13/8/2019

Anaemia

→ Anaemia is a group of disease charcterized by a decrease in either Haemoglobin (8) the volume of RBCs. which results in used oxygen carrying capacity.

Classification:
- → Based on morphology of RBCs.
- → Etiology
- → Pathophysiology.

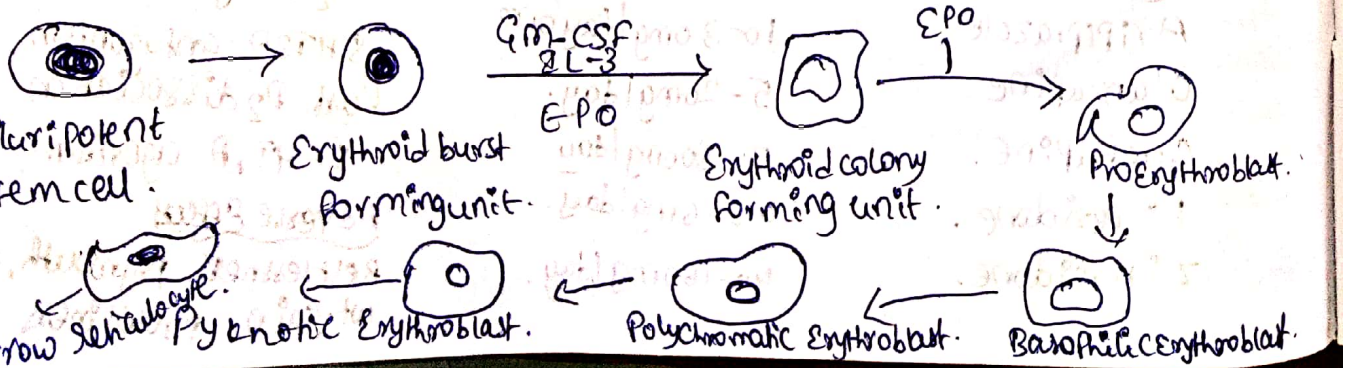
→ vitamin B_{12} deficiency.
→ folic acid deficiency.
→ Iron deficiency
→ sickle cell anaemia.
→ Thalassemia.
→ Hemolytic anaemia.
→ chronic disease Anaemia.

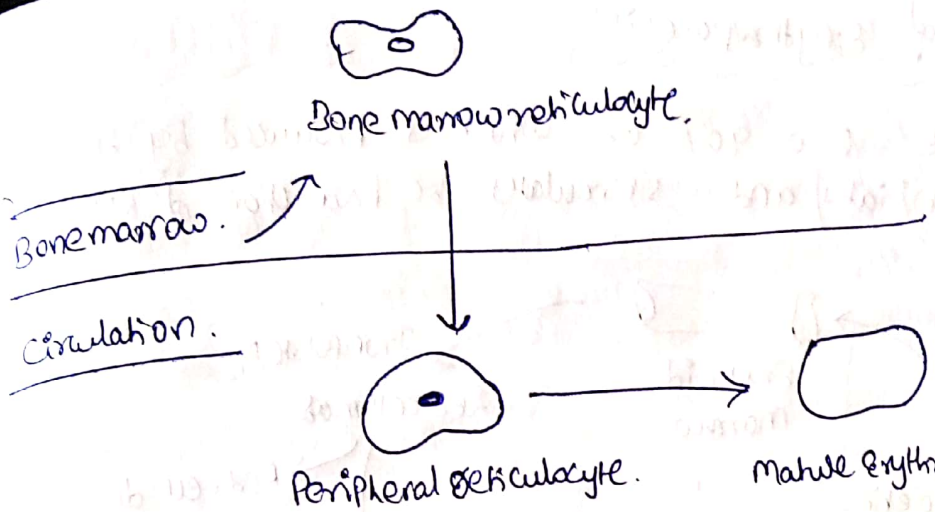
Anaemia classified by RBC size.

Macrocytic anaemia. (large sized RBCs)	Microcytic anaemia (small RBCs)	Normocytic anaemia. (normal size but less number of RBCs)
Eg: vit B_{12} folic acid	Eg: Iron deficiency anaemia.	Eg: Chronic disease.

Development of RBCs:

→ In humans RBC's are formed in marrow. of the vertebrae, ribs, sternum, clavicle, pelvic, crest & proximal epiphyses of the long bones.





GM-CSF - Granulocyte macrophage colony stimulating factor.

→ Pluripotent stem cell yields an Erythroid burst forming unit.

→ EPO, Interleukins, GM-CSF stimulate this cell.

↓

Erythroid colony forming unit.

