الجامعة التقنية الشمالية
المعهد التقني / الموصل
قسم تقنيات المختبرات الطبية

امراض الدم

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٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.

Sixteenth modular unit

Hemostasis

٤/ the text :-

Hemostasis: prevention of blood loss.

The hemostatic response to vascular damage depend on the interaction between the blood vessel wall, ciculating platelets and blood Coagulation factors. The mechanism of hemostasis:-

a-Vasoconstriction :physioloical reflex constriction of adjacent small arteries and arteiols, leading to slowing of blood flow. To the injured area which allows contact activation of platelets and Coagulation factor.

b-Formation of platelet plug, platelet have ٣ function

a- adhesion b-release c-aggregation

these ٣ functions lead to formation of platlate plug which close injured part of b.v .

c- Coagulation or clotting mechanism initiated and ended through formation of fibrin thread or network. d-Clot retraction : occur and slow lysis of the blood clot occur and find repair of injured tissue or b.v take place. Platelet reaction in blood Coagulationand primary haemostatic.

plug formation:

Vessel injury, collagen exposure

↓

Platelet adhesion

↓

Platelet release reaction

↓

Thromboxane A٢, ADP

↓

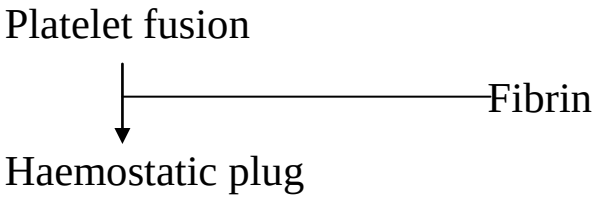
Platelet → aggregation

Plateletfactor ٣

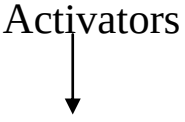
↓

For coagulation

↓



Fibrinolysis : it is a normal haemostatic response to vascular injury, trauma, exercise or emotional stress in which plasminogen coenzyme is converted the active proleolytic enzyme plasimin by activators [from vascular wall or from the tissues] and by the activated factor XI١.
Plasmin will digest fibrin, fibrinogen and other proteins by hydrolysis of peptide bonds into soluble split product [fibrin degradation product FDP]. Then FDP are competitive inhibitors of thrombin , the smaller FDP are competition inhibitor of fibrin polymerisation. Free plasmin is nentralised by circulating antiplasmins this will prevent the widespread destruction of fibrinogen and other coagulation proteins such as factor VI١١ and V.
Plasminogen: it is abetaglobulin proenzyme present in blood and tissue fluid, it is converted to the proleolytic enzyme plasmin by activators in the process of fibrinolysis .
Plasmin: it is a serine protease enzyme which is responsible for digestion of fibrin bond fibrinogen and other proteins by hydrolysis of peptide leading to formation of soluble split produced from plasminogen and from certain Activators .
Fibrin degradation products: Are the end results of the action of plasmin enzyme on the action of plasmin enzyme on the fibrin plug in the process of fibrinolysis.



Fibrin ⟶ soluble split ⟶ products F.D.P

[Fibrinolysis]

٥/ Post test:-

١-**What are the processes involved in the mechanism of hemostasis.**

٢-**Draw a diagram showing the process of plug Formation,**

Note Chick your answers in key answer next pages.

٦/ Key answer:-

(٢,٥) degree each

-pre test:-

١-Hemostasis :-Prevention of blood loss.

٢-Fibrinolysis:-a normal hemostatic response to vascularInjury in which plasminogen coenzyme is converted to active plasmine which will digest Fibrin, fibrinogen, and other proteins to fibrin degradation products.

٣-plasminogen:-It is a beta globulin pro enzyme present in the blood and tissue fluid , and it is converted to the protulytic enzymeplasminby activators in the process of hemolysis,

٤-Plasmine:-It is a serine protease enzyme which is responsible for the digestion of fibrin , fibrinogen , and other proteins,by hydrolysis of peptide bonds leading to formation of fibrin degradation products.

Post test:-

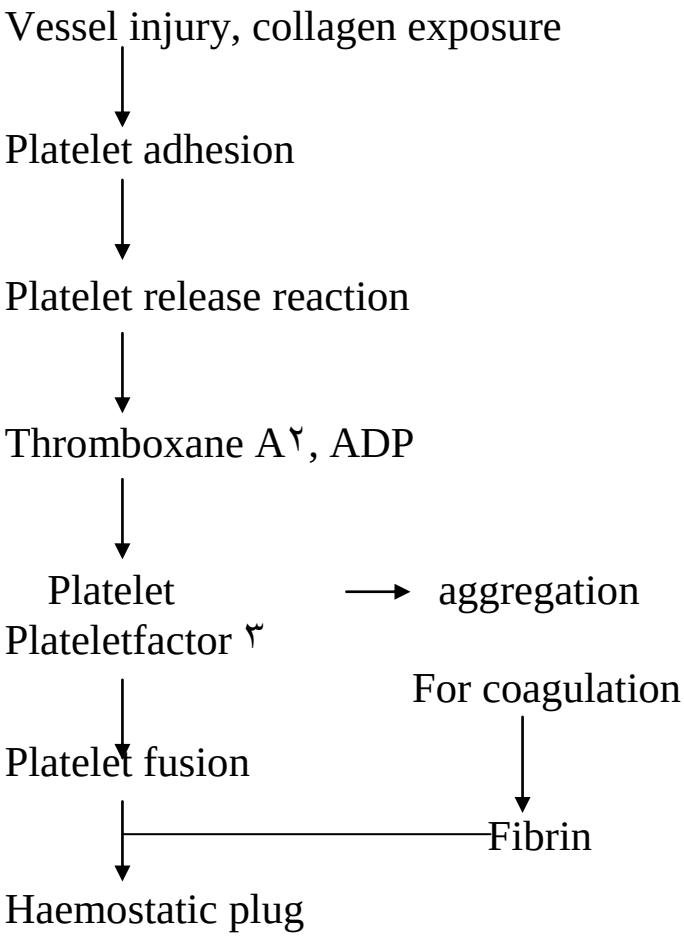
١- A-vasoconstriction,

B-Formation of platelet plug.

C-Coagulation or clotting mechanism.

D-Clot retraction.

٢-plug formation:



٧/ Sources:-

١-Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.

٢-A short text book of hematology, R.B Thompson ٥th. Edt.

٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.

Seventeenth & Eighteenth modular unit

Coagulation factors , names &figures
Coagulation mechanism

٤/ the text :-

The Coagulation Factors:

Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Thromboplastin
Factor IV	Ca++
Factor V	Proaccelerin
Factor VI	absolete(not present)
Factor VII	Proconvertin
Factor VIII	Antihemophilic
Factor IX	Christmas Factor (Plasma thromboplastin component)
Factor X	Stuart-prower Factor
Factor XI	Plsama Thromboplastin Antecedent
Factor XII	Hagemen Factor (Contact Factor)
Factor XIII	Fibrin stabilizing Factor (fibrinase)

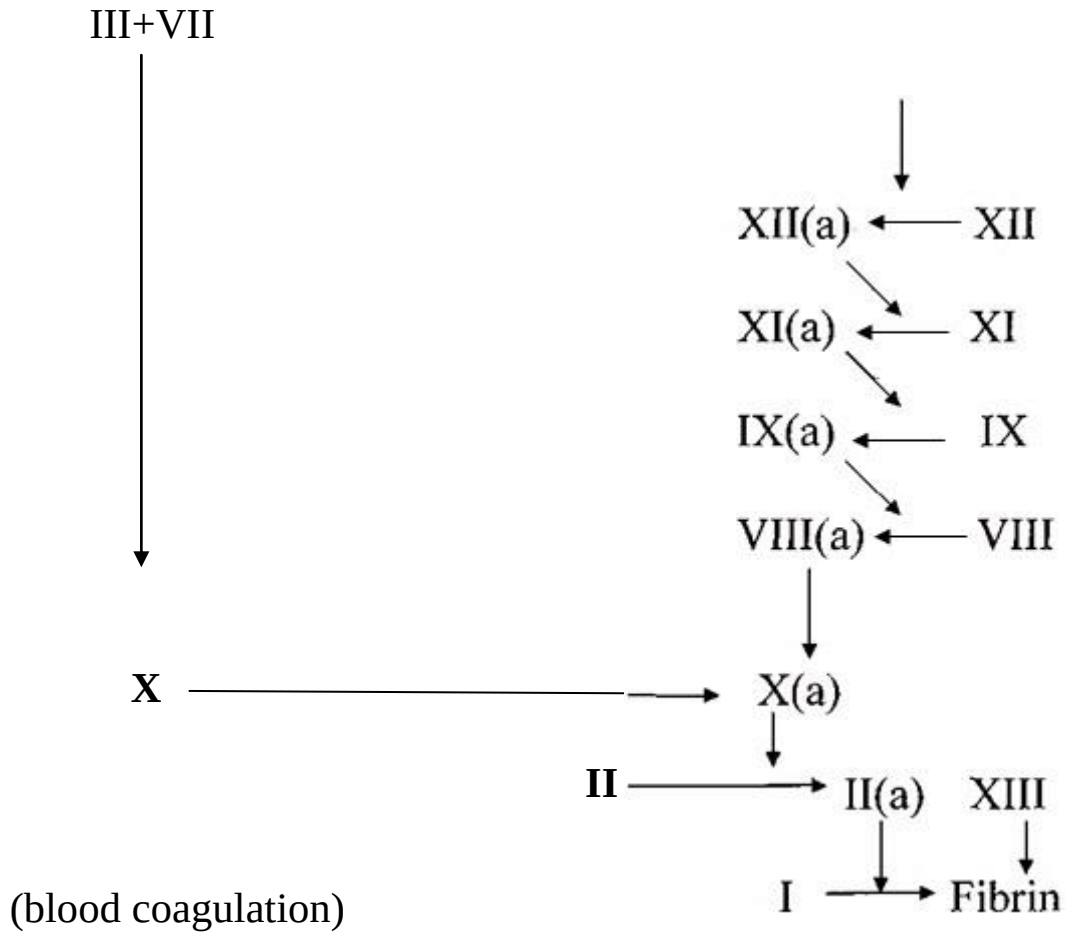
Factor I,V,VIII and XIII Lost during coagulation process not present in serum.

