



BLOOD PHYSIOLOGY (1+2)

Control of Erythropoiesis, Iron Metabolism and Hemoglobin (3)

Red: very important.

Green: only found in males' slides. Purple: only found in females' slides.

Gray: notes.

Physiology Team 436 - Foundation block lectures 8+9+10

Lecture: If work is intended for initial studying. Review: If work is intended for revision.

Objectives

- Describe : physical and chemical characteristics of blood
- Describe: Cellular and non-cellular blood components
- Describe: different stages of RBC differentiation.
- Describe: features of RBC maturation
- Describe: regulation of RBC production and erythropoietin hormone secretion in response to hypoxia.
- Describe: essential elements needed for RBC formation
- Describe: the process of Vitamin B12 absorption and its malabsorption.
- Describe: the fate of old RBC.
- Describe: anemia and its causes
- Recognize: blood functions.
- Recognize: clinical conditions associated with high level of erythropoietin in the blood.
- Recognize: sites of RBC formation at different developmental age.

- Recognize: the causes of polycythemia.
- ▶ Define: Erythro-poiesis; leuco-poiesis, thrombo-poiesis.
- Recognize: hemoglobin structure and its functions.
- Discuss: Iron metabolism (absorption, storage and transport).
- Describe essential elements needed for RBC formation.
- Describe the process of Vitamin B12 absorption and its malabsorption.
- Recognize hemoglobin structure and its functions.
- Discuss iron metabolism (absorption, storage and transport) .
- Describe the fate of old RBC.
- Describe anemia and its causes .
- Recognize causes of polycythemia .
- Understand steps of erythropoiesis & its regulation.

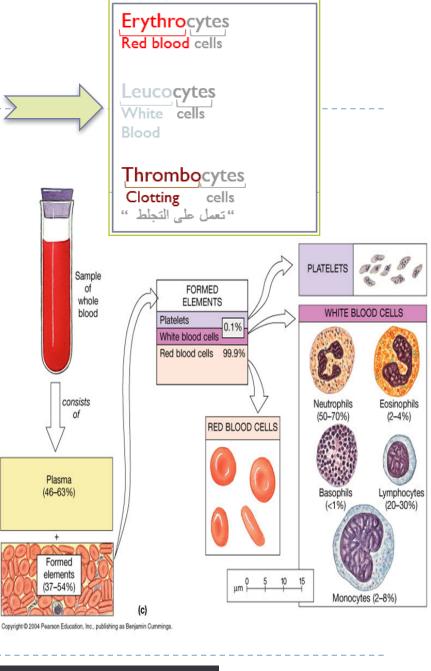
Blood Composition

I.Cellular components:

- Red Blood Cells(Erythrocytes)
- White BloodCells(_eucocytes)
- Platelets (Thrombocytes)
- NOTE: red blood cells are in millions
- Platelets are hundred thousands
- white blood cells are in thousands.

2. Plasma (ECF):

- 98% water + ions
 + plasma proteins e.g.
 (Albumin, globulin,
 Fibrinogen)
- #notice: it's the same ionic composition as interstitial fluid. (Na, K, PO4, etc)



Characteristics of Blood

Viscosity

- 3-4 times than Water.
- Blood relative viscosity: (4-5) mainly depends on the numbers of RBC.
- Plasma relative viscosity: (1.6-2.4) is mainly involved in plasma protein.

pН

- Slightly alkaline, with a pH of 7.35-7.45.
- It has a salty metallic taste and is Sticky.
- Hb acts as blood buffer.

Temperature

• about 37C (slightly higher than normal body temp).

Color

- Bright red = O2 rich;
- Dull red = O2 poor

Osmolarity

 Plasma osmolality is about 300 mmol/L (Equal to 0.9% NaCl Solution=Isotonic).

Regeneration

• Tremendous regenerative capacity.

Characteristics of Blood

Plasma osmotic pressure:

- Is 300 mmol/L or 770kPa
- Crystal osmotic pressure: results from NaCl and modulates water distribution between inside and outside cells.
- Colloid osmotic pressure: results from albumin and regulates water distribution between inside and outside of capillaries.

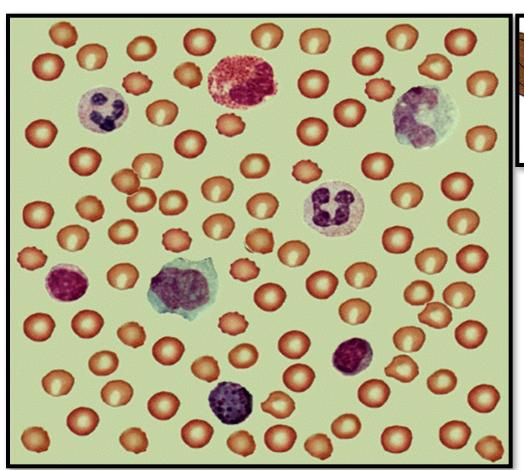
Specific gravity:

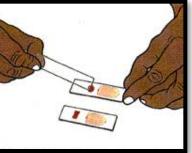
- Total blood: (1.050-1.060) more influenced by RBC.
- Plasma: (1.025-1.030) more influenced by plasma protein.
- RBC: (1.090-1.092) more influenced by hemoglobin.

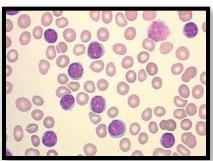
Erythrocyte sedimentation rate (ESR)

- It the red blood cell descending distance per hour.
- Normal male 0¬15mm/h.
- Normal Female 0¬20mm/h.

Blood Film





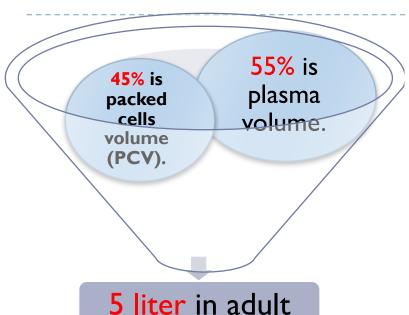


نقطه دم نضعها على الشريحه الأولى ثم نحضر شريحه أخرى ونسحب الدم قليلا (مثل المناكير لما تسحبينه بالفرشه).

نستفيد من الـ Blood Film:
القدرة على معرفة لو كان هناك انيميا
او لا وشكل الـ Cells
ونستطيع أيضا أن نرى الـ White
وكم عددها.

Blood Volume

The volume of blood cells in a sample of blood after it has been centrifuged (separation of contents).



Plasma: Straw colored liquid that serves as a transport medium for blood and platelets. It is called **Serum**

when fibrinogen removed after coagulation.

Ratio of the volume of red blood cells to the total volume of blood.

يساعدنا في التشخيص أشياء كثير زي الانيميا.

(coagulating factor) is Plasma = 55% of whole blood Plasma contains: Electrolytes, clotting **Platelets** factors, antibodies, "Buffy coat" blood gases, nutrients, <1% and wastes. White blood cells Packed cell Red blood cells = volume, or-45% of whole blood hematocrit

every month half a liter of blood due to menstruation

Because females lose

Males => 5 to 5.5 L

Females => 4 to 4.5

Functions of the Blood

I. Transport

- Respiration: O2, CO2
- > Trophic: nutrients to the tissue
- Excretive: waste products (metabolites) from tissues to excretory organs
- Regulative: hormones
- Waste product ex)

metabolism process.

2. Homoeostasis

Urea (creatinine) + product for any

- Regulation of:
 - I) Body temperature by redistributing blood between skin and internally
 - 2) ECF pH
 - 3. Protecting against Infections: White Blood Cells, Antibodies
 - 4. Blood clotting: to prevent blood loss
 - Homoeostasis => Keeping the internal environment constant

[او راح تموت الخليه]

Blood stop

Hemostasis => Stopping of the flow of blood [stop bleeding]

Formation of Blood Cells: Haemopoiesis

Erythro-poiesis:

Formation of RBC (erythrocytes)

Erythropoiesis RBC formation" تصنیع

Leuco-poiesis:

Formation of WBC (leucocytes)

Leucopoiesis WBC formation

Thrombo-poiesis:

Formation of platelets (thrombocytes)

* Note: Active cellular marrow is called red marrow; inactive marrow that is infiltrated with fat is called yellow marrow.

Thrombopoiesis
Clotting formation
cells

Cyte: Mature cell
Blast: Still not mature cell

Red Blood Cells (RBCs)

Surface view



Sectioned view

Males-Il aie lia

الشهرية.

عند الـ Females أقل بسبب الدورة

الوحدات غير مهمه مو مهم نعرفها لما تجي بالاختبار يجيبون كل الخيارات نفس الوحده. لكن الارقام حفظ.

Functions

- ➤ Transport of: O2 and CO2
- ➤ Buffer (keeps pH level at 7.4)

لان الدم فيه هيموجلوبين فهو يحاول يوازن الـ pH

Shape & Size

>Flat Biconcave Disc

الزيادة مساحة السطح.

- **≻Non-nucleated**
- **≻No** mitochondri

وجود النواة في ال RBCتلزم في حالة تصنيع البروتين (الهيمو جلوبين), و"بعد النضج التام "تختفي النواة لتنقل أكبر كمية من الاكسجين – على الهيموجلوبين- وبكفاءة اعلى.

- >Flexible
- ≻Diameter 7-8µmx2.5µmx1 µm.
- **Average volume 90-95 μm3**
- \triangleright Number = 4.7 5 x 106
- \rightarrow Hb = 14-16 g/dl in the blood
- Plt is negatively charged

ثلاث مزايا بشكل الـRBCs مهمه جداً:

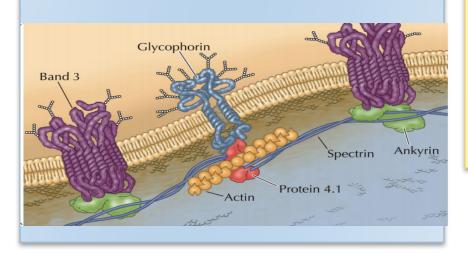
- I. <u>Flexible</u> so it can go through the capillaries.
- 2. Flat biconcave is the best shape to let the gases exchange easily.
- 3. <u>Storage</u>: the shape of the RBCs can store big amounts of RBCs so it allows more gas exchange.

 زی اثاث ایکیا

Red Blood Cells Cytoskeleton

Skeletal protein network

- Spectrin
- Actin
- Ankyrin
- Tropomyosin
- Proteins 4.1 and 4.9



The red cell, as it continuously circulates, must be able to undergo extensive passive deformation and to resist fragmentation. These two essential qualities require a highly deformable yet remarkably stable membrane. Blood cells that lyse(breakdown) without difficulty at low ionic strength are a sign of Hereditary Spherocytosis.

RBCs Enzyme- Carbonic Anhydrase

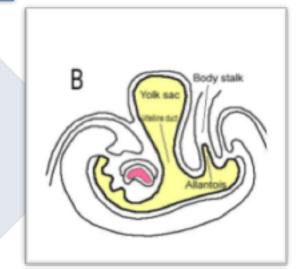
Carbonic anhydrase is an enzyme that catalyzes the reversible reaction between carbon dioxide (CO2) and water to form carbonic acid (H2CO3), increasing the rate of this reaction several thousand fold. It plays a major role in CO2 transport.

Production of RBCs

RBCs are only nucleated in fetus

Inutero:

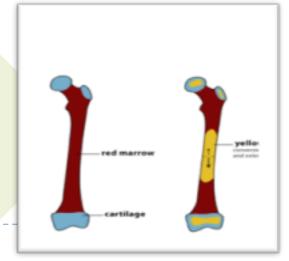
- Early few weeks (Ist 4 months): embryo nucleated RBCs are formed in yolk sac. (nucleus is needed for division)
- Middle trimester: mainly in <u>liver & spleen & lymph nodes.</u>
- Last months: RBCs are formed in bone marrow of all bones

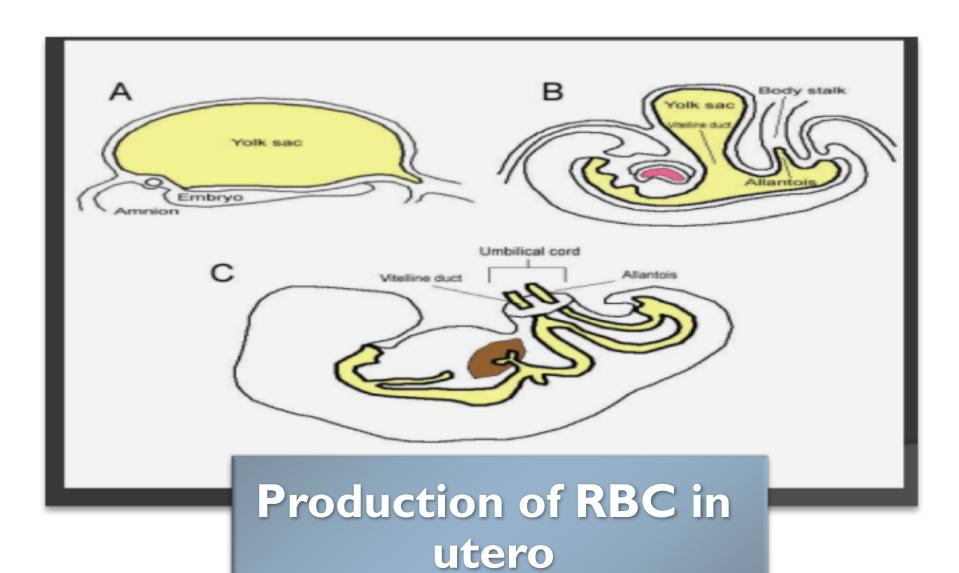


After Birth:

- P Bone marrow of flat bones (e.g. scapula, skull,..) continue to produce RBC into adult life.

 In children: all bones produce RBCs until 5 years old.
- **Shaft** of long bones <u>stop</u> producing RBC at puberty while **epiphysis** <u>continues</u>.
- In adults: after 20, membranous bones such as vertebrae, sternum, ribs, and ilia produce RBCs



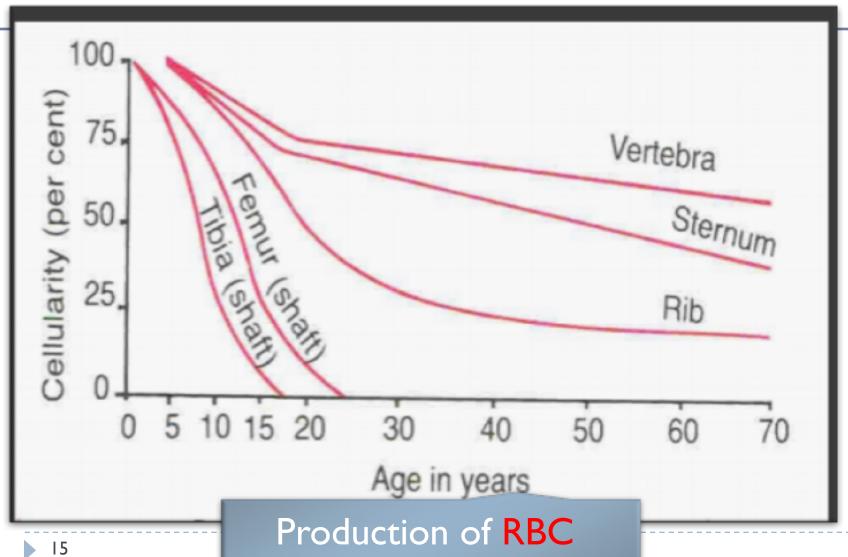


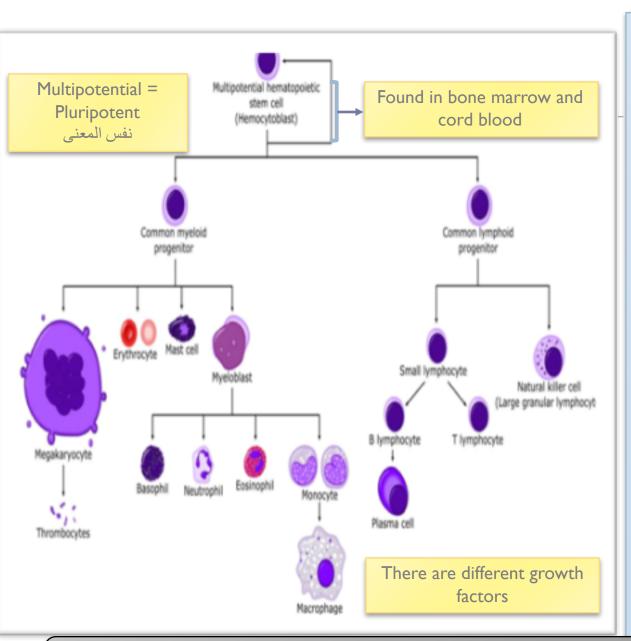
Normal bone marrow conversion yellow marrow conversion begins centrally red marrow and extends periperally and axially cartilage Infant Childhood Adolescent Adult <1 year 1-10 years 10-20 years >25 years

Note: Children need RBC more than adults for their growth.

As mentioned in the previous slide: (After birth)

- -Flat bones (Sternum, Ribs) and the Vertebras (Irregular bones) continue to produce RBCs.
- -Shafts of long bones (Femur, Tibia) stop producing RBCs after puberty.





شرح محتوى الصورة:

All blood cells are formed from (stem cells) stem cells have two paths:

I- First Path:

"myeloid" → that forms
RBCs + some types of
WBCs +

2-Second Path:

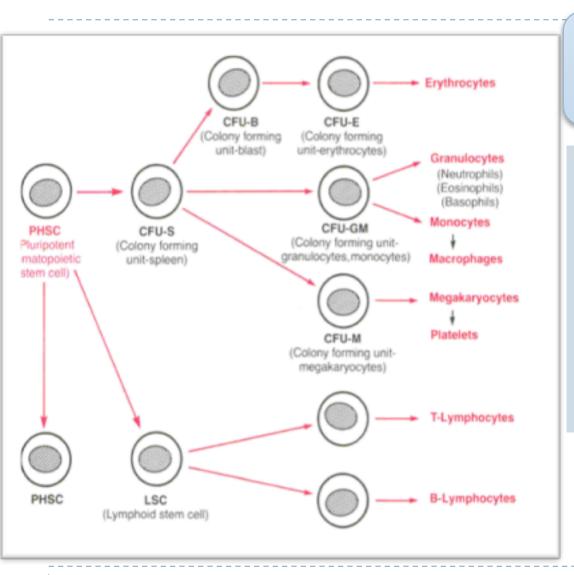
" lymphoid" → that forms lymphocytes (another type of WBC)

Lymphocytes are always special ;)

Note: Stem cells can differentiate into a lot of different cells.

Myeloblast gives white blood cells.

Genesis (Production) of RBCs



Pluri-potential hemato-poietic stem cells: give rise to (create) all the other blood cells

committed cells

- Committed stem cells for RBC
- Committed stem cells for WBC

Growth of different stem cells are controlled by different growth factors

Note

Colony-Forming Unit

cells produce colonies of their own type

Stages of RBCs Differentiation (development): 7 Days

Committed stem cell:

Proerythro-blast (first identifiable cell)

Basophil erythro-blast

Poly-chromatophil erythro-blast

Ortho-chromatic erythro-blast

Reticulocytes (loses nucleus)

Mature erythrocytes

Reticulocytes: First cell to appear in Circulation Matures in 24-48 Hours.

Contain remnants of the Golgi apparatus & mitochondria.

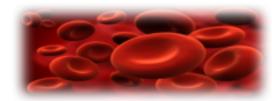
In cases of rapid

fast RBC

production →

reticlocytes in

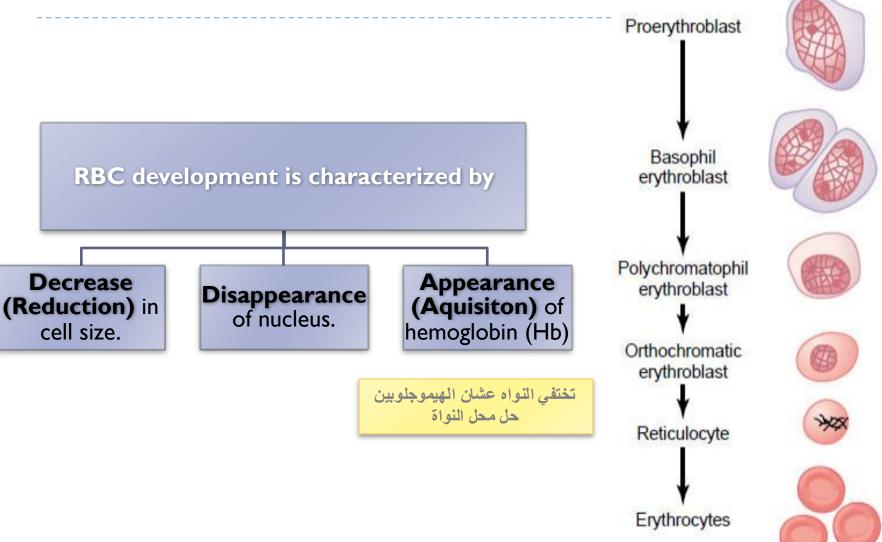
the circulation



Note: RBC goes into stages to get its concave structure, **Reticulo-cyte** is the stage where the cell loses its nucleus and is covered by a net.

GENESIS OF RBC

Erythro-poiesis

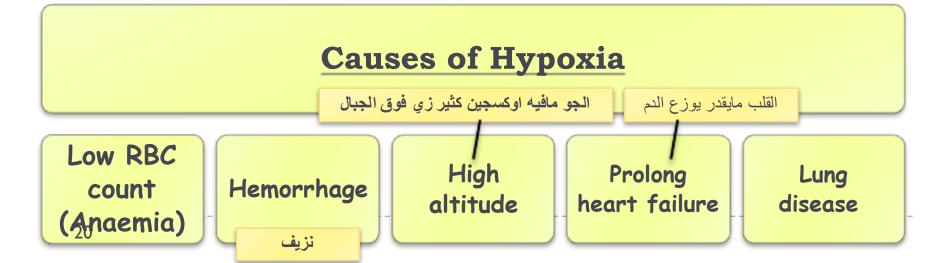


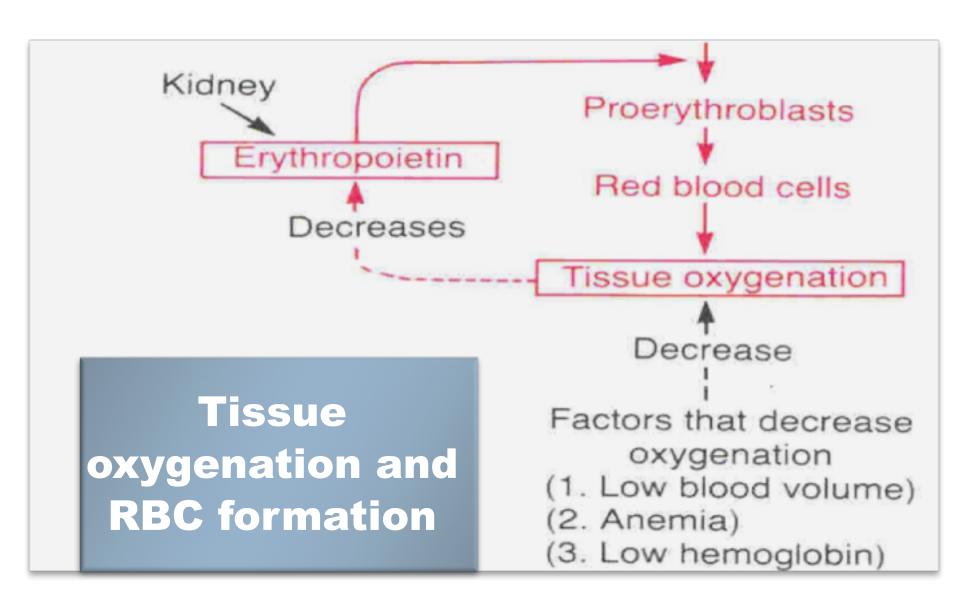
Regulation of RBC Production

- Erythro-poiesis
- stimulated by: erythro-poietin hormone

لما يكون مستوى الاوكسجين في الدم قليل (و هذا يسمى hypoxia) تروح الـ kidney عثنان توازن الـ اسمه Erythropoietin

(which is produced by: the kidney in response to hypoxia (low oxygen in the blood)





Erythro-poietin (Hormone)

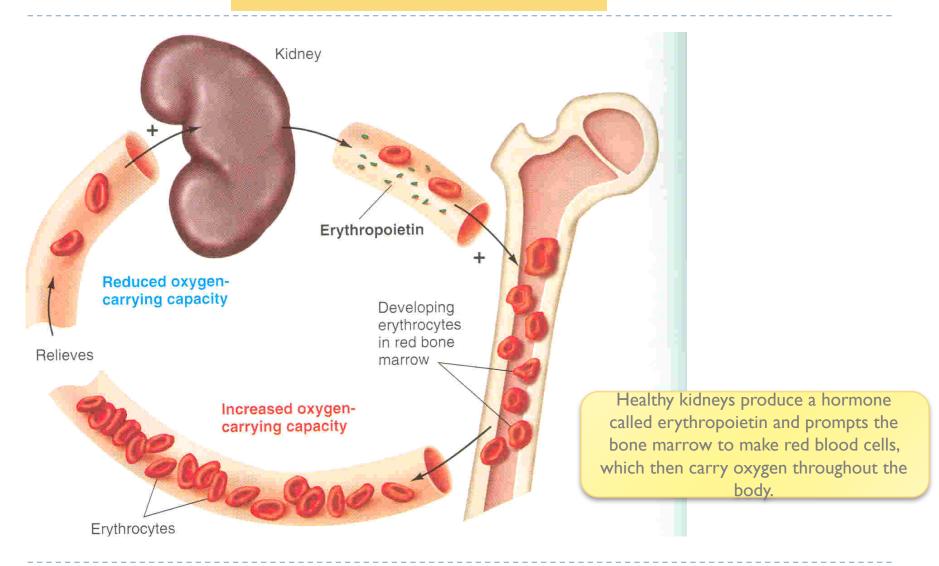
- Glycoprotein
- 90% from renal cortex (kidney)
- 10% from the liver.
- Stimulate: the growth of early stem cells.
- Does not affect: maturation process of RBCs.
- Can be measured in plasma & urine.
 - Conditions like: anemia, High altitude, Heart failure, Lung Disease result in:

 High erythropoietin levels polycythemia Polycythemia = RBCs level is up Erythropoietin => works when RBCs level is down

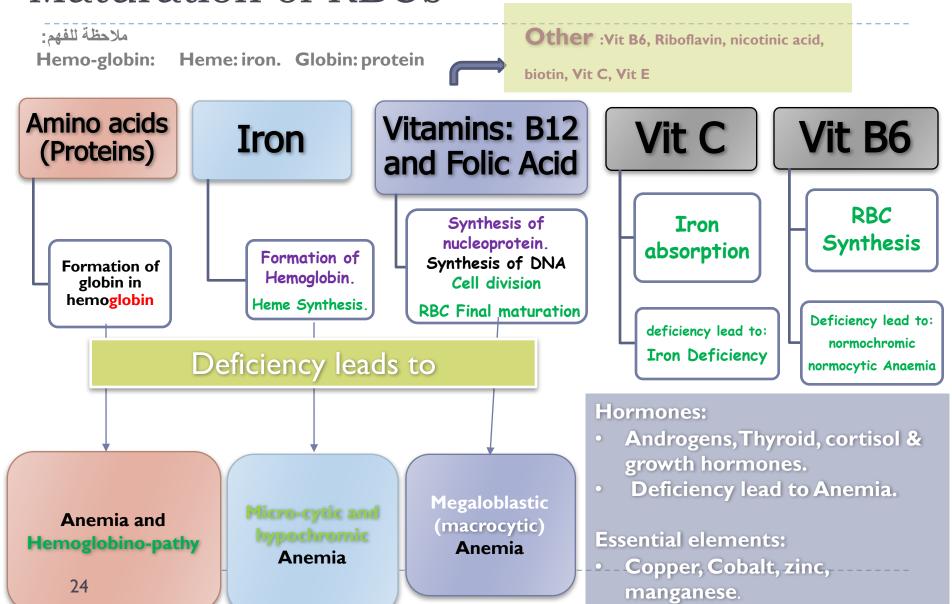
أي كلمه تنتهي بمقطع mia أي كلمه تنتهي بمقطع

The hormone controls the early stages of RBC formation (production of proerythroblasts from stem cells), not the middle or last stages, so erythropoietin makes the cells pass more rapidly through the erythroblastic stages and can increase it to 10 or more times than normal.

Role of the kidneys in RBC formation:



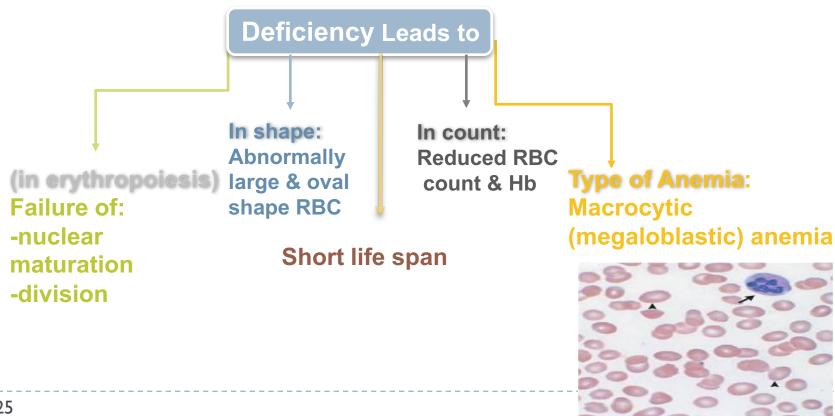
Essential Elements for Formation and Maturation of RBCs



Most of this slide is found only in females' slides.

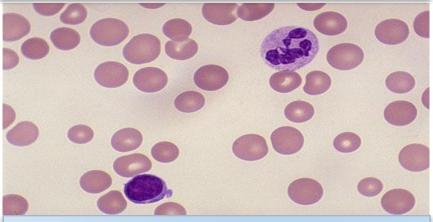
Vitamin B12 & Folic acid

- Important for **DNA synthesis and final maturation** of RBC.
- (Important for all stages of maturation of RBCs) *
- Dietary source: meat, milk, liver, fat, green vegetables.



MACROcytic (Megaloblastic) Anemia

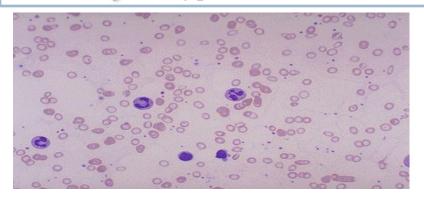
It is caused by the deficiency of vit B12 and Folic Acid



Note

- 1- The hyper-segmented Neutrophil (WBC)
- 2- The RBC are almost as large as the lymphocyte (WBC).
- 3-There are fewer RBCs.

MICROcytic hypochromic Anemia



- **★** The RBC's are smaller than normal
- **★** Have an increased zone of <u>central</u> <u>pallor</u>.
- ★ Increased anisocytosis (variation in size)
- Increased poikilocytosis (variation in shape)
- ★ Causes: Iron deficiency and Thalassemia.

Microcytic hypochromic anemia

smaller size of each RBC

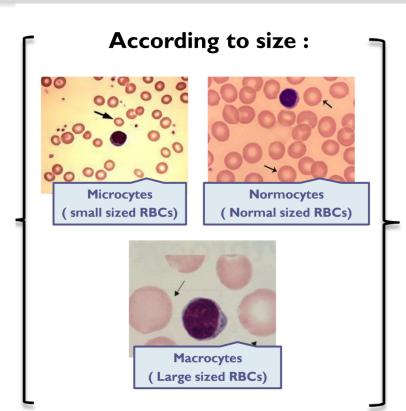
less hemoglobin in each RBC

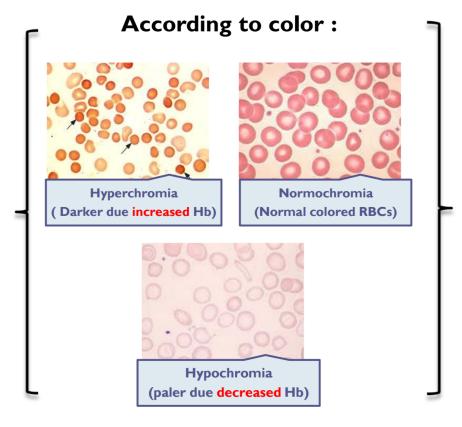
(MCV<80 fl)

(MCH<27pg)

MCV: the average volume of RBCs.

MCH: the average mass of hemoglobin per RBC.





Mal-absorption of vit.B12

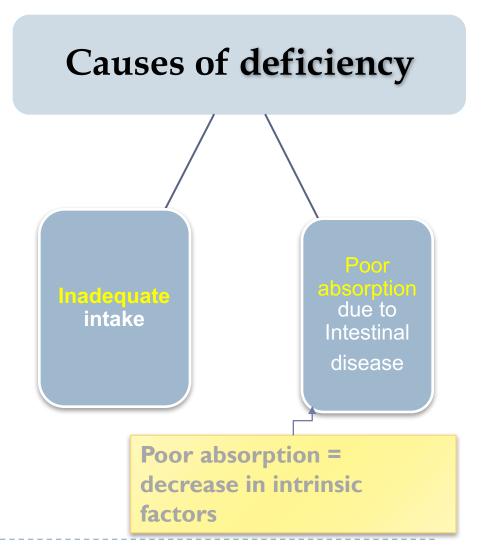
Pernicious Anemia

الـ Stomach فيه الـ Stomach فيه الـ Intrinsic factor وهي اللي تطلع لي الـ

- ★ VBI2 absorption needs <u>intrinsic factor</u> secreted by parietal cells of stomach خلایا جدار المعدة
- ★ VB12 + intrinsic factor is absorbed in the terminal Ileum.

لازم الـ VBI2 يكون ماسك المتصلف . بالـ Intrinsic factor عشان تمتصه .

• Terminal ileum = اخر حته في Small intestine الـ



Iron Metabolism (Fe):

Iron is needed for the synthesis of hemoglobin, myoglobin cytochrome oxidase, peroxidase & catalase.

Total Iron in the body = 3-5/4-5g

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Note: Females' Slides
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★ 65% - 75%.. Haemoglobin (3g)
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- ★ 5% other hems
- ★ 1% bound to transferrin (betaglobulin) in blood
- ★ 15-30% stored iron in the form of ferritin in the liver, spleen and bone marrow.

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★ 4% ...... Muscle Hb (myoglobin)
```

- ★ 1% Enzymes (cytochrome)
- ★ 0.1% Plasma iron: (transferrin)

Note: Males' Slides

عشان كذا لما ناخذ iron ينصحون نشرب معه عصير برتقال (فيتامين سي) ليه؟ لانه يساعد بالامتصاص

Iron Absorption:

اللي عندهم Stomach diseases عندهم اللي عندهم in vitC

- **★** Iron in food is mostly in oxid zed form (Ferric, F⁺³)
- **★** Better absorbed in reduced form (Ferrous, F⁺²)
- **★** Iron in stomach is reduced by gastric acid, Vitamin C.

يساعد في الامتصاص Vitamin C

- **★** What does rate of iron <u>absorption</u> depend on?
 - -The amount of iron stored.
- ★ When does rate of iron absorption decrease?
- * when iron stores are saturated (When all the apoferritin is saturated).

-Ferritin: intracellular iron-storage protein

-Ferritin that is not combined with iron is called apoferritin.

Transport and Storage of Iron

- Iron transportation:
- in plasma in the form of <u>Transferrin</u> (apotransferrin + iron).
- Normally 30-40 saturated with Fe: (plasma iron 100-130ug/100ml)
- When transferrin is 100% saturated with Fe:(plasma iron 300ug/100ml)

Haemosiderin: Iron storage complex only found in cells (not in circulating blood) appears to be I. a complex of ferritin. 2. denatured ferritin. 3. other material.

(not a good supplier of iron when needed)

- Iron storage:
 - ★ Ferritin : (apoferritin + iron) (Loose bond)
 - ★ <u>Haemosiderin</u>: insoluble complex molec
 (Firm bond)
- نفقد الـ Iron عن طريق جرح بالجلد أو قص الأظافر والشعر

- ★ Sites: liver, spleen & bone marrow
- Daily loss of iron is 0.6 mg in male & 1.3mg/day in females.
- Diet provides 10-20 mg iron per day.

Iron excretion

Iron losses

feces: unabsorbed, dead epithelial cells

bile and saliva.

Skin: cell, hair, nail, in sweat.

Urine

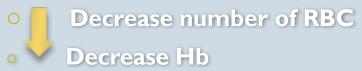
Menstruation, pregnancy and child birth

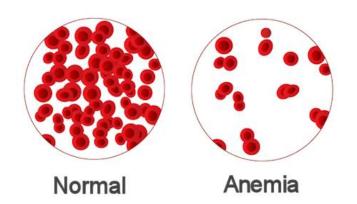
Destruction of RBCs

- RBC life span in circulation = 120 days.
- Metabolic active cells.
- Old cells have a fragile cell membrane, the cell will rupture as it passes in narrow sinusoidal <u>capillaries</u> of the spleen, bone marrow & liver.
- Released Hb is taken up by <u>macrophages</u> in liver, spleen & bone marrow:
 - Hb is broken into its component:
 - Polypeptide → amino acids → amino acid pool (protein pool = storage).
 - Haem
 - Iron → recycled (reused) → iron storage (ferritin form).
 - prophyrin → biliverdin → bilirubin (secreted by the liver into bile) (excess destruction of RBC can cause Jaundice)

Anemia:







★ Normal ranges of Hb:

- Men: Hb 13.5 to 17.5 g/dL
- Women: Hb 12.0 to 15.5 g/dL
- Infants: Hb 14 19 g/dL

★Symptoms:

Fatigue

Tired

Dyspnea

(shortness of breathing)

Pallor

Tachycardia

heart failure.

Greek word (an-haîma) meaning "without blood"

Causes of Anemia



Causes of anemia

I- Blood loss

- ★ Acute ⇒ accident (RBC return to normal in 3 to 6w)
- **★** Chronic **→ microcytic** hypochromic anemia (ulcer, worms)

2- Decrease RBC production

1- Nutritional causes

- ★ Iron ➡ microcytic Hypochromic anemia
- ★ Vit B12 & Folic acid **→** megaloblastic anemia

2- Bone marrow failure:

Destruction by cancer, radiation, drugs → Aplastic anaemia.



Abnormal cells or Hb

- **★** Spherocytosis
- ★ sickle cells

Incompatible blood transfusion

Erythroblastosis fetalis

Spherocytosis = مشكله بالـ cell membrane تتكسر الـ RBCsبسرعه

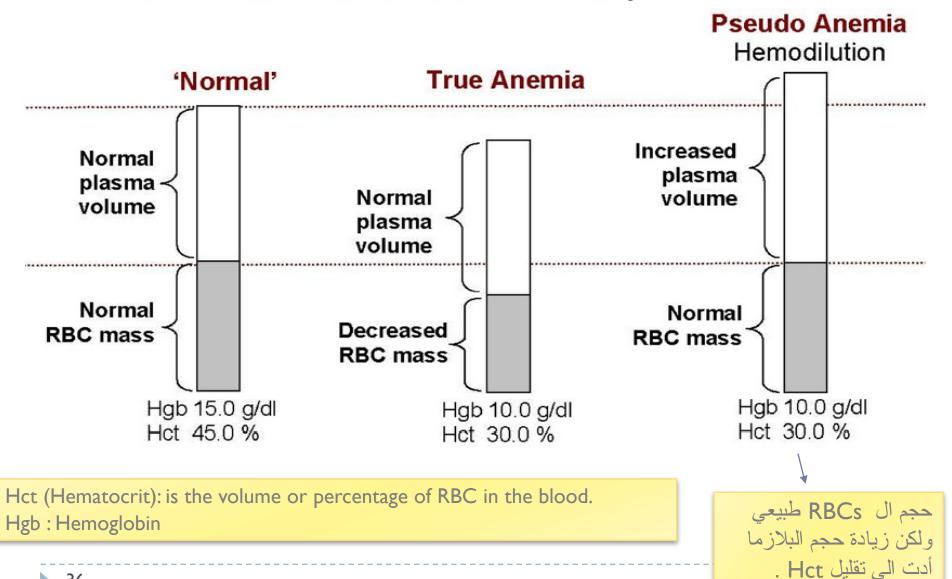
تغير في شفره وحده = Sickle cells فحدثت طفره وراثي.

Incompatible blood transfusion = لما يُنقل للشخص دم غير مناسب

Acute = عاد Chronic = 384 الدم على فترات زي الدوره الشهريه مثلاً + اللي عنده قرحه بالمعده . بواسير . ديدان بالامعاء



RBC Mass and Plasma Volume Relationship



Polycythemia

Polycythemia

"Increased number of RBC or high concentration of Hb (hemoglobin) in the RBCs"

Types:

- True
- Absolute

Primary (Polycythemia Rubra Vera - PRV): uncontrolled RBC production."

نقص الاوكسجين = Hypoxia



Secondary to hypoxia:
high altitude
(physiological), chronic
respiratory or cardiac
disease

- Primary =) بالمناعه
- عند النساء اكثر) يصير الجلد محمر.
- Secondary =

يعني لما يصير hypoxia يحدث hypoxia يعدث المعنى يحدث المعنى المعنى يحدث المعنى يحدث المعنى يحدث المعنى يحدث المعنى يحدث المعنى المعنى يحدث المعنى المع

Polycythemia Cont.

Polycythemia is either caused by:

- I- Increase in RBC, therefore, increase in hemoglobin.
- 2- Increase in hemoglobin content of RBC WITHOUT increase in RBC count.
 - 3- Decrease in plasma therefore hemoglobin is more dominant and apparent.

End result always: an increase in hemoglobin.

Relative:

Haemoconcentration
» loss of body fluid in vomiting,
diarrhea and sweating.

Note: Polycythemia is always due to an ABNORMAL increase or decrease.

Structure of Hemoglobin (Hb)

مهم معرفه الـStructure

Hb molecules is made of 4 chains, each formed of heme & polypeptide chain (globin)



Polypeptide chain

Polypeptide chain

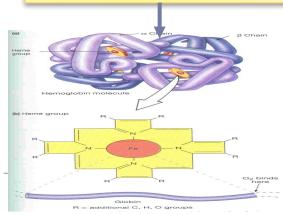
Polypeptide chain

Polypeptide chain

Heme groups

Hemoglobin structure:

Hemoglobin holds/contains:
(4 MOLECULES of hydrogen) OR (8 ATOMS of hydrogen)



Protoporphyrin ring + iron (F2+)

Types of Hb

normal

Hb A $(\alpha_2\beta_2)$ 2 alpha, 2 beta **chains**. (adult Hb)

Most common (98%)

Hb A2 $(\alpha_2\delta_2)$ (2%)

gamma

Hb F $(\alpha_2\gamma_2)$ (Hb of intrauterine life). (80-90%)

abnormal

Abnormality in the polypeptide chain

abnormal Hb (hemoglobin-pathy) e.g thalassemias, sickle cell (HbS). Hb F = high nifty of O2 + يكون بالبيبي , ولما يكبر يتحول Hb A

Function of Hemoglobin

Carbon monoxide: اول اكسيد الكربون يمسك بالهيموجلوبين ولا يخليه يوصل الـO2 لانه binds irreversibly فيصير اختناق زي شب النار بالخيام او الدفايات بغرف مغلقه بدون تهويه .

In smokers:

Hb binds to CO₂= carboxyhemaglobin

of CO2

Hb reversibly binds to O₂ to form oxyhemoglobin, affected by pH, temperature, H+ Carriage of 02 **Function** of HB buffer

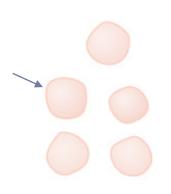
Quantity of Hemoglobin in Blood

- RBCs have the maximum ability to concentrate hemoglobin in the cell fluid up to about 34 grams in each 100 milliliters of cells.
- Each gram of hemoglobin can combine with 1.34 ml of oxygen if Hb is 100% saturated with O2.

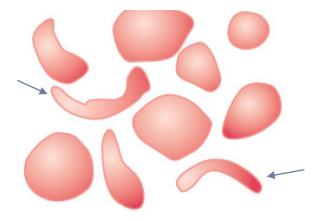
O₂Carrying Capacity of Blood:

- It is the amount of O2 carried by 100 ml of blood.
- Calculated by: Hb conc x 1.34.
- \circ **Example:** 16 x 1.34 = 21.4 ml

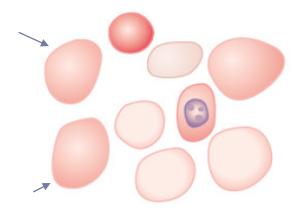
Different Cell Morphology



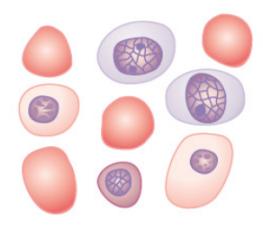
Microcytic, hypochromic anemia



Sickle cell anemia

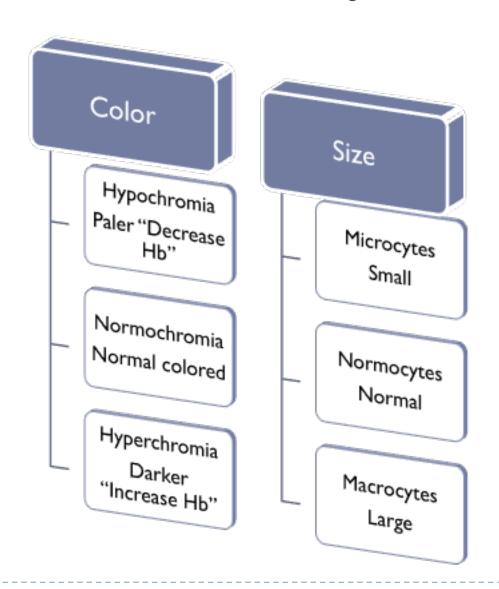


Megaloblastic anemia



Erythroblastosis fetalis

Classification of RBCs by Size & Color



RBC Indices

Mean corpuscular Volume (MCV)

(= 80 TO 90 fl OR 83 Cubic um) Mean corpuscular Hemoglobin (MCH)

(= 27 –32 picogram)

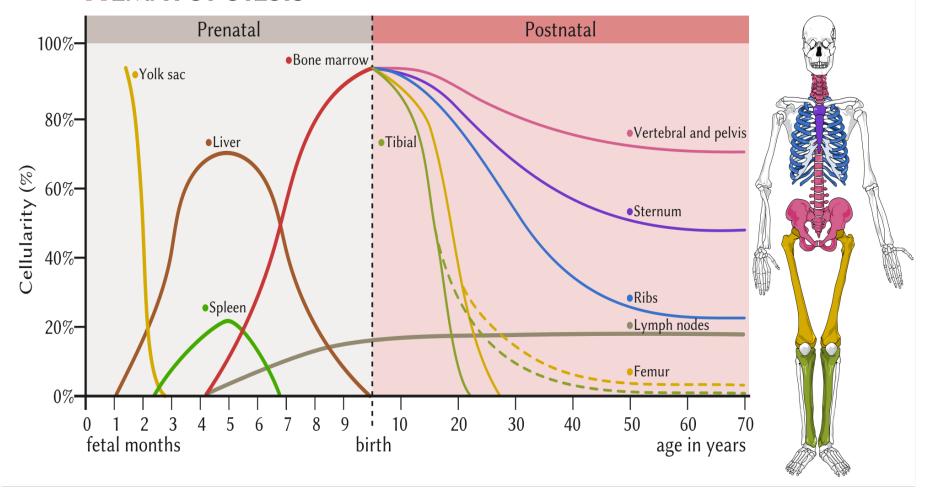
Mean corpuscular Hemoglobin Concentration (MCHC)

(MCHC= 30 –36 gm/dl)

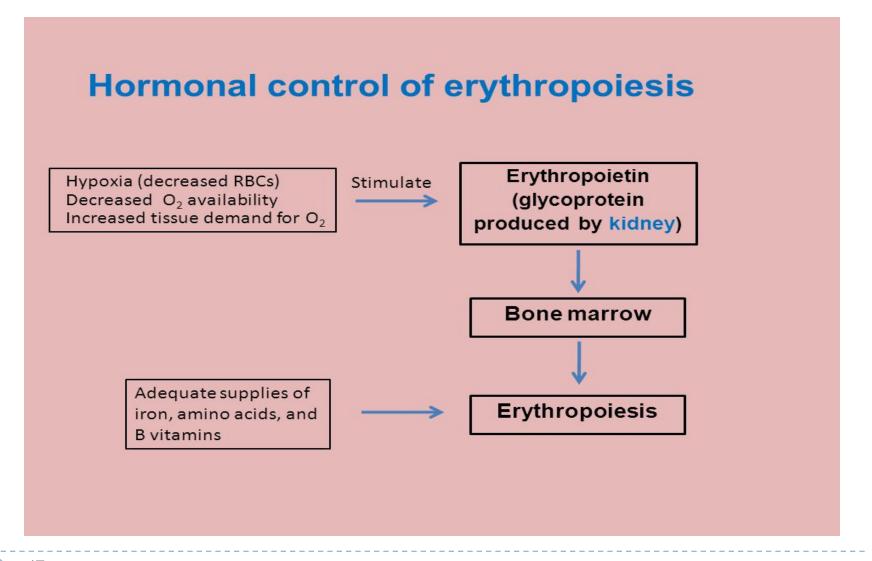
* F1: fimto liter

*gm/dl: gram per Deci liter

HEMATOPOIESIS•



Control of Erythropoiesis



Percentages & Numbers

Blood volume: 5 liter in adult

55%plasma45% is packed cells volume (PCV)1% buffy coat

Plasma (ECF): 98% water

Diameter 7-8μmx2.5μmx1 μm. Average volume 90-95 μm3 Number 4.7 - 5 x106 Hb 14-16 g/dl in the blood

Total Iron in the body 3-4-5 g

Normally: 30-40% saturated with Fe: plasma iron 100-130ug/100ml When transferrin is 100% saturated with Fe: plasma iron 300ug / 100ml **Daily loss of iron** is 0.6 mg in male & 1.3 mg/day in females.

Normal ranges of Hb:

Men: 13.5 to 17.5 g/dL

Women: 12.0 to 15.5 g/dL

Infants : 14 – 19 g/dL

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دمعة، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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