Symptoms & Signs of IDA :

>> symptoms of Anemia syndrome due to hypoxia
>> Frontal blading , Koilonychia , Angular chelittis , glossitis , Pica , Restless leg syndrom

✓ IDA + Dysphagia + Esophageal web >> Plummer-Vinson syndrome (PVS)
✓ Association : Celiac disease , Crohn's , Achlorhydria , Colon cancer , PUD , heavy menstruation ..etc

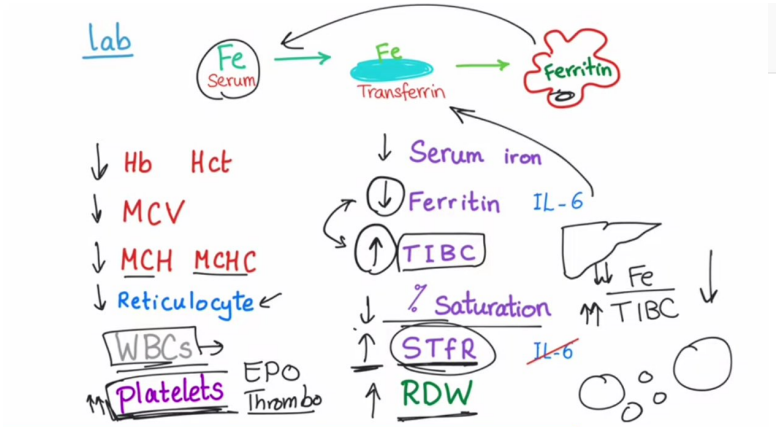


** Regarding the labs :

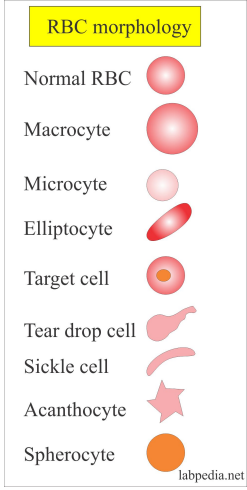
✓ Low HB
✓ Low MCV
✓ Low MCH
✓ High RDW
✓ Low Reticulocytes

✓ Low serum Fe
✓ Low ferritin
✓ High Total iron-binding capacity (TIBC) — test measures the blood's ability to attach itself to iron and transport it around the body. High as the body try to compensate for low Fe by increasing tranferrin and increasing Transferrin receptor
✓ High Soluble Transferrin receptor (STFR)
✓ Low % Transferrin saturation with iron → low as there's low Fe and high tranferrin

✓ Normal WBCs (except if there's inflammation)
✓ High or normal platelets (high due to EPO similarity to TPO & also as an acute phase reactant)



**** Note** : Most accurate test that gives the diagnosis of IDA definitely : Bone marrow biopsy , but it's painful and invasive so we depend on labs
** TIBC & STFR can be used to see if the iron stores are depleted when the patient has ongoing inflammation or whatever makes ferritin elevated as an acute phase reactant