Factor V and VIII are labile coagulation Factors . Factor II, VII, IX and X are Vit K dependent Factors.

Coagulation Mechanism:

When the cells of blood Vessele wall are damaged both interinsic and extrinsic path ways are activated, Tissue fluid (Factor III)which is normaly extrinsic to the blood stream comes in contact with the plasma and activates factor VII. At the same time factor XII comes into contact with collagen which has been exposed by the vascular injury and this activates the intrinsic pathway which initiates other factors in sequence. The intrinsic pathway contains both hemophilic factors (VIII and IX) at this stage both systems join in a final common pathway to form platelet phospholipid. In the final stages thrombin convert fibrinogen to fibrin the cross linkage of fibrin strands is strengthened by factor XIII

Extrinsic Pathway	Intrinsic Pathway
Tissue injury	Collagen contact



(blood coagulation)

Coagulation tests uses (Importance)

١-Bleeding time : Is a screeming test for platelet function [platelet count and the ability of the platelet to form platelet plug directly affect the bleeding time.] prolong bleeding time in: low platelet count below ٥٠٠٠٠/ul And in platelet dysfunction.

٢-prothrombin time:

a-It is ascreening test for detecting deficiencies in factors II, V, VII and X, I (rare).

b-follow up test or patient receiving coumarin drugs (warfarin) Prolong prothrombin time occur in: a-Vit K dehiciency.

c-Certain liver diseases .

d-specific coagulation deficiencies.

e-Cumarin drug.

٣-Activated partial thromboplastin time:[APTT]:

a-It is the most useful test for routine screening of Coagulation disorders in the interinsic system .

b-The method of choice for monitoring heparin therapy Normal range between ٣٠-٤٠Sec.

Prolong APTT; due to deficiency in the internsic Coagulation factor c- due to presence of inhibiters.

Thrombin time: it measures the availability of functional fibrinogen. Prolong thrombin time in fibrinogen deficiency. ٢-impaired fibringin Function.

٥/ Post test:-

١-Draw a diagram showing the stages of blood coagulation (fibrin formation).

Note Chick your answers in key answer next pages.

٦/ Key answer :-

١-Pre test :- **(٥) degrees each.**

١- a-Fibrinogen. b-Antihemophilic factor

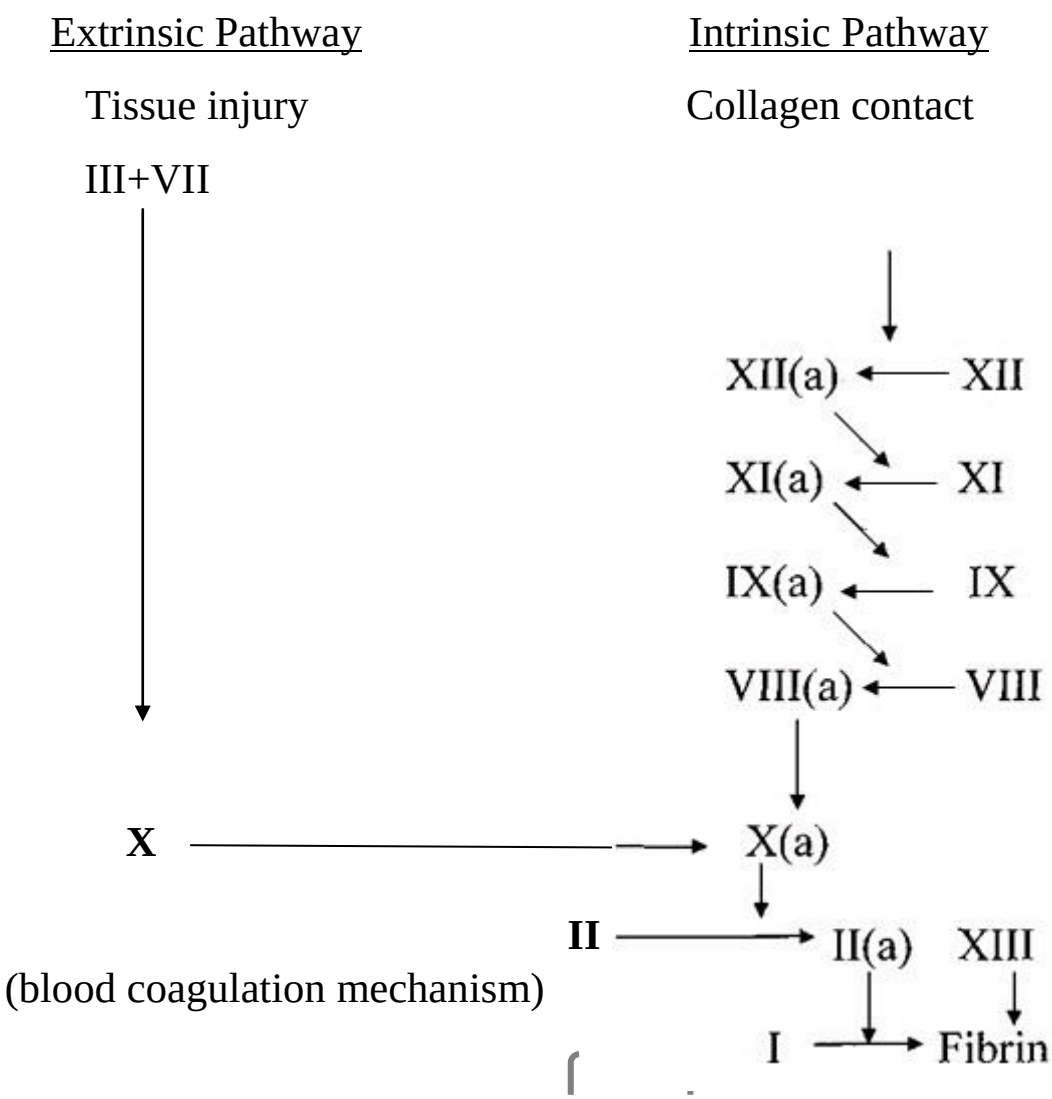
c-Christmas factor. d- prothrombin

e-Fibrin stabilizing factor.

٢-a- Prothrombin time :-It is a screening test for detecting deficiencies in factor II, V, VII, X,and factor I (rare)
And a follow up test for patient receiving cumarine therapy.
b-APTT:- IT is the most useful test for routine screening of coagulation disorder in the intrinsic system.

٢-Post test:-

-(١٠) degrees



(blood coagulation mechanism)

٧/ Sources:-

١-Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.

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nineteenth modular unit

Heorrhagic disorder types ,hemostasis due to blood vessles disorder

٤/ the text :-

Types of bleeding:-

١-Mucous membrane bleeding

٢-Subcutaneous bleeding

٣-Internal bleeding

Bleeding disorder due to vascular defect:-

١-Bruises

٢-Petechiae

٣-Ecchymosis

٤-Autoimmune vascular purpura.

a-The allergic purpura.

b-Drug induced vascular purpura.

c-Purpura fulminance.

٥-Infections :-

(Bacterial,viral,ricketsial ,protozoal).

٦-Structural mal formation:-

a--Telangectasia:-a vascular malformation involve vessels all over the body which are dilated tortuous and disorganized,The walls of affectedvessels are markedly thinned,vascular support is poor,and vascular ,As a result bleeding may occur after trivial trauma or arise spontaneously,The vascular abnormality is inherited as an autosomal dominant

Trait.

b-Hereditary disorder of connective tissues (Osteogenesis imperfecta)

c-Acquired disorder of connective tissue (cortico steroid purpura ,Senile purpura).

٧-Miscellaneous (paraproteinemia, snake venum,Auto erythrocytes sensitization etc.

٥/ Post test:-

١-Mention the types of autoimmune vascular purpura.

Note Chick your answers in key answer next pages.

٦/ Key answer

Pre test:-

١- Types of bleeding:-

١-Mucous membrane bleeding

٢-Subcutaneous bleeding

٣-Internal bleeding

٢- a-Bruises b-ecchymosis

Post test:-

٣-٤-Autoimmune vascular purpura.

٤- a-The allergic purpura.

٥- b-Drug induced vascular purpura.

٦- c-Purpura fulminance.

