وزارة التعليم العالي والبحث العلمي
الجامعة التقنية الشمالية
المعهد التقني الدور

الحقيبة التعليمية

القسم العلمي: الإسعاف الفوري

اسم المقرر: علم الدم	

المرحلة / المستوى: الثاني

الفصل الدراسي: الثاني	

السنة الدراسية: 2024/2023

اسم المقرر:	**علم الدم**						
القسم:	الإسعاف الفوري						
الكلية:المعهد	المعهد التقني الدور						
المرحلة / المستوى	الثاني						
الفصل الدراسي:	الثاني						
عدد الساعات الاسبوعية:	نظري	15	عملي	15			
عدد الوحدات الدراسية:	3						
الرمز:	IMA 216						
نوع المادة	نظري		عملي		كلهما	√	
هل يتوفر نظير للمقرر في الاقسام الاخرى							
اسم المقرر النظير	/						
القسم	/						
رمز المقرر النظير	/						

معلومات تدريسي المادة

اسم مدرس (مدرسي) المقرر:	**بكر حاتم عبدالوهاب حيدر**
اللقب العلمي:	**لا يوجد**
سنة الحصول على اللقب	**لا يوجد**
الشهادة :	**بكالوريوس طب اسنان**
سنة الحصول على الشهادة	**2023**
عدد سنوات الخبرة (تدريس)	**1 سنة**

الوصف العام للمقرر

علم الدم هو فرع من العلوم الطبية يدرس الدم ومكوناته ووظائفها، ويعتبر جزءًا مهمًا من علم الأحياء وعلم الأمراض. يهتم علم الدم بدراسة خصائص الدم، مثل تركيبه الكيميائي، ووظائفه الفيزيولوجية، والمساهمة في الدفاع عن الجسم ونقل العناصر الغذائية والأوكسجين إلى الخلايا.

يحتوي الدم على مكونات مختلفة مثل الكريات الحمراء التي تحمل الأكسجين، والصفائح الدموية التي تلعب دورًا في عملية تخثر الدم، واللقاحات التي تساعد في مكافحة العدوى، بالإضافة إلى البروتينات والهرمونات والعناصر الأخرى.

علم الدم يلعب دورًا حيويًا في تشخيص الأمراض المختلفة مثل فقر الدم وانخفاض عدد الصفائح الدموية وأمراض الجهاز المناعي والسرطانات الدموية. كما يستخدم علم الدم في عمليات نقل الدم والتبرع بالدم وفحوصات التحاليل الطبية لتقييم صحة الفرد.

الاهداف العامة

- تعلم الطلاب عن أنواع الخلايا المكونة للدم مثل الكريات الحمراء، والكريات البيضاء، والصفائح الدموية، وكيفية تأثيرها على وظيفة الجسم بشكل عام.
- -تعريف الطلاب بأمراض الدم واضطراباته شرح الأمراض المختلفة التي تؤثر على الدم مثل فقر الدم، وأمراض التجلط، وأمراض نقص الصفائح الدموية وسرطان الدم.
- تعليم الطلاب كيفية إجراء تحاليل الدم المختلفة وفهم النتائج المختبرية المرتبطة بصحة الدم
- تعريف الطلاب بعملية التخثر الدموي وأهميتها في وقف النزيف ومنع فقدان الدم الزائد

الأهداف الخاصة

1- تعرف الطالب على أنواع الدم وماهي ميزات كل نوع .
2- تعلم الطالب كيفية سحب عينات الدم من المريض وفصلها عن طريق جهاز الطرد المركزي
3- تعلم كيفية حساب كريات الدم البيض والحمراء والصفيحات الدموية .

الأهداف السلوكية او نواتج التعلم

- الأهداف السلوكية لمادة علم الدم تتعلق بالسلوكيات أو الأداء الذي يجب أن يتحلى به الطالب عند اكتسابه المعرفة والمهارات في هذا المجال. إليك بعض الأمثلة على الأهداف السلوكية لمادة علم الدم:
- القدرة على جمع العينات الدموية بدقة واتقان**: يجب على الطالب أن يظهر مهارات عالية في تقنيات جمع العينات الدموية، مثل رسم الدم من الوريد بشكل صحيح دون إلحاق الضرر بالمريض.
- معرفة وفهم المعدات الطبية المستخدمة في تحاليل الدم**: ينبغي على الطالب أن يظهر فهماً عميقاً للأدوات والمعدات المستخدمة في مختبر علم الدم، وكذلك كيفية استخدامها بأمان وفعالية.

- الالتزام بمعايير السلامة والنظافة**: يجب على الطالب أن يتعلم ويتبنى ممارسات السلامة اللازمة للوقاية من الإصابة بالعدوى أثناء التعامل مع الدم والمواد البيولوجية الأخرى.
- قدرة التفاعل الفعّال مع المرضى**: يتعين على الطالب أن يكون لديه مهارات تواصل جيدة للتعامل مع المرضى، بما في ذلك القدرة على توضيح الإجراءات وتهدئة المرضى المتوترين.
- القدرة على تحليل النتائج وتقديم التقارير بدقة**: يجب على الطالب أن يكون قادراً على تفسير النتائج التي يحصل عليها من التحاليل الدموية وتقديم تقارير شاملة ودقيقة بناءً على هذه النتائج.
- تتنوع الأهداف السلوكية باختلاف المناهج والبرامج التعليمية، ولكن هذه الأمثلة تعكس الجوانب الأساسية التي قد تشملها مادة علم الدم بغرض تحقيق تعلم فعال ومفيد للطلاب.

المتطلبات السابقة

- اذكر أي متطلبات سابقة قد يحتاجها الطالب قبل التسجيل في المقرر، مثل مواد دراسية سابقة أو مهارات معينة.

الأهداف السلوكية او مخرجات التعليم الأساسية		
ت		آلية التقييم
1	الأهداف المعرفية: يستطيع الطالب تعريف علم الدم وفهم مكوناته وأهميته في التشخيص الطبي. يستطيع الطالب تحديد ووصف المكونات الرئيسية للدم ووظائفها. يستطيع الطالب شرح عملية تكوين خلايا الدم في نخاع العظم والمراحل المختلفة لتكون خلايا الدم. يميز الطالب بين الأمراض المختلفة المتعلقة بالدم مثل فقر الدم، الهيموفيليا، وسرطانات الدم.	تقارير، واجبات، امتحانات نظرية شفوية وتحريرية نصف فصلية وفصلية
2	الأهداف المهارية: يتقن الطالب تقنيات جمع عينات الدم وتحليلها.يستخدم الطالب بشكل صحيح المجاهر وأجهزة التحليل المختلفة لفحص مكونات الدم. يفسر الطالب نتائج فحوصات الدم ويستطيع الربط بينها وبين الحالات المرضية المحتملة.يقوم الطالب بإجراء تحاليل مخبرية متنوعة تتعلق بمكونات الدم ووظائفه.	تقارير، واجبات، امتحانات نظرية شفوية وتحريرية نصف فصلية وفصلية
3	الأهداف العاطفية: يظهر الطالب التزامًا بأخلاقيات المهنة واحترام خصوصية المرضى عند التعامل مع العينات والبيانات. يظهر الطالب دقة وتفانيًا في إجراء التحاليل والتعامل مع النتائج.	تقارير، واجبات، امتحانات نظرية شفوية وتحريرية نصف فصلية وفصلية

4	الأهداف التطويرية: يبدي الطالب رغبة في التعلم المستمر والتحديث فيما يخص التطورات الحديثة في علم الدم. يتقن الطالب أسس البحث العلمي ويستطيع تطبيقها في مشاريع بحثية تتعلق بعلم الدم.	تقارير، واجبات، امتحانات نظرية شفوية وتحريرية نصف فصلية وفصلية

أساليب التدريس (حدد مجموعة متنوعة من أساليب التدريس لتناسب احتياجات الطلاب ومحتوى المقرر)

الاسلوب او الطريقة	مبررات الاختيار
1.المناقشة	تقديم الخلاصة والفهم للموضوع
2.الالقاء	اكتساب الطالب مهارة تفسير النصوص
3.المحاضرة	محدد وواضح ويطبق بسهوله وهو التقليدي

الفصل الثاني						
عنوان الفصل	الوقت					
التوزيع الزمني	النظري	العملي	العنوان الفرعي	طريقة التدريس	التقنيات	طرق القياس
الأسبوع الأول	1	2	مقدمة عن الدم, دراسة محتوى الدم.	محاضرة	السبورة / شرائح البوربوينت / التعليم الإلكتروني	
الأسبوع الثاني	1	2	تكوّن الدم عند الجنين والأطفال والبالغين.	محاضرة	السبورة / شرائح البوربوينت / التعليم الإلكتروني	
الأسبوع الثالث	1	2	خلايا الدم الحمراء الطبيعية، أهميتها، تركيبها، تكوين الكريات الحمر ووظيفتها.	محاضرة	السبورة / شرائح البوربوينت / التعليم الإلكتروني	
الأسبوع الرابع	1	2	زيادة كريات الدم الحمر، الأسباب، العلامات السريرية والتشخيص المختبري	محاضرة	السبورة / شرائح البوربوينت / التعليم الإلكتروني	
الأسبوع الخامس	1	2	دراسة مورفولوجيا كريات الدم الحمراء في الصحة والمرض. الاختلالات في حجم كرات الدم الحمراء (R.B.C).	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع السادس	1	2	الاختلالات في اشكال كرات الدم الحمراء.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع السابع	1	2	الاختلالات في الوان كرات الدم الحمراء.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع الثامن	1	2	نسبة الهيموجلوبين الطبيعي في الدم واحتوائه وأهميته.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع التاسع	1	2	دراسة أنواع Hb الطبيعية.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع العاشر	1	2	أنواع ال Hb المتغايرة	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع الحادي والثاني عشر	1	2	فقر دم. التعريف والتصنيف والأنواع. الأسباب والعلامات السريرية والنتائج المختبرية.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	

الاسبوع الثالث عشر	1	2	خلايا الدم البيضاء وظيفتها وأنواعها ونضجها وتشوهاتها وأمراضها	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع الرابع عشر	1	2	تخثر الدم، تعريفه وأنواعه. عوامل التخثر، أنواع اضطراب تخثر الدم.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	
الاسبوع الخامس عشر	1	2	سرطان الدم تعريفه وتصنيفه.	محاضرة	عرض تقديمي، شرح، أسئلة وأجوبة, مناقشة	

المحتوى العلمي

MODULAR UNIT 1

Hematology: is the science which deals with blood contains in normal and abnormal (healthy and diseases).

Hematology study aid to:

1-know the causes of bloody diseases.

2-Diagnosis of these diseases.

3-Treatment of these diseases.

Blood:

Blood is a connective tissue in fluid form composed from blood cells suspended in a liquid called blood plasma.

It is considered as the **'fluid of life'** because it carries oxygen from lungs to all parts of the body and carbon dioxide from all parts of the body to the lungs.

It is known as '**fluid of growth**' because it carries nutritive substances from the digestive system and hormones from endocrine gland to all the tissues. The blood is also called the '**fluid of health'** because it protects the body against the diseases and gets rid of the waste products and unwanted substances by transporting them to the excretory organs like kidneys.

PROPERTIES OF BLOOD:

1- **Color**: Blood is red in color. Arterial blood is scarlet red because it contains more oxygen and venous blood is purple red because of more carbon dioxide

2- **Volume**: Average volume of blood in a normal adult is 5 L. In a newborn baby, the volume is 450 ml. It increases during growth and reaches 5 L at the time of puberty. In females, it is slightly less and is about 4.5 L. It is about 8% of the body weight in a normal young healthy adult, weighing about 70 kg.

3- **Reaction and pH:** Blood is slightly alkaline and its pH in normal conditions is 7.4.

4- **Specific gravity:** Specific gravity of total blood : 1.052 - 1.061 Specific gravity blood cells : 1.092 - 1.101 Specific gravity of plasma : 1.022 - 1.026.

5- **Viscosity:** Blood is five times more viscous than water. It is mainly due to red blood cells and plasma proteins.

COMPOSITION OF BLOOD:

Blood contains of the:
1-cellular portion called blood cells.

2-liquid portion: there are two types known:

1- Serum

2-Plasma

BLOOD CELLS:

Three types of cells are present in the blood contain 45% of blood volume and consist of :

1. Red blood cells or erythrocytes ,is most common cells.
2. White blood cells or leukocytes
3. Platelets or thrombocytes

Plasma:

Plasma is a straw-colored clear liquid part of blood. It contains 91% to 92% of water and 8% to 9% of solids. The solids are the organic(glucose, acid fatty , amino acid, urea ,lactic acid ..) and the inorganic substances (Na, Chloride,…etc) gives the normal values of some important substances in blood, contain coagulative factors added to blood protein(albumin, fibrinogen, immunoglublin) .

Serum:

Serum is the clear yellow-colored fluid that oozes from blood clot. When the blood is shed or collected in a container, it clots. In this process, the fibrinogen is converted into fibrin and the blood cells are trapped in this fibrin forming the blood clot. After about 45 minutes, serum oozes out of the blood clot. For clinical investigations, serum is separated from blood cells and clotting elements by

centrifuging. Volume of the serum is almost the same as that of plasma (55%). It is different from plasma only by the absence of fibrinogen, i.e. serum contains all the other constituents of plasma except fibrinogen. Fibrinogen is absent in serum because it is converted into fibrin during blood clotting. Thus, Serum = Plasma – Fibrinogen

Functions of blood:

1-Nutritive function : Nutritive substances like glucose, amino acids, lipids and vitamins derived from digested food are absorbed from gastrointestinal tract and carried by blood to different parts of the body for growth and production of energy.

2-Respiratory function :Transport of respiratory gases is done by the blood. It carries oxygen from alveoli of lungs (statured with O2at 89-99% at rest) to different tissues and carbon dioxide from tissues to lung (alveoli).

3-Excretory function :Waste product formed in the tissues during various metabolic activities are removed by blood and carried to the excretory organs like kidney, skin, liver, etc. for excretion.

4-Transport of hormones and enzymes: Hormones which are secreted by ductless (endocrine) glands are released directly into the blood. The blood transports these hormones to their target organs/tissues. Blood also transports enzymes .

5-**Regulation of water balance** :Water content of the blood is freely interchangeable with interstitial fluid. This helps in the regulation of water content of the body.

6- **Regulation of Acid-Base balance:** Plasma proteins and hemoglobin act as buffers and help in the regulation of acid-base balance .

7- **Regulation of body temperature** : Because of the high specific heat of blood, it is responsible for maintaining the **thermoregulatory** mechanism in the body, i.e. the balance between heat loss and heat gain in the body.

8-**Storage function**: Water and some important substances like proteins, glucose, sodium and potassium are constantly required by the tissues. Blood serves as a readymade source for these substances. And, these substances are taken from blood during the conditions like starvation, fluid loss, electrolyte loss, etc.

9- **Defensive function**: Blood plays an important role in the defense of the body. The white blood cells are responsible for this function. Neutrophils and monocytes engulf the bacteria by phagocytosis. Lymphocytes are involved in development of immunity. Eosinophils are responsible for detoxification, disintegration and removal of foreign proteins.

10- **Transport of Hydrogen ion**: some oxyhemoglobin loses O2 and become deoxyhemoglobin this compound binds to hydrogen ion in much greater affinity than oxygenated blood.

11- **Hadraulic function:** The restriction of blood flow can be used in specialized tissue to engorge blood in it like in jumping in which blood forced flow and engorge into the leg under pressure resulting straighter them giving powerful for jumping without need to bulky muscular leg.

Pre –Test: - Enumerate the functions of blood?

1- Nutritive function

2- Respiratory function

3- Excretory function

4-Transport of hormones and enzymes

5-Regulation of water balance

6- Regulation of Acid-Base balance

7- Regulation of body temperature

8-Storage function

Post-Test?

Q1 – Define the blood?

Blood is a connective tissue in fluid form composed from blood cells suspended in a liquid called blood plasma.

MODULAR UNIT 2

Erythropoiesis:

DEFINITION :

Erythropoiesis is the process of the origin, development and maturation of erythrocytes. Hemopoiesis or hematopoiesis is the process of origin, development and maturation of all the blood cells. This process start by stem cell which is non-recognizable morphologically. This is a well-defined and recognizable lineage of nucleated red cell in the marrow is called Erythroblast which produced from stem cell. Erythroblast give pronormoblast which suffer from many changes resulting erythrocyte ,these changes are :

1-Reduction in cell size.

2-reduction in nucleus size.

3-Ripening of cytoplasm.

Maturation time from pronoroblast until erythrocyte 7 days. there are stagespresent in erythropoiesis :

1-**Multiplication maturation stage:** it start from erythroblast until intermediate normoblast.

2- maturation stage: it include late normoblast and reticulocyte.

3-Rlease stage : it contain reticulocyte and erythrocyte.

Site of Hemopoiesis (Erythropoiesis):

-In Fetal Life :

In fetal life, the erythropoiesis occurs in three stages:

1- **Mesoblastic Stage** :I is start from few days after fertilization of ova until less than the first two months of embryonic life, the RBCs are produced from mesenchyme (mesoderm) of yolk sac.

2- **Hepatic Stage** :It begin 2-7 month of embryonic life, liver is the main organ that produces RBCs. Spleen and lymphoid organs are also with minimal role involved in erythropoiesis.

3- **Myeloid Stage** :After 3 months of embryonic life, the RBCs are produced from red bone marrow and liver.

Sites of haemopoiesis

Fetus	months (yolk sac) months (liver, spleen) months (bone marrow)
Infants	marrow (practically all bones)
Adults	ebrae, ribs, sternum, skull, sacrum and pelvis, proximal ends of femur

IN NEWBORN BABIES, CHILDREN AND ADULTS:

In newborn babies, growing children and adults, RBCs are produced only from the red bone marrow.

1. Up to the age of 20 years: RBCs are produced from red bone marrow of all bones (long bones and all the flat bones).
2. After the age of 20 years: RBCs are produced from membranous bones like vertebra, sternum, ribs, scapula, iliac bones and skull bones and from the ends of long bones. After 50 years of age, the proportion of active marrow decline as fat increase , the shaft of the long bones becomes yellow bone marrow because of fat deposition and looses the erythropoietic function. In adults, liver and spleen may produce the blood cells if the bone marrow is destroyed or fibrosed. Collectively bone marrow is almost equal to liver in size and weight.