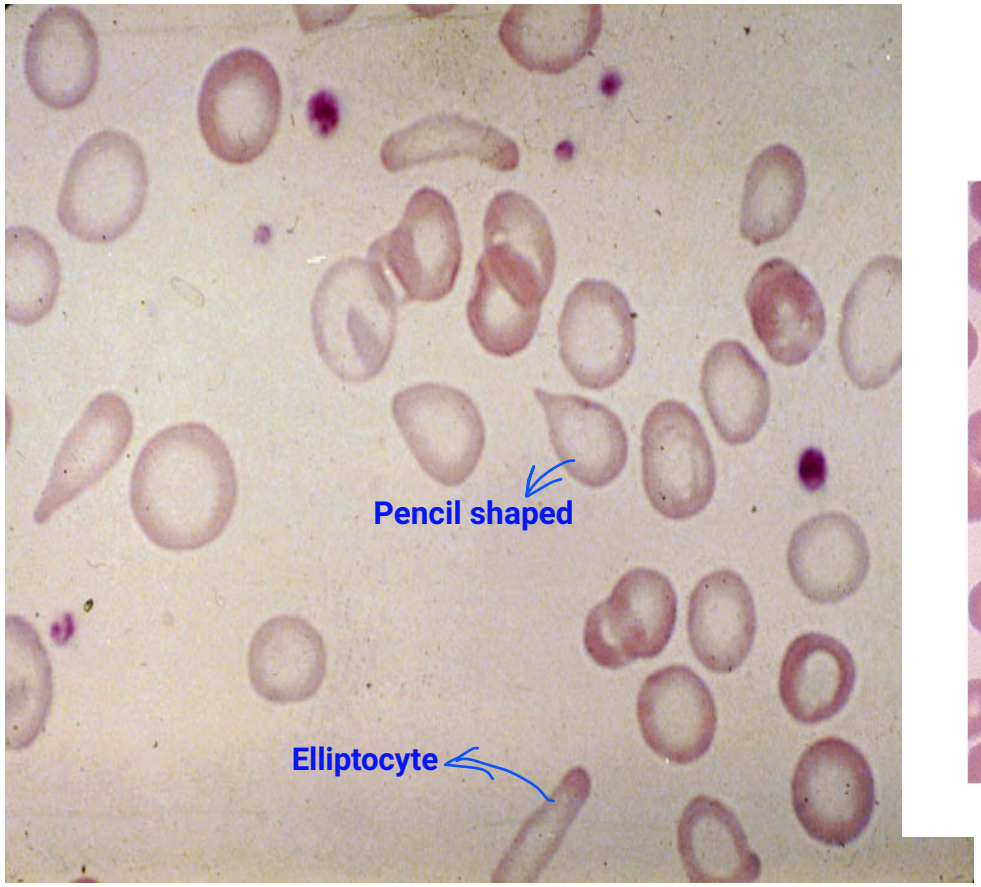
✓ Iron Deficiency Anemia blood film :

Microcytosis + Severe Hypochromia + Anisocytosis + Poikylocytosis

abnormal shaped red blood cells

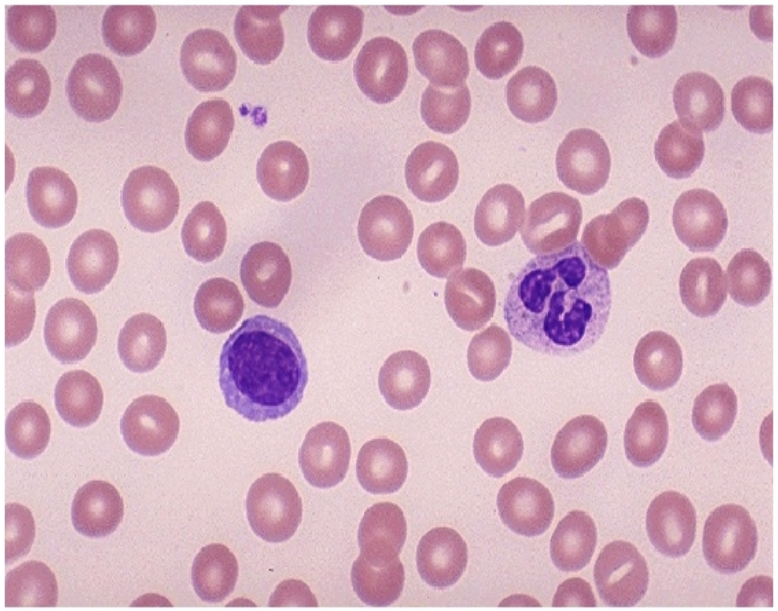
having RBCs that are unequal in size.

