Notes

24

HAEMOSTASIS

24.1 INTRODUCTION

Haemostasis means "arrest of bleeding". During haemostasis several mechanisms interact to slow blood flow, block the vessel wall defect with a platelet plug (primary haemostasis), convert fibrinogen to a jelly like fibrin clot (coagulation of blood) and later re-establish the flow of blood through a mechanism of slow clot lysis (fibrinolysis).

OBJECTIVES

After reading this lesson, you will be able to:

- describe the 4 phases of Haemostasis
- describe the coagulation of blood
- explain Von Willebrand's Disease
- explain the causes of thrombocytopenia
- discuss bleeding Time test
- interpret PT/APTT/TT
- explain INR
- describe D – dimmer

24.2 HAEMOSTASIS

Haemostasis means "arrest of bleeding". During haemostasis several mechanisms interact to slow blood flow, block the vessel wall defect with a platelet plug (primary haemostasis), convert fibrinogen to a jelly like fibrin clot (coagulation of blood) and later re-establish the flow of blood through a mechanism of slow clot lysis (fibrinolysis). These complex physiological processes may be divided into phases:

A. Vascular Phase.

B. Platelet Phase.

C. Coagulation Phase and

D. Fibrinolytic Phase.

During haemostasis all the phases interact. It is convenient to consider them under these headings when investigating a patient with haemostatic problems.

A. The Vascular phase

The blood vessel plays a major role in maintaining the blood in a liquid state. The entire surface of the vessel wall is lined by a single layer of endothelial cells (EC) which rest on a basement membrane. The blood inside the blood vessel is not in touch with the sub-endothelial tissues. The EC secrete a major protein called the von Willebrand factor (VWF) into the plasma and sub-endothelium. External to the basement membrane lies the sub-endothelium rich in collagen, elastin, fibronectin, tissue factor (TF), VWF etc. External to the sub-endothelium lies the smooth muscle layer of variable thickness depending on the type of vessel. External to the smooth muscle layer is the adventitial layer. Figure 24.1.

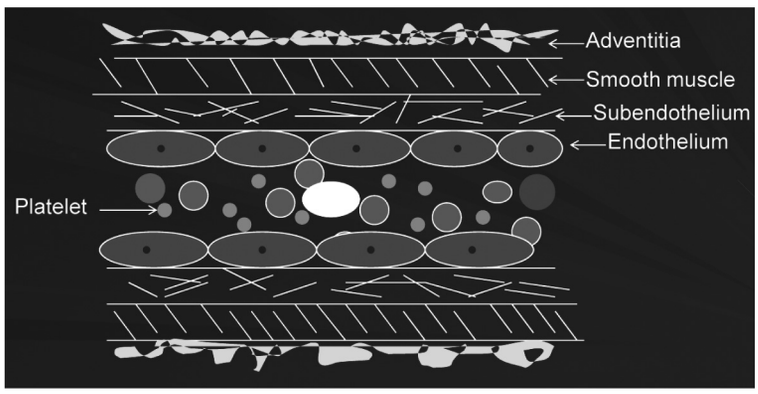


Fig. 24.1: The Blood Vessel Structure

Table I summarizes the role of the Vascular Phase.

Table I. Role of Vascular Phase in Haemostasis.

Blood vessel	Property	Function
Endothelial cell	Non reactive surface	Smooth blood flow Platelets are repelled
	VWF	1. Binds to platelet GPIb-IX and GPIIb-IIIa and mediates platelet adhesion to vessel wall. 2. Carries FVIII and prevents its early degradation.
	Antiplatelet activity	Negative charge on EC repels platelets, prostacyclin production and local degradation of ADP

	Anticoagulant property	1. Heparan sulphate on EC + antithrombin III inactivate serine proteases ie, thrombin, FXIa, FIXa etc. 2. Thrombin + Thrombo-modulin on EC activate Protein C and S which inactivates FVa and FVIIIa
	Fibrinolytic activity	EC releases plasminogen activator
Sub endothelial tissues	Collagen, elastin, VWF etc	Activate platelets
	Tissue factor	Complexes with FVII to form tissue thromboplastin for extrinsic pathway
Smooth muscle	Vasoconstriction and dilatation	Regulates blood flow