It is also as active as liver. Though bone marrow is the site of production of all blood cells, comparatively 75% of the bone marrow is involved in the production of leukocytes and only 25% is involved in the production of erythrocytes.

But still, the leukocytes are less in number than the erythrocytes, the ratio being 1:500. This is mainly because of the lifespan of these cells. Lifespan of erythrocytes is 120 days whereas the lifespan of leukocytes is very short ranging from one to ten days. So the leukocytes need larger production than erythrocytes to maintain the required number.

Stages of maturation :

Blood cell formations have 3 stages to recognize into erythrocytes, leucocytes,and platelets :

1- **Multiplication maturation stage :** it occur by division of the cells toincrease its number.
2- **Gradual maturation stage :** include development and recognizable of the cells .
3- **Relase stage :**it occur after maturation stage when migrate all the mature cells to peripheral blood stream

PROCESS OF ERYTHROPOIESIS:

Stem cells :

Stem cells are the primary cells capable of self-renewal and differentiating into specialized cells . **Hemopoietic stem cells** are the primitive cells in the bone marrow, which give rise to the blood cells. Hemopoietic stem cells in the bone marrow are called **uncommitted pluripotent hemopoietic stem cells** (PHSC). PHSC is defined as a cell that can give rise to all types of blood cells. In early stages, the PHSC are not designed to form a particular type of blood cell. And it is also not possible to determine the blood cell to be developed from these cells: hence, the name uncommitted PHSC (Fig.). In adults, only a

few number of these cells are present. But the best source of these cells is the umbilical cord blood. When the cells are designed to form a particular type of blood cell, the uncommitted PHSCs are called **committed PHSCs**. Committed PHSC is defined as a cell, which is restricted to give rise to one group of bloodcells

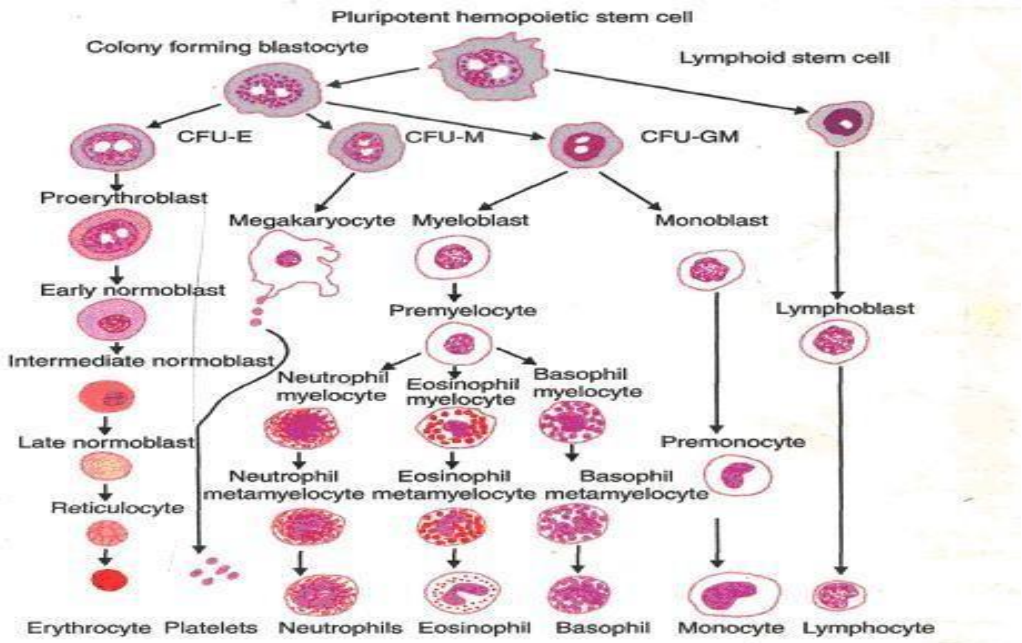
Committed PHSCs are of two types:

1. Lymphoid stem cells (LSC) which give rise to lymphocytes and natural killer (NK) cells.
2. Colony forming blastocytes, which give rise to myeloid cells. Myeloid cells are the blood cells other than lymphocytes. When grown in cultures, these cells form colonies hence the name colony forming blastocytes. Different units of colony forming cells are:

Colony forming unit-erythrocytes (CFU-E) – Cells of this unit develop into erythrocytes.

Colony forming unit-granulocytes/monocytes (CFU-GM) – These cells giverise to granulocytes (neutrophils, basophils and eosinophils) and monocytes.

Colony forming unit-megakaryocytes (CFU-M) – Platelets are developed from these cells



E 10-2: Stages of erythropoiesis. CFU-E = Colony forming unit—Erythrocyte, CFU-M = Colony forming unit—Megakaryocyte, CFU-GM = Colony forming unit—Granulocyte/Monocyte

STAGES OF ERYTHROPOIESIS:

Various stages between CFU-E cells and matured RBCs are (Fig. 10.2):

1. Proerythroblast
2. Early normoblast
3. Intermediate normoblast.
4. Late normoblast
5. Reticulocyte
6. Matured erythrocyte

1- Proerythroblast (Megaloblast)

Proerythroblast or megaloblast is the rounded or oval first cell derived from CFU-E. It is very large in size with a diameter of about 12-20 µ. Its nucleus is large and occupies the cell almost completely(80% of cytoplasmic space). The nucleus has two or more nucleoli and a reticular network. Proerythroblast does not contain hemoglobin. The cytoplasm is basophilic in nature have ferritin granules. Proerythroblast multiplies several times and finally forms the cell of next stage called early normoblast. Synthesis of hemoglobin starts in this stage. However, appearance of hemoglobin occurs only in intermediate normoblast.

2- Early Normoblast:

The early normoblast is little smaller than proerythroblast with a diameter of about 10-16 µ. In the nucleus still large have chromatin Condensation and deeply staining, the nucleoli disappear. The condensed network becomes dense. The cytoplasm is basophilic in nature. So, this cell is also called basophilic erythroblast. This cell develops into next stage called intermediate normoblast .

3- Intermediate Normoblast Cell:

is smaller than the early normoblast with a diameter of 8-14 µ. The nucleus is still present (small). But, the chromatin network shows further condensation. The hemoglobin starts appearing. Cytoplasm is already basophilic. Now,

because of the presence of hemoglobin, it stains with both acidic as well as basic stains. So this cell is called polychromophilic or polychromatic erythroblast. This cell develops into next stage called late normoblast

4-Late Normoblast :

Diameter of the cell decreases further to about 8 -10 µ. Nucleus becomes very small with very much condensed chromatin network and it is known as ink- spot nucleus. Quantity of hemoglobin increases. And the cytoplasm becomes almost acidophilic. So, the cell is now called orthochromic erythroblast. In the final stage of late normoblast just before it passes to next stage, the nucleus disintegrates and disappears. The process by which nucleus disappears is called pyknosis. The final remnant is extruded from the cell. Late normoblast develops into the next stage called reticulocyte.

5-Reticulocyte:

Reticulocyte is flat non-nucleate, disc shaped ,otherwise known as immature RBC. It is slightly larger than matured RBC. The cytoplasm contains the reticular network or reticulum, which is formed by remnants of disintegrated organelles. Due to the reticular network, the cell is called reticulocyte. The reticulum of reticulocyte stains with supravital stain. In newborn babies, the reticulocyte count is 2% - 6% of RBCs, i.e. 2 - 6 reticulocytes are present for every 100 RBCs. The number of reticulocytes decreases during the first week after birth. Later, the reticulocyte count remains constant at or below 1% of RBCs. The number increases whenever production and release of RBCs increase. Reticulocyte is basophilic due to the presence of remnants of disintegrated Golgi apparatus, mitochondria and other organelles of cytoplasm. During this stage, the cells enter the blood capillaries through capillary membrane from site of production by diapedesis. Important events during erythropoiesis is given in Table (1) .

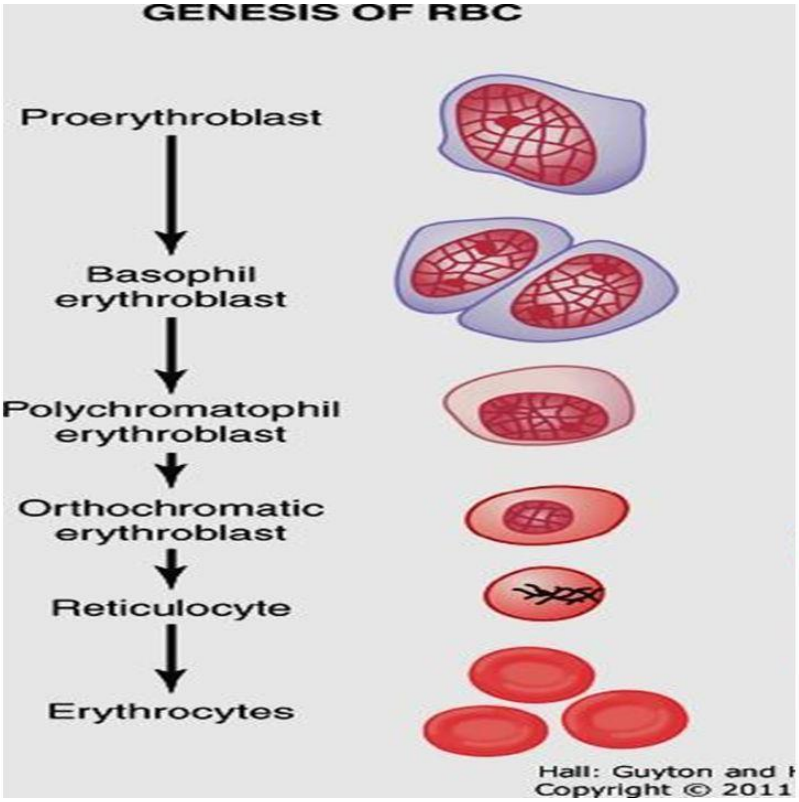
6-Matured Erythrocyte:

Reticular network disappears and the cell becomes the matured RBC and attains the biconcave shape. The cell decreases in size to 7.2 µ diameter. The matured RBC is with hemoglobin but without nucleus. It requires 7 days for the development and maturation of RBC from proerythroblast. It requires 5 days up to the stage of reticulocyte. Reticulocyte takes 2 more days to become the matured RBC.

Table (1) : Important events during erythropoiesis

Stage of erythropoiesis	Important event
Proerythroblast	Synthesis of hemoglobin starts
Early normoblast	Nucleoli disappear
Intermediate normoblast	Hemoglobin starts appearing
Late normoblast	Nucleus disappears
Reticulocyte	Reticulum is formed. Cell enters capillary from site of production
Matured RBC	Reticulum disappears Cell attains biconcavity

Genesis of RBC:



Control of erythropoiesis :

This control system operates in the following manner :

1- Alteration in hemoglobin concentrations of the blood lead to changes in tissue oxygen tension within the kidney (hypoxia).

2- In response to hypoxia ,secreted hormones called erythropoietin which induce primitive marrow cells to differentiate into pronormoblast then resulting an increase in production of erythrocyte .

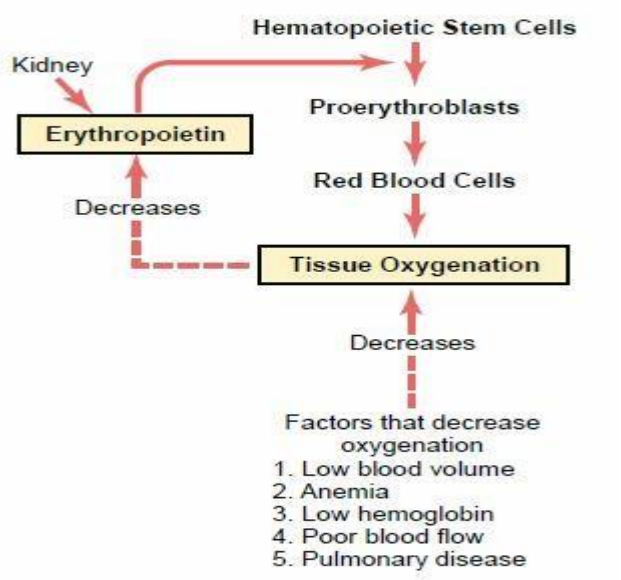
3- This in turn leads to an increase in size of the erthron and an increase in tissue oxygen levels .

Figure :Tissue oxygenation and RBC formation

Factors Necessary for Erythropoiesis:

Development and maturation of erythrocytes require variety of factors, whichare classified into three categories:

1. General factors
2. Maturation factors
3. Factors necessary for hemoglobin formation



GENERAL FACTORS:

General factors necessary for erythropoiesis are:

Erythropoietin

Thyroxine

Hemopoietic growth factories

Vitamins

Erythropoietin: (erythropoiesis stimulating factor)

Is glycoprotein containing sialic acid ,hexoamin ,and hexoses. In human, kidney is the major source (90%) of Erythropoietin production, it is that the renal tubular epithelial cells secrete Erythropoietin, but liver and other organs also contributes (10%). Erythropoietin detected in both urine and plasma

.Normal value of Erythropoietin in urine men is (1) unit /day but in women is about 50% (0.5 unit / day) .

Erythropoietin level increase in urine in :

1-Iron deficiency anemia .

2-Perncious anemia .

3-Sickel cell anemia.

4-Leukemia.

5-Acute hypoxia .

6-Polycythemia with tumor .

Erythropoietin level reduced in :

1-Anemia associated with abnormal hemoglobin which reduced oxygen affinity ,ex hemoglobin saettel.

2-polycythemia vera.

3-Anemia with renal insufficiency.

4- Chronic disorder (cancer, infection ,rheumatoid arthritis).

Factor that decrease oxygenation:

1-Low blood volume.

2-Anemia.

3- Low hemoglobin

4-Poor blood flow.

5-Pulmonary disease.

Maturation Factors :

Vitamin B12, intrinsic factor and folic acid are necessary for the maturation ofRBCs.

1- Vitamin B12 (Cyanocobalamin)

Vitamin B12 is the maturation factor necessary for erythropoiesis.

Source

Vitamin B12 is called extrinsic factor since it is obtained mostly from diet. Its absorption from intestine requires the presence of intrinsic factor of Castle. Vitamin B12 is stored mostly in liver and in small quantity in muscle. When necessary, it is transported to the bone marrow to promote maturation of RBCs. It is also produced in the large intestine by the intestinal flora.

Action

Vitamin B12 is essential for synthesis of DNA in RBCs. Its deficiency leads to failure in maturation of the cell and reduction in the cell division. Also, the cells are larger with fragile and weak cell membrane resulting in macrocytic anemia. Deficiency of vitamin B12 causes pernicious anemia. So, vitamin B12 is called antipernicious factor.

2- Intrinsic Factor of Castle

Intrinsic factor of castle is produced in gastric mucosa by the parietal cells of the gastric glands. It is essential for the absorption of vitamin B12 from intestine. In the absence of intrinsic factor, vitamin B12 is not absorbed from intestine. This leads to pernicious anemia. Deficiency of intrinsic factor occursin:

Severe gastritis

Ulcer

Gastrectomy.

Hematinic principle

Hematinic principle is the principle thought to be produced by the action of intrinsic factor on extrinsic factor. It is also called or antianemia principle. It is a maturation factor.

3-Folic Acid

Folic acid is also essential for maturation. It is required for the synthesis of DNA. In the absence of folic acid, the synthesis of DNA decreases causing failure of maturation. This leads to anemia in which the cells are larger and appear in megaloblastic (proerythroblastic) stage. And, anemia due to folic acid deficiency is called megaloblastic anemia.

Factors Necessary for Hemoglobin formation : Various materials are essential for the formation of hemoglobin in the RBCs. Deficiency of these substances decreases the production of hemoglobin leading to anemia. Such factors are:

1. First class proteins and amino acids: Proteins of high biological value are essential for the formation of hemoglobin. Amino acids derived from these proteins are required for the synthesis of protein part of hemoglobin, i.e. the globin.

2. Iron: Necessary for the formation of heme part of the hemoglobin.

3. Copper: Necessary for the absorption of iron from the gastrointestinal tract (appears to be catalyst in hemoglobin formation)

4. Cobalt and nickel: These metals are essential for the utilization of iron during hemoglobin formation. Cobalt is an essential constitutent of vitamin B12.

5. Vitamins: Vitamin C (play apart in folate metabolism), riboflavin, nicotinic acid and pyridoxine are also essential for the formation of hemoglobin. Vitamin E supposed to be important for hemopoiesis in infants only

MODULAR UNIT 3

Erythrocyte ,Red blood cells (RBC):

Mature Red blood cells (RBCs) also known as erythrocytes (erythros = red) are the non-nucleated. red color of the red blood cell is due to the presence of the coloring pigment called hemoglobin. RBCs play a vital role in transport of respiratory gases. RBCs are larger in number compared to the other two blood cells, and marked by glycoprotein that defines the different blood types .

Normal value :

RBC count ranges between (4.7 - 6.1 million/cu mm) of blood in adult males, it is (4.2-5.4 million/cu mm) in adult females,

Normal shape:

Normally, the RBCs are disk shaped and biconcave (dumbbell shaped). In fixed blood smears appear circular , non-nucleus and lack organelles. Central portion is thinner and periphery is thicker. The biconcave contour of RBCs has some mechanical and functional advantages.

Advantages of Biconcave Shape of RBCs:

1. Biconcave shape helps in equal and rapid diffusion of oxygen and other substances into the interior of the cell.

2. Large surface area is provided for absorption or removal of different substances.

3. Minimal tension is offered on the membrane when the volume of cell alters.

4. Because of biconcave shape, while passing through minute capillaries, RBCs squeeze through the capillaries very easily without getting damaged.

Normal size :

Diameter: 7.2 µ (6.9 to 7.4 µ).

Thickness : At the periphery it is thicker with 2.2 µ and at the center it is thinner with 1 µ. This difference in thickness is because of the biconcave shape. Surface area : 120 sq µ. Volume : 85 to 90 cu µ.