= increased RDW



Notice the increased central pallor >>> Hypochromia

Normal Smear

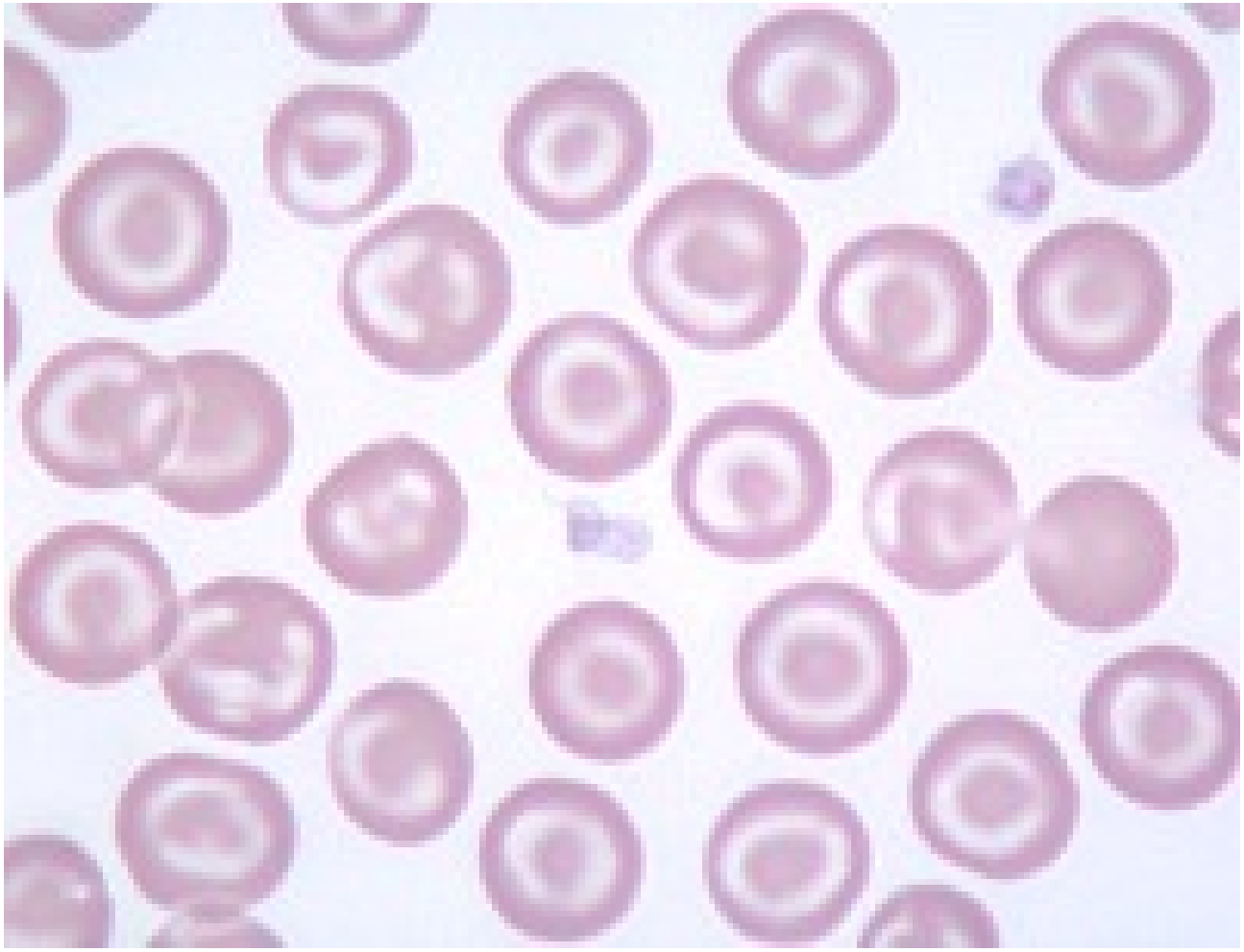


Biconcave shaped RBCs with central pallor that doesn't exceed 1\3 of the total volume of the cell

Target cells can be seen in IDA but must be associated with Anisocytosis

Hypochromia with target cells but without Anisocytosis: Thalassemia Trait

suggest the Dx of



TRANSPORT PROTEINS/Fe

- DMT1 (Divalent Metal Transporter 1)

(Tranports from lumen into the enterocytes)

- FERROPORTIN1

(Transports from enterocytes to circulation)

What is HEPICIDIN??