Table I:- EC – endothelial cell, VWF – von Willebrand factor, GP – glycoprotein

B. The Platelet Phase

Platelets are formed from megakaryocytes in bone marrow. The normal platelet count is 150- 450 x10^9/l. The life span of the platelet is 8 - 9 days. On a stained blood smear platelets are anucleate, round or discoid bodies, 1 – 2 mm in size with fine purple pink granules. The platelet has a phospholipid cell membrane into which are inserted glycoproteins (GP) which act as major cell receptors and antigens of the platelets. The role of platelets in haemostasis may be summarized as follows:

1. **Adhesion**. When EC is damaged platelets adhere to sub-endothelial tissues. Normal platelet number, presence of the receptor GPIb-IX complex on the platelet membrane (receptor for VWF), VWF in plasma and normal structure of collagen are necessary for adhesion. Figure 24.2

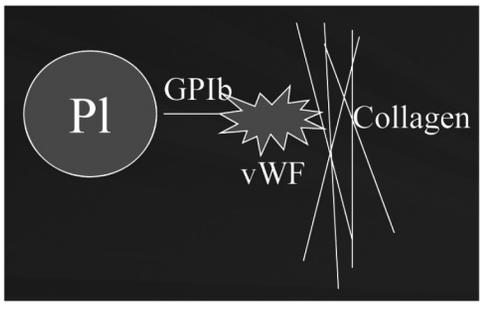
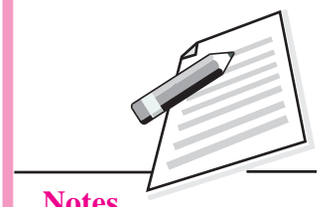


Fig. 24.2: Platelet Adhesion

2. **Aggregation**. Platelets then stick to one another to form the primary platelet plug. Normal platelet number, presence of GPIIb-IIIa complex on the



platelet surface (receptor for fibrinogen), plasma fibrinogen and calcium ions are necessary for platelet aggregation. Figure 24.3.

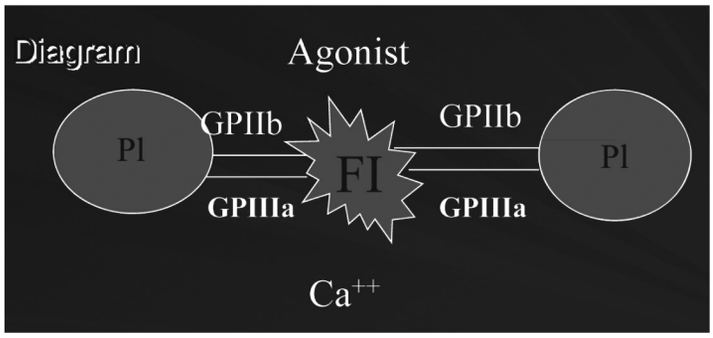


Fig. 24.3: Platelet Aggregation

3. **Platelet Release reaction**. As platelets aggregate they release their a and d granule contents which further sustain the aggregation response.
4. **The phospholipid surface** for the formation of coagulation complexes during blood coagulation is provided by the plasma membrane of the platelets.
5. **Clot retraction.** The GPIIb-IIIa complex on platelets anchor fibrin strands and pull them together to ensure a strong fibrin clot.
6. **Wound healing.** Platelet derived growth factor (PDGF) released from a granules promotes fibroblast proliferation and healing.

The platelet plug that is formed provides primary haemostasis. This must be reinforced with fibrin deposition to sustain haemostasis.

Table II lists some of the **abnormal platelet - vessel wall interactions** which result in bleeding.