Normal structure:

Red blood cells are non•nucleated. Only mammal, which has nucleated RBC is camel. Because of the absence of nucleus in human RBC, the DNA is also absent. Other organelles such as mitochondria and Golgi apparatus also are absent in RBC. Because of absence of mitochondria, the energy is produced from glycolytic process. Red cell does not have insulin receptor and so the glucose uptake by this cell is not controlled by insulin. It is cannot synthesis of protein or carry out oxidative reactions associated mitochondria or undergo mitosis. RBC has a special type of cytoskeleton, which is made up of actin and spectrin. Both the proteins are anchored to transmembrane proteins by means of another protein called ankyrin. Absence of spectrin results in hereditary spherocytosis. In this condition, the cell

is deformed, losses its biconcave shape and becomes globular (spherocytic). The spherocyte is very fragile and easily ruptured (hemolyzed) in hypotonic solutions .

Properties of Red blood cells:

Rouleaux formation : When blood is taken out of the blood vessel, the RBCs pile up one above another like the pile of coins. This property of the RBCs is called rouleaux (pleural = rouleau) formation . It is accelerated by plasma proteins globulin and fibrinogen

Specific gravity : Specific gravity of RBC is 1.092 to 1.101

Packed cell volume :

Packed cell volume (PCV) is the proportion of blood occupied by RBCs expressed in percentage. It is also called hematocrit value. It is 45% of the blood and the plasma volume is 55%

Suspension stability :

During circulation, the RBCs remain suspended uniformly in the blood. This property of the RBCs is called the suspension stability.

Physiology of mature Red blood cells :

1-A surface membrane **.**

2-Cytoplasm which is divided into : a-hemoglobin b- stroma

Erythrocyte membrane : is made from three layers **:**

1-Outer layer from glycoprotein molecules which carry the mucopolysaccharides ,blood group antigens and absorbed protein .

2-Middle layer is a phospholipid bilayer stabilized by cholesterol .

3- Inner layer has protein molecules extending toward the cell interior.

The erythrocyte surface bears a negative charge .

Hemoglobin content : It has 28% from the erythrocyte mass.

Metabolism : Erythrocyte has two metabolic pathways :

Glycolysis and glutathione metabolism .

The energy derived from glycolysis is used to maintain selective exchanges of ions a cross unite membrane that result in potassium retention and sodium expulsion.

Life span of Red blood cells :

Average lifespan of RBC is about 120 days after the lifetime the senile (old) RBCs. About 1% of erythrocytes removed from circulation by phagocytes are destroyed in reticuloendothelial system particularly those of splenic pulp .

Determination of Lifespan of Red Blood Cells:

Lifespan of the RBC is determined by radioisotope method. RBCs are tagged with radioactive substances like radioactive iron or radioactive chromium. Life of RBC is determined by studying the rate of loss of radioactive cells from circulation.

Fate of Red blood cells:

When the cells become older (120 days), the cell membrane becomes more fragile. Diameter of the capillaries is less or equal to that of RBC. Younger RBCs can pass through the capillaries easily. However, because of the fragile nature, the older cells are destroyed while trying to squeeze through the capillaries. The destruction occurs mainly in the capillaries of red pulp of spleen because the diameter of splenic capillaries is very small. So, the spleen is called ‘graveyard of RBCs. Destroyed RBCs are fragmented and hemoglobin is released from the fragmented parts. Hemoglobin is immediately phagocytized by macrophages of the body, particularly the macrophages present in liver (Kupffer cells), spleen and bone marrow.

Hemoglobin is degraded into iron , globin and porphyrin. Iron combines with the protein called apoferritin to form ferritin, which is stored in the body and reused later. Globin enters the protein depot for later use. Porphyrin is degraded into bilirubin, which is excreted by liver through bile. Daily 10% RBCs, which are senile, are destroyed in normal young healthy adults. It

causes release of about 0.6 g/dL of hemoglobin into the plasma. From this 0.9 to 1.5 mg/dL bilirubin is formed.

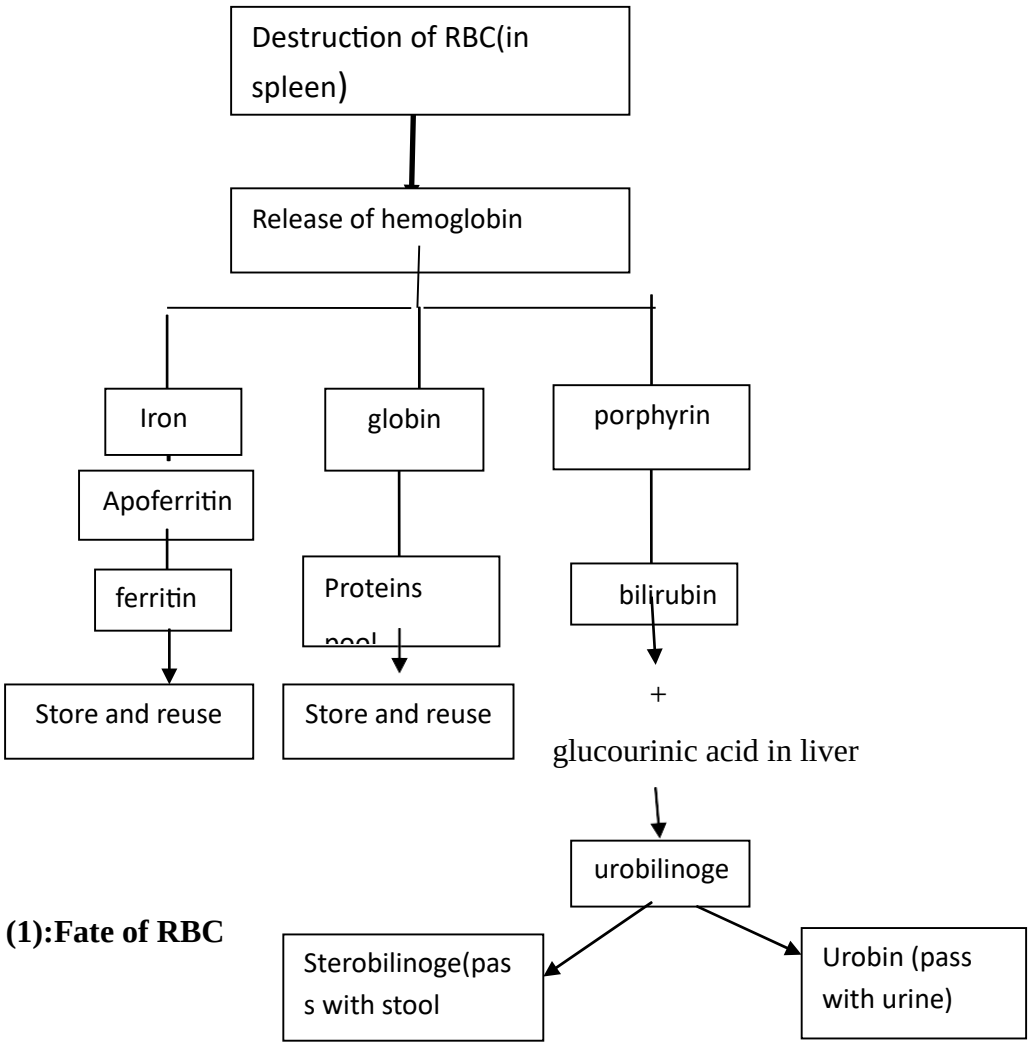


Figure (1):Fate of RBC

FUNCTIONS OF RED BLOOD CELLS :

Major function of RBCs is the transport of respiratory gases. Following are the functions of RBCs:

1-Transport of Oxygen from the Lungs to the Tissues Hemoglobin in RBC combines with oxygen to form oxyhemoglobin. About 97% of oxygen is transported in blood in the form of oxyhemoglobin.

2-Transport of Carbon Dioxide from the tissues to the lungs Hemoglobin combines with carbon dioxide and form carbhemoglobin. About 30% of carbon dioxide is transported in this form.

RBCs contain a large amount of the carbonic anhydrase. This enzyme is necessary for the formation of bicarbonate from water and carbon dioxide. Thus, it helps to transport carbon dioxide in the form of bicarbonate from tissues to lungs. About 63% of carbon dioxide is transported in this form. **3-Buffering Action** in Blood Hemoglobin functions as a good buffer. By this action, it regulates the hydrogen ion concentration and thereby plays a role in the maintenance of acid• base balance.

4-In Blood Group :Determination RBCs carry the blood group antigens like A antigen, B antigen and Rh factor. This helps in determination of blood group and enables to prevent reactions due to incompatible blood transfusion.

MODULAR UNIT 4

Polycythemia, causes, clinical signs and laboratory diagnosis

Variation in number of Red blood cells :

PHYSIOLOGICAL VARIATIONS :

A . Increase in RBC Count:

Increase in the RBC count and hemoglobin per liter (High PCV) is known as polycythemia leading to increase blood viscosity. It occurs in both physiological and pathological conditions. When it occurs in physiological conditions it is called physiological polycythemia. The increase in number during this condition is marginal and temporary. It occurs in the following conditions:

1. Age at birth, the RBC count is 8 to 10 million/cu mm of blood. The count decreases within 10 days after birth due to destruction of RBCs causing physiological jaundice in some newborn babies. However, in infants and growing children, the cell count is more than the value in adults.

2. Sex Before puberty and after menopause in females the RBC count is similar to that in males. During reproductive period of females, the count is less than that of males (4.5 million/cu mm).

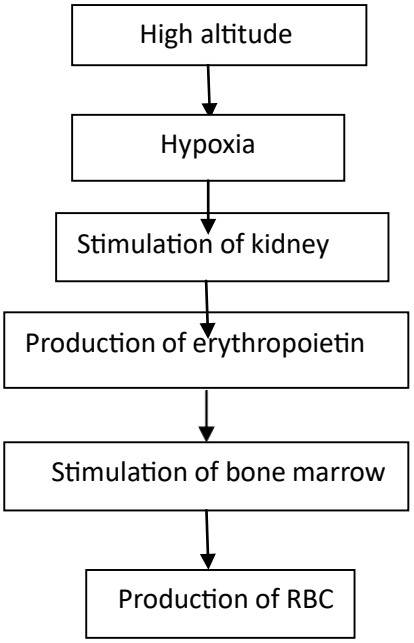
3. High altitude Inhabitants of mountains (above 10,000 feet from mean sea level) have an increased RBC count of more than 7 million/cu mm. It is due to hypoxia (decreased oxygen supply to tissues) in high altitude. Hypoxia stimulates kidney to secrete a hormone called erythropoietin. The erythropoietin in turn stimulates the bone marrow to produce more RBCs.(figure 2)

4. Muscular exercise :there is a temporary increase in RBC count after exercise. It is because of mild hypoxia and contraction of spleen. Spleen stores RBCs. Hypoxia increases the sympathetic activity resulting in secretion of adrenaline from adrenal medulla. Adrenaline contracts spleen and RBCs are released into blood .

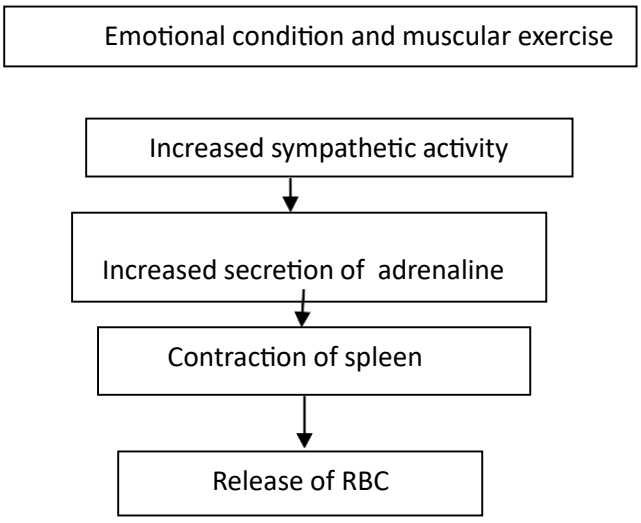
5. Emotional conditions RBC count increases during the emotional conditions such as anxiety. It is because of increase in the sympathetic activity as in the case of muscular exercise.(figure 3)

6. Increased environmental temperature: increase in atmospheric temperature increases RBC count. Generally increased temperature increases all the activities in the body including production of RBCs.

7. After meals :there is a slight increase in the RBC count after taking meals. It is because of need for more oxygen for metabolic activities.



Fig(2) Physiological polycythemia in high altitude



Figure(3): Physiological polycythemia in emotional conditions and exercise

B. Decrease in RBC Count

Decrease in RBC count occurs in the following physiological conditions:

1-High barometric pressures At high barometric pressures as in deep sea, when the oxygen tension of blood is higher, the RBC count decreases.

2-During sleep RBC count decreases slightly during sleep and immediately after getting up from sleep. Generally, all the activities of the body are decreased during sleep including production of RBCs.

3. Pregnancy In pregnancy, the RBC count decreases. It is because of increases the plasma volume also resulting in hemodilution. So, there is a relative reduction in the RBC count

PATHOLOGICAL VARIATIONS:

Pathological polycythemia is the abnormal increase in the RBC count. Red cell count increases above 7 million/ cu mm of the blood. Polycythemia is of two types:

1-primary polycythemia

2-secondary polycythemia

Or other classification of polycythemia :

1-True (absolute) polycythemia :divided in to :

a. primary polycythemia (Idopathic poly. or stear poly. ,Neoplastic poly.)

b. secondary polycythemia

2-Relative polycythemia

Primary Polycythemia – Polycythemia Vera:

Primary polycythemia is otherwise known as polycythemia vera. It is a disease characterized by persistent increase in RBC count above 14 million/cu mm of blood due to mutation HSCs or RBC progenitors in bone marrow, RBC production occurred out of erythropoietin control. This is always associated with increased white blood cell count above 24,000/cu mm of blood. Polycythemia vera occurs in myeloproliferative disorders like malignancy of red bone marrow.

Lab diagnosis:

Increase in RBC, Hb. PCV, WBC, and Platelets count

Secondary Polycythemia:

This is secondary to some of the pathological conditions (diseases) such as:

1- Associated with hypoxia :

a. Respiratory disorders like chronic pulmonary disease (emphysema).

b. Congenital heart disease .

c. Ayerza's disease (condition associated with hypertrophy of right ventricle and obstruction of blood flow to lungs).

d. Chronic carbon monoxide poisoning.

e. Poisoning by chemicals like phosphorus and arsenic.

f. Repeated mild hemorrhages.

g-hypoventilation syndrome associated with obesity (pick wickian syndrome).

h- heavy smoking (carboxyhaemoglobin).

I- Metahaemoglobinemia (rarely).

2- Due to inappropriate erythropoietin increase in :

A-Benign and malignant tumors of kidney ,liver, C.N.S. Uterus, Ovary.

B-Renal diseases (hydronephrosis, vascular impairment ,cyst, renal artery stenosis

3- Associated with adrenocortical steroids or androgens :

a-adrenal hypercriticism .

b-Virilizing tumor.

c-Androgens used therapeutically and blood doping (as in athletes).

4- Associated with chronic chemical exposure :

a-nitrites, sulfonamide , other substances producing methaemoglobin and sulphaemoglobin .

b-C obalt ,shellac components ,various alcohols .

All these conditions lead to hypoxia which stimulates the release of erythropoietin. Erythropoietin stimulates the bone marrow resulting in increased RBC count.

Lab diagnosis: increase in RBC ,PCV, Hb only but the WBC and Platelets at normal range .

Symptoms and signs of polycythemia:

Increase RBC count lead to increase in blood viscosity make shortage oxygen delivery to tissue causes very cyanosis degree and symptoms:

Symptoms:

-Headache ,pruritus, dyspnea,

-Weakness ,itching Pruritis (aquagenic) ,Dizziness

-Visual disturbance (blurred vision) ,Weight loss

-high blood pressure .

-fever and night sweats, Red skin (face, hands , and feet).

-Hemorrhage in gastrointestinal tract ,uterine, cerebral.

-Thrombosis in arterial ,cardiac ,cerebral ,peripheral venous ,deep or superficial leg venous .

-Gout (due to raise of uric acid production) and peptic ulceration rarely .

Signs

-Splenomegaly 66-70%

-Skin plethora 67%

-Hepatomegaly 40%

-Conjunctival plethora 59%

-Systolic Hypertension 72%

2) Relative polycythemia :

It which there is increased in total plasma in the body and the total number of RBC is normal, it is called " Pseudopolycythemia" which caused by concentration of plasma by :

a-stress

b-D ehydration :water deprivation, vomiting

c-Plasma lose :burns, enteropathy .

b. irregulation of fluid in the body

this condition is occur in the middle age .

Laboratory finding :

1- Raised erythrocytes count ,hematocrite, and hemoglobin.

2-Neutrophilic leukocytosis (50% cases) and in some cases basophilic .

3-Raise neutrophilic alkaline phosphatase score .

4- Raised platelets count (50% cases).

5- increase serum vitamin B 12 binding capacity.

6- bone marrow hyper cellular with prominent megakaryocytes

Diagnosis-Revised WHO Criteria:

- Major criteria

-Hemoglobin >18.5 g/dL in men, 16.5 g/dL in women

-Presence of JAK2 617V>F or other functionally similar mutation such as JAK2 exon 12 mutation

-Minor criteria

-Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation

-Serum erythropoietin level below the reference range for normal

-Endogenous erythroid colony formation in vitro

Workup:

-H/H-Sa O2

-EPO- JAK2 screen (95-100% pts with PV haveJAK2 mutation)

-Bone marrow

EEC: endogenous erythroid colony formation.

MODULAR UNIT 5

Morphology of RCB in health and disease:

1-Discuss aspects of red cell morphology related to size

Normal RBC:

-Size: Normocyte ,measure 6.2-8.2µm (7.2µm)

-Colour: Normochromic

In disease abnormality in the RBC pictures due to four causes:

1- Abnormal erythropoiesis which may be effective or ineffective.

2- Inadequate hemoglobin formation.

3- Damages or changes effect erythrocytes after leaving bone marrow.

4- Attempts by bone marrow to compensate for anemia by increase erythropoiesis .

These process result respectively in the following abnormalities of erythrocytes .

Abnormal erythrocyte morphology is found in pathological states that may be :

- abnormalities in size (anisocytosis).

- In shape (poikilocytosis).

-In hemoglobin content or the presence of inclusion bodies in erythrocyte.