- HEPICIDIN is the key regulator of iron in our body.
- Is a peptide hormone. produced by the liver
- Its molecular weight is 25 Kda.
- Highly folded structure.
- Present in inactive form;prohepcidin(60aa) and its active form is hepicidin(25aa).

- Hepcidin lowers iron absorption in the intestine ,lowers iron releasing from hepatocytes and macrophages

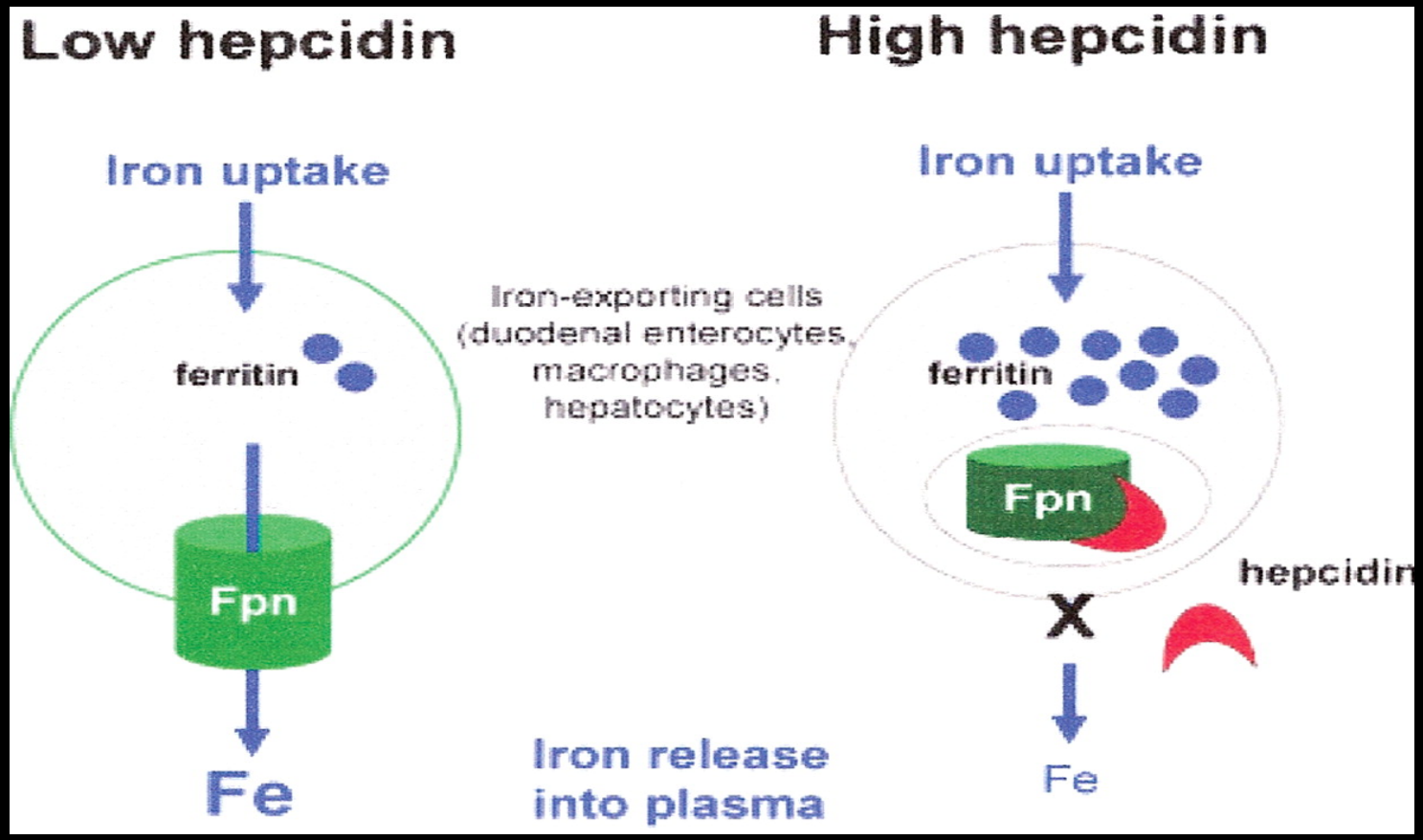
High Hepcidin =

Serum iron is decreased

Mechanism of action of hepicidin

- The major mechanism of hepicidin is THE
1. REGULATION OF TRANSMEMBRANE IRON TRANSPORT.
- It binds to FERROPORTIN ,forms hepicidin-
2. ferroportin complex ,which is degraded in the lysosomes and iron is locked inside the cells(mainly enterocytes,hepatocytes and macrophages).

Hepicidin/Ferroportin



Hepicidin Regulation

So when hepicidin levels are low ,iron exporting cells have abundant ferroportin and thus releases iron into plasma.When hepicidin concentration increases it binds to ferroportin and thus iron is retained in the cells.

Affecting levels of Hepcidin

- Hypoxia/Anemia leads to decrease in hepcidin
- Inflammation leads to increase in hepcidin

✓ Anemia or hypoxia >> low Oxygen >> Low Hepcidin >> high Uptake of diet iron & high Iron release from hepatocytes and macrophages >> high iron serum levels