Table II Abnormalties in Primary Haemostasis

Defect	Condition
Abnormal collagen (adhesion defect)	Ehlers Danlos syndrome, Marfans syndrome, Senile purpura
Absence of GPIb-IX (adhesion defect)	Bernard Soulier syndrome
Absence of VWF (adhesion and coagulation defect)	Von Willebrand's disease
Absence of GPIIb-IIIa (aggregation defect)	Glanzmann,s thrombasthenia, drug induced.
Absence of FI (aggregation + coagulation defect)	Afibrinogenemia

Absence of a or d granules or both (release defect)	Gray platelet syndrome and d storage pool disorder
Absence of receptors for ADP, collagen epinephrine, arachidonic acid etc.	Aggregation and release defects, drug induced
Absence of phospholipid release	Scott syndrome
Absence of enzyme systems	"aspirin" like defects

INTEXT QUESTIONS 24.1

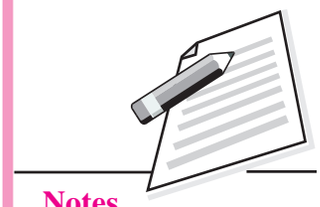
1. Haemostasis means .....
2. The endothelial cells of blood vessel secrete a protein called ..... factor
3. Platelets are formed from ..... in bone marrow
4. Normal platelet count is .....
5. When endothelial cell is damaged ..... adheres to sub-endothelial tissues
6. ..... ions is necessary for platelet aggregation
7. ..... factor promotes fibroblast proliferation and healing
8. Absence of phospholipid release causes ..... syndrome

C. The Coagulation Phase

In this phase liquid blood coagulates into a stable jelly like clot. Table III lists the coagulation proteins.

Table III Coagulation Factors

Factor	Synonym	Production site	Plasma half life	Replacement
FI	Fibrinogen	Liver	3 - 5 days	CRYPPT.
FII*	Prothrombin	Liver	2.5 – 3 days	FFP, PCC
FIII	Tissue factor	Subendothelium	-	-
FIV	Calcium ions	-	-	-
FV**	Labile factor Proaccelerin	Liver, mega-karyocyte	0.5 day	FFP



FVII*	Stable factor, Proconvertin	Liver	3 – 4 hours	FFP, Plasma, rFVII
FVIII**	Anti haemo-philic globulin	Liver	8 – 12 hours	CRYPPT. FFP, FVIII conc.
FIX*	Christmas factor	Liver	1 day	FFP, Plasma, PCC, FIX conc.
FX*	Stuart Prower factor	Liver	1.5 days	FFP, Plasma, PCC
FXI	Plasma thromboplastin antecedent	Liver	3 days	FFP
FXII	Hageman factor	Liver	2 days	FFP
FXIII	Fibrin stablising factor	Liver	9 – 10 days	CRYPPT, FFP
	Prekalleikrein**			FFP
	High molecular weight kinnin-ogen**			FFP

Table III: *Vitamin K dependent factors, ** cofactors. FFP – fresh frozen plasma, CRYPPT – cryoprecipitate, PCC – prothrombin complex

Blood coagulation takes place in a series of enzyme reactions, each successive step being catalysed by the active enzyme formed in the previous step. The process gains speed and force like a cascade. During the process the activated enzymes form **complexes** on phospholipid membranes in the presence of calcium ions. This localizes the clotting process to the site of injury. The complexes are formed by the vitamin K dependent factors (F II, VII, IX and X). These factors are produced in the liver in their precursor form. They bear g glutamic (Gla) residues at the amino terminal end of the molecule. A post ribosomal modification in the hepatocyte involves carboxylation of the Gla residues in the presence of a carboxylase, vitamin K, carbon dioxide and oxygen. The g carboxy glutamic acid residues of these proteins bind calcium ions which then serve as a bridge to bind the proteins to phospholipid surfaces.

For ease of understanding the Coagulation Phase has been divided into (a) Intrinsic Pathway (b) Extrinsic Pathway and (c) Common Pathway as shown in Figure 24.4