1-Variation in erythrocyte size (anisocytosis)

In healthy ,Red blood cells have a diameter within 6-8.5M (7.2M) can vary in size from smaller than normal, microcytes, to larger than normal, macrocytes. When red cells of normal size, microcytes and macrocytes are present in the same field, the term anisocytosis.

1-Microcytosis:

Morphology:

- Decrease in the red cell size. Red cells are smaller than ± 7µm in diameter (>6µm) .The nucleus of a small lymphocyte (± 8,µm) ,is a useful guide to the size of a red blood cell. Smaller than a nucleus of the lymphocyte, MCV is decrease to less than 80fL,the area of central pallor is greater than 1/3 of the cell ,low hemoglobin content as a result from fragmentation of the number erythrocytes or macrocytic as occur with many types of abnormal erythropoiesis.

Found in:

- Iron deficiency anemia
- Thalassemia
- Sideroblastic anemia
- Lead poisoning
- Anemia of chronic disease
- liver disease
- alcoholism

2-Macrocytosis:

Morphology:

Increase in the size of a red cell. Red cells are larger than 9µm in diameter(diameter of 9-12 microns,1.5-2 times larger than normal red cells).They are uniform in size ,it occur when there is increased erythropoiesis. May be round or oval in shape, and MCV is also increase (above 80-100fL) and increase hemoglobin content, the diagnostic significance being different.

Found in :

- Folate and B12 deficiencies (oval)
- Ethanol (round)
- Liver disease (round)
- Reticulocytosis (round)
-Megaloblastic anemia
-Aplastic anemia
- Hemolytic anemia

3-Megalocytes

-Megalocytes are large (greater diameter may measure 12pm) often oval shaped cell with increased haemoglobin content with MCV exceed 120fL, they

are result of decreased DNA synthesis, frequently due to vitamin B12 and/orfolic acid deficiencies, and associated with some leukaemia chemotherapy .

-Decreased DNA synthesis causes the nucleus in the developing red cells tomature at a slower than normal rate.

4- <u>Pseudomacrocytes</u>

-appears larger than the lymphocyte but in contrast to megalocytes has an areaof central pallor.

-size is the result of exaggerated flattening and thus the presence of the centralpallor.

-in patients with cirrhosis of the liver, obstructive jaundice, post splenectomy.

two types of macrocytes:-

1- True macrocytes (megalocytes).

2- Increased MCV, MCH2- Pseudomacrocytes. Normal MCV, MCH.

MODULAR UNIT 6

II- **Variation of red cells shape (Poikilocytosis)** RBCs may have different shapes:

1- Spherocytosis /Microspherocytes:

Morphology:

Red cells are more spherical. Lack the central area of pallor on a stained bloodfilm,cells which have a decreased surface-to-volume ratio.

-Their diameter is less and their membrane thickness greater than normal redcells

-they appear to be round, darkly-stained cells without central pallor.

-Associated with abnormalities in membrane protein, lipid loss and excessiveflux Na+ across the membrane.

Found in :

- Hereditary spherocytosis (genetic defect of RBC cell membrane)
- Immune hemolytic anemia

- Zieve's syndrome
- Microangiopathic hemolytic anemia.

Target Cells: (Codocytes)

Morphology:

Red cells are thinner than normal ,they have an area of increased staining which appears in the area of central pallor then stained peripheral ring adhere to the cell membrane surrounded them .

-It appear less staining than normal one.

-Codocytes appear in conditions which cause the surface of the red cell to increase disproportionately to its volume.

-This may result from a decrease in haemoglobin, as in iron deficiency anaemia, or an increase in cell membrane.

Found in

-Obstructive liver disease

- Severe iron deficiency

-Thalassemia

-Sickle cell anemia

-Haemoglobinopathies (S and C)

- Post splenectomy

-obstructive jaundice

This deformity happen due to loss of elasticity of red cell membrane becauseof changes in composition of membrane and its change in :

1- Fat composition.
2- Effect of bile salt regarded on blood in obstructive jaundice, these salts are fat emulsifier which cause the loss of elasticity of red cell membrane.

Ovalocytes:

Morphology:

oval shape red blood cell

Found in:

- Thalassemia major.
- Hereditary ovalocytosis.
- Sickle cell anemia
-megaloblastic anemia

Elliptocytosis

Morphology:

The red cells are oval or elliptical in shape. Long axis is twice the short axis .Less than 1% of red cells in normal blood are oval.

Found in:

-Hereditary elliptocytosis .

- Megaloblastic anemia.
- Iron deficiency .
- Thalassemia .
- Myelofibrosis

Tear Drop Cells (Dacrocyte):

Morphology:

Red cells shaped like a tear drop or pear which could be considered to bediscocytes with a single drawn out spicule .

Found in:

- Bone marrow fibrosis.
- Megaloblastic anemia .
- Iron deficiency .
- Thalassemia
- Tumor metastasis ,myeloid metaplasia (in bone marrow).

-Tuberculosis.

Blister cell:

Morphology:

Have accentric hallow area.

Found in: Microangiopathic hemolytic anemia.

Schistocytosis:

Morphology:

Fragmentation of the red cells. red cell fragments which are formed when fibrin strands come in contact with circulating red cells. The strands cut a small piece from the original cell.

Found in:

1- certain genetically disorders as thalassemia and hereditary elliptocytosis

2-Aqcuired disorders of red cell formation (megaloblastic anemia, Iron deficiency anemia).

3-As the sequences of mechanical stress in Microangiopathic hemolytic anemia, Mechanical hemolytic anemia.

4-As a result of direct thermal injures as in severe burns.

Stomatocytosis:

Morphology:

Red cells with a central linear slit or stoma. Seen as mouth-shaped form inperipheral smear.

- The cause for this deformity is decrease pH.

Found in:

- Alcohol excess (alcoholism) .
- Alcoholic liver disease .
- Hereditary stomatocytosis .
- Hereditary spherocytosis

Echinocyte ,Burr (crenation) cell:

Morphology:

Red cell with uniformly spaced, short pointed projections(spicules). Red cell with 30 or more, short blunt projections which are regularly distributed on their surface on their surface. They are small cells or fragment cells, they are:

a-small fragments of cells of varying shape, sometimes round in shape withsharp angles or spines .

b-large cells or irregular or round contour from which fragments have beensplit off.

c- normal un fragmented adult red cells and reticulocyte.

Found in:

- hemolytic anemia
  - Uremia.
  - Megaloblastic anemia.

-pyruvate kinase deficiency

-neonatal liver disease

Keratocytes (horn cell):

Morphology:

Part of the cell fuses back leaving two or three horn-like projections. Thekeratocyte is a fragile cell and remains in circulation for only a few hours.

Found in:

- Uraemia .
- Severe burns .
- EDTA artifact .
- Liver disease

Acanthocytosis (spiny cells):

Morphology:

are red blood cells with irregularly spaced projections (3-12 spicules), theseprojections very in width but usually contain a rounded end.

-Smaller than normal and have little or no central pallor.

-Acanthocytes refer to abnormal phospholipid metabolism (have an excess ofcholesterol)

-Large numbers of these cells on a smear can be of diagnostic significance.

Found in:

- Hereditary acanthocytosis,50-100% of blood cells.

-Liver disease (cirrhosis),rarely in hepatitis.

- Post splenectomy
- Anorexia nervosa and starvation

-lipid disorders

Rouleaux Formation:

Morphology:

Stacks of RBC's resembling a stack of coins. Stacking of RBCs due to increased plasma proteins coating RBCs (in patient with high ESR) .

Found in:

- Hyperfibrinogenaemia
- Hyperglobulinaemia
- Chronic inflammatory disorders.
- Multiple myloma

Red cell-agglutination:

Morphology:

Irregular clumps of red cells. Antibody-mediated Irregular clumping , temperature dependent. Several types of irregular contracted cells can be distinguished in toxin or drug or chemical induced hemolytic anemia.

Found in:

- Cold agglutinins
- Warm autoimmune hemolysis

Sickle Cells (Drepanocytes):

Morphology:

Sickle shaped red, are formed as a result of the presence of hemoglobin S inthe red cell.

-As the red cell ages, it becomes less flexible or deformable and becomes rigid as it passes through the low oxygen tension atmosphere of the small capillaries in the body.

-In the absence of oxygen, hemoglobin S polymerizes into rods, causing the sickle cell shape.

Sickle cells can be somewhat pointed at the ends,

Found in:

Hb-S disease

-Most sickled cells can revert back to the discoid shape when oxygenated.

-About 10% of sickled cells are unable to revert back to their original shapeafter repeated sickling episodes.

Nucleated red blood cells.

These red blood cells are released from the bone marrow early into the blood stream, due to the need for oxygen. Normal red blood cells do not contain a nucleus on a peripheral smear.

Envelope Form Cell:

Found in

-Thalassaemia

-Sickle cell anemia

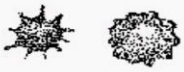
Knizocyte:

-A streak of hemoglobin through the centre of the cell.

-In some hemolytic anemia cases.

Terminolo	Description	Condition
Target Cells	Central Hemoglobin; target shaped	Liver Disease; Thalassaemia, Abnormal Hb; Iron Deficiency
Echinocyte	Short specula's, equally-spa	Uremia, Hypokalemia, Artifact
Acanthocyte	Speculated, Irregular	Liver disease (Alcohol), Post-spleenoctomy.
Spherocyte	Spherical, no central pallor	HS, immune Hemolytic anemia
Shistocyte	Fragmented RBC, Helmet c	MAHA, burns
Ovalocyte	Oval / Elliptical shaped	Hereditary elliptocytosis, Megaloblastic anemia.
Sickle Cell	Bipolar speculated shape “ banana” shaped	Hb S-containing hemoglobinopathy
Teardrop cell	Single elongated extremity	Myelophthistic changes
Bite cells	Irregular gap in membrane	G6PD deficiency

TABLE I. TERMS USED TO DESCRIBE POIKILOCYTOSIS

Appearance/New Name	Meaning of Greek Stem	Old Name	Significance
Acanthocyte 	Spine	Acanthocyte	Abetalipoproteinemia, cirrhosis
Codocyte 	Bell	Target cell	Thalassemia, retention jaundice
Dacryocyte 	Tear	Tear drop	Thalassemia, hemoloytic anemia, myelofibrosis
Drepanocyte 	Sickle	Sickle cell	Sickle cell anemia
Echinocyte 	Sea Urchin	Burr cell Crenated cell	Anemia, artifact
Elliptocyte* 	Oval	Elliptocyte	Hereditary ellipocytosis

Appearance/New Name	Meaning of Greek Stem	Old Name	Significance
Keratocyte 	Horn	-------	Intravascular coagulation (DIC), fibrin deposits in blood vessels or synthetic heart valves
Knizocyte 	Dimple	-------	Hemolytic anemia Hereditary spherocytosis
Leptocyte 	Thin	Target cell	Thalassemia, retention jaundice
Schizocyte 	Cut	Schistocyte	(same as Keratocyte)
Spherocyte	Sphere	Spherocyte	Hereditary spherocytosis; Some hemolytic anemias
Stomatocyte 	Mouth	Stomatocyte	Hereditary stomatocytosis; Acquired hemolytic anemias; May be artifact

Erythrocyte Inclusions with Wright's stain

Inclusion	Composition	Appearance	Condition
Basophilic stippling	Precipitated ribosomes	Evenly dispersed fine or co granules	- Lead poisoning Thalassaemia , other anemia.
Howell-Jolly bodies	DNA in origin Nuclear Fragment	Dense, round blue granule	Post – Splenectomy
Pappenheimer bodies	Iron-containing granules	Small blue granules in clus	Anemia's
Heinz bodies	Denatured Hemoglobin	Round blue precipitates	G6PD
Cabot Rings	Remnants of Nuclear membrane	Reddish-blue thread like ri	Severe anemia, Lead poisoni
Organism		Small blue inclusion	Malaria Babesiosis

Abnormality with inclusion bodies :is the presence foreign bodies in inside erythrocyte, includes :

1-Howell-Jolly Bodies:

There are nuclear remnant ,they appear as small round cytoplasmic red cell inclusion with same staining characteristics as nuclei, may be seen in sickle cell anemia. These bodies are DNA that densely staining dark purple (violet) particles within the red blood cell.

Found in

1- Post splenectomy
2- Megaloblastic anemia
3- Leukemia

2- Siderotic Granules (Pappenheimer Bodies):

These are iron containing granules in red blood cells that are seen because theiron is aggregated with mitochondria and ribosomes. They appear as faint

violet or magenta specks, often in small clusters, due to staining of the associated protein.

They are associated with:

-severe anemia and thalassemia.

- hemolytic anemia,

-infections

-post-splenectomy.

3- Basophilic stippling:

Considerable numbers of small basophilic inclusions in red cells is granules of RNA seen within the red blood cell. The granules stain blue to purple distributed throughout the cell surface.

Found in

-Thalassemia

-Megaloblastic anemia

-Hemolytic anemia

- Liver disease

-Toxicities such as Heavy metal poisoning

4- Heinz Bodies:

Represent denatured hemoglobin deep purple bodies (methemoglobin - Fe+++) within a cell, some laying close to periphery of the red cells and other attach to outer surface .With a supravital stain like crystal violet, Heinz bodies appear as round blue precipitates.

Presence of Heinz bodies indicates red cell injury and is usually associated with G6PD-deficiency.They are found in some forms of hemolytic anemia.

5- Cabot Rings:

Reddish-blue threadlike rings or figure 8 pattern in RBCs of severe anemia's. These are remnants of the nuclear membrane or remnants of microtubules and. Very rare finding in patients with

-Megaloblastic anemia.

-severe anemia.

-lead poisoning.

-Dyserythropoiesis

6- Parasites of Red Cell:

Two organisms are have a tendency to invade the RBCs

1- All 4 species of the malaria parasite will invade RBCs. We will see the Plasmodium of different species in RBCs..

2- Theileria microti (Bebesia microti).

7- Erythroblast:is used as genetic term to describe all nucleated erythrocyte .In normal marrow the pronormoblast is the first cell, recognizable as definitely belonging to erythroid series .From it the erythrocyte develops through a succession of maturing erythroblast, early normoblast ,intermediate normoblast, late normoblast developing erythrocyte.

The process of normoblastic maturation is characterized by the following progressive changes :

a- **Diminution in cell size**.

b- **Ripening of cytoplasm** in stain proportion ,this is accompanied by change in color from deep blue to pink due to progressive formation of acidophil staining haemoglobin and simultaneous loosening of the ribose nucleic acid which responsible for basophilic of the cytoplasm .

c- **Diminution of the nucleus :**this is manifest by loss nucleoli, decrease in total size and size relative to cytoplasm progressive clumping and condensation of the chromatins and Deeping in color ,the time for maturation from pronormoblast to mature red blood cell about 7 days.

8- pronormoblast.

9- early normoblast

10- intermediate normoblast.

11- late normoblast.

12- Reticulocyte

MODULAR UNIT 7

Red Cell Morphology

Discuss aspects of red cell morphology related to color

III -Variation In Erythrocyte Color

-A normal erythrocyte has a pinkish-red color with a slightly lighter-coloredcenter (central pallor) when stained with a blood stain, such as Wright stain.

-The color of the erythrocyte is representative of hemoglobin concentration inthe cell.

-Under normal conditions, when the color, central pallor, and hemoglobin areproportional, the erythrocyte is referred to as Normochromic.

RBC Color

-the central area (1/3 of the cell) is white, while buff-colored haemoglobin isvisible in the outer 2/3 of the cell.

- The unit to measure the amount of hemoglobin per cell is mean corpuscular hemoglobin, or MCH .
- The MCH is simply the average amount of hemoglobin in one red blood cell, from a particular sample .
- Its reference range is 27pg – 31pg , meaning that there is typically between 27pg and 31pg of hemoglobin in a single red blood cell
  - The other unit for haemoglobin content of a red blood cell is mean corpuscular haemoglobin concentration (MCHC).
  - The MCHC is reflective of the concentration of packed red blood cells (so blood excluding plasma) that is haemoglobin.
  - It basically translates to the amount of haemoglobin present in the cellular component of blood, and thus excluding plasma. Its reference range is 32g/dL – 36g/dL

-A decreased amount of haemoglobin is referred to as hypochromasia or hypochromic.

-MCHC values of 30% or less reflect this condition.

-Hyperchromasia and hyperchromia, refer to a hypothetical situation ratherthan an actual occurrence.

1-Hypochromia

Is used to describe a decrease in intensity of hemoglobin color at varying degree . Increased central pallor and decreased hemoglobin concentration, the central pallor occupies more than the normal third of the red cell diameter. Hypochromia is associated with decrease in MCHC. However cell which are thinner than normal may appear slightly hypochromic but MCHC is still normal .

There are two conditions that a RBC must satisfy in order to be classified as a hypochromic cell. These are:

1- The central zone of pallor of the RBC must be greater than 1/3 of the diameter of the cell.

2-The MCH must be below 27pg/cell and/or the MCHC must be below 32g/dL.

Found in

-Iron deficiency anemia

-Thalassemia

-Sideroblastic anemia .

-any of the conditions leading to Microcytosis.

❖ They are two possible causes :-

1-Abnormal thinness of erythrocyte.

2-A lowered hemoglobin concentration result from impaired hemoglobin synthesis as in sideroblastic anemia .Rarely, the failure of globin synthesis cause lower hemoglobin as in thalassemia

2- Hyperchromia\Polychromasia

Mean increase the intensity of stain of erythrocyte in which central area of pallow is

lost so the cell appear more deep staining, this appearance due to increase in thickness of cell not in to increase concentration of hemoglobin so MCHC normal. Red cells stain shades of blue-gray as a consequence of uptake of both eosin (by hemoglobin) and basic dyes (by residual ribosomal RNA). Often slightly larger than normal red cells and round in shape - round macrocytosis (high MCV).

Found in

Any situation with reticulocytosis –for example bleeding, hemolysis or response to heamatinic factor replacement.

-Megaloblastic anemia or spherocyte in spherocytosis occur due to increase cell thickness.

3- Polychromasia (reticulocyte) /polychromatophilia :

Young erythrocyte which have not yet completely with lost their nucleic acid(residual RNA) affinity for basic component of the Romanowsky stains andassumes a degree of blue staining proportional to the amount of RNA ,it isnormally present only in small number in peripheral blood film, they stain asreticulocyte.It general marked polychromasia indicated active bloodregeneration,they are slightly larger than normal mature erythrocyte(macrocyte). Polychromasia term used to indicate the increased presence ofnon-nucleated immature erythrocyte (polychromatophilic erythrocyte) Appears as bluish gray color of RBC on Wrights stain smear due to prescienceRNA . Residual RNA indicates immaturity of cell.