↓

EPO is sensitive to this colony unit

↓

formation of proErythroblasts.

↓

Basophilic Erythroblasts → Polychromatic Erythroblasts → Pyknotic Erythroblasts → Reticulocytes.

↓

Erythrocytes.

→ During this process the nucleus becomes smaller with each division finally disappearing. in the normal Erythrocyte.

→ Hb & iron are incorporated into the gradually maturing RBC which is eventually is released from the marrow into the circulating blood as reticulocyte.

→ maturation take place approximately in 1 wk

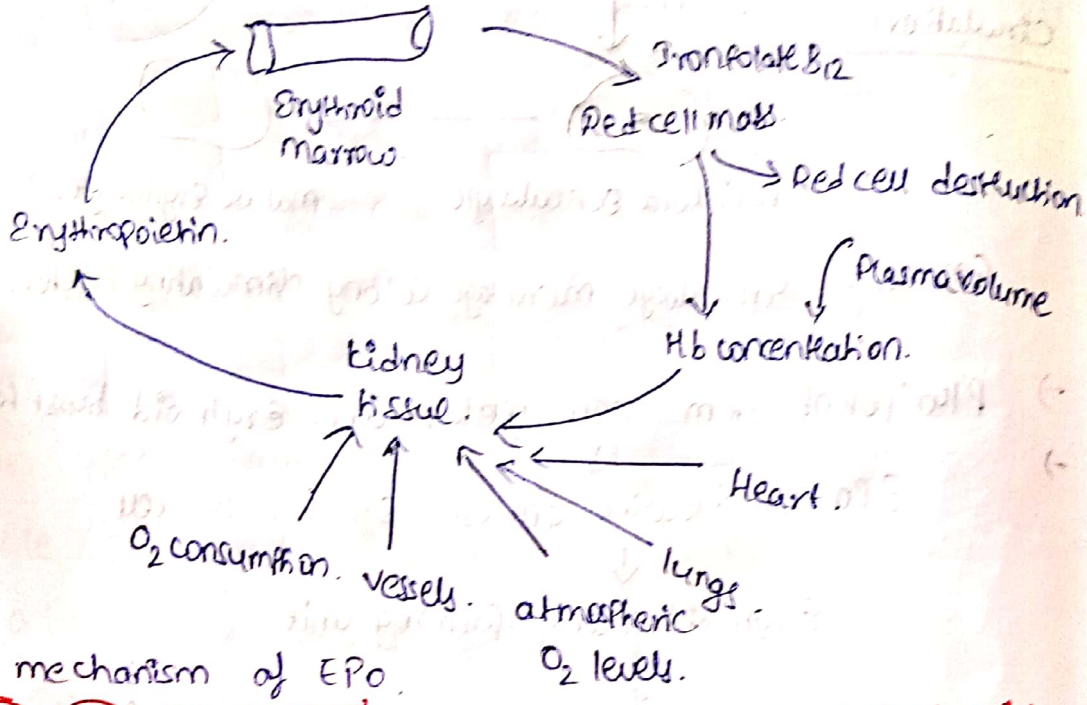
→ Reticulocyte loses its nucleus & becomes an Erythrocyte within several days.

→ The circulating Erythrocyte is a non-nucleated, nondividing cell.

→ more than 90% of protein content of the Erythrocyte consists of the oxygen

Stimulation of Erythropoiesis:

→ The hormone EPO 90% of which is produced by the kidneys, initiates and stimulates the production of RBCs.



main mechanism of EPO.

→ Preventing apoptosis / Programmed cell death of Erythroid Precursor cells.

→ Proliferation & subsequent maturation.

~~oxygen tension~~

↓ tissue oxygen concentration signals.

↓

Kidneys to ↑se the production & release of EPO into the plasma.

↓

↑se Production & maturation of RBCs.

→ under normal circumstances RBC mass kept at an almost constant level by EPO matching new erythrocyte production to the natural rate of loss of RBCs.

→ Reticulocytosis is an indication of ↑sed RBC Production.

Synthesis of Hemoglobin:

→ Hb consists of protein component with two α-chains & two β-chains.

→ Each chain linked with heme group consists of a Porphyrin ring structure with an iron atom chelated at its center, which is capable of binding Oxygen.

Substrate succinyl co.A
↓
glycine requires presence of.
Pyridoxine phosphate (vit B_6) as a catalyst.

→ following its synthesis in the cytoplasmic mitochondria of the RBC.

Heme diffuses into Extramitochondrial space.
↓
Combines with the completed α & β-chains.
↓
Formation of Hb.