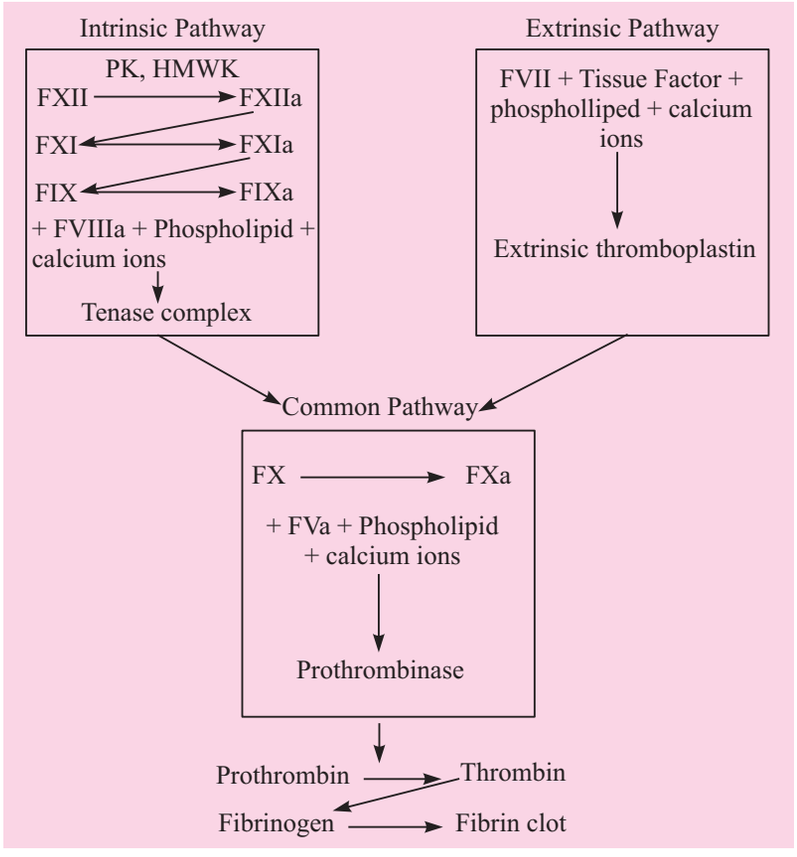


Fig. 24.4: Schematic representation of the coagulation pathways

In the Intrinsic pathway, when blood comes into contact with a non endothelial surface, FXII is activated to FXIIa. Prekallikrein and High Molecular Weight Kinninogen are cofactors. FXIIa activates FXI to FXIa which in turn activates FIX. FIXa complexes with phospholipid (PL) in the presence of calcium ions and activated FVIII to form a complex called tenase or intrinsic thromboplastin.

In the Extrinsic Pathway, when blood comes in contact with tissue factor present in the subendothelium, FVII is activated and forms a complex with TF, PL and calcium ions to form extrinsic thromboplastin.

In the Common Pathway, both intrinsic and extrinsic thromboplastins activate FX. FXa forms a complex, Prothrombinase, with FVa, PL and calcium ions. Prothrombinase converts prothrombin to thrombin. Thrombin is a potent serine protease which splits off fibrinopeptides A and B from fibrinogen to produce fibrin monomers. Fibrin monomers polymerize to form fibrin clot.

Thrombin also activates FV, FVIII, FXI and FXIII. In the body the activation of FVII through TF and the generation of small amounts of thrombin is the

dominant pathway. Once thrombin is generated the process is sustained through the intrinsic pathway.

FXIIIa acts on the fibrin clot in the presence of calcium ions to stabilize it.

The extrinsic and common pathways are tested "in vitro" by the Prothrombin time (PT) and the intrinsic and common pathways are tested by the activated partial thromboplastin time (APTT). The final conversion of FI to fibrin is tested by the Thrombin Time (TT). Since FXIIIa acts only after fibrin formation, its activity is not evaluated by PT or APTT.

Disorders of the coagulation pathway due to a **single factor** deficiency are usually inherited disorders. Haemophilia A or FVIII deficiency is the most common example. Multifactor deficiencies are usually acquired as seen in severe liver disease, disseminated intravascular coagulation or massive transfusion of bank blood

D. The Fibrinolytic Phase.

Fibrinolysis achieves recanalization of a blood vessel blocked by fibrin deposition. Plasminogen is a protein made in the liver and circulates in blood. Plasminogen is converted to the active enzyme, plasmin, by the action of tissue plasminogen activator (tPA) released from damaged EC. Plasminogen activators are also present in milk, semen, prostatic bed etc. Plasmin that is formed is immediately inactivated by circulating antiplasmin. Small amounts of plasmin adsorbed onto fibrin strands digest fibrin from within the clot. Fibrin breaks down to form fibrin degradation products (FDP) which are cleared by macrophages. Plasmin can also digest fibrinogen.

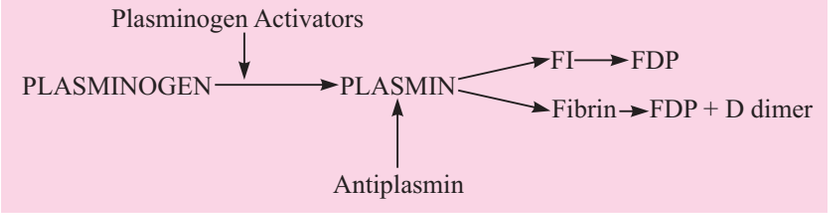


Fig. 24.5: The Fibrinolytic Pathway

Localization of the haemostatic process.

Uncontrolled and disseminated fibrin deposition is prevented by several mechanisms:-

1. Formation of membrane bound complexes localizing clot formation to site of injury.
2. Blood flow removes and dilutes activated coagulation factors.

Notes

3. Presence in plasma of normal inhibitor proteins which inactivate the activated coagulation factors. These are
   (a) Antithrombin III formed by the liver and complexed to heparan sulfate and inactivates the serine proteases – Thrombin, FXIa, FXa, FIXa, FVIIa.
   (b) Proteins C and S which are vitamin K dependent factors which inactivate FVa and FVIIIa.
   (c) Antiplasmin inactivates plasmin.
   (d) Tissue factor pathway inhibitor inhibits tissue factor.

Abnormalties of Haemostasis may result in **Bleeding** (Congenital or Acquired) and **Thrombosis** (Arterial or Venous)

INTEXT QUESTIONS 24.2

1. The extrinsic and common pathways are tested by ..... test
2. The intrinsic and common pathways are tested by ..... test
3. Final conversion of F1 to fibrin is tested by ..... test
4. Abnormalities of Haemostasis may result in ..... and .....

24.3 BLEEDING DISORDERS

All patients who present with bleeding need to be investigated. **It is also good practice to screen patients for a bleeding tendency prior to subjecting a patient to any form of surgery.** Preoperative evaluation of haemostasis occurs at two levels – an adequate history and screening tests.

History. Specific questions should be directed to

(a) Is there a history of a bleeding tendency? If so, what was the **age of onset** of the problem? Onset in childhood is associated with congenital causes. Recent onset suggests an acquired disorder eg. drug induced or liver disease.

(b) What is the **type of bleeding**? Bleeding into the skin and from mucosal surfaces – bruising, epistaxis, gum bleeding, menorrhagia suggest a vascular or platelet related problem. Bleeding into subcutaneous tissues, haematoma formation and haemarthrosis suggest a coagulation factor deficiency.

(c) **Delayed wound healing**, bleeding from umbilical stump, intracranial bleeds and frequent abortions are associated with FI and FXIII defects.

(d) Assess **severity of bleeding tendency** from frequency of episodes, days of hospitalization, transfusion requirements.

(e) Detailed history of **drug intake** especially of antiplatelet agents should be taken.

(f) **Family history**. In general haemophilia A and B are sex linked recessive disorders, von Willebrand's disease is autosomal dominant and all other coagulation factor deficiencies and platelet disorders are autosomal recessive in nature.

24.4 SCREENING TESTS FOR HAEMOSTASIS

These tests detect most abnormalities in haemostasis. If found to be abnormal the patient is referred for definitive tests which may be available only in specialized laboratories.

24.4.1 Blood Samples to be taken for screening tests are:

(a) 1 – 2 ml blood in EDTA anticoagulant for complete blood count. Platelet count done from a finger prick is not reliable.

(b) 4.5 ml venous blood mixed with 0.5ml of 3.2% sodium citrate for plasma clotting tests.

Blood must be taken from a clean venepuncture. If sampling is to be done from a central line, it must be flushed with normal saline, the first 4 – 5 ml of blood discarded and then the sample for tests must be drawn. The sample must be processed within 1 – 2 hours.

24.4.2 Tests to be done are:-

24.4.2.1 Platelet count. All platelet counts must be verified by a blood smear.

24.4.2.2 Bleeding Time. (BT) This measures the platelet vessel wall interaction. Two methods are available – the Template method (normal 2-9minutes) and the Ivy method (normal 2 – 6minutes). The BT is very operator dependent. It is accepted now that the BT is not indicated as a routine screening test and that a history taken well is just as reliable. **The BT is a poor predictor of abnormal surgical bleeding** and need not be done prior to surgery. Indications for doing BT are assessment of platelet function 4 –5 days after stopping asprin, assessing platelet function when patient has mild thrombocytopenia (platelet count > $50x10^9/l$), diagnosis of VWD and platelet dysfunction and to evaluate response to FFP, cryoprecipitate or desmopressin in VWD prior to surgery.

24.4.2.3 Prothrombin time (PT) is the time taken for citrated plasma to clot on the addition of tissue thromboplastin and calcium chloride. It measures

the extrinsic and common pathways and will detect abnormalities of FI, II, V, VII and X. A control plasma is always run with the test. PT is considered prolonged if the test and control values show a greater than 3 second difference. The normal PT by the manual technique is 12 - 14 seconds. A mild elevation of the PT is an early indication of deranged hepatocelluar dysfunction. For patients on oral anticoagulants the PT is reported as **the INR or International Normalised Ratio** to avoid problems that arise from the use of thromboplastins of varying sensitivities. Commercial thromboplastins are assigned an ISI (International Sensitivity Index) value after comparisons with a WHO standard. The ISI is used to calculate the INR. The INR is calculated as:

INR = (Patient's PT ÷ Mean normal PT)^{ISI} The normal INR is 0.9 – 1.2.

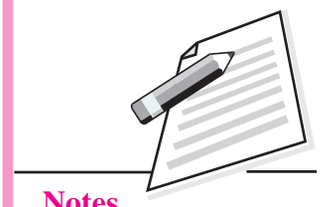
24.4.2.4 Activated partial thromboplastin time (APTT) has replaced the old and insensitive Clotting Time (CT) test. The APTT measures all the coagulation factors except FVII and FXIII. The normal manual APTT is 30 – 35". A greater than 5 second difference from the control is significant. A persistently short APTT (<25") indicates a hypercoagulable state. The APTT is used to monitor heparin therapy.

24.4.2.5 Thrombin time (TT) measures clottable fibrinogen. The normal TT is 12 –14" and a greater than 2 seconds difference from control is significant. TT is increased in deficiency of FI, dysfibrinogenemia, in the presence of heparin and with elevated levels of FDP.

24.4.2.6 Correction studies. When the PT/APTT/or TT are prolonged a correction study is performed by mixing equal parts of the test plasma and control plasma and repeating the test with the mixture. If the prolonged time is corrected, the study indicates a factor deficiency. Lack of correction indicates the presence of an inhibitor in the patient's plasma. Common inhibitors are heparin, lupus anticoagulant or an antibody to one of the coagulation factors.

24.4.2.7 Tests of fibrinolysis. For screening purposes it is sufficient to detect increased fibrinolysis in a patient using latex agglutination kits or ELISA techniques which demonstrate the presence of fibrin degradation products (FDP) and D-dimers.

24.4.2.8 Screening test for FXIII activity. Since FXIII acts after clot formation, the plasma clotting tests do not measure FXIII activity. A screening test called clot solubility in 5M urea or 1% acetic acid is performed to screen for FXIII activity.



INTEXT QUESTIONS 20.3

1. INR stands for .....
2. Normal INR is .....
3. Normal prothrombin tine is .....
4. Activated partial thromboplastin time measures are coagulation factors except ..... & .....
5. Normal Activated partial thromboplastin time is .....
6. Normal thrombin time is .....

24.5 COMMON BLEEDING PROBLEMS

24.5.1 Vascular Disorders

Many disorders of abnormal blood vessel structure are present as inherited or acquired conditions. Many of these disorders are present as syndromes and recognized because of typical signs. They present with easy bruising and purpura.

Von Willebrand's Disease

This is an inherited disorder of vascular dysfunction. The VWF is normally produced by the endothelial cells and secreted into plasma. The VWF has two functions (1) to mediate platelet adhesion to subendothelial collagen and (2) to carry FVIII and prevent it from being destroyed. VWD is an autosomal dominant disorder and occurs in both males and females.

Laboratory Diagnosis

1. Haemoglobin, PCV, RBC count are normal unless there is blood loss.
2. Platelet count is normal, morphology is normal.
3. Bleeding time is increased
4. Prothrombin time is normal, Thrombin time is normal
5. APTT is increased
6. FVIII activity is decreased
7. FXIII is normal

Treatment is infusion of FFP or cryoprecipitate both of which contain VWF.

24.5.2 Platelet Disorders

Thrombocytopenia is the most commonly encountered haemostatic problem. The availability of platelet concentrates for replacement therapy has made surgery possible for such patients.

Causes of Thrombocytopenia

A. Failure of Platelet Production in bone marrow.

Aplastic anaemia, Leukemia, Radiation, chemotherapy, Alcholism, Megaloblastic anaemia, marrow infiltration by tumour, lymphoma.

B. Increased destruction of platelets

(a) Immune causes – ITP (immune thrombocytopenic purpura), SLE, drug induced, post transfusion, malaria, viral infections, neonatal.

(b) DIC

(c) Hemolytic uremic syndrome, TTP

(d) Sepsis

C. Abnormal distribution of platelets – splenomegaly

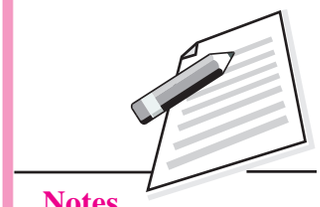
D. Dilutional – massive transfusion

Laboratory diagnosis

1. Complete blood counts shows thrombocytopenia
2. Platelet morphology may be abnormal depending on the cause for low platelets
3. Bleeding Time variably prolonged
4. Plasma clotting tests are normal unless there is factor consumption
5. Bone marrow examination to determine cause of thrombocytopenia

Disorders of Platelet Function are given in Table II

Coagulation Factor Deficiency: The deficiency of a single factor is usually due to an inherited deficiency. The commonest factor deficiency is Haemophilia A which is FVIII deficiency. Haemophilia B or deficiency of FIX is less common. Both haemophilias present with haematoma formation and haemarthrosis and are inherited as sex linked recessive disorders. Clinically severe form of the disorder has less than 1% factor activity and is associated with spontaneous bleeding by one year of age. Moderate deficiency has 2 – 5% factor activity and is associated with bleeding following trauma and haemarthrosis. Mild form of the disease has 5 – 15% factor activity and is asymptomatic unless the patient is subjected to trauma or surgery. The APTT will detect these patients whereas the CT will definitely miss them.



Laboratory Diagnosis

1. Haemoglobin, PCV, RBC normal or variably deranged.
2. MCV, MCH,MCHC,RDW normal
3. WBC count normal
4. Platelet count normal
5. Bleeding Time normal
6. PT normal
7. APTT prolonged
8. TT normal
9. FVIII/FIX assay.

Rare disorders of other coagulation factors are autosomal recessive and may involve any of the coagulation factors.

Acquired Disorders

(a) Liver disease – Most of the coagulation factors are made in the liver and hence chronic liver disease is associated with multifactor deficiency characterized by prolonged PT, APTT, low fI and increased D-dimers.

(b) Vitamin K deficiency.

Vitamin is a fat soluble vitamin which is needed for the normal formation of the Vitamin K dependent factor – FII,FVII, FIX and FX. Vitamin K needs bile for absorption. Deficiency is seen in

(a) Newborns: This is called haemorrhagic disease of the new born. It occurs because the liver of the newborn is immature and mother's milk lacks vitamin K. PT and APTT are markedly prolonged and TT is normal

(b) Obstructive jaundice

(c) Liver disease.

(d) Oral anticoagulants used to prevent thrombosis are vitamin antagonists

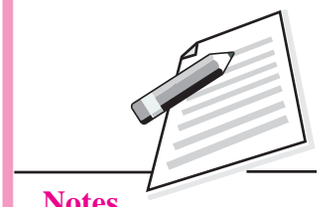
(c) Thrombotic Disorders

Thrombosis in blood vessels may be arterial (eg heart attack, stroke) or venous (eg Deep vein thrombosis). The conditions that are associated with thrombosis are usually acquired. They may rarely be inherited due to the decreased levels of