Found in :

-Reticulocyte

-Target cell – also called leptocyte ,the Maxican hat cell or codocyte.

-An RBC with a peripheral ring of Hb plus a central condensation of Hb inthe area of pallor or “bull’s eye appearance“

- Found in patients with hemoglobinpathay and thalassemia Reticulocyte

4-Anisochromasia (Dimorphism)

Refer to different abnormality of color in same field , indicates the presence ofboth normochromic and hypochromic

Found in :

-Iron deficiency anemia .

-Responding to iron therapy or after blood transfusion of normal blood topatient with hypochromic .

-sideroblastic anemia.

What Abnormal Results Mean

This test is used to diagnose the cause of anemia. The following are the typesof anemia and their causes:

-Normocytic/ normochromic (NC/NC) anemia is caused by sudden blood loss,prosthetic heart valves, sepsis, tumor, long-term disease or aplastic anemia.

-Microcytic/ hypochromic anemia is caused by iron deficiency, lead poisoning,or thalassemia.

-Microcytic/ normochromic anemia results from a deficiency of the hormoneerythropoietin from kidney failure.

-Macrocytic /normochromic anemia results from chemotherapy, folate deficiency, or vitamin B-12 deficiency.

MODULAR UNIT 8

The normal Hb of the blood, contain and importance

Hemoglobin (Hb): The red respiratory protein of erythrocytes ,Iron- bearing protein, red globular proteins which have a molecular weight of about 68000-64,500 deltons which is the main component of the RBC ,gives the red cell its color. In adult has about 630gm of hemoglobin containing about 2.2gm of Iron .64,500 consisting of approximately 3.8% heme and 96.2% globin which is the main component of the RBC ,gives the red cell its color

Hb function:-

Hb is found in RBCs each100ml of arterial oxygenated blood carriers 19ml oxygen in combination with Hb and about 0.3ml of O2 in plasma.

its main function :

-Transport of O2 from lung to tissues.

-Transfer of CO2 from tissue to lungs.

-Buffering action, maintains blood pH as it changes from oxyhemoglobin (carrying O_2) to deoxyhemoglobin (without $_{O2}$)

In the lungs, 1 g of hemoglobin combines readily with 1.36cc of oxygen by oxygenation to form oxyhemoglobin.

-Each red cell has 640 million molecules of Hb.

-Haemoglobin (Hb), protein constituting 1/3 of the red blood cells weight

Synthesis : Majority synthesized at the polychromatophilic normoblast, stage begins in proerythroblast

65% at erythroblast stage

35% at reticulocyte stage

Structure: Is a tetramers, 2 pairs un like polypeptide chains (consist of 4 polypeptide subunits)

-**Heme group**: protoporphyrin is linked at a specific site to each globin polypeptide chain ,made up of ringed structure called pyrrol rings, the building materials used to synthesis hem within the developing erythrocyte are amino acid glycine and succinic acid ,one molecule of glycine acid and one of succinic acid condense to give delta aminolaevulinic acid (A.L.A) .Two molecules of A.L.A are called aminolaevulinic acid anhydrase .

Four of pyrrol rings react to form a tetra pyrrol rings ,additional structures of pyrrol rings form the protoporphyrin at the last stage link to Iron

Structures of Heme : a)Porphyrin ring

b)Ferrous iron

-Globin chain: major component of hemoglobin, some globin are made daily, four chains a)2 (α) Alpha chains (141)amino acid

b)2 Beta chains (146) amino acid

Heme: porphyrin ring with central iron. Iron is the site of attachment with O2.

Synthesis of Haem & globin produced at two different sites in the cells : Haem in mitochondria

Globin in polyribosomes

Processes necessary for normal synthesis of Hb :-

-Adequate iron supply & delivery

-Adequate synthesis of protoporphyrins

-Adequate globin synthesis

Chain of Events:

-Iron delivery & supply: Iron is delivered to the reticulocyte by transferrin

-Synthesis of protoporphyrins: Occurs in the mitochondria of RBC precursors mediated by EPO and vitamin B^6

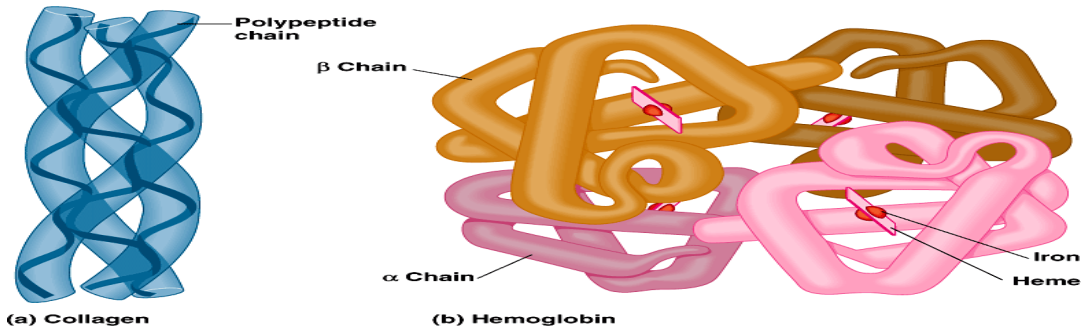
Protoporphyrin + iron = heme

Regulation : Stimulated by tissue hypoxia

Hypoxia causes the kidneys to increase production of EPO, which increases RBC and hemoglobin production

There are 4 heme groups each attached to on globin chain. So one Hb molecule can carry up to 4 O2 molecules.

According to sequence of amino acids in the primary structure of each chain, there are four types of chains: α, β, γ and δ.



Hemoglobin Reference Ranges

-Adults

Male 14-17.5 g/dL

Female12-15 g/dL

-Children

Birth 13.5-20.0 g/mL 6-12 years 11.5-15.5 g/mL

Iron in Hemoglobin is ferrous or ferric ? Why ?

• Iron in ferrous form (6 coordination)

4 bind with protoporphyrin

1 bind to histidine (globin)

1 free bind to O2 or CO2 respectively

• Where in ferric form we well have one bond missing (malfunctional hemoglobin)

• Heme and globulin are not isolated, the bind together by Iron.

Gas Transportation

• **Why we use hemoglobin as a transporter for oxygen ?**

1. Because of low solubility of oxygen in water.

2. Hemoglobin have a regulatory effect on oxygen concentration in lungs and tissues.

Note : all tissue required of oxygen and 20% of CO2 from metabolic wastes transport via Hb.

MODULAR UNIT 9

Types of Hb:

Hb A or HbA1: is the normal Hb in adults represents about 97% of total Hb, it is composed of 2 α and 2 β chains.

HbA2: minor adult Hb, comprised 3% of normal adult Hb. Composed of 2 α and 2 δ chains consider as diagnostic aid in beta-thalassemia and megalobastic anemia and decrease in Iron deficiency anemia and sideroblastic anemia .

Hb Gower (Gower-1 (ζ2ε2), Hb Gower-2 (α2Aε2) or Hb Portland (ζ2γ) : embryonic hemoglobin's produced in the first three months of embryonic development, when blood cells are produced in the yolk sac.

HbF(fetal Hb): is the main Hb during fetal life and about 60% of normal Hb at birth then disappear gradually. It is composed of 2α and 2 γ chains.It have many character like :

1-Hb F has greater affinity for O2 than HbA so ensure O2 transfer from maternal circulation to fetus RBCs through placenta.

2-Hb F has special property of remarkable resistance to denaturation of extremes pH.

The erythrocyte of newborn contain about 80% Hb F,20% Hb A and less than 0.5% Hb A2.Hb F falls steadily following birth at about six months of age, it is increase in Varity of acquired hematological disorders include megaloblastic anemia ,sickle cell anemia ,and leukemia .

HBA1C : has glucose residues attached to β-globin chains – increased amounts in DM . ***HbA1c could be used as a monitor for the control of the blood glucose level during the last 2 months for diabetic patients***

	Hb A	Hb A_2	Hb F
structure	$\alpha_2ß_2$	$\alpha_2\delta_2$	$\alpha_2\gamma_2$
Normal %	96-98 %	1.5-3.2 %	0.5-0.8 %

Nonfunctional hemoglobin:

1- Carboxyhemoglobin

-Oxygen molecules bound to heme are replaced by carbon monoxide.

-Slightly increased levels of carboxyhemoglobin are present in heavy smokers and as a result of environmental pollution. Can revert to oxyhemoglobin.

2- Methemoglobin

Iron in the hemoglobin molecule is in the ferric (Fe^3) state instead of the ferrous (Fe^2) state. Incapable of combining with oxygen. The NADH-dependent enzyme methemoglobin reductase is responsible for converting methemoglobin back to hemoglobin

Can occur as a result of strong oxidative drugs or to an enzyme deficiency. Can revert to oxyhemoglobin

3- Sulfhemoglobin

Hemoglobin molecule contains sulfur. Caused by certain sulfur-containing drugs or chronic constipation. .Cannot revert to oxyhemoglobin and may cause death.

MODULAR UNIT 10

Mutations in hemoglobin (hemoglobinopathies):

Hemoglobinopathies are members of a family of genetic disorders caused by:

1- Production of a *structurally abnormal* hemoglobin molecule

(Qualitative hemoglobinopathies)

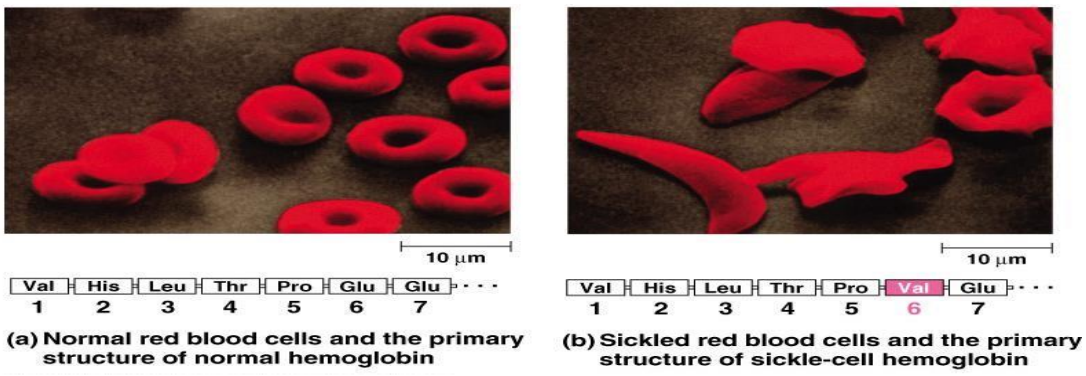
Or: 2- Synthesis of *insufficient quantities* of normal hemoglobin

(Quantitative hemoglobinopathies)

Or: 3- both (rare).

1-Sickle cell anemia (Hb S disease):

It is a genetic disorder of blood caused by mutation in β-globin chain resulting in the formation of Hb S. The mutation occurs in 6th position of β-chain where glutamic acid is replaced by valine (non polar). Valine residues aggregate together by hydrophobic interactions leading to precipitation of Hb within RBCs. RBCs assume sickle-shaped leading to fragility of their walls and high rate of hemolysis.



(a) Normal red blood cells and the primary structure of normal hemoglobin

(b) Sickled red blood cells and the primary structure of sickle-cell hemoglobin

Such sickled cells frequently block flow of blood in narrow capillaries and block blood supply to tissue (tissue anoxia) causing pain and cell death.

Note: The lifetime of erythrocyte in sickle cell is less than 20 days, compared to 120 days for normal RBCs.

Patients may be :

- Heterozygotes (Hb AS): mutation occurs only in one β-globin chain. These patients have sickle cell trait with no clinical symptoms and can have normal life span. HbS 35% while HbA 65% .

Or: Homozygotes (Hb SS): mutation occurs in both β-globin chain with apparent anemia and its symptoms. 90% HbSS and 10% HbA .

Symptoms:

a-pain in stomach, legs ,arm**.**

b- patients is tired and nervous.

c-ulceration in lower part of legs.

d-prolong arm and legs.

2-**Hb C disease:** Like HbS, Hb C is a mutant Hb in which glutamic acid in 6th position of β-chain is replaced by lysine. RBCs will be large oblong and hexagonal. Found primarily in blacks, in area of west Africa , the gene may be as high as 28%. About 2% of blacks Americans are AC heterozygote while 1out of 10,000 are CC homozygote .it is the second most commonly variant worldwide .

The heterozygous form (HbAC) is lack any clinical manifestation (asymptomatic),erythrocyte life is normal contain about 30% Hb C and 50-60% Hb A and slightly increase amount of HbA2.Stained blood film of AC show increase numbers of target cell.

The homozygous form (Hb CC) causes anemia, tissue anoxia and severe pain.

3- Thalassemia: A group of genetic diseases in which a defect occur in the rate of synthesis of one or more of Hb chains(imbalance occurs in the synthesis of globin chains),but the chains are structurally normal. This due to defect or absence of one or more of genes responsible for synthesis of α or β chains leading to premature death of RBCs.

Types:

β -thalassemia: When synthesis of β chains is decreased or absent. There are two copies of the gene responsible for synthesis of β chains. Individuals with β globin gene defects have either :

-β -thalassemia minor (β –thalassemia trait) : when the synthesis of only one β –globin gene is defective or absent. Those individuals make some β chains and usually not need specific treatment.

β -thalassemia major (Cooley anemia): if both genes are defective.

Babies will be severely anemic during the first or second year of life and so require regular blood transfusion. Bone marrow replacement is more safe treatment (why?).

α-thalassemia: in which synthesis of α globin chain is defective or absent. There are four copies of gene responsible for synthesis of α globin chains so patients may have:

i - Silent carrier of α-thalassemia with no symptoms: if one gene is defective

ii- α-thalassemia trait: if two genes are defective.

iii- Hb H disease: if 3 α globin genes are defective, with mild to moderate anemia. The produced Hb will be β4 which is called HB H. Oxygen delivery to tissues will be blocked because Hb H (β4) has high affinity to O2 and not deliver it to tissues.

iv- Hydrops fetalis: when all 4 α globin genes are defective. It causes fetal death because α globin chains are required for synthesis of Hb F.

4 -Hb D

Hb D Punjab present in punjab region of India and Pakistan. Studies indicate that Hemoglobin D-Punjab accounts for over 55% of the total hemoglobin variants there. it is also sometimes called “D Los Angeles”. Hemoglobin D is the 4th most common hemoglobin variant. It developed as a response to the selective pressures of malaria in these regions of Asia.

1 -these individuals have normal Hb values with no evidence of hemolysis.

2-erythrocyte indices within normal limit.

3-some individuals have decreased osmotic fragility.

4 -individuals doubly heterozygous for Hb D and B thalassemia.

5-usually individuals have mild anemia and minimal hemolysis.

6-People with hemoglobin D trait have slightly more hemoglobin A than hemoglobin D.

7 -Hemoglobin D Disease can cause mild hemolytic anemia and mild to moderate splenomegaly. The anemia usually occurs in the first few months of life, as fetal hemoglobin decreases and hemoglobin D increases

5 -Hb E

is an abnormal hemoglobin with a single point mutation in the β chain. At position 26 there is a change in the amino acid, from glutamic acid to lysine. Hemoglobin E is very common among people of Southeast Asian, Northeast Indian, Sri Lankan and Bangladeshi descent. The βE mutation affects β-gene expression creating an alternate splicing site in the mRNA at codons 25-27 of the β-globin gene. Through this mechanism, there is a mild deficiency in normal β mRNA and production of small amounts of anomalous β mRNA. The reduced synthesis of β chain may cause β-thalassemia

AE heterozygotes are commonly encountered ,they have no hematological abnormalities .As in Ac and As heterozygotes, the proportion of Hb E decease in individuals who have α-thalassemia.

6-Hb G Accra(korle-B4)

It is encountered quite frequently in central Africa.

Hemoglobin G-Philadelphia can arise from one of two different mutations in the α-globin gene. Although both produce the same protein, the mutations occur in different ethnic groups and produce different patterns of abnormal hemoglobins.

1-there is no clinical or hematological manifestation associate with either the heterozygote or the homozygote state .

2-the erythrocyte from an individual homozygote for Hb krole B4 have normal appearance on blood smear.

3-No target cell

7 -Hb H

It is a tetramer composed of four normal ß chains .this abnormal hemoglobin is seen in some individuals with α-thalassemia.

8 -Hb I

it is most commonly encountered Alpha chain variant. They have no apparent clinical or hematological abnormalities. Heterozygous have about 25% Hb I and 75% Hb A ,this proportion is similar to other alpha chain variant and indirect evidence that each parent contributes two alpha chain gene .

Myoglobin (Mb) :

- It is formed of one heme molecule attached to one globin chain.

- It is found only in red skeletal muscles and cardiac muscle. It gives their tissues their characteristic red color.

-Myoglobin has much higher affinity for oxygen than hemoglobin. So it is unable to release it to tissues. In contrast, Hb reacts with oxygen reversibly to give it to tissues. Myoglobin concentration is increased in blood in a disease called myocardial infarction and in case of muscle trauma and myopathies.

MODULAR UNIT 11,12

Anemia: definition, classification and types

Anemia is the blood disorder, deficiency in the oxygen-carrying capacity of the blood due to a diminished erythrocyte mass.

characterized by the reduction in:

1. Red blood cell (RBC) count

2. Hemoglobin content

3. Packed cell volume (PVC).

Generally, reduction in RBC count, hemoglobin content and PCV occurs because of:

1. Decreased production of RBC:

a) low erythropoietin

b) Decreased marrow response to erythropoietin

2. Increased destruction of RBC (hemolysis)

3. Excess loss of blood from the body (bleeding).

All these incidents are caused either by inherited disorders or environmental influences such as nutritional problem, infection and exposure to drugs or toxins.

Anemia is a laboratory diagnosis:

Less than normal range of hematological parameters (CBC):

-RBC,WBC, ,platelets count ,hemoglobin concentration and PCV.

-Mean cell volume (MCV): is below 80 fL in microcytic anemia ,higher than 100fL in macrocytic anemia .