✓ inflammation >> high Interleukin-6 >> High Hepcidin >> Low iron serum levels >> anemia of chronic disease or inflammation

Disease States

- Hepcidin deficiency, physiological = Haemochromatosis
- Hepcidin excess – anaemia of chronic disease

Red > anemia in general
blue > IDA

Case one

24 yr old female complains of

Symptoms of "Anemia Syndrome" due to tissue hypoxia

Dizziness, Fatigue, Shortness of breath especially on exertion and Headaches for the last 4 months. She has been losing scalp hair.

Hints indicating IDA

She does not eat red meat and has reported heavy menstrual bleeding.

Her physical exam is shown

Lab and Xray test are shown

Likely Diagnosis

✓ Normal MCV >> 80-100 FL
✓ Normal RDW >> 11.5-15%
✓ Normal MCH >> 29±2 picograms
✓ Normal Ferritin >> 12-150 in females
12-300 in males

Case One …..continuation

Lab: Hb 8, MCV 72, RDW 19, MCH 20pg. WBC 8000/Normal dif.Plts 380000

Bld Film: microcytic, hypchromic, anisocytosis, poikilocytosis, Retics (corrected) o.8%

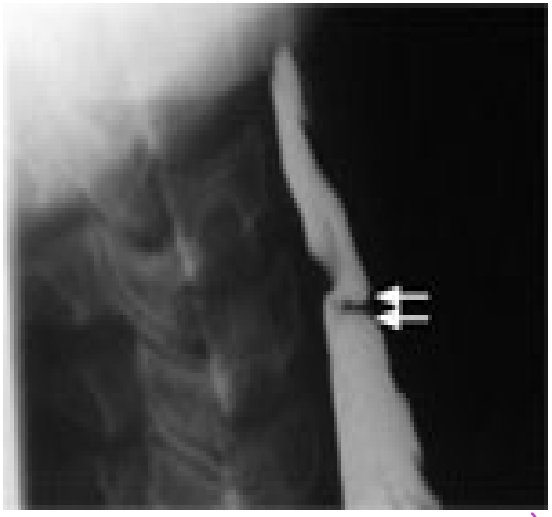
Serum Ferritin 2

Spooning of the nails (koilonychia)

Pallor seen on conjunctiva

A

Angular cheilitis



>> Upon Esophagogram and endoscopy the patient was found to have Esophageal web
✓Esophageal web + Dysphagia + IDA >>> Plummer-Vinson syndrome (PVS)

Hb Electrophoresis?? Serum B12, Folate??