→ When RBC's destruction exceeds marrow Production capacity. anaemia develops, the Hb value ↓se to a steady state level at which Production = destruction.

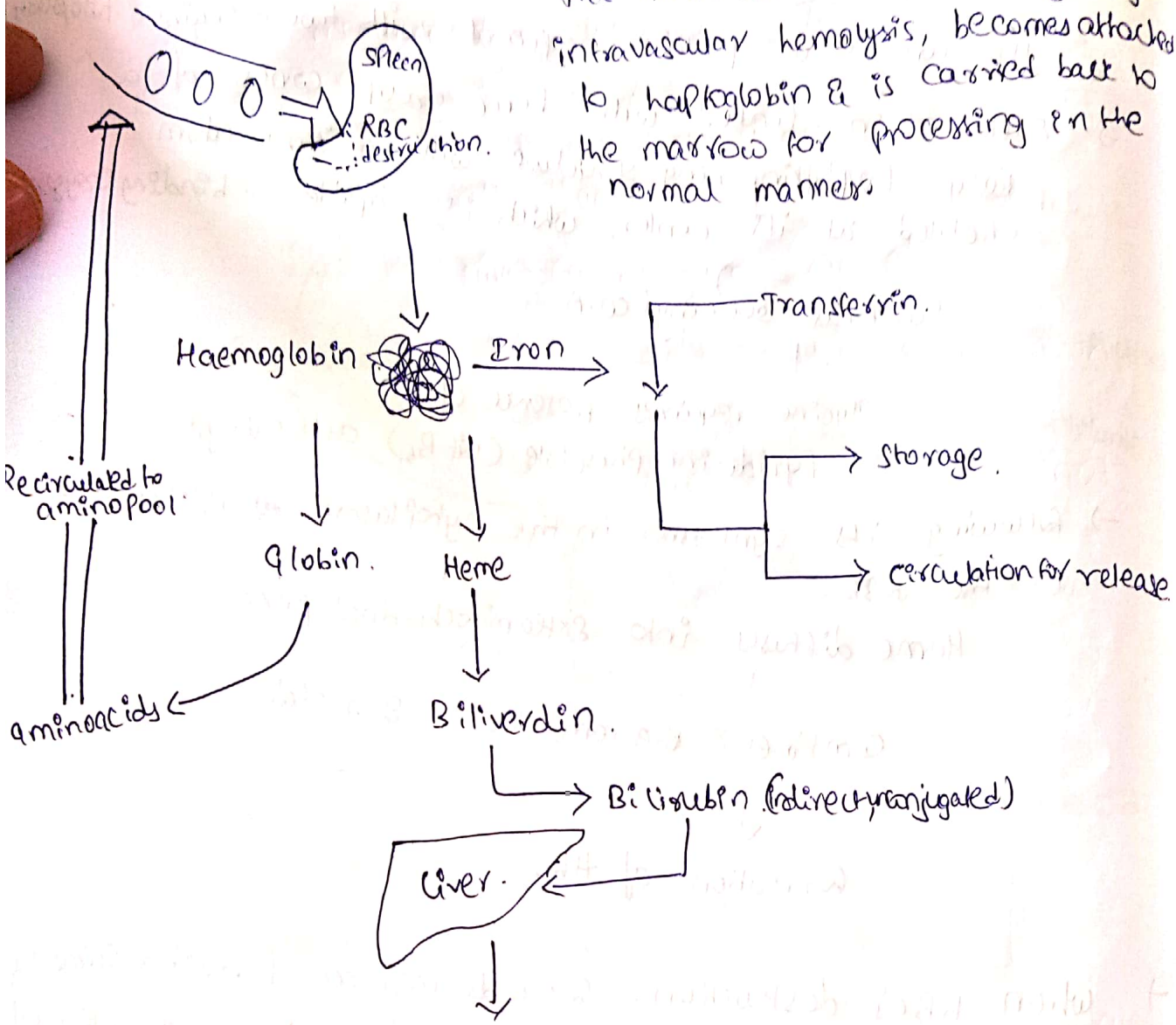
Destruction of RBCs:

→ Phagocytic breakdown destroys older blood cells, Primarily in the spleen but also in the bone marrow.

→ Heme oxygenase acts on the porphyrin heme structure to form biliverdin & to release its iron.

→ Iron returns to the iron pool to be reused, although biliverdin is further catabolized to bilirubin.

The Hb in RBCs, which is destroyed by intravascular hemolysis, becomes attached to haptoglobin & is carried back to the marrow for processing in the normal manner.