- Reticulocyte count important to determine is a hypo-proliferative or hyper-proliferative anemia or observed the treatment progress in hypo-proliferative anemia.

-Blood bilirubin: High bilirubin (unconjugated bilirubin) indicate the jaundice which due to haemolysis (hemolytic anemia)or megaloblastic anemia.

-Iron blood : Iron level be low in Iron deficiency anemia which due to shortage in Iron storage in human body led to defect in haemoglobin synthesis .Microcytic ,hypochromic anemia observed in Iron deficiency anemia.

	Men	**Women**
Hemoglobin (g/dL)	14-17.4	12.3-15.3
Hematocrit (%)	42-50%	36-44%
RBC Count (10^6/mm^3)	4.5-5.9	4.1-5.1
Reticulocytes	1.6 ± 0.5%	1.4 ± 0.5%
WBC (cells/mm^3)	~4,000-11,000	
MCV (fL)	80-96	
MCH (pg/RBC)	30.4 ± 2.8	
MCHC (g/dL of RBC)	34.4 ± 1.1	
RDW (%)	11.7-14.5%	

Laboratory Definition of Anemia:

Hgb: Women: <12.0 g/dL

Men: < 13 g/dL

Hct: Women: < 36

Men: < 39

Clinical symptoms and Signs of anemia:

The severity of symptoms may vary widely depending on :

1-The degree(severity) of anemia.

2-Time period over which anemia developed.

3-Age of patient.

4-The Hb oxygen dissociation curve.

5-Other medical conditions that are present.

-Decreased oxygenation

Exertion dyspnea (shortness of breath)

Dyspnea at rest

Weakness ,Headache, Fatigue

Tachycardia ,Bounding pulses and Roaring in the Ears

Widened pulse pressure (increase systolic blood pressure with a decreased diastolic blood pressure)

Lethargy, confusion

-Decreased volume

Signs :physical examination:

Fatigue - pale apparent in conjunctive ,palms, and face, nail beds (all mucous membrane in all side of the body) .

Muscle cramps

Postural dizziness

syncope

CLASSIFICATION OF ANEMIA:

Anemia is classified by two methods:

1. Morphological classification

2. Etiological classification.

MORPHOLOGICAL CLASSIFICATION:

Morphological classification depends upon the size and color of RBC.

a- Size of RBC is determined by mean corpuscular volume (MCV).

b-Color is determined by mean corpuscular hemoglobin concentration (MCHC).

By this method, the anemia is classified into four types.

1-Normocytic Normochromic Anemia:

Size (MCV) and color (MCHC) of RBCs are normal. But the number of RBC is less (as in hematological malignancies(chronic lymphocytic and large granular lymphocytic leukemia),rheumatic diseases, and infections).

2. Macrocytic Normochromic Anemia

RBCs are larger in size with normal color. RBC count is less. (causes is impaired DNA synthesis in the bone marrow leading to megaloblastic changes in the red cell precursors ,and from other mechanism as alcoholism, liver diseases, hypothyroidism ,and hemolysis or hemorrhage)

3-Macrocytic Hypochromic Anemia

RBCs are larger in size. MCHC is less, so the cells are pale (less colored).

4-Microcytic Hypochromic Anemia

RBCs are smaller in size with less color (Iron deficiency, anemia of chronic disease, thalassemia).

Normal ranges:

-Normocytic (MCV 90-100)

-Macrocytic (MCV >100)

-Microcytic(MCV<80)

Table: Morphological classification of anemia

Type of anemia	Size of RBC (MCV)	r of RBC(MCHC)
Normocytic normochromic	normal	normal
Normocytic hypochromic	normal	less
Macrocytic hypochromic	large	less
Microcytic hypochromic	small	less

ETIOLOGICAL CLASSIFICATION:

On the basis of etiology (study of cause or origin), anemia is divided into five types:

1. Hemorrhagic anemia

2. Nutrition deficiency anemia

3. Hemolytic anemia

4. Aplastic anemia

5. Anemia of chronic diseases.

1-Hemorrhagic Anemia

Hemorrhage refers to excessive loss of blood. Anemia due to hemorrhage is known as hemorrhagic anemia. It occurs both in acute and chronic hemorrhagic conditions .

Acute hemorrhage:

Acute hemorrhage refers to sudden loss of a large quantity of blood as in the case of accident. Within about 24 hours after the hemorrhage, the plasma portion of blood is replaced. However, the replacement of RBCs does not occur quickly and it takes at least 4 to 6 weeks. So with less number of RBCs, hemodilution occurs. However, morphologically the RBCs are normocytic and normochromic. Decreased RBC count causes hypoxia, which stimulates the bone marrow to produce more number of RBCs. So, the condition is corrected within 4 to 6 weeks.

Chronic hemorrhage :

It refers to loss of blood by internal or external bleeding, over a long period of time. It occurs in conditions like peptic ulcer, purpura, hemophilia and menorrhagia due to continuous loss of blood, lot of iron is lost from the body causing iron deficiency. This affects the synthesis of hemoglobin resulting in less hemoglobin content in the cells. The cells also become small. Hence, the RBCs are microcytic and hypochromic .

MODULAR UNIT 13

White blood cells (WBC)

White blood cells (also called leukocytes or leucocytes and abbreviated as WBCs) They are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders .

All white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells. Leukocytes are found throughout the body, including the blood and lymphatic system.

All white blood cells have nuclei, which distinguishes them from the other blood cells, the a nucleated red blood cells (RBCs) and platelets .

Types of white blood cells can be classified in standard ways. Two

pairs of broadest categories classify them either :

- By structure (granulocytes or a granulocytes)
- by cell lineage (myeloid cells or lymphoid cells).

These broadest categories can be further divided into the five main types :
neutrophils, eosinophil (acidophilic), basophils, lymphocytes, and monocytes.

These types are distinguished by their physical and functional characteristics .

- Monocytes and neutrophils are phagocytic .
- Further subtypes can be classified; for example, among lymphocytes, there are B cells, T cells, and NK cells.

-The number of leukocytes in the blood is often an indicator of disease, and thus the white blood cell count is an important subset of the complete blood count .

-The normal white cell count is usually between 4,000 to 11,000 white blood cells per microliter of blood.

-An increase in the number of leukocytes over the upper limits is calledleukocytosis

-It is normal when it is part of healthy immune responses, which happen frequently. It is occasionally abnormal, when it is neoplastic or autoimmune inorigin.

-A decrease below the lower limit is called leukopenia. This indicates a weakened immune system.

Etymology:

The name "white blood cell" derives from the physical appearance of a bloodsample after centrifugation.

White cells are found in the buffy coat, a thin, typically white layer ofnucleated cells between the sediment red blood cells and the blood plasma .

The scientific term leukocyte directly reflects its description. It is derived fromthe Greek roots leuk- meaning "white" and cyt- meaning "cell ."

The buffy coat may sometimes be green if there are large amounts of neutrophils in the sample, due to the heme-containing enzyme myeloperoxidase that they produce.

Types

All white blood cells are nucleated, which distinguishes them from the anucleated red blood cells and platelets.

- ❖ Types of leukocytes can be classified in standard ways. Two pairs of broadest categories classify them either :
- by structure : a-granulocytes

b-a granulocytes

- by cell lineage: a- myeloid cells

b-lymphoid cells.

- ❖ These broadest categories can be further divided into the five main types: neutrophils, eosinophil, basophils, lymphocytes, and monocytes.

These types are distinguished by their physical and functional characteristics.Monocytes and neutrophils are phagocytic. Further subtypes can be classified.

- Granulocytes are distinguished from a granulocytes by their:

-nucleus shape (lobed versus round, that is, polymorphonuclear versus mononuclear).

- by their cytoplasm granules (present or absent, or more precisely, visible on light microscopy or not thus visible)

- The other dichotomy is by lineage :

- Myeloid cells (neutrophils, monocytes, eosinophil and basophils)

- lymphoid cells (lymphocytes) by hematopoietic lineage (cellular differentiation lineage).

-Lymphocytes can be further classified as

- T cells, B cells
- natural killer cells.

Neutrophil

Neutrophils are the most abundant white blood cell, constituting 60-70% of the circulating leukocytes. and including two functionally unequal subpopulations:

-neutrophil-killers

-neutrophil-cagers .

Function :

They defend against bacterial or fungal infection. They are usually first responders to microbial infection; their activity and death in large numbers form pus .

 Neutrophils are active in phagocytosing bacteria and are present in large amount in the pus of wounds. These cells are not able to renew their lysosomes (used in digesting microbes) and die after having phagocytosed a few pathogens.

Neutrophils are the most common cell type seen in the early stages of acute inflammation.

The life span of a circulating human neutrophil is about 5.4 days.

Characters:

They are commonly referred to as polymorphonuclear (PMN) leukocytes, although, in the technical sense, PMN refers to all granulocytes .

-They have a multi-lobed nucleus, which consists of 3-5 lobes connected byslender strands.

-This gives the neutrophils the appearance of having multiple nuclei, hence thename polymorphonuclear leukocyte .

-The cytoplasm may look transparent because of fine granules that are palelilac when stained .

Eosinophil :

Eosinophil compose about 2-4% of the WBC total. This count fluctuatesthroughout the day, seasonally, and during menstruation .

Functions:

It rises in response to allergies, parasitic infections, collagen diseases, anddisease of the spleen and central nervous system .

They are rare in the blood, but numerous in the mucous membranes of therespiratory, digestive, and lower urinary tracts.

They primarily deal with parasitic infections .

Eosinophil are also the predominant inflammatory cells in allergic reactions.The most important causes of eosinophilia include allergies such as asthma.

They secrete chemicals that destroy these large parasites, such as hook wormsand tapeworms, that are too big for any one WBC to phagocytize .

Characters:

In general, their nucleus is bi-lobed. The lobes are connected by a thin strand.

The cytoplasm is full of granules that assume a characteristic pink-orangecolor with eosin staining.

Basophil:

They are the rarest of the white blood cells (less than 0.5% of the total count) and share physicochemical properties with other blood cells, they are difficult to study.

Function:

Basophils are chiefly responsible for allergic and antigen response by releasing the chemical histamine causing the dilation of blood vessels .

They excrete two chemicals that aid in the body's defenses: histamine and heparin .

- Histamine is responsible for widening blood vessels and increasing the flow of blood to injured tissue. It also makes blood vessels more permeable so neutrophils and clotting proteins can get into connective tissue more easily .
- Heparin is an anticoagulant that inhibits blood clotting and promotes the movement of white blood cells into an area. Basophils can also release chemical signals that attract eosinophil and neutrophils to an infection site

Characters:

The nucleus is bi- or tri-lobed, but it is hard to see because of the number ofcoarse granules that hide it.

They can be recognized by several coarse, dark violet granules, giving them ablue hue.

Lymphocyte:

Lymphocytes are much more common in the lymphatic system than in blood .

Characters:

Lymphocytes are distinguished by having a deeply staining nucleus that may be eccentric in location, and a relatively small amount of cytoplasm.

Lymphocytes include:

1- B cells make antibodies that can bind to pathogens, block pathogen invasion, activate the complement system, and enhance pathogen destruction.

2-T cells:

a- **CD4+ helper T cells**: T cells displaying co-receptor CD4 are known as CD4+ T cells. These cells have T-cell receptors and CD4 molecules that, in combination, bind antigenic peptides presented on major histocompatibility complex (MHC) class II molecules on antigen-presenting cells. Helper T cells make cytokines and perform other functions that help coordinate the immune response. In HIV infection, these T cells are the main index to identify the individual's immune system integrity.

b- **CD8+ cytotoxic T cells:** T cells displaying co-receptor CD8 are known as CD8+ T cells. These cells bind antigens presented on MHC I complex of virus-infected or tumor cells and kill them. Nearly all nucleated cells display MHC I.

c- **γδ T cells possess an alternative T cell receptor** (different from the αβ TCR found on conventional CD4+ and CD8+ T cells). Found in tissue more commonly than in blood, γδ T cells share characteristics of helper T cells, cytotoxic T cells, and natural killer cells.

3-**Natural killer cells** are able to kill cells of the body that do not display MHC class I molecules, or display stress markers such as MHC class I polypeptide-related

sequence A (MIC-A). Decreased expression of MHC class I and up-regulation of MIC-A can happen when cells are infected by a virus orbecome cancerous.

Monocyte :

Characters:

They have the kidney shaped nucleus and are typically a granulated. They alsopossess abundant cytoplasm.

Function:

Monocytes, the largest type of WBCs, share the "vacuum cleaner" (phagocytosis) function of neutrophils, but are much longer lived as they have an extra role: they present pieces of pathogens to T cells so that the pathogens may be recognized again and killed. This causes an antibody response to be mounted .

Monocytes eventually leave the bloodstream and become tissue macrophages, which remove dead cell debris as well as attack microorganisms. Neither dead cell debris nor attacking microorganisms can be dealt with effectively by the neutrophils

Unlike neutrophils, monocytes are able to replace their lysosomal contents and are thought to have a much longer active life.

Fixed leucocytes :

Some leucocytes migrate into the tissues of the body to take up a permanent residence at that location rather than remaining in the blood. Often these cells have specific names depending upon which tissue they settle in, such as fixed macrophages in the liver, which become known as Kupffer cells. These cells still serve a role in the immune system.

- Histiocytes
- Dendritic cells (Although these will often migrate to local lymph nodes upon ingesting antigens)
- Mast cells
- Microglia

Disorders:

- The two commonly used categories of white blood cell disorders divide them **quantitatively** into those :

  - causing excessive numbers (**proliferative disorders**):there is an increase in the number of WBC .This increase is commonly reactive (ex. Due to infection)

but may also be cancerous.

  - causing insufficient numbers (**leukopenias**): there is decrease in the number of WBC

Leukocytosis is usually healthy (e.g., fighting an infection), but it also may bedysfunctionally proliferative .

- WBC **proliferative disorders** can be classed as
- Myeloproliferative
- lymphoproliferative .

Some are autoimmune, but many are neoplastic.

Another way to categorize disorders of white blood cells is qualitatively. There are various disorders in which the number of white blood cells is normal but the cells do not function normally.

Neoplasia of WBCs can be benign but is often malignant. Of the various tumors of

the blood and lymph, cancers of WBCs can be broadly classified as leukemias and lymphomas, although those categories overlap and are often grouped as a pair.

Leucopenia :

A range of disorders can cause decreases in white blood cells. This type ofwhite blood cell decreased is usually the neutrophil .

In this case the decrease may be called:

- neutropenia or granulocytopenia .
- Less commonly, a decrease in lymphocytes (called lymphocytopenia or lymphopenia) may be seen.

Neutropenia

Neutropenia can be acquired or intrinsic.

A decrease in levels of neutrophils on lab tests is due to :a-

either decreased production of neutrophils.

b-increased removal from the blood.

Causes:

1- Medications - chemotherapy, sulfas or other antibiotics, phenothiazenes, benzodiazepines, antithyroids, anticonvulsants, quinine, quinidine, indomethacin, procainamide, thiazides

2- Radiation

3- Toxins - alcohol, benzenes

4- Intrinsic disorders - Fanconi's, Kostmann's, cyclic neutropenia, Chédiak–Higashi

5- Immune dysfunction - disorders of collagen, AIDS, rheumatoid arthritis

6- Blood cell dysfunction - megaloblastic anemia, myelodysplasia, marrow failure, marrow replacement, acute leukemia

7- Any major infection

8- Miscellaneous - starvation, hypersplenism

Symptoms:

neutropenia are associated with the underlying cause of the decrease in neutrophils. For example, the most common cause of acquired neutropenia is drug-induced, so an individual may have symptoms of medication overdose or toxicity. Treatment is also aimed at the underlying cause of the neutropenia. One severe consequence of neutropenia is that it can increase the risk of infection.

Lymphocytopenia

Defined as total lymphocyte count below $1.0x10^9$/L, the cells most commonly affected are CD4+ T cells. Like neutropenia, lymphocytopenia may be acquired or intrinsic and there are many causes. This is not a complete list.

Causes:

Inherited immune deficiency-severe combined immunodeficiency, commonvariable immune deficiency, ataxia-telangiectasia ,

Blood cell dysfunction - aplastic anemia

Infectious diseases - viral (AIDS, SARS, West Nile encephalitis, hepatitis, herpes, measles, others), bacterial (TB, typhoid, pneumonia, rickettsiosis, ehrlichiosis, sepsis), parasitic (acute phase of malaria).

Medications - chemotherapy (antilymphocyte globulin therapy, alemtuzumab, glucocorticoids).

1- Radiation

2- Major surgery

3- Miscellaneous - ECMO, kidney or bone marrow transplant, hemodialysis, kidney failure, severe burn, carcinoma

Immune dysfunction - arthritis, systemic lupus erythematosus

Nutritional/Dietary - alcohol abuse, zinc deficiency

Like neutropenia, symptoms and treatment of lymphocytopenia are directed atthe underlying cause of the change in cell counts.

Proliferative disorders:

An increase in the number of white blood cells in circulation is called leukocytosis.

This increase is most commonly caused by inflammation.

There are four major causes :

1-increase of production in bone marrow.

2-increased release from storage in bone marrow.

3-decreased attachment to veins and arteries.

4-decreased uptake by tissues.

Leukocytosis may affect one or more cell lines and can be neutrophilic, eosinophilic, basophilic, monocytosis, or lymphocytosis.

Neutrophilia :

Neutrophilia is an increase in the absolute neutrophil count in the peripheralcirculation .

Normal blood values vary by age. Neutrophilia can be caused by a directproblem with blood cells (primary disease). It can also occur as a consequence

of an underlying disease (secondary). Most cases of neutrophilia are secondaryto inflammation.

Primary causes :

Conditions with normally functioning neutrophils – hereditary neutrophilia, chronic idiopathic neutrophilia

Down syndrome

Leukocyte adhesion deficiency

Familial cold urticaria

Leukemia (chronic myelogenous (CML)) and other myeloproliferative disorders

Surgical removal of spleen

Secondary causes:

1- Infection

2- Chronic inflammation – especially juvenile rheumatoid arthritis, rheumatoid arthritis, (for example, tuberculosis), and chronic hepatitis

3- Cigarette smoking – occurs in 25–50% of chronic smokers and can last up to 5 years after quitting

4- Stress – exercise, surgery, general stress

5- Medication induced – corticosteroids (for example, prednisone, β-agonists, lithium)

6- Cancer – either by growth factors secreted by the tumor or invasion of bone marrow by the cancer

7-Increased destruction of cells in peripheral circulation can stimulate bone marrow. This can occur in hemolytic anemia and idiopathic thrombocytopenic purpura

Eosinophilia

A normal eosinophil count is considered to be less than 0.65×109/L.