S Fe, TIBC??, BM ??? GI endoscopy??, Investigate for bleeding disorder: VWD?, celiac disease?

Gyne consulation

GI consultation

Treatment/ Follow up of Case 1

1- Oral Iron: Fe gluconate, sulphate

2- educate

3- IV Fe?? Fe sucrose/carboxymaltose or new Fe dextran

Follow up: check CBC every month : expected Hb rise ± 1g/ 10 days. Check Ferritin at 3 months. Follow other investigations and consulations

Differential Diagnosis of Microcytic Anaemia

- Thalassaemia syndromes
- Certain haemoglobinopathies (Hb C)
- True (classical) iron deficiency secondary to blood loss, iron-poor diet, increased iron needs, *Helicobacter pylori* infection or gastric pathology
- Anaemia of chronic inflammatory diseases
- Certain forms of sideroblastic anaemia
- Genetic forms of iron deficiency anaemia

Case **Two**

60 yr old male complains of :Dizziness, Fatigue, Shortness of breath especially on exertion and Headaches for the last 2 months. He has constipation and weight loss 5 kg over 2 months.

Lab: Hb 8, MCV 72, RDW 19, MCH 20pg. WBC 8000/Normal dif.Plts 380000

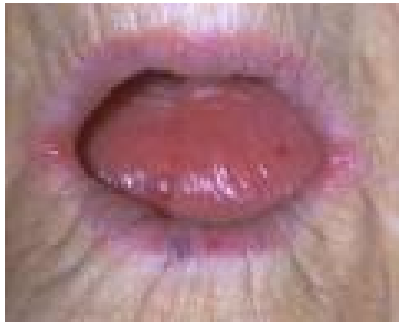
Bld Film: microcytic, hypchromic, anisocytosis, poikilocytosis, Retics (corrected) o.8%

Serum Ferritin 2. FOB x 3 positive in 2.

Case One B

Findings:

Angular Chelittis & Glossitis

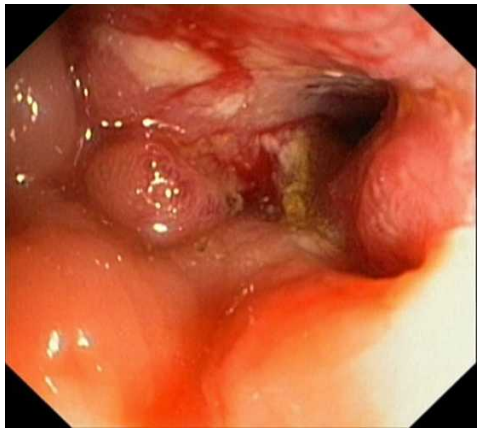


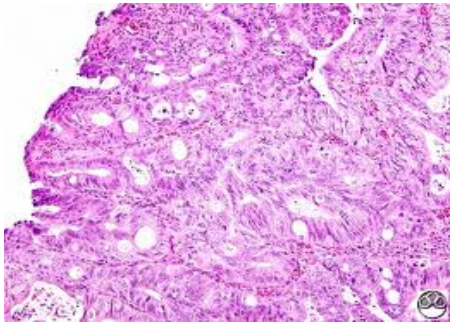
koilonychia

after doing Colonoscopy > biopsy > histology

Diagnosis: Colon adenocarcinoma Mod. dif.

causes chronic blood loss > IDA





Always Look for a cause for IDA.

Anemia must have a full identification

Anemia is **not a final diagnosis**

IRON DEFICIENCY ANEMIA **IS NOT** A DIAGNOSIS PER SAY.

ALWAYS PUT A LABEL TO IT:

IDA DUE TO UPPER GI BLEEDING DUE TO GASTRIC CANCER