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Twentieth modular unit

Hemostasis due to platelet disorder

٤/ the text :-

Platelets

The platelets are small bodies present in the plasma, produced in the bone marrow by fragmentation of the cytoplasm of the megakaryocytes. The normal platelet life span is ٧- ١٠ days. The normal platelet count (١٥٠٠٠٠-٤٠٠٠٠٠ /μL). The main platlet diameter ١-٣ μm. The main function of platelet is the formation of mechanical plug during the normal hemostatic response to vascular injury.

Platelet production **;-**

the platelet are produced in the bone marrow from a hemopoietic stem cell which differentiate into the megakaryoblast then into megakaryocytes, which by a process of nuclear replication enlarging the cytoplasmic volume as the number of nuclei increases .At the ٨ nucleus stage the cytoplasm becomes granular and platelets are thenliberated.

Platlet function;-

the main function of the platelet is the formation of the mechanical

plugs during the normal hemostatic response to vascular injury which take place as follows:

١ - platelet adhesion : the platelet adhere to the exposed subendothelial connective tissues, this function depend upon the factor VIII also depend on a surface membrane glycoprotein.

٢- The release reaction : collagen exposure or thrombin action results in the release of platelet granule contents which include ADP, serotonin, fibrinogen, lysosomal enzymes and heparin neutralizing factor, platelet prostaglandin lead to formation of thromboxane A٢ which lowers platelet Cyclic AMP level and initiates the release reaction.

٣- Platelet aggregation : released ADP and thromboxan A٢ cause additional platelet to aggregate at the site of vascular injury results in the formation of platelet mass.

٤- Platelet procoagulant activity.

٥- Platelet fusion: High concentration of ADP, the enzymes released during the release reaction and thromboasthinin contribute to the irreversible fusion of platelet aggregated at the site of vascular injury.

١- The growth factor found in the specific granules of platelets stimulate vascular healing.

Diseases:-

Disorders leading to reduced platelet count:-

*Thrombocytopenia.

-Idiopathic thrombocytopenic purpura-also known as immune thrombocytopenic purpura.(ITP)

-Thrombotic thrombocytopenic purpura

-Drug induced thrombocytopenia.

*Gaucher's disease.

*Aplastic anemia.

Alloimmune disorder

* Fetomatrrnal alloimmune thrombocytopenia

* Some transfusion reactions.

Disorders leading to platelet dysfunction or reduced count:-

*HELLP syndrome

*Hemolytic uremic syndrome

*Chemotherapy

*Dengue

*Alpha-Delta platelet storage pool deficiency.

Disorders featuring an elevated count:-

*Thrombocytosis, includingbenign essential thrombocytosis (elevated counts either reactive Or as an expression of Myeloproliferative disease)

Disorders of platelet aggregation or adhesion :-

*Bernard –Soulier syndrome

*Von Willebrand disease

*Gray platelet syndrome

Disorder of platelet metabolism:-

*Decreased cyclooxygenase activity

*storage pool defect.

Disorder that indirectly compromise platelet function:-

*Hemophilia

٥/ Post test:-

-(٢)Degree each.

١-Mention (٣)types of purpura in which platelet count is Reduced.

٢-Mention (٢)disorders featuring an elevated platelet count.

Note Chick your answers in key answer next pages

٦/ Key answer:-

-Pre test :-

١-(٧-١٠)

٢-Megakaryoblast

٣-Thrombocytosis.

٤-Thromocytopenia

٥-Hemophilia

-Post test:-

١- Idiopathic thrombocytopenic purpura-also known as immune thrombocytopenic purpura.(ITP)

٢-Thrombotic thrombocytopenic purpura

٣-Drug induced thrombocytopenia.

٢-a- Benign essential thrombocytosis.

b-Myeloproliferative disease.

٧/ Sources:-

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٢ ١st modular unit

Hemostasis due to coagulative disorder

٤/ the text :-

Fibrinogen deficiency:-

The protein fibrinogen is the soluble precursor of fibrin to which it is converted by the action of the enzyme thrombin, in the third stage of coagulation,There are several forms of fibrinogen deficiency,Which are usually inherited as a recessive In one which is extremely rare there is total failure to synthesize fibrinogen ,so there is sever hemostatic defect and death may occure.In other caseses there is hypo fibrinogenemia and the condition is much less sever.

Hypoprothrombinemia:-

Prothrombin is the pro enzyme of thrombin , The proteolytic enzyme which acts upon fibrinogen to form fibrin in the final stage of coagulation.

Causes of hypo prothrombinemia :-

A-Acquired

١-Diatery deficincy of vitamine K

٢-Defective synthesis of vitamin K by intestinal Bacteria.

٣-Defective absorption of vitamin K

٤-Defective synthesis of prothrobin.

a-Liver disease.

b-Presence of vitamin K antagonists

٥-Miscellaneous.

B-Congenital (very rare).

Clinical picture:- The type of bleeding is similar to that found in other conditions associated with coagulation defects Large ecchymoses,intra muscular hemorrhages are common and there is usually persistent and sever bleeding following trauma ,Hematuria ,Petechial hemorrhages are characteristic.

Factor VIII deficiency:-

Hemophilia A: it is a sex-linked hereditary disorder of blood coagulation, affecting male only while female are carriers for the defective chromosome.

Only small percentage is due to spontaneous – mutation. The defect is an absence or low level of plasma factor nVI١١ clotting activity (VlllrC), both VI١١ related antigens (VlllR.AG) and (VlllrWF) is unaffected. The symptoms appear early in life as recurrent painful haemartherosis and

muscle hematomas, prolong bleeding after trauma like tooth extraction, hematuria, gastrointestinal bleeding, intracranial hemorrhage is rare. Hemophilic pseudotumours may appear in long bones, toes due to repeated periosteal hemorrhage.

Laboratory Diagnosis:-

١- Prolongation of the partial thromboplastin time.

٢- Bleeding time normal.

٣- Platelets count normal.

٤- Prothrombin time normal.

٥-Factor VI١١: c low.

٦- Factor IX normal.

Treatment:- factor VI١١ with factor VI١١ concentrate replacement or cryoprecipitate .

Factor IX deficiency:-

HEMOPHILIA B (christmas disease):-

Hemorrhagic hereditary disorder due to deficiency of factor IX.

Laboratory diagnosis:-

١- APTT prolongs. ٢- Whole blood clotting time prolong.

٣- Low factor IX. ٤- Bleeding time normal.

٥- prothrombin time normal.

Treatment :- Factor IX concentrate , stored plasma replacement.

Vonwillebrands disease :- it is an inherited disorder of coagulation autosomal dominant ,the primary defect is due to reduced synthesis of

VIII, VIII R : AG associated with abnormal platelet function. It is charactrised by post traumatic hemorrhage , mucous membrane bleeding eg. (epistaxis), muscle hematoma and hemarthrosis are rare.

Lab. Findings:- prolong bleeding_time, low level of factor VIII , clotting activity (VIII C) is low , low level of VIII related protein (VIII R-AG) , defective platelet aggregation with ristocetin.

Treatment : cryopricipitation.

Note:- factors causing platelet aggregation (ADP, collagen, thrombin, adrenalin).

٥/ Post test:-

١-What are the lab. findings of hemophilia type B?

٢-What are the lab.findings of VonWillebrand disease?

Note Chick your answers in key answer next pages

٦/ Key answer :-

Pre test:- ١-factor VIII. ٢-Factor IX . ٣-Firinogen

٤-Factor VIII,VIII-RG and platelet dysfunction

Post test:-

١-Laboratory diagnosis:-

١- APTT prolongs. ٢- Whole blood clotting time prolong.

٣- Low factor IX. ٤- Bleeding time normal.

٥- prothrombin time normal.

٢-Lab. Findings:- prolong bleeding_time, low level of factor VIII , clotting activity (VIII C) is low , low level of VIII related protein (VIII R-AG) , defective platelet aggregation with ristocetin.