Causes:

1-Eosinophil counts are higher in newborns and vary with age

2-time (lower in the morning and higher at night)

3-exercise

4- environment

5- exposure to allergens.

Eosinophilia is never a normal lab finding. Efforts should always be made to discover the underlying cause, though the cause may not always be found.

MODULAR UNIT 14

Hemostasis ,definition and types.

The role of blood vessels and platelets in hemostasis

Definition :

Hemostasis: The cessation of blood loss from a damaged vessel .

There are three haemostatic components:

1- The **extra-vascular** (The tissues surrounding blood vessels) involved in hemostasis when local vessel is injured.

It plays a part in hemostasis by providing back-pressure on the injured vessel through swelling and trapping of escaped blood.

2- The **vascular** (The blood vessels through which blood flow) it depends on the size, amount, of smooth muscle within their walls and integrity of the endothelial cell lining.

3- The **intra-vascular** (The platelets and plasma proteins that circulate within the blood vessels).

These components are involved in Coagulation (clot or thrombus formation) or Fibrinolysis (clot or thrombus dissolution).

The normal hemostatic response to vascular damage depends on closely interaction.

between:

1- blood vessel wall

2- circulating platelets.

3- blood coagulation factors .

The five major components of haemostatic response:

1- plateltes

2- coagulation factors

3- coagulation inhibitors4- fibrinolysis

5-blood vessel

Problems with structure or function of platelets

Platelets are small disc shaped cells which are formed in the bone marrow. Platelets play a crucial role in helping blood to clot. The primary functions of platelets are:

1- adhesion

2- aggregation

3- activation and secretion

A defect in any one of these functions will result in an increased tendency to bleed. Approximately 70-80% of platelets circulate in the bloodstream while the remainder are stored in the spleen. The average platelet lasts about 10 days.

❖ **Reduced function**

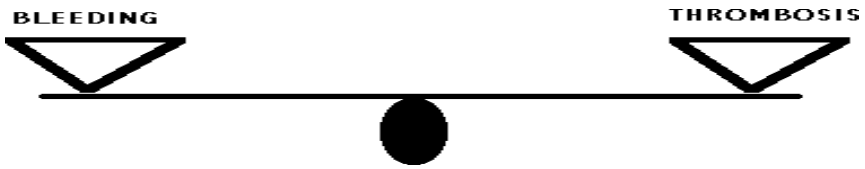
- Thrombocytopathy(term not used much)

❖ **Reduced count**

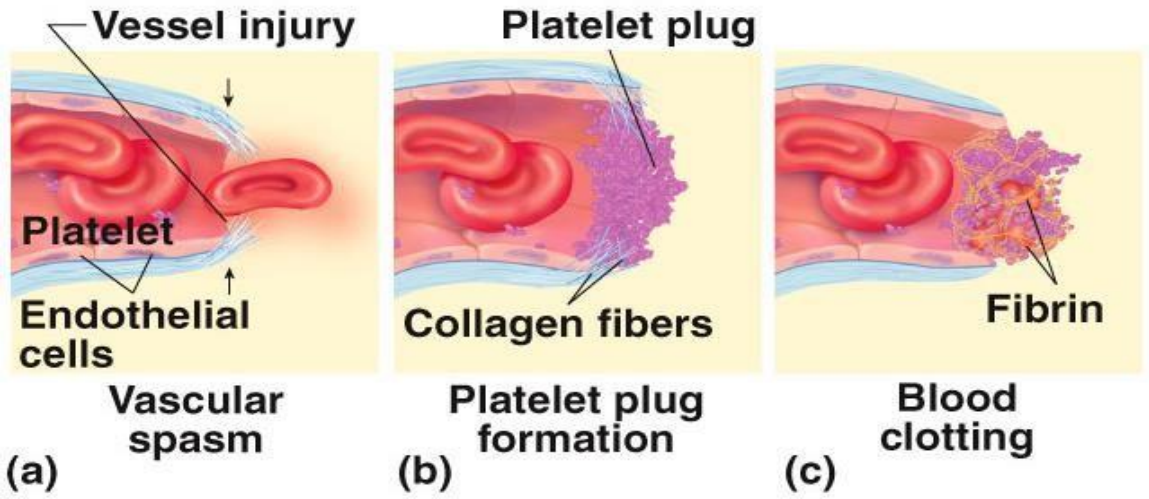
- Thrombocytopenia

Concepts of Normal Hemostasis

Under normal conditions, the formation and dissolution of thrombi is maintained in a delicate balance. (fig).



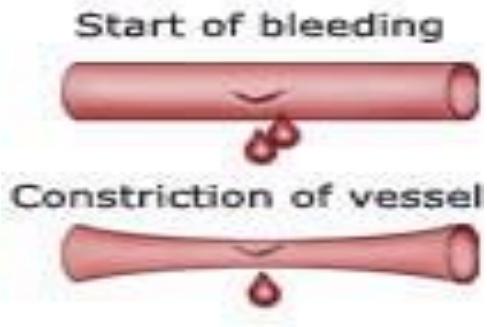
Following an injury to blood vessels several actions may help prevent blood loss, including:



1-Local vasoconstriction:

-is due to local spasm of the smooth muscle (sympthetic reflex)

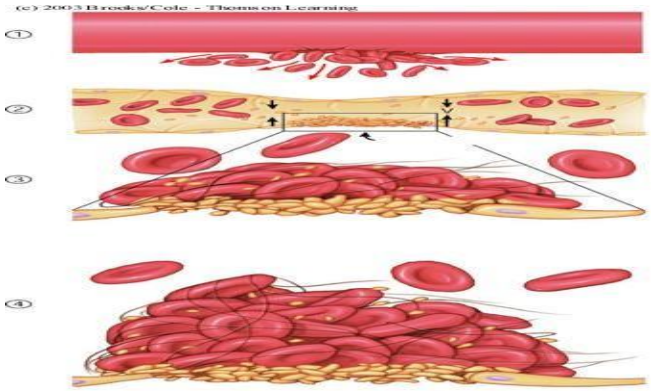
-can be maintained by platelet vasoconstrictors



1-Formation of platelet aggregate

-Injured blood vessel releases ADP, which attracts platelets (PLT)

-PLT comming in contact with exposed collagen release: serotonin, ADP, Thromboxane-A 2(TXA2), which accelerate vasoconstriction and causes PLT to swell and become more sticky



2-Formation of blood clot

-In the formation of the clot, an enzyme called thrombin converts *fibrinogen* into insoluble protein, *fibrin*

-Fibrin aggregates to form a network at the site of vascular damage.

Coagulation Processes :

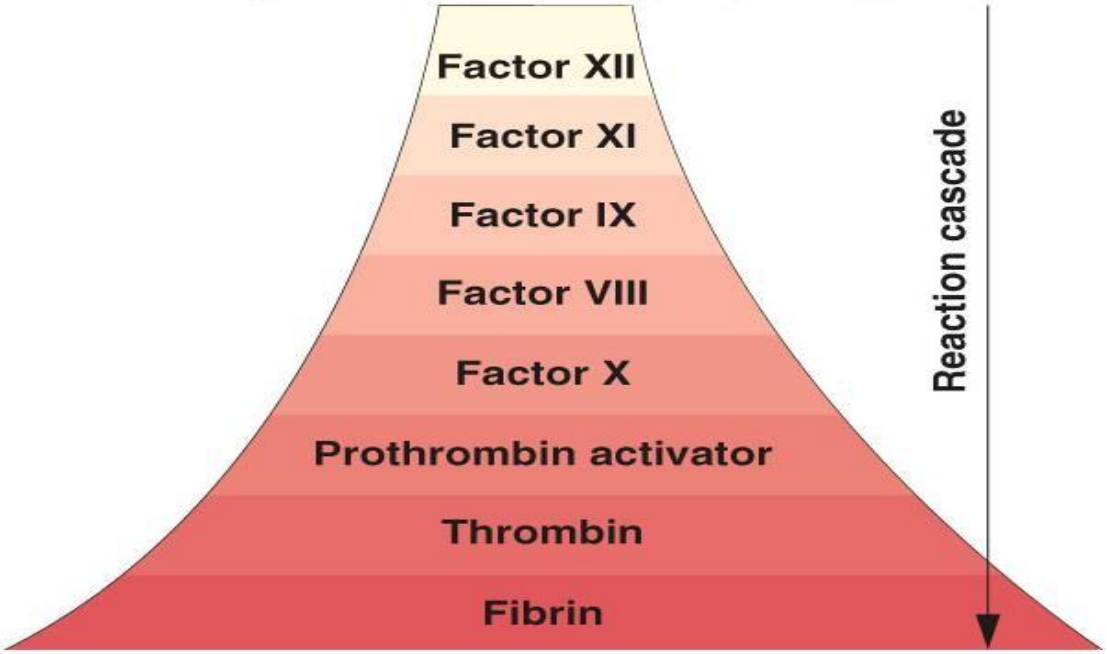
Coagulation: Is the process whereby on vessel injury, Plasma protein, Tissue factors and Calcium interact on the surface of the platelets to form a *Fibrin clot*.

Platelets provide a surface for the coagulation reaction, and interact with fibrin to form a stable platelet fibrin clot.

Tissue factors (except Ca and Tissue Thromboplastin) normally circulate in the plasma as inactive proteins.

-On activation some factors form enzymatic proteins known as Seiren Proteases that activate other specific factors in the coagulation sequence.

Coagulation factors,name and figures :



The three pathways that makeup the classical blood coagulation pathway

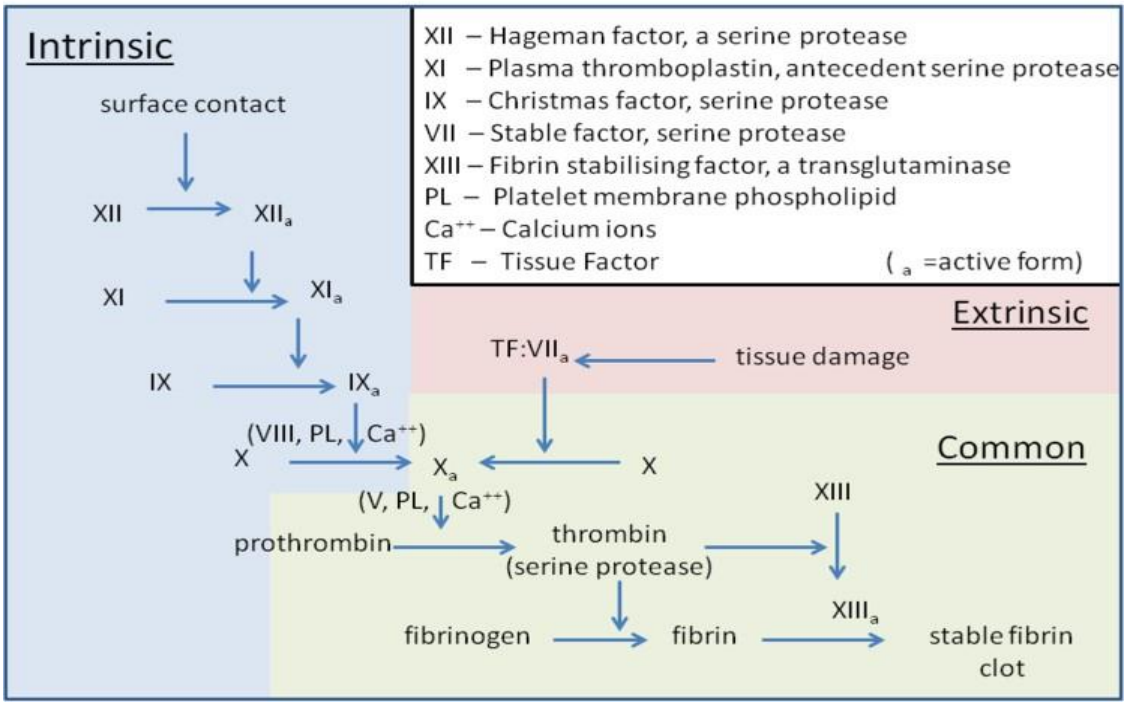


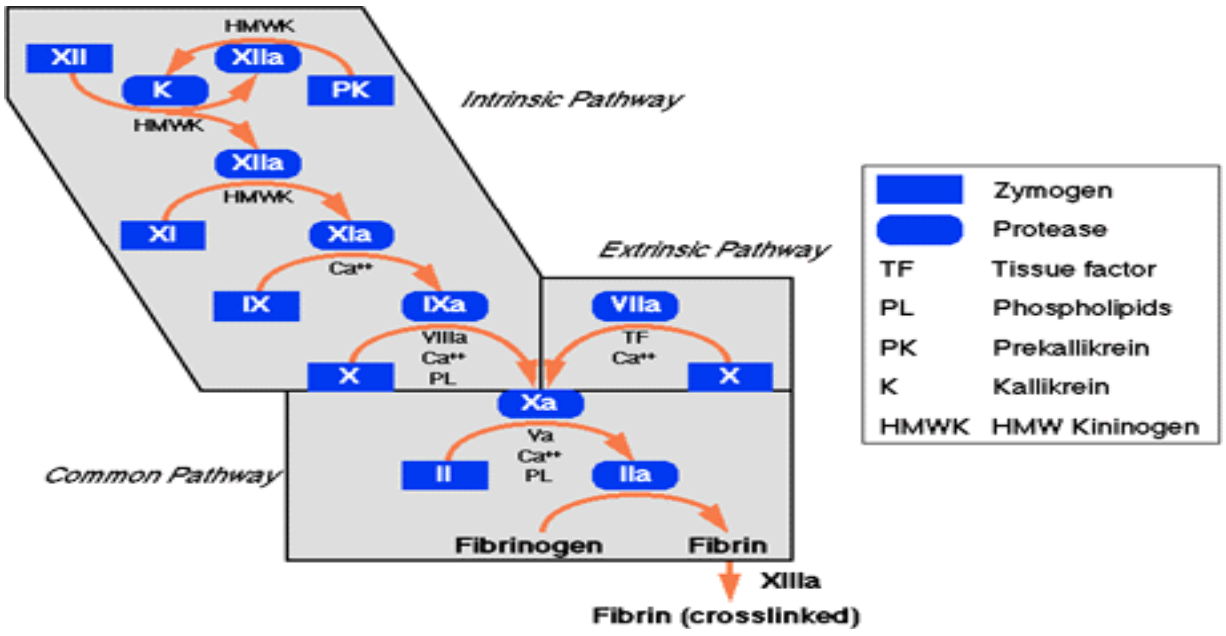
Table 18.9 Clotting Factors (Procoagulants)

Number	Name	Origin	Function
I	Fibrinogen	Liver	Precursor of fibrin
II	Prothrombin	Liver	Precursor of thrombin
III	Tissue thromboplastin	Perivascular tissue	Activates factor VII
V	Proaccelerin	Liver	Activates factor VII; combines with factor X to form prothrombin activator
VII	Proconvertin	Liver	Activates factor X in extrinsic pathway
VIII	Antihemophiliac factor A	Liver	Activates factor X in intrinsic pathway
IX	Antihemophiliac factor B	Liver	Activates factor VIII
X	Thrombokinase	Liver	Combines with factor V to form prothrombin activator
XI	Antihemophiliac factor C	Liver	Activates factor IX
XII	Hageman factor	Liver, platelets	Activates factor XI and plasmin; converts prekallikrein to kallikrein
XIII	Fibrin-stabilizing factor	Platelets, plasma	Cross-links fibrin filaments to make fibrin polymer and stabilize clot
PF_1	Platelet factor 1	Platelets	Same role as factor V; also accelerates platelet activation
PF_2	Platelet factor 2	Platelets	Accelerates thrombin formation
PF_3	Platelet factor 3	Platelets	Aids in activation of factor VIII and prothrombin activator
PF_4	Platelet factor 4	Platelets	Binds heparin during clotting to inhibit its anticoagulant effect

Coagulation mechanism is composed of an extrinsic and intrinsic pathway, which eventually merge into one .

-The intrinsic system is more complex and present only in „higher" life forms *(e.g. birds and reptiles possess only extrinsic system)*

-The complex sequence of events that produce fibrin are divided into three stages



Stage I: Formation of prothrombin activator

1-Extrinsic pathway:

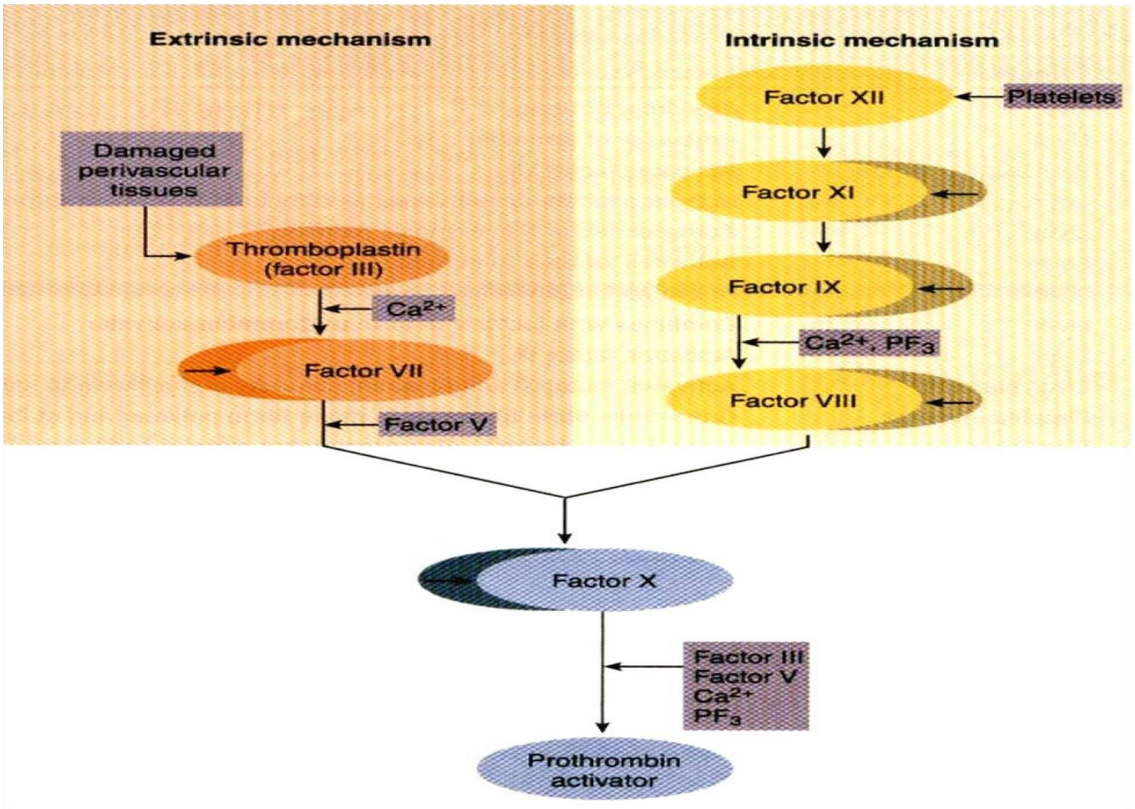
When blood comes in contact with injured tissue - tissue thromboplastin (F III) interacts with proconvertin (F VII), and Ca^{2+} activating Stuart factor (F X).

2-Intrinsic pathway:

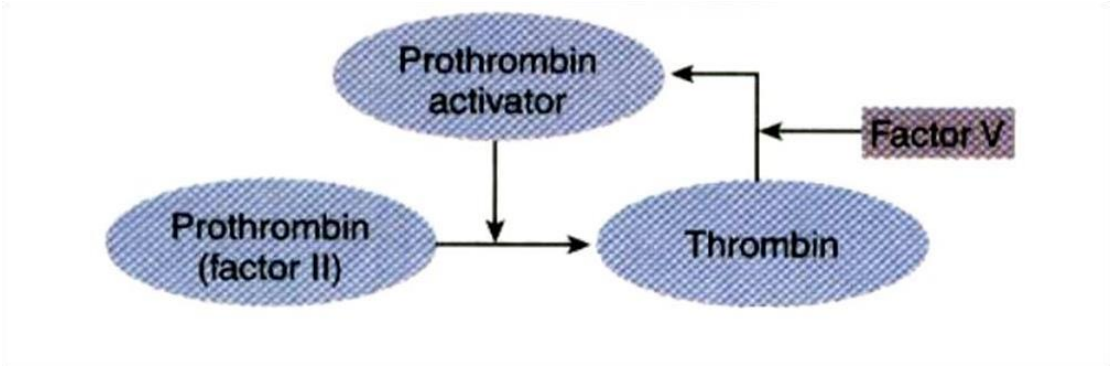
Exposed collagen activates Hageman factor (F XII). Activated F XII activates plasma enzyme – plasma thromboplastin antecedent (PTA; F XI, which in the presence of Ca^{2+} activates Christmas factor (F IX). F IX interacts with antihemophilic factor (F VIII), Ca^{2+} to form a complex that activates Stuart factor (F X) .

3. Common pathway:

Activated F X in the presence of Ca^{2+} forms complexes with accelerin (F V) to form prothrombin activator.



Stage II: conversion of prothrombin to thrombin

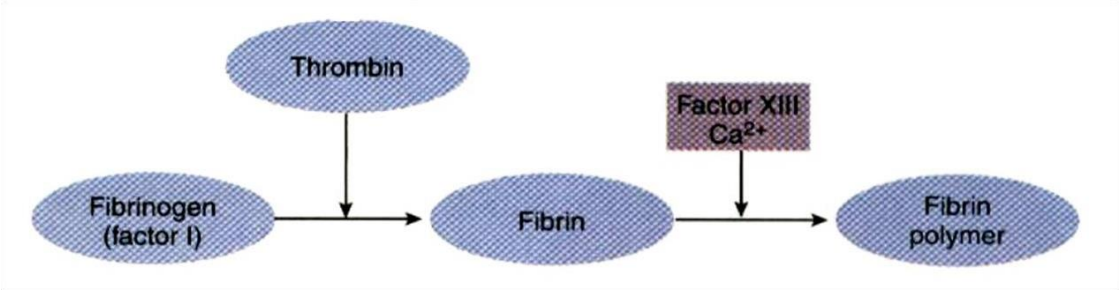


-Prothrombin – inactive precursor of enzyme thrombin

-In the presence of prothrombin activator and Ca^{2+} prothrombin is converted to thrombin

-Thrombin itself increases its own rate of formation (positive feedback mechanism).

Stage III: conversion of fibrinogen to fibrin



-Fibrinogen – plasma protein produced by the liver

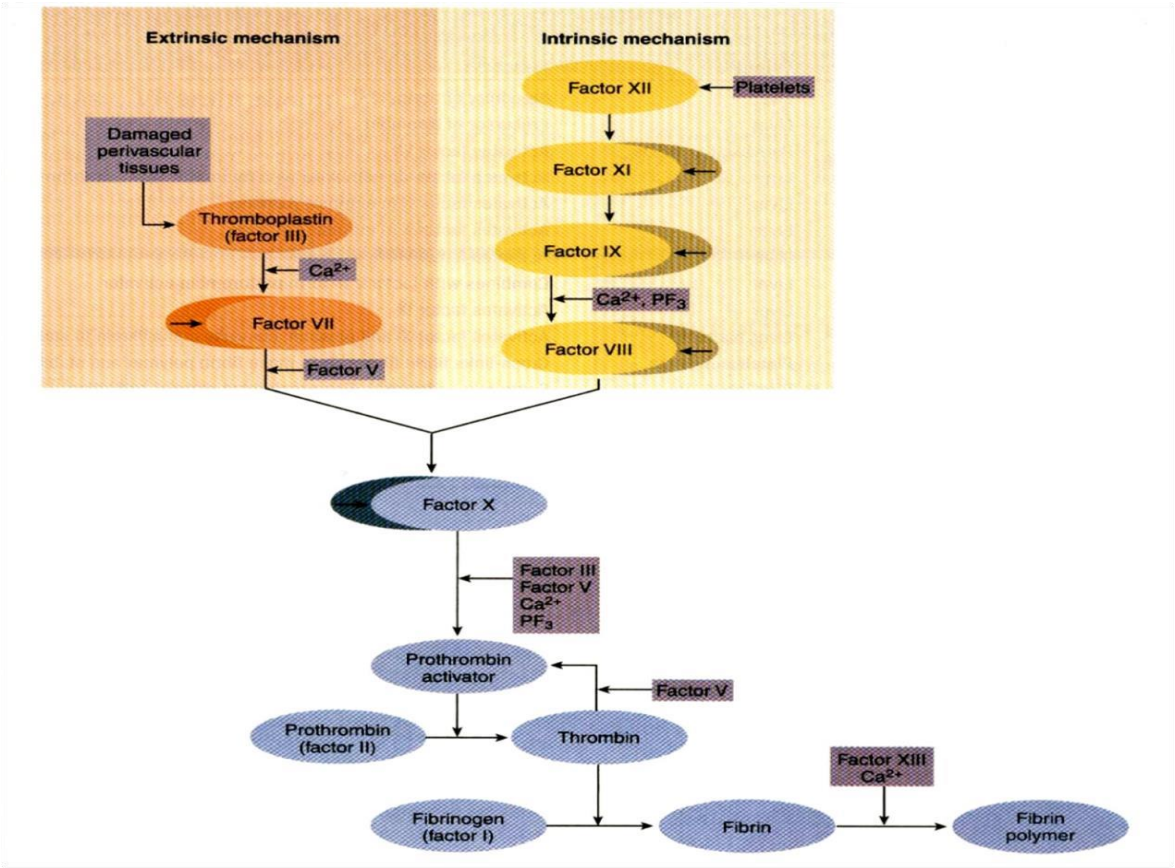
-Thrombin converts fibrinogen to fibrin

-Thrombin also activates fibrin-stabilizing factor (F XIII), which in the presence of Ca^{2+}, stabilizes the fibrin polymer through covalent bonding of fibrin monomers.

Calcium ions:

-Are required for promotion and acceleration of almost all blood clotting reactions.

Except: activation of XII and XI (intrinsic mechanism).


Extrinsic mechanism
Intrinsic mechanism
Damaged perivascular tissues
Thromboplastin (factor III)
Ca^{2+}
Factor VII
Factor V
Factor XII
Platelets
Factor XI
Factor IX
Ca^{2+}, PF_3
Factor VIII
Factor X
Factor III
Factor V
Ca^{2+}
PF_3
Prothrombin activator
Factor V
Prothrombin (factor II)
Thrombin
Factor XIII
Ca^{2+}
Fibrinogen (factor I)
Fibrin
Fibrin polymer

MODULAR UNIT 15

Leukemia

- Group of malignant disorders of the hematopoietic tissues characteristically associated with increased numbers of white cells in the bone marrow and / or peripheral blood :

– Bone marrow

– Lymph system

– Spleen

- Occurs in all age groups

- Results in an accumulation of dysfunctional cells because of a loss of regulation in cell division

  - Progressive
  - Often thought of as a childhood disease
  - The number of adults affected with leukemia is 10 times that of children

Etiology and Pathophysiology:

- No single causative agent
- Most from a combination of factors

– Genetic and environmental influences

- Associated with the development of leukemia

– Chemical agents

– Chemotherapeutic agents

– Viruses

– Radiation

– Immunologic deficiencies

Classification:

- Acute versus chronic

– Cell maturity

• Acute: clonal proliferation of immature hematopoietic cells (the formation of blood or blood cells)

• Chronic: mature forms of WBC; onset is more gradual

– Nature of disease onset

○ Acute leukemia: appears suddenly, progresses rapidly, death within months – blasts found in peripheral blood

○ Chronic leukemia: undetected for months, survival time average of 3 years

○ Effects: normal cell percentages disrupted; impaired clotting; infections.

- Type of leukemia:

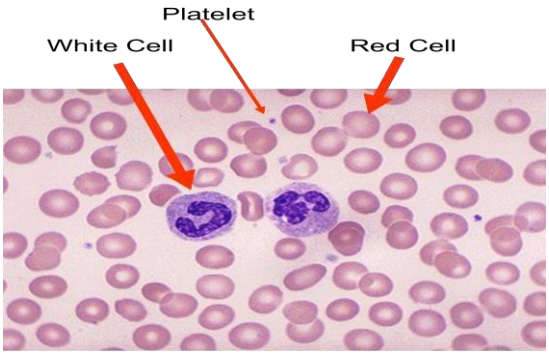
– Acute lymphocytic leukemia (ALL)

– Acute myelogenous leukemia (AML)

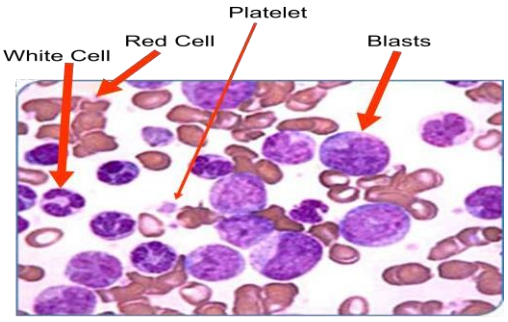
• Also called acute nonlymphoblastic leukemia (ANLL)

– Chronic myelogenous leukemia (CML)

– Chronic lymphocytic leukemia (CLL)



Normal human blood



Blood with leukemia

AML

French-American-British (FAB) Classification

M0: Minimally differentiated leukemia

M1: Myeloblastic leukemia without maturation

M2: Myeloblastic leukemia with maturation

M3: Hypergranular promyelocytic leukemia

M4Eo: Variant: Increase in abnormal marrow eosinophils

M4: Myelomonocytic

leukemiaM5: Monocytic

leukemia

M6: Erythroleukemia (DiGuglielmo's disease)

M7: Megakaryoblastic leukemia

Myelogenous Leukemia:

- Leukemia characterized by proliferation of myeloid tissue (as of the bone marrow and spleen) and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the circulating blood.
- Myeloid tissue is a biologic tissue with the ability to perform hematopoiesis. It is mainly found as the red bone marrow in bones, and is often synonymous with this. However, myeloid can also be present in the liver and spleen .
- A myelocyte is a young cell of the granulocytic series, occurring normally in bone marrow, but not in circulating blood (except when caused by certain diseases).
- Granulocytes are a category of white blood cells characterized by the presence of granules in their cytoplasm. They are also called polymorphonuclear

leukocytes (PMN or PML) because of the varying shapes of the nucleus, which is usually lobed into three segments.

- The myeloblast is a unipotent stem cell, which will differentiate into one of the actors of the granular series**.**

Acute Myelogenous Leukemia (AML):

- Leukemia characterized by proliferation of myeloid tissue (as of the bone marrow and spleen) and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the circulating blood
- One fourth of all leukemias

– 85% of the acute leukemias in adults(Rare in childhood & incidence increases with age)

  - Abrupt, dramatic onset (insidious nonspecific onset)

– **Signs and Symptoms of AML:**

-Pallor due to anemia, fever due to ineffective WBC, petechiae (skin bruising) due to thrombocytopenia, bone pain.

– Serious infections, abnormal bleeding

- Uncontrolled proliferation of myeloblasts

– Hyperplasia of bone marrow and spleen

Acute Lymphocytic Leukemia (ALL):

- Most common type of leukemia in children
- 15% of acute leukemia in adults
- Immature lymphocytes proliferate in the bone marrow.
- Signs and symptoms may appear abruptly

– Fever, bleeding

- Insidious with progressive

– Weakness, fatigue

- Central nervous system manifestations

Chronic Myelogenous Leukemia (CML):

- Excessive development of mature neoplastic granulocytes in the bone marrow

– Move into the peripheral blood in massive numbers

– Ultimately infiltrate the liver and spleen

- *Philadelphia chromosome*

– The chromosome abnormality that causes chronic myeloid leukemia (CML) (9 &22)

– Genetic marker

- Chronic, stable phase followed by acute, aggressive (blastic) phase.

Chronic Lymphocytic Leukemia (CLL):

- Production and accumulation of functionally inactive but long-lived, mature-appearing lymphocytes
- B cell involvement
- Lymph node enlargement is noticeable throughout the body

– ↑ incidence of infection

- Complications from early-stage CLL is rare

– May develop as the disease advances

– Pain, paralysis from enlarged lymph nodes causing pressure

Hairy Cell Leukemia:

- 2% of all adult leukemias
- Usually in males > 40 years old
- Chronic disease of lymphoproliferation

– B lymphocytes that infiltrate the bone marrow and liver.

- Cells have a “hairy” appearance
- Symptoms from

– Splenomegaly, infection, vasculitis

- Treatment

– alpha-interferon, pentostatin, cladribine

Unclassified Leukemias

- Subtype cannot be identified
- Malignant leukemic cells may have

– Lymphoid, myeloid, or mixed characteristics

- Frequently these patients do not respond well to treatment

– Poor prognosis.

Leukemia

Clinical Manifestations

- Relate to problems caused by

– Bone marrow failure

• Overcrowding by abnormal cells

• Inadequate production of normal marrow elements

• Anemia, thrombocytopenia, ↓ number and function of WBCs.

- Relate to problems caused by

– Leukemic cells infiltrate patient’s organs

• Splenomegaly

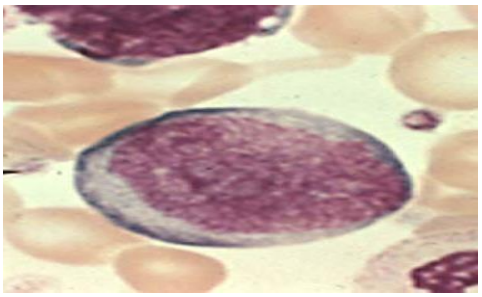
• Hepatomegaly

• Lymphadenopathy

- Bone pain, meningeal irritation, oral lesions

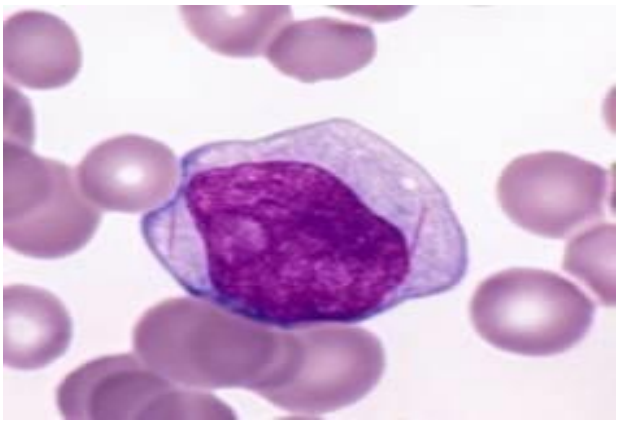
Diagnostic Studies:

- To diagnose and classify
  - Peripheral blood evaluation (CBC and blood smear)
  - Bone marrow evaluation
- To identify cell subtype and stage
  - Morphologic, histochemical, immunologic, and cytogenic methods.



Typical Labs of AML:

- Leukocytosis
- Blastemia
- Leukemic hiatus
- Auer rods – only found in myelocytic blasts
- Thrombocytopenia
- Anemia
- >20% blasts in Bone Marrow

Auer Rods 

CD markers

- The **cluster of differentiation** (**cluster of designation**) (often abbreviated as **CD**) is a protocol used for the identification and investigation of cell surface molecules providing targets for immunophenotyping of cells.
- The CD markers can be used to identify the type of cell.
- CD 13 and CD 33 in flowcytometry
- Cytochemistries-stains that can be used to differentiate leukemias
- Myeloperoxidase
- Sudan black B
- Choloroacetate esterase (specific)
- Nonspecific estera

- **المصادر الاساسية:**

- **Essentials of Blood Banking and Transfusion Medicine - Sally V. Rudmann, Ph.D - 2002**
- **Modern Blood Banking & Transfusion Practices - Denise M. Harmening - 2012**
- **Transfusion Medicine and Hemostasis: Clinical and Laboratory Aspects - Christopher D. Hillyer, MD, Beth H. Shaz, MD, PhD, James C. Zimring, MD, PhD, Thomas C. Abshire, MD - 2013**

- رمز الاستجابة السريع QRC