Clinical Presentation of Anaemia:

Signs & Symptoms:

- Fatigue.
- Dizziness.
- Irritability.
- weakness.
- vertigo
- Shortness of breathe
- Chest pain.
- Tachycardia.
- Used mental activity.

9/8/19 Diagnostic tests:

① Hb: gld amount of Hb per volume of whole blood.
→ higher value is seen in males due to stimulation of RBC production by androgenic steroids.

② Haematocrit: % actual volume of RBCs in a unit volume of whole blood.
It is approximately 3 times the Hb value.

③ RBC: actual count of RBCs per unit of blood.

④ RBC indices. — MCV (average volume of RBCs)
MCH. (amount of Hb in RBC).

MCHC: mean cell Haemoglobin concentration.
The conc^n of Hb per volume of cells is the MCHC.

⑤ Total Reticulocyte count: Indirect assessment of new RBC (1%) production.
↳ How quicely immature RBCs are produced by bone marrow & released into the blood.

⑥ Red cell distribution width: (RDW)
Higher RDW is the more variable. is the size of RBCs.

⑦ Peripheral blood smear: provides.
→ Information on the functional status of bone marrow & defects in RBC production.
→ On variations in cell size & shape.

⑧ Serum iron: The level of serum iron is the conc^n of iron bound to Hansferrin.
↳ approximately one third bound to iron

(a) Total iron binding capacity:

→ An indirect measurement of the iron-binding capacity of serum transferrin.

→ TIBC evaluation is performed by adding an excess of iron to plasma to saturate all transferrin with iron.

→ Each transferrin molecule carry two iron atoms.

→ The excess iron is removed & the serum iron conc^n determined.

→ Unlike the serum iron level the TIBC does not fluctuate over hours (&) days.

→ TIBC usually is higher than normal when body iron stores are low.

(b) Percentage transferrin saturation:

$$\text{Transferrin saturation} = \frac{\text{serum iron}}{\text{TIBC}} \times 100.$$

It reflects the extent to which iron binding sites are occupied on transferrin & indicates the amount of iron readily available for Erythropoiesis.

Transferrin normally is 20% to 50% saturated with iron.

(c) Serum ferritin:

→ Concentration of ferritin (storage iron) is proportional to total iron stores

→ Ferritin levels indicate the amount of iron stored in the liver, spleen, & bone marrow cells.

① Iron deficiency anaemia:

→ The normal iron content of the body is approximately 3 to 4 g.

→ Iron is a component of Hb, myoglobin & cytochromes.

2g - Hb.

140mg - proteins such as myoglobin.

3mg of iron is bound.

1000mg of iron exists as storage iron in the form of ferritin. or hemosiderin.

→ The rest of the iron is stored in other tissues such as cytochromes.

→ Hepicidin is a regular of intestinal iron absorption. iron recycling, & iron mobilization from hepatic stores.

Hepicidin is a peptide made in liver distributed in plasma & excreted in urine.

↓

Hepcidin inhibits efflux of iron through ferroportin.

↓

~~Hepcidin inhibits efflux of iron~~

Hepcidin synthesis is increased by iron loading & ↓sed by anemia & hypoxia.

↓

Hepcidin is induced during infections. & inflammation. which allows iron to sequester in macrophages hepatocytes & enterocytes.

→ Daily recommended dietary allowance for iron is 8mg. in adult males.

Post menopausal females - 18mg. in menstruating females.

→

Etiology:

→ Prolonged iron negative balance.
  ↳ ↑sed loss of iron.
  ↳ ↓sed intake absorption.

→ Trauma

→ malignancies.

→ Pregnancy.

Pathophysiology:

→ Iron is a cofactor for oxidative metabolism, dopamine & DNA synthesis and free radical function in neutrophils.

→ Iron deficiency anaemia can be associated with abnormal neurotransmitter function & altered immunologic & inflammatory defenses..

→ Impaired Hb synthesis d/t reduced iron supply.

→ Generalized defect in cellular proliferation.

→ Survival of Erythroid precursor & Erythrocytes is reduced.

Treatment:

Dietary supplementation:

Good sources of Iron.

Total cereal	1 cup	18 mg
Grape nut cereals	1 cup	18 mg
Instant cream of wheat	1 cup	8.2 mg
Instant Plain oat meal	1 cup	6.7 mg
Wheat germ	1 oz	2.6 mg
Baked potato	1 medium	2.7 mg.

Dose of iron = whole blood haemoglobin deficit (g/dl) x body wt. (lb).

Calculating Doses of Parenteral Iron Dextran

For patients with iron deficiency anaemia.

Adults + children > 15kg.

Dose(mL) = 0.0442 (Desired Hb - Observed Hb) x LBW + (0.26 x LBW)

LBW males = 50kg + 2.3 x (inches over 5ft)

LBW females = 45.5kg + 2.3 x (inches over 5ft).

children 5-15 kg.

Dose (mL) = 0.0442 (Desired Hb - Observed Hb) x W + (0.26 x W).

for pts with anemia secondary to blood loss.

mg of iron = blood loss x Haematocrit.

Oral iron products.

	Elemental iron %	Elemental iron Provided.
Ferrous Salt.	20%.	60-65mg/324-325mg tablet. 18mg iron/5mL syrup 44mg iron/5mL Elixir. 15mg iron/0.6ml drop.
Ferrous Sulfate.	30%	65mg/200mg tablet. 60mg/187mg tablet. 50mg/160mg tablet.
Ferrous Gluconate.	12%	36mg/325mg tablet.
Ferrous fumarate.	33%.	33mg/100mg tablet. 63-66mg/200mg. tablet. 15mg/0.6mL drop.
Carbonyl iron	100%.	50mg Caplet.

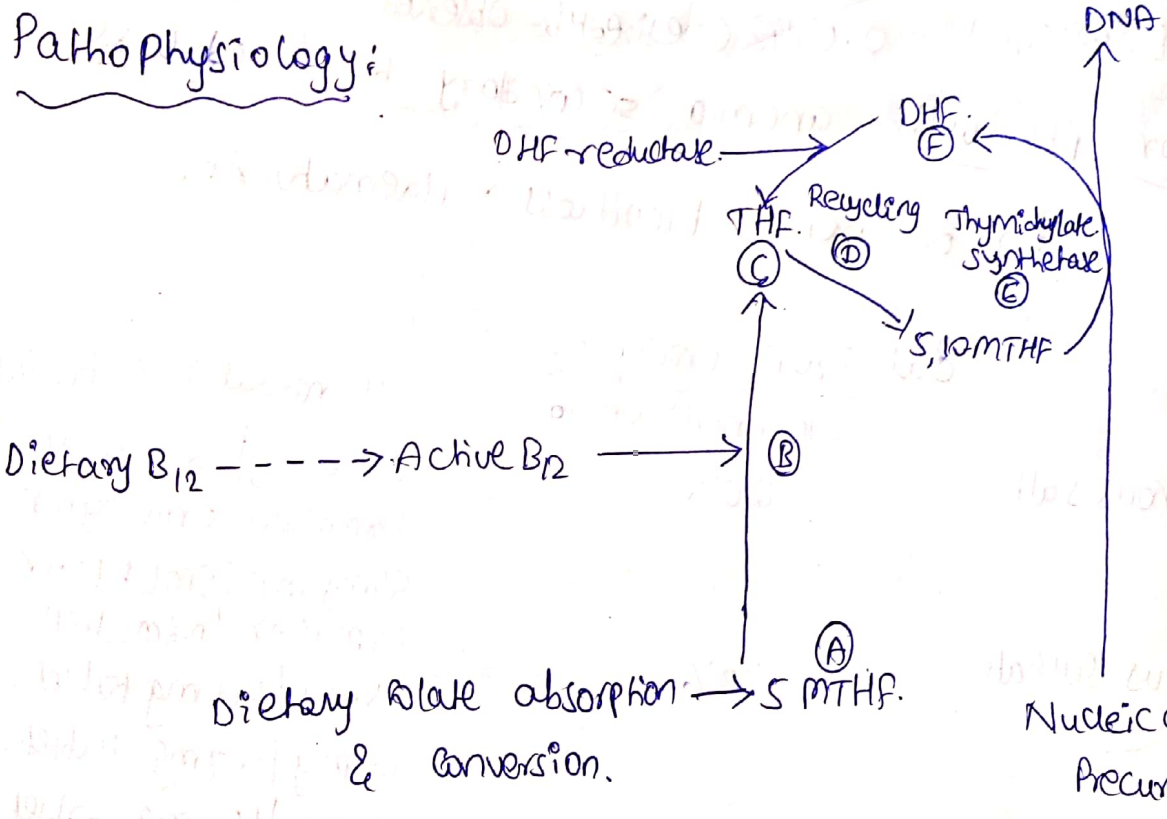
Megaloblastic Anemias:

→ Macrocytosis as seen in megaloblastic anemias, is caused by abnormal DNA metabolism resulting from Vit B_{12} (&) Folate deficiency.

Etiology:

→ Inadequate intake.
→ Malabsorption syndromes
→ Inadequate utilization.
→ Chronic alcoholics.

Pathophysiology:

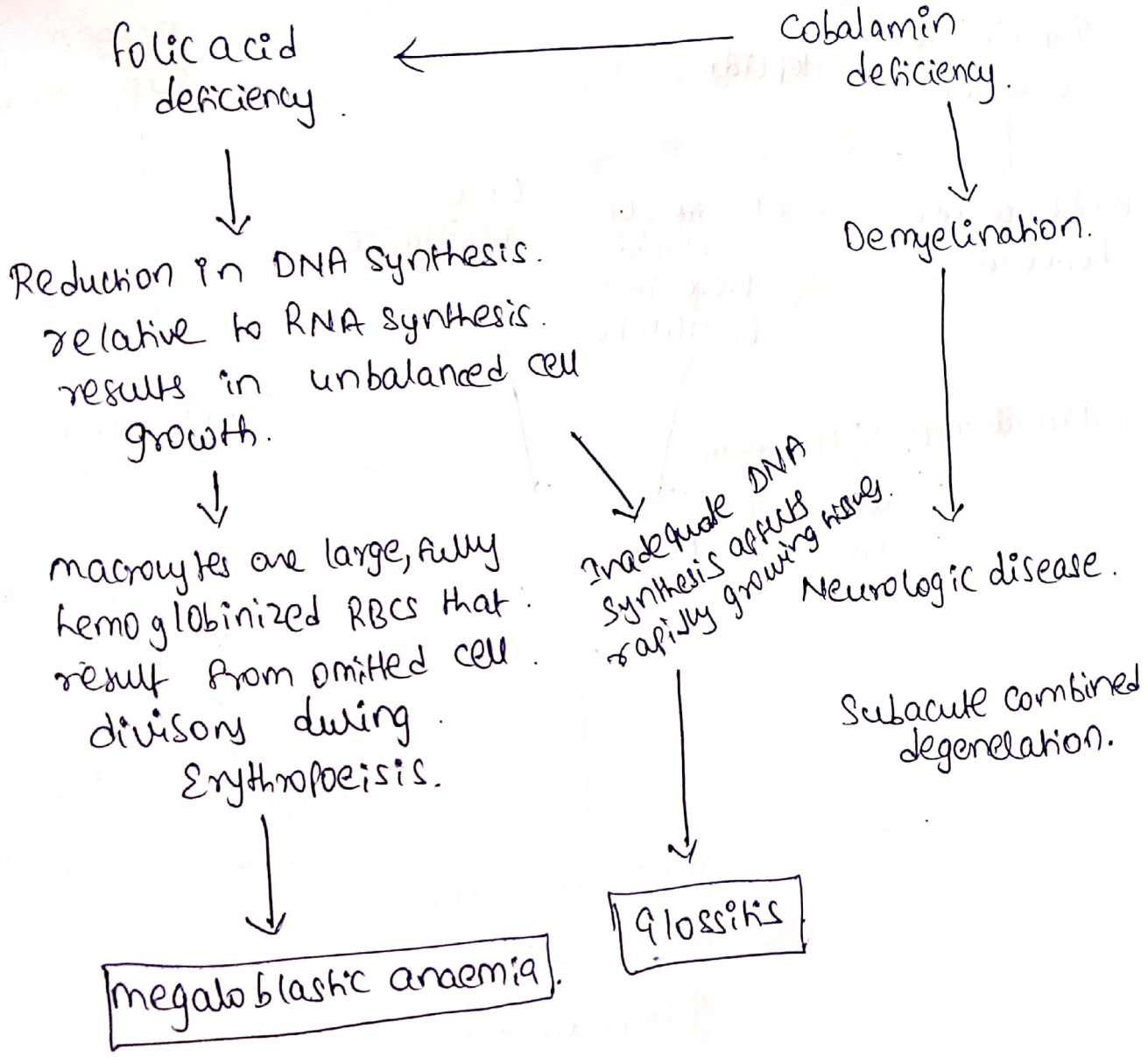


→ Vit B_{12} works closely with folate in the synthesis of building blocks for DNA & RNA.

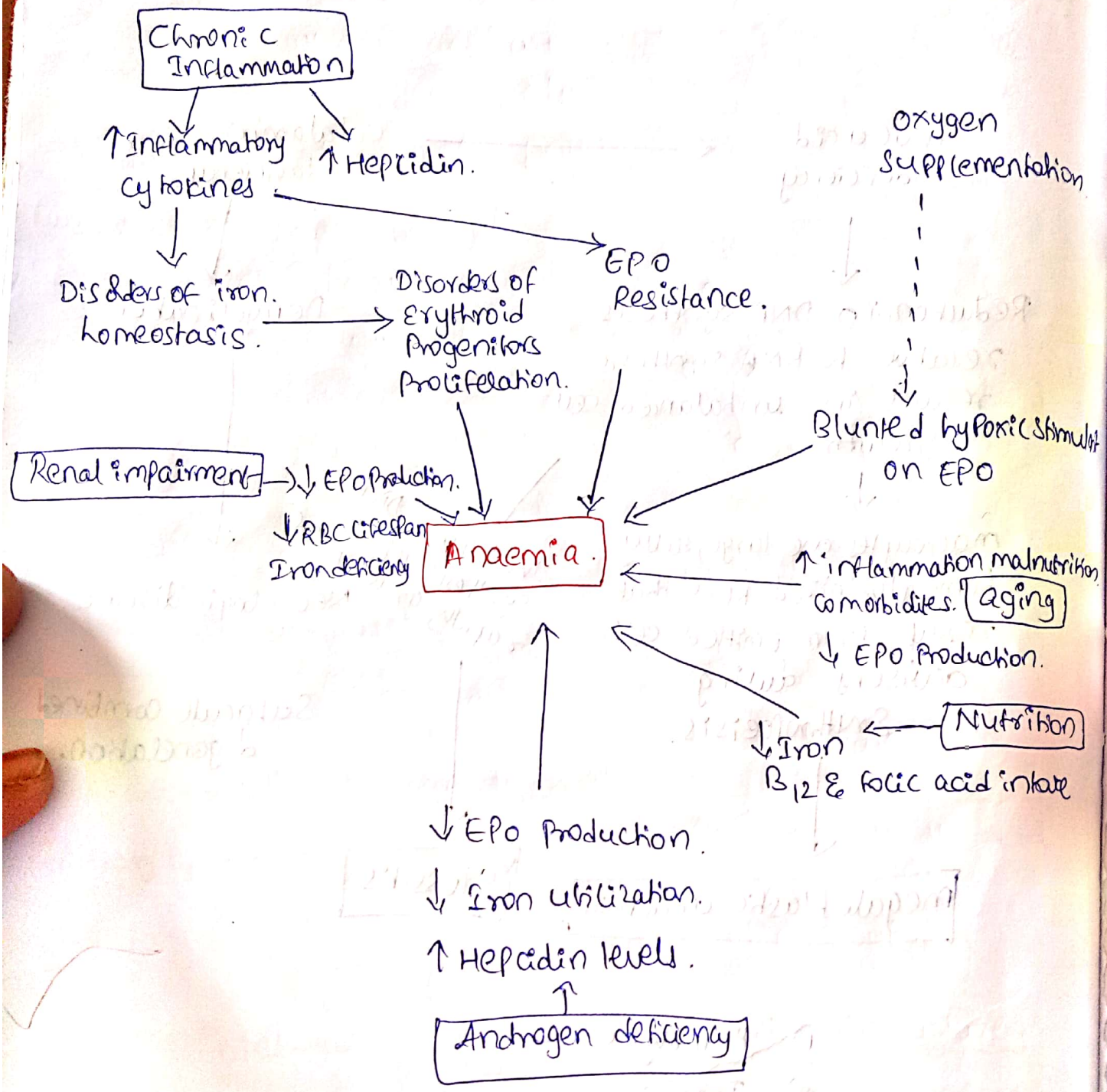
→ Vit B_{12} is essential in maintaining the integrity of the neurologic system.

→ Vit B_{12} plays a role in fattyacid synthesis & Energy production.

Relationship b/w cobalamin & folate deficiency:



1) Hemolytic
2) Iron
3) Pernicious.
4)



→ Influencing factors of RBC maturity.

vitamin B_{12}.

folic acid (DNA metabolism).

Thalassemia

→ A blood disorder involving lower than normal amount of an oxygen carrying Protein.

→ Thalassemia is an inherited blood disorder charcterised by less oxygen carrying protein & fewer red blood cells in the body than normal.

Types of thalassemia:

Alpha thalassemia → Results in the genes for the α-globin component of Hb.

Beta thalassemia.

α-thalassemia.

Etiology:

→ Mutation in the DNA of cells that Produce Hemoglobin

→ Inheritance.

Pathophysiology:

→ Results when there is disturbance in α-globin from any or all four of the α-globin genes.

→ α-globin genes, are Encoded on Chromosome 16.
β-globin gene, are Encoded on Chromosome 11.

→ A normal person carries a linked pair of α-globin genes each 2, from maternal & Paternal Chromosome,

There α-thalassemia occurs when there is a disturbance in production of α-globin from any or all four of the α-globin genes.

→ Either functional point mutations, frame shift mutations nonsense mutations, & chain termination mutations occur within or around the coding sequences of the α-globin gene cluster hemoglobin is impaired.

→ when that occur protein synthesis may be inhibited.

→ Normal production of α-chains is absent which results in excess production of gamma globin chains in the fetus & newborn (d) β-globin chains in adults & children.

→ The β-globin chains are capable of forming soluble tetramers. (β-4 or HbH)

→ α-form Hb is still unstable & precipitates with in the cell

↓

forming insoluble Heinz bodies.

↓

Heinz bodies damage the RBCs.

↓

further damage to Erythrocyte precursors.

↓

Ineffective Erythropoiesis in the bone marrow

↓

hypochromia & microcytosis of circulating RBCs.

Clinical Presentation

Signs & symptoms:

→ Shortage of RBCs. (Anaemia)
→ Paleskin.
→ weakness.
→ fatigue
→ Enlarged liver & spleen.
→ Abnormal in urinary system.
→ Premature delivery.
→ Jaundice

Treatment:

→ Regular blood transfusions & folate supplements.

→ Persons who receive significant number of blood transfusions need a treatment called chelation therapy, to remove excess of iron from the body.

→ Bone marrow transplant (esp in children)

→ Folic acid - Oral (250-1000mcg per day)

Folic acid - Injection. (1-5 mg/day (I.V, I.M, & S.C).

Deferoxamine - Injection I.M 1000 mg initial. then 500 mg every 4 hours for two doses (Total 6g/day based upon condition of patient)

ADRs: blue lips, skin. vision/hearing problems. bloody diarrhea. cough, wheezing, stuffy nose, fever.

S.C - 1000 - 2000mg/day 8-24 hours.

I.V should be used only for pts in a state of cardiovascular collapse & then only by slow infusion Bcoz deferoxamine can cause heart problems. (should not exceed)

Rate of infusion should not exceed 15mg/kg/Hr. for the first 1000mg administered.

β - Thalassemia.

→ It is a genetic blood disorder that reduces the production of Hemoglobin.

→ genetic deficiency in the synthesis of β-globin chains

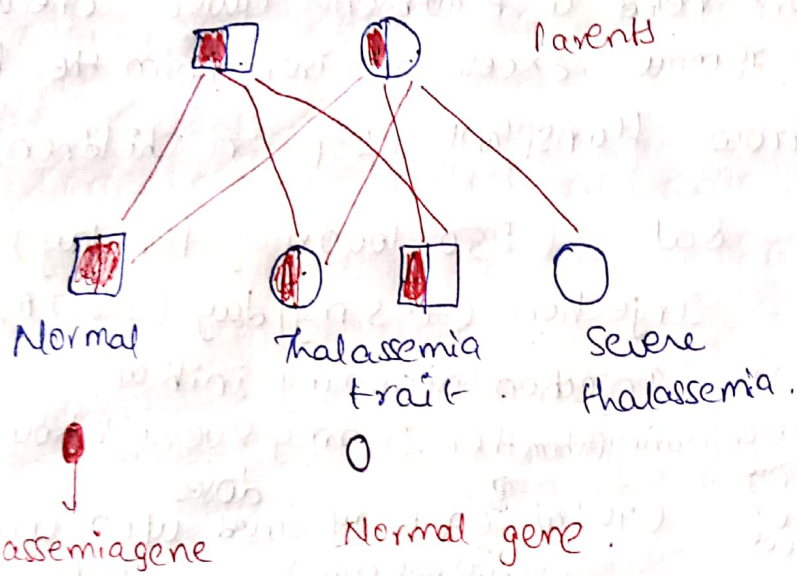
→ Cooley's anemia - severe form - Presence of two abnormal genes — ↓ & complete lack of beta globin production.

Thalassemia minor
└ one normal gene & one with a mutation.

→ mild to moderate anemia.

Etiology & Pathophysiology

→ Inherited in an autosomal recessive pattern. which means both copies of Hemoglobin beta (HBB) gene in each cell have mutations.



→ when there is a mutations in the HBB gene it prevents the production of any beta-globin.

→ absence of beta globin is referred to as beta (β^0) thalassemia.

→ A lack of beta globin leads to a reduced amount of functional hemoglobin.

Clinical Presentation:

→ Fatigue & weakness
→ Pale skin(&) jaundice.
→ Protuding abdomen. & Enlarged spleen & Liver.
→ dark urine.
→ Poor appetite.
→ Abnormal facial bones & Poor growth.
→ Delayed puberty.

Treatment :

Deferoxamine. — 500-1000mg I.M Everyday.

Deferasirox.