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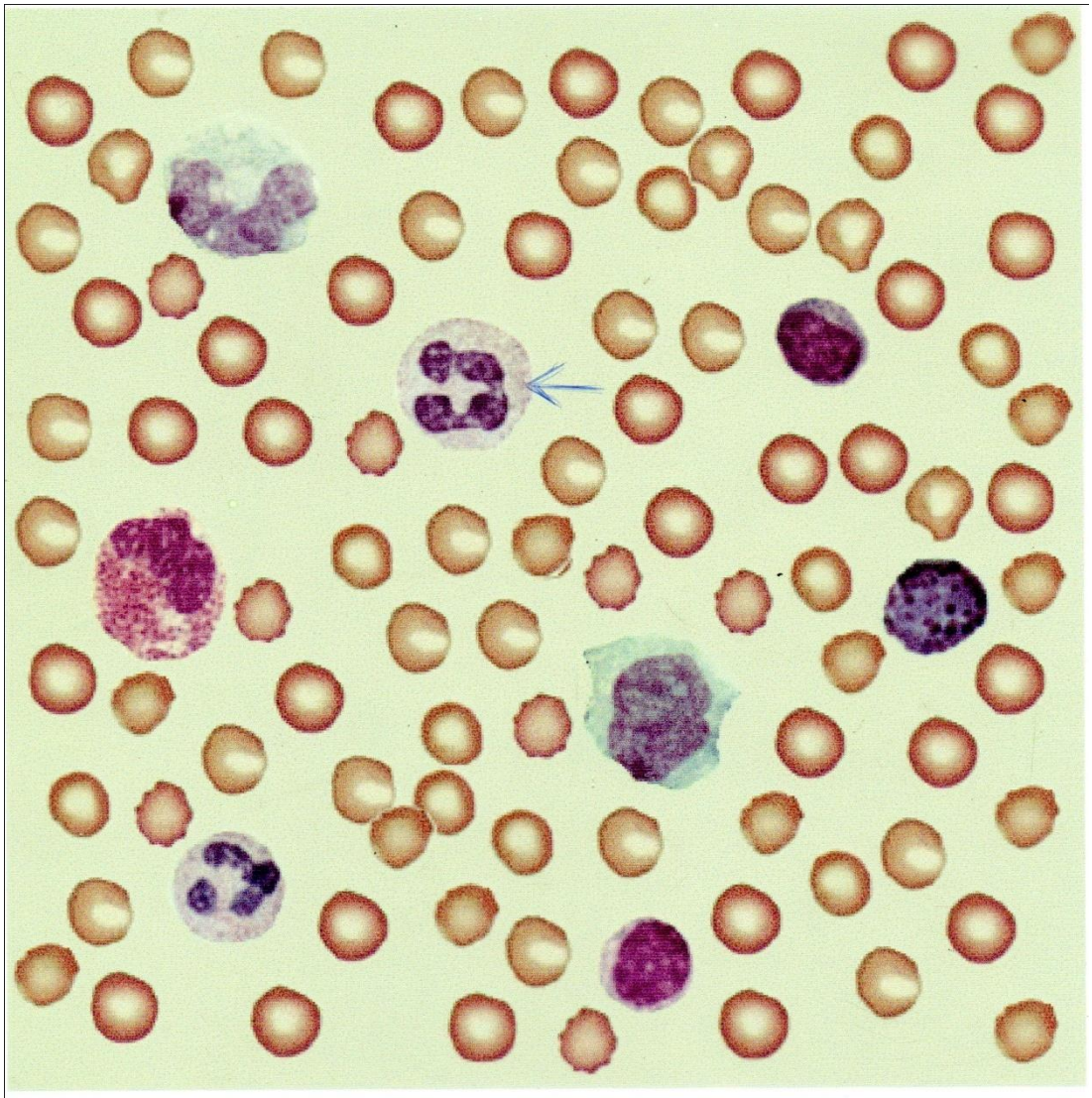
٢ ٣nd, ٢ ٣rd,modular units

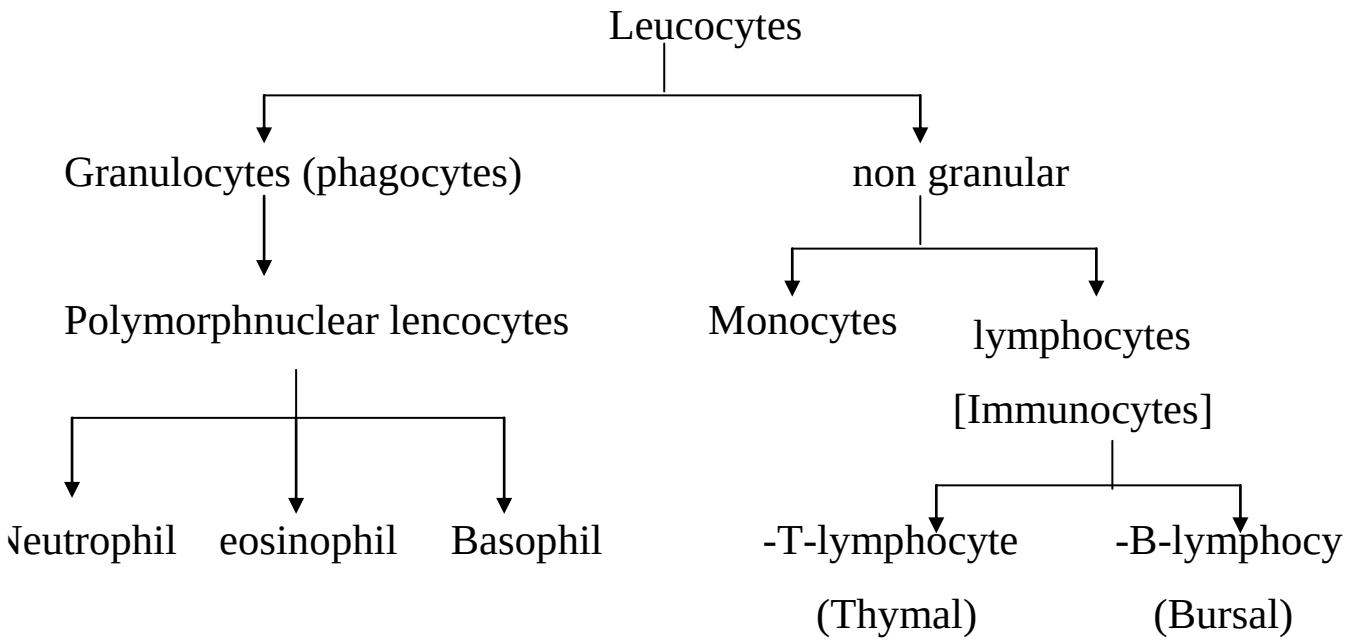
The white blood cells,types,&maturation



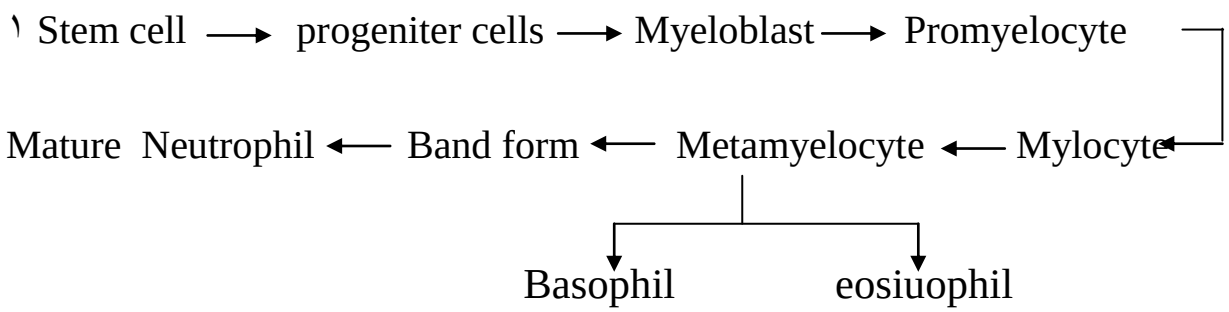
Normal WBC (Leucocytes)

The white blood cells [Leucocytes]:

The Leucocytes of the peripheral blood are two main varieties depending on the presence or absence of cytoplasmic granules.



Granulopoiesis;- All forms of granulocytes are produced in the bone marrow:



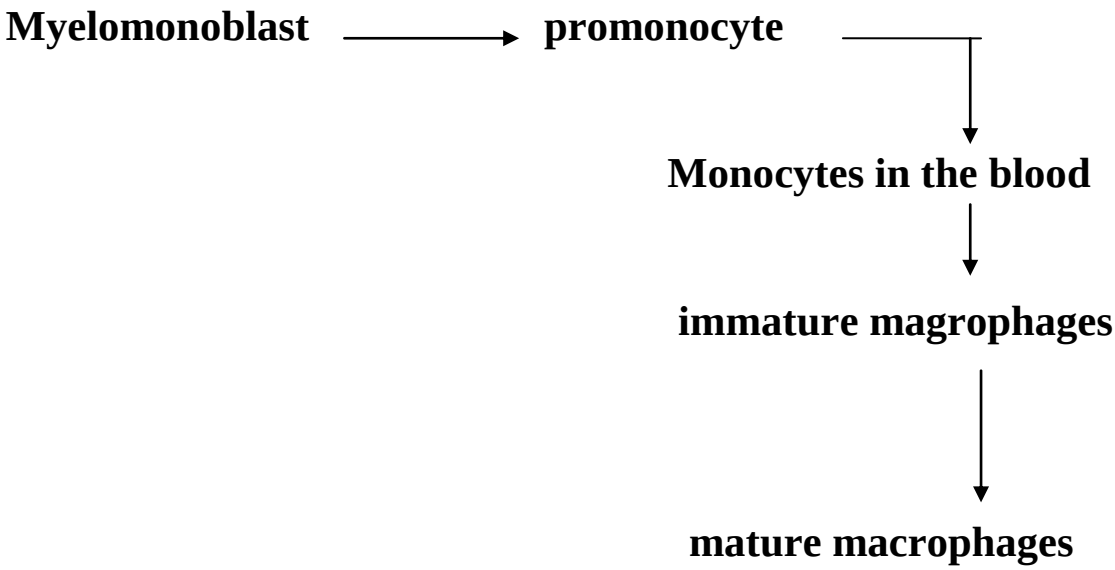
The normal differential leucocyte count:

Cell type	%	Absolute No.s
Neutrophils	٤٠-٧٥	٢,٥ – ٧,٥ X ١٠ ٩/ℓ
Eosinophils	١-٦	٠,٠٤ – ٠,٤ X ١٠ ٩/ℓ
Basophils	<١	٠,٠١ – ٠,١ X ١٠ ٩/ℓ
Monocytes	٢-١٠	٠,٢X٠,٨ X ١٠ ٩/ℓ
Lymphocytes	٢٠-٤٥	١,٥ – ٤ X ١٠ ٩/ℓ

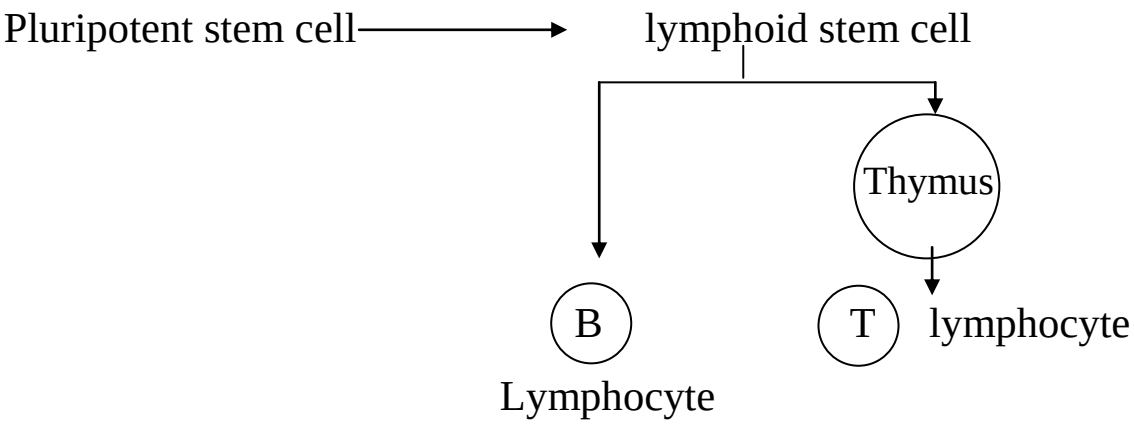
The granulocytes spend about ١٠ hours in the circulation before moving into the tissues, where they perform their phagocytic function they then

Leucopoietin:- a hormone that control the various compartment of the

Monocytes formation:-



Lymphocyte formation: [lymphopoiesis] in man the bone marrow and thymus (and in the foetus, the yolk sac and liver) are the primary lymphopoietic organs.



The secondary or reactive tissuse is that found in the lymph nodes, the spleen and lymphoid tissue of the alimentary arid respiratory tract.
The granulocyte precursors:- These cells don't normally appear in the peripheral blood.

١-**Myeloblast**: Is the earliest recognizable precursor, a cell of variable size ١٠-٢٠! !m in diameter which has a large nucleus with fine chromatin and usually ٢-٥ nucleoli. The cytoplasm is basophilic and no cytoplasmic granules are present. The normal B.M contains up to ٤٪ of myeloblasts.

Promyelcytes: Larger than the myeloblast, contain primary granules in the cytoplasm.

Myelocytes: Originated from the division of promyelocyte in the B.M, it has specific or secondary granules. The nuclear chrome is more condensed and the nucleoli are not visible.

Metamyelocytes: Originated from the division of myelocytes in the B.M. it is non dividing cells which have an indented or horseshoe -shaped nucleus and cytoplasm filled with primary and secondary granules. It different into ٣ types of cells.

Band or juvenile neutrophil: This cells is a stage of neutrophil maturation between the metamyelocytes and fully mature neutrophil this cell may occur in the peripheral blood, it doesn't contain the clear filamentous distinction between lobs which is seen in the mature neutrophiles.

The Neutrophil: This cell ١٢-١٥ micron in diameter has dense nucleus consisting of between ٢ and ٥ lobes and a pale cytoplasm with an irregular out line and containing many fine pink or violet pink granules.

The neutrophil granules are of two types:

a- primary: appear in the promyelocyte stage contains myeloperoxidase acid phosphatase and other hydrolases.

b- Secondary: appear at the myelocyte stage contains a Ikaline phosphatase and lysosome.

Function of neutrophil:

١-They are actively motile phagocytes they are the first lencocytes to reach to the site of inflammation this function is called chemo taxis (cell mobilization) in which the phagocyte is attracted to the bacteria or site of inflammation by chemo tactic substance or by complement component.

٢-**phagocytosis**: in which the foreign material e.g bacteria, fungi…..etc or dead cells are phagocytosed.

٣- **killing**: killing of the bacteria by oxygen-dependent and oxygen independent path ways.

٤- Important source of pyrogenic material which act directly on the thermoregulatory centre.

Neutrophilia : An increase in circulating neutrophils level greater than ٧,٥X١٠^{٩}/ℓ.

Causes :

١. Bacterial infection.

٢. Inflammation and tissue necrosis.

٣. Metabolic disorders curaemia,acidosis .

٤. Neoplasm of all types

clinical feature :- fever .

lab diagnosis:- blood film a- "shift to the left" in the peripheral blood differential count of WBC i.e. an increase in the member of band forms and the occasional prescience of more primitive cells.

The presence of cytoplasmic toxic granules and Dohle bodies (condensation of RNA).

-An elevation in the neutrophil alkaline phosphatase level.

Neutropenia : low level of neutrophil in the blood below ١٥X١٠^{٩}/ℓ the neutropenia may be selective or accur as part of panaytopenia.

Causes:

١-Drugs

٢- viral infections

٣- fulminant bacterial in fection (typhoid,miliary tuberculosis).

٤- hypersensetivity.

٥- autoimmune.

٦-SLE.

٧- pancytopenia.

Clinical picture: recurrent infections.

Variations in neutrophil morphology:

١- Hyper segmented neutrophil: The nucleus has more than ٥ lobes occur in megaloblastic anemia.

٢- Dohle bodies: occur in infections.

٣- The drumstick: appeare on the nucleus of proportion of neutrophils in normal females and this due to the prescence of two X chromosomes.

Eosinophils: These cells are similar to neutrophils except the cytoplasmic granules are coarser and more deeply red stained and there rarely more than three nuclear lobes.

Function :

١- have special role in allergic responses .

٢- in defenses against parasites.

٣- in removal of fibrin formed during inflammation.

Eosinophilia: An increas in blood eosinophil above ٠,٤X١٠^{٩}/ℓ.

Causes:

١- parasitic diseases ex. Worm infestation .

٢- Allergic diseases ex. Asthma hay fever.

٣-skin diseases example: psoriasis, dermatitis.

٤-pulmonary eosinophilia.

٥-eosinophilic leukaemia.

Basophils:- The basophil is produced in the bone marrow occasionally seen in normal peripheral blood. In the tissues they become mast cells they have IgE attachment sites. They have many cytoplasmic granules which overlie the nucleus and contain heparin and histamine.

Function:

١- Chemotaxis (but have slower motility than neutrophil).

٢-Phagocytosis.

٣-Secretory function the water soluble granules contain histamin, heparin etc...

Basophil leucocytosis:- An increase in blood basophils above ٠,١X١٠٩/L

It is rare ex: granulocytic leukaemia, polycythemia vera, small pox chicken pox.

Monocyte: Larger than other peripheral blood leucocyte (١٦-٢٠Mm in dimeter)and have large central oval or indented nucleus with clumped chromatin. The cytoplasm stain faint blue and contain many fine vacules giving a ground glass appearance. Cytoplasmic granules are also often present. The monocyte precusor in the bone marrow are difficult to distinguish from myeloblast and monocyte.

Function: Thy are large macrophages capable of phagocytosis and pinocytosis :

١ -Defence mechanism against intracellular parasites including certain bacteria, fungi and protozoa.

٢-Removal of damaged and old cells.

٣-Process antigen formation for lymphocytes.

٤-Production of secretion of various substances like lySosomal enzymes.

Lymphocytes:- type of WBC also called immunocytes they are produced by the bone marrow, lymph nodes, spleen, thymus. They divided morphologically in to three types, small, medium and large with size variation of ٨-١٦ Mm in diameter. The larger the lymphocyte the more the cytoplasm.

Function:

١-they are vital to the immune system. They produce circulating antibodies and express cellular immunity.

There are two subpopulations of lymphocytes:

١- B-lymphocytes . ٢- T- lymphocytes.

B- lymphocytes : are generally short lived and constitute about ٢٠ % of lymphocyte in the peripheral blood . they are derived from the bone marrow and was so named because they are previously discovered in birds in an organ called bursa of fabricious . The B- lymphocytes are primarly responsible for the production of anti bodies. They may transform into plasma cells , they have immunoglobulin receptors on there surface, and produce and secrete specific antibodies. :

T- Lymphocytes; (thymus dependent lymphocytes):

They have antigens attached to their outside surface .They are long lived, There main function is cell mediated immunity including graft rejection and delayed hyper sensitivity.

Lymphocytosis*:* -Increase number of lymphocytes often occur in infants and young children .

Causes ;

١- infection .

a-Acute [Infectious mononucleosis, Rubella, Cytomegallic virus].

b-Chronic [tuberculosis, toxoplasmosis , brucellosis].

٢-thyrotoxicosis.

٣-chronic lymphocytic leukaemia.

Lymphopenia*:* Rare may occur in sever bone marrow failure , immuno suppressive therapy, Hodgkin's disease.

INFECTIOUS MONONUCLEOSIS

It is also called [glandular fever].;-a disease characterised by fever^ sore throat, lymphadenophathy and atypical lymphocytes in the blood. These thought to be T-cells reacting against B-lymphocytes infected with Epstein- Barr [EB jvirus. Individuals with out antibodies to this virus are prone to the infection ,the majority of patient

٥/ Post test:-

١-Draw a diagram showing the process of granulocytes formation,

٢-Draw a diagram showing the process of monocytes . Formation.

٣-Draw a diagram showing the process of lymphocytes formation

Note:- Chick your answers in key answer next pages.

٦/ Key answer:-

-pre test:-

The normal differential leucocyte count:

Cell type	%	Absolute No.s
Neutrophils	٤٠-٧٥	٢,٥ – ٧,٥ X ١٠ ٩/ℓ
Eosinophils	١-٦	٠,٠٤ – ٠,٤ X ١٠ ٩/ℓ
Basophils	<١	٠,٠١ – ٠,١ X ١٠ ٩/ℓ
Monocytes	٢-١٠	٠,٢X٠,٨ X ١٠ ٩/ℓ

- **Post test:-**

١--

Granulopoiesis;- All forms of granulocytes are produced in the bone marrow:

١ Stem cell → progeniter cells → Myeloblast → Promyelocyte → Mylocyte → Metamyelocyte → Band form → Mature Neutrophil

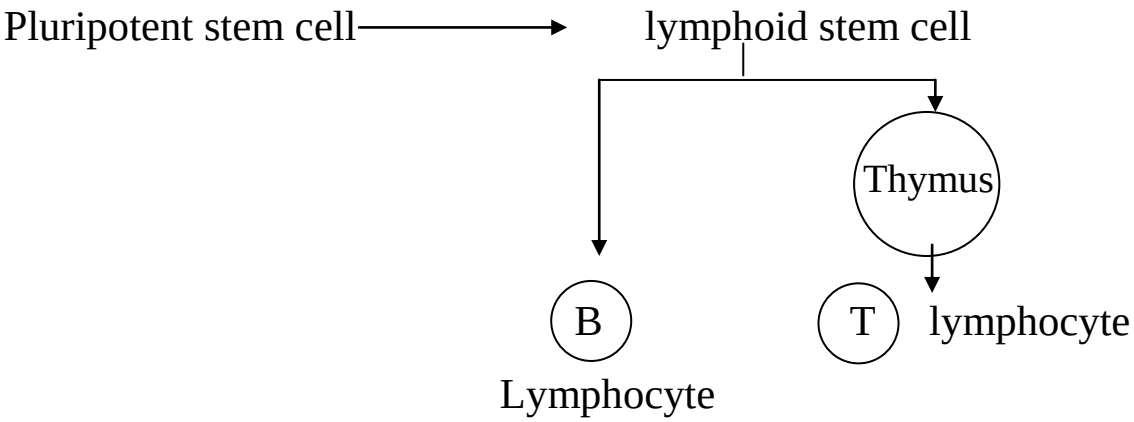
Metamyelocyte → Basophil

Metamyelocyte → eosinophil

٢-monocyte formation:-

Myelomonoblast → promonocyte → Monocytes in the blood → immature magrophages → mature macrophages

٣-Lymphocytes formation:-



٧/ Sources:-

١-Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.

٢-A short text book of hematology, R.B Thompson ٥th. Edt.

٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.

٢ ٤th modular unit

The functions of WBC

٤/ the text :-

Function of neutrophil:

١-They are actively motile phagocytes they are the first leucocytes to reach to the site of inflammation this function is called chemo taxis (cell mobilization) in which the phagocyte is attracted to the bacteria or site of inflammation by chemo tactic substance or by complement component.

٢-**phagocytosis**: in which the foreign material e.g bacteria, fungi…..etc or dead cells are phagocytosed.

٣- **killing**: killing of the bacteria by oxygen-dependent and oxygen independent path ways.

٤-Important source of pyrogenic material which act directly on the thermoregulatory centre.

Functions of eosinophils:-

١- have special role in allergic responses .

٢- in defenses against parasites.

٣-in removal of fibrin formed during inflammation.

Functions of basophilis:-

١- Chemotaxis (but have slower motility than neutrophil).

٢-Phagocytosis.

٣-Secretory function the water soluble granules contain histamin, heparin etc...

Functions of monocytes:-

They are large macrophages capable of phagocytosis and pinocytosis :

١ -Defence mechanism against intracellular parasites including certain bacteria, fungi and protozoa.

٢-Removal of damaged and old cells.

٣-Process antigen formation for lymphocytes.

٤-Production of secretion of various substances like lySosomal enzymes.

Functions of lymphocytes:-

They are vital to the immune system. They produce circulating antibodies and express cellular immunity.

a- The B- lymphocytes are primarly responsible for the production of anti bodies. They may transform into plasma cells , they have immunoglobulin receptors on there surface, and produce and secrete specific antibodies.

b-The T-lymphocytes main function is cell mediated immunity including graft rejection and delayed hyper sensitivity.

٥/ Post test:-

١-Heparin secreted by:-

a-lymphocytes **b-Monocytes**

c-Basophils **d-eosinophils**

٢-Increase in allergic response:-

a-Eosinophil **b-lymphocytes**

c-Neutrophil **d-Monocyte**

٣-Secretion of pyrogenic material:-

a-neutophil **b-Lymphocytes**

c-Eosinophils **d-monocytes**

٤-Delayed hypersensitivity :-

a-B-Lymphocytes **b-T-Lymphocytes**

c-Neutrophilis **d-Basophil**

٥-Become mast cell in the tissues

a.Eosinophil **b. Basophil**

c.Neutrophil **d. Lymphocytes**

Note Chick your answers in key answer next pages.

٦/ Key answer :-

(٢) degree each

١-Pre test :-

١-Neutrophil.

٢-Basophil,

٣-monocyte.

٤-monocyte.

٥-lymphocyte

٢-Post test:-

-(٢) degree each

١-c

٢-a

٣-a

٤-a

٥-b

٧/ Sources:-

١-Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.

٢-A short text book of hematology, R.B Thompson ٥th. Edt.

٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.

٢٥t & ٢٦th modular unit

Leukocytosis & leukopenia

٤/ the text :-

Neutrophilia : An increase in circulating neutrophils level greater than ٧,٥X١٠^{٩}/ℓ.

Causes :

١. Bacterial infection.

٢. Inflammation and tissue necrosis.

٣. Metabolic disorders curaemia,acidosis .

٤. Neoplasm of all types

clinical feature :- fever .

lab diagnosis:- blood film a- "shift to the left" in the peripheral blood differential count of WBC i.e. an increase in the member of band forms and the occasional prescience of more primitive cells.

The presence of cytoplasmic toxic granules and Dohle bodies (condensation of RNA).

-An elevation in the neutrophil alkaline phosphatase level.

Neutropenia : low level of neutrophil in the blood below ١٥X١٠^{٩}/ℓ the neutropenia may be selective or accur as part of panaytopenia.

Causes:

١-Drugs

٢- viral infections

٣- fulminant bacterial in fection (typhoid,miliary tuberculosis).

٤- hypersensetivity.

٥- autoimmune.

٦-SLE.

٧- pancytopenia.

Clinical picture: recurrent infections.

Variations in neutrophil morphology:

١- Hyper segmented neutrophil: The nucleus has more than ٥ lobes occur in megaloblastic anemia.

٢- Dohle bodies: occur in infections.

٣- The drumstick: appeare on the nucleus of proportion of neutrophils in normal females and this due to the prescence of two X chromosomes.

Eosinophilia: An increas in blood eosinophil above ٠,٤X١٠^{٩}/ℓ.

Causes:

١- parasitic diseases ex. Worm infestation .

٢- Allergic diseases ex. Asthma hay fever.

٣-skin diseases example: psoriasis, dermatitis.

٤-pulmonary eosinophilia.

٥-eosinophilic leukaemia.

Basophil leucocytosis:- An increase in blood basophils above ٠,١X١٠٩/L

It is rare ex: granulocytic leukaemia, polycythemia vera, small pox chicken pox.

Lymphocytosis*: -*Increase number of lymphocytes often occur in infants and young children .

Causes ;

١- infection .

a-Acute [Infectious mononucleosis, Rubella, Cytomegallic virus].

b-Chronic [tuberculosis, toxoplasmosis , brucellosis].

٢-thyrotoxicosis.

٣-chronic lymphocytic leukaemia.

Lymphopenia*:* Rare may occur in sever bone marrow failure , immuno suppressive therapy, Hodgkin's disease.

Monocytosis:- a rise in blood monocyte above ٠,٨x١٠٩/l

Causes :-

١-Chronic bacterial infection.

٢-protozoal infection.

٣-Chronic neutropenia.

٤-Hodgkin disease and other malignancies.

٥-Chronic meylomonocytic leukemia

٥/ Post test:

Complete the following statement

١-In monocytosis the number of monocytes increase above----------.

٢-In worm infestation the numberof----------increases.

٣-In megaloblastic anemia some neutrophils ---------

٤-One of the chronic infections in which there is Lymphocytosis is----------,

٥-Lymphocytosis often occur in --------and young children

Note Chick your answers in key answer next pages.

٦/ Key answer :-

_Pre test :-

١-Causes of neutropenia:-

١-Drugs

٢-viral infection

٣-Fulminant bacterial infection(military tuberculosis,typhoid)

٤-Hypersensitivity.

٥-auto immune

٦-SLE

٧-Pancytopenia

٢-Causes of lymphopenia:-

١-Sever bone marrow failure

٢-immunosupressive therapy

٣-Hodgkin disease

-post test -

١-٠,٨X١٠^{٩}/l

٢-eosinophils

٣-hyper segmented neutrophil

٤-Miliary tuberculosis

٥-Infants

٧/ Sources:-

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٢٧th modular unit

Leukemia,definition and classification

The leukaemias

Definition:- The leukaemias are group of disorder characterized by the accumulation of abnormal white cells in the bone marrow which may lead to bone marrow failure, a raised circulating white cell and infiltrate other organs.

The common features of leukaemias in general.

١- Abnormal WBC in the peripheral blood.

٢- Raised total WBC count.

٣- Evidence of B.M, failure (i.e. anemia, neutrogena, thrombopocitopenia),

٤- Involvement of other organs (liver , spleen , lymph nodes, skin , brain)

Aeitiology:-

١- neoplasia; uncontrolled proliferation of the cell,

٢- Infection: viral.

٣- Radiation: particularly of the bone marrow.

٤- Familial.

Chromosome changes : the Philadelphia chromosome found in majority of patient with chronic granulocytic leukaemias.

Classification of leukaemias

Acute	Chronic
١- Myeloblastic (AML)	Chronic granulocytic (CGL)
Ml Myeloblastic (poorly differentiated)	Chronic lymphocytic (CLL)
M٢ Myeloblastic (well differentiated)	Unusual types:-Hairy cell
M٣ promyelocytic	leukaemia Pro lymphocytic
M٤ myelomonocytic	Dysmyclopoietic syndrome
M٥ monocytic	
M٦ erythroleukaemia	
٢- Lymphoblastic (ALL)	
a- common (non T- non B)	
b- Thy-ALL	
c- B-Cell ALL	

٥/ Post test:-

-١-Define leukemia

٢-What are the possible causes of it?

Note Chick your answers in key answer next pages.

٦/ Key answer

-Pre test:-

Classification of leukaemias

Acute	Chronic
١- Myeloblastic (AML)	Chronic granulocytic (CGL)
Ml Myeloblastic (poorly differentiated)	Chronic lymphocytic (CLL)
M٢ Myeloblastic (well differentiated)	Unusual types:-Hairy cell
M٣ promyelocytic	leukaemia Pro lymphocytic
M٤ myelomonocytic	Dysmyclopoietic syndrome
M٥ monocytic	
M٦ erythroleukaemia	
٢- Lymphoblastic (ALL)	

-post test:-

١- **Definition**:- The leukaemias are group of disorder characterized by the accumulation of abnormal white cells in the bone marrow which may lead to bone marrow failure, a raised circulating white cell and infiltrate other organs.

٢- **Aeitiology:-**

١- neoplasia; uncontrolled proliferation of the cell,

٢- Infection: viral.

٣- Radiation: particularly of the bone marrow.

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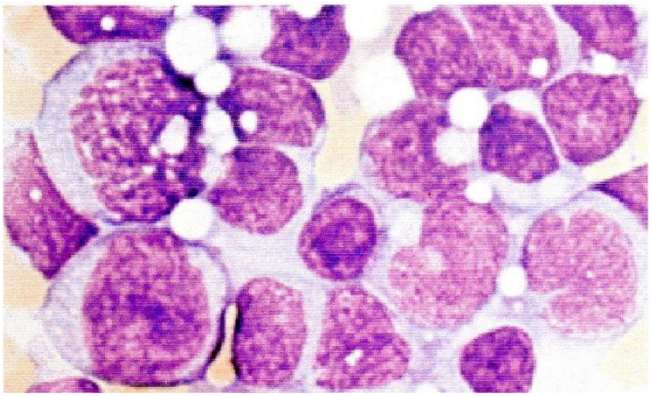
٨th edt.

٢٨th modular unit

Acute & chronic myeloid leukemia



Acute myelohlastic leukaemias:

A condition in which (the white blood cells count show moderate lo marked elevation with ٦٠٪ or more of the cells being myeloblasts. The bone marrow show an increased number of myeloblasts. it occur in all age groups, they are the common form of leukemia in adults. The variants of AMI. are not sharply sperated from each other and there treatment and prognosis are basically similar.

Clinical features : similar lo ALL.

Laboratory findings: l-Auer rods may be present in the cytoplasm of the myeloblast. normochromic normocytic anaemia.

٢-Thrombocytopcnia.

٣-The W.B.C' count may be decreased, normal or increased.

٤-Blood film exam show variable number of blast cell- myeloblast promyelocytcs. myelocytes. A granular neulrophils.

٦-The bone marrow shows an increase number of myeloblast.

٧-**Special tests**: periodic shiff (PAS) positive with fine granules.

٨-leucocytes alkaline phosphatase decreased.

Chronic granulocytic leukaemia

(Chronic myeloid myelogenous leukaemia)

It comprises ٢٠٪ of all leukaemias seen mostly in middle age characterise by replacement of normal bone marrow by cells with an abnormal chromosome (number ٢٢) which is called the Philadelphia or ph chromosome it is an acequired bnormality that is present in all dividing granulocytic erythroid and megakaryocytic cells in the marrow in the

blood film the ful range of granulocyte precursors from myeloblasts to mature neutrophils

PHILADELPHIA CHROMOSOME:-it is ashortened chromosome ٢٢ it result from a reciprocal translocation of part of the long arms of chromosome ٢٢ to the long arms of chromosome ٩.

laboratory findings:-

١- Leucocytosis

٢- A complete spectrum of nuceloid cells is seen in the peripheral blood the levels of neutrophils and myelocytes exceed those of blast cells and promyelocyte.

٣- Philadelphia chromosome on cytogenic analysis (٩٠٪) in blood or B.M

٤- Bone morrow hyper cellularity with granulocytic predominance.

٥- Low neutrophil alkaline phosphatase.

٦- Nor mochromic normocytic anaemia.

٧- Platelet count may be normal .

٨- Serum vit B١٢ and vit B١٢ binding capacity .

FEATURES

١- Weight loss

٢- Lassitude, anorexia , neight sweat

٣- Splenomegaly

٤- Features of anaemia

٥- Bruising epistaxis .

Treatment: Cytotoxic drug (B٤ sulpher, allopurinol) splenic radiation splenectomy prognoses ٣-٤ years survival. it may transform in to acute blast cell leukaemia

٥/ Post test:-

١-What are the laboratory findings in CML?

٢-What is the blood picture in AML

Note Chick your answers in key answer next pages.

٦/ Key answer

١-Pre test:-

١-a

٢-b

٣-d

٤-c

٥-a

٢-Post test:-

١-Chronic granulocytic leukaemia:-

laboratory findings

١- Leucocytosis ٥٠

٢- A complete spectrum of nuceloid cells is seen in the peripheral blood the levels of neutrophils and myelocytes exceed those of blast cells and promyelocyte.

٣- Philadelphia chromosomeon cytogenic analysis (٩٠٪ of ca) in blood or b.m

٤- Bone morrow hyper cellularity with granulocytic predominance.

٥- Low neutrophil alkaline phosphatase.

٦- Nor mochromic normocytic anaemia.

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٢-Blood film exam show variable number of blast cell myeloblast promyelocytcs. myelocytes. A granular neulrophils.

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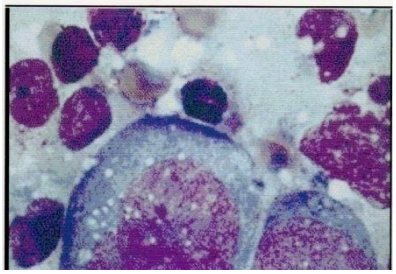
٢ ٩th modular unit

Acute & chronic lymphoid leukemia

CLL



Acute lymphoblastic leukaemias:-

This type of leukemia gnerally assosiated with a predominance of undifferentiated cells of the lymphoid series in the bone marrow or thymus , it is the commonest form in children. The incidence is higher at ٣-٤ Y with a secondary rise after the age of ٤٠.

Clinical feature:-

١- feature of anemia (pallor, lethargy).

٢- infection.

٣- bleeding tendency.

٤- tender bones.

٥- lymph adenopalhy.

٦- moderate splenomegaly and hepatomegaly.

Lab. Findings:

١- Normochromic normocytic anemia.

٢- the whiter cell count may be decreased, normal or increased up to at least $٢٠٠X١٠^{٩}/I$

٣- thorombocytopenia.

٤- blood film: show variable number of lymphoblast.

٥-B.M.: show hypercellularity with marked proliferation of lymphoblast with increased reliculin fibers.

٦- immunological markers and enzyme assay help in subdividing ALL into non-B, non-T etc… also help to differential ALL from AMI..

٧-rairsed TdT enzyme.

Mangement:

١-platelet concentrate and fresh blood are used .

٢-cyloloxic drugs these drugs will damage the capacity of the cells for reproduction leading to remission state (reduced or no abnormal cells found on examination).

٣-Treatment of anemia, infection, etc…

CHRONIC LYMPHOCYTIC LEUKAEMIA CLL

Account for ٢٥٪ of leukaemias , occur chiefly in the elderly with amale predominance it is characterized by accumulation of large numbers mature lymphocytes to ٥٠-١٠٠ times the normal lymphoid mass in the blood , bone marrow spleen and livrer in most cases the cells are B-lymphocytes but in a few they are all T-cells , with advanced disease there

is often bone marrow failure , generalised discrete lymphadenopathy and sometimes soft tissue lymphoid masses.

Immunological failure result from reduced humeral and cellular Immune process.

٥/ Post test:-

١-What are the clinical features of ALL?

٢-What are the varients ofCLL?

Note Chick your answers in key answer next pages.

٦/ Key answer :-

(٢) degree each

Pre test:-

١-a

٢-b

٣-b

٤-b

٥-a

-Post test:-

(٢) degree each

Clinical features of ALL

١- feature of anemia (pallor, lethargy).

٢- infection.

٣- bleeding tendency.

٤- tender bones.

٥- lymph adenopalhy.

٦- moderate splenomegaly and hepatomegaly.

VARIANTS OF CLL:

١- CLL may be asymptomalic_especiall in elderly .

٢- More aggressive in younger patient ٣-٥٠y old.

٣- ١٠٪-١٥٪ of all may deveTopTa secondary autoimmune hemolytic anaemia with +ve direct combs test

٤- Prolymphocytic leukaemia is a variant of CLL characterise by massive splenommegaly and lymphocytes exceeding ٤٠٠*١٠/١ but abscent lymph node enlargement

٧/ Sources:-

١- **Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.**

٢-A short text book of hematology, R.B Thompson ٥th. Edt.

٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.

٣٠th modular unit

Acute & chronic monocytic leukemia
Malignant Lymphomas other than ALL &CLL

Monocytic leukaemia:-

is a type of myeloid leukemia characterized by a dominance of monocytes in the marrow. When the monocytic cells are predominantly monoblasts it is subclassified into the **monoblastic leukemia**.

Like myeloid leukemia, monocytic leukemia is almost always broken down into "acute" and "chronic":

- acute monocytic leukemia
- chronic monocytic leukemia

Acute monocytic leukemia is far more commonly referenced than the chronic variety. However, the chronic variety is a valid diagnostic entry.

CHRONIC MYELOMONOCYTIC LEUKAEMIA:

In this type the absolute monocyte count is raised, The total WBC is lower than that in CGL . Abscent Philadelphia chromosome there is an increase ratio of monocyte in the blood and myeloblast in the bone marrow, agranular pseudo-pelger cells (cells between granulocytes and monocytes)may be seen in the peripheral blood . Low platelet and low absolute neutrophinl count. Ring sidero blast may be seen in the B.M

Pre Leukaemia :- This is anumber of chronic acequired bone marrow abnormalities , which may progress in some patient to leukaemia usually of the acute myeloblastic variety. Examples patients with a/Acequired sideroblatic anaemia, b/Aplastic anaemia c/Red cell aplasia d/Mild dysmelo poietic syndrome (qualitative and quanlitative abnormalities occur in all the three myeloid cell lines)

MALIGNANT LYMPHOMAS

CLASSIFICATION :

١- Hodgkins disease

٢- Non hodgkins disease in both there is replacement of normal lymphoid structure by collections of abnormal cells.

HODJKEN DISEASE: Is a smalignant tumour closely related to the other malignant lymphomas but it is distinguished from other lymphomas by the prescence of reed -steruberg cells (This is alarge cell .varying in size from ٥٠-١٠٠ Mm or more with abundant cytoplasm and irregular

margins the nucleus may be single or multilobed with large nucleoli, these cells are present in the involved tissue they may be derived from histiocytes) the disease involved the lymph nodes and then progress within the lymphatic system.then it may progress to involve the non lymphatic tissue.

CLINICAL FEATURES:

١- Painless asymmetrical firm discrete enlargement of the superficial lymph nodes.

٢- Spleenomegaly

٣- Mediastinal lymph node enlargement .

٤- Cutaneous hodjkins disease occurs as late complication

٥- fever (pel ebstein).٦- pruritis ٧-neight sweat,٨-weight loss.

HAEMATOLOGICAL FINDINGS:-

١- Normochromic normocytic anaemia

٢- marrow infilteration and marrow failure

٣- Neutrcphiiia due to a neutrophil increase.

٤- Neutrophil alkaline phosphtase level.

٥- Eosinophilia

٦- advanced disease associated with lymphopenia ٧-ESR.

HISTOLOGICAL FINDINGS AND DIAGNOSIS:

examination of excised lymph node show the reed-sternberg cell. Lymphocytes histiocytes, poly morph eosinophils plasma cells fibrosis. Chest x-ray show mediastinal lymph nodes liver biopsy,spleen and liver ultrasound show deposits of diffuse enlargement.

CLASSIFICATION OF HODJKEN DISEASE:

١- Lymphcyte predominant

٢- nodular sclerosis

٣- mixed cellularity

٤- lymphocyte depleted (poorer prognosis)

TREATMENT

١- Raddio therapy stag I ,ll ,

٢- chemotherapy stage III and Iv (Vincristine mustine)

PROGNOSIS ٥Y survival stage I, II ٨٥٪, ٧٠٪ stage III, ٤٠-٥٠٪ stage Iv

NON -HODGKINIS LYMPHOMA :

A malignant lymphoma it can be classified morphologically in to ٤ categories

I:Nodular

١-lymphocytic, well differentiated

٢- lymphocytic poorly differentiated

٣-lymphocytic and histiocytic

٤-histiocytic

II Difuse (Similar in classification to nodular)

Ill Mixed histiocytes and lymphocyte

VI Undifferentiated stem cells.

The difference between hodjken and non hodjken is that the pattern of spread is not as regular and a ggreater propotion of patients present with extranodal disease or leukaemic menitestation

The difuse type tend to be more aggressive and have poor prognsis

CLINICAL FEATURE:

١- superficial lymph adenopathy

٢- fever

٣- Anaemia

٤- neight sweat

٥- weight loss

٦- osophasyngeal involvement

٧- enlargement of liver and spleen .

٨- skin involoement.

HEMALOTOGICAL FINDINGS :

No٢ mochromic normocytic anaemia

Neutropenia thrombocytopenia

Blood chemistry : uric acid Abnormal liver function test. ,.

Chest X-ray to detect thoracic involverment liver biopsy.

FREATMENT Radiotherapy +chemotherapy.

MULTIPLE MYELOMA

(Myelomatosis) Is a neoplastic proliferation of plasma cells, characterized by lytic bone lesions , plasma cell accumulation in the bone marrow and presence of monoclonal protein in serum and urine ٨٪ of cases occur over the age of ٤٠.

Clinical feature : Bone pain (especially backache) ,features of anaemia, repeated infection ,

Renal failure which lead to hypercalcaemia, poly dipsia, poly uria. Abnormal bleeding tendency . purpura , hemorrhage ,C.N.S. symptoms

DIAGNOSIS : In ٩٨٪ of patients monoclonal proteins occurs in serum or (urine :-(Bence Jones protein).) The serum paraprotein is IgG in ٢/٣ rd of cases IgA in ١/٣rd rare IgM or IgD or mixed cases . Normal serum Immunoglobulin (IgG, IgA, IgM) are depressed.
Bence Jones protein : it is monoclonal proteins consists of free light chains , either kappa or lambda appear in urine of patient with multiple myeloma B.M show plasma cells
Osteolytic areas in the bone seen by X -ray . especially seen clearly in the skull.
Normochromic , normocytic anaemia . Rouleax formation is marked . high ESR .
Serum calcium elevation . Normal Alkaline phosphatase. raised serum urea and . serum creatinine.

٥/ Post test:-

What are the hematologicl findings in :-

a-Hodjken disease

b-Chronic mtelomocytic leukemia.

Note Chick your answers in key answer next pages.

٦/ Key answer:-

Pre test:- **(٢,٥)degree each**

١-Pseudo pelger Cells.

٢-Bilateral mediastinal Lymph nodes.

٣-Reed-sterenberge Cells.

٤-Bence Jones protein

Post Test:-

١- a-Normochromic normocytic anemia.

b-Marrow infilteration and marrow failure.

c-Neutrophilia

d-increase lactate dehydrogenase

e-Eosinophilia

f-Advanced disease associated with lymphopenia.

g-High ESR.

٢-a-Absolute monocyte count is raised

b-Abscent philadilphia chromosome.

c-There is an increase monocytet in the blood and myeloblast in the B.M.

d-Pseudo –pelger cells in the peripheral blood.

e-low platelet and low absolute neutrophil count

ring sideroblast may be seen in the bone marrow.

٧/ Sources:-

١-Essential hematology , By A.V. Hoffbrand , J.E.Pettit ,P.A.Moss. ٤th.edt.

٢-A short text book of hematology, R.B Thompson ٥th. Edt.

٣-Clinical hematology ,Maxwell M. Wintrobe, ٨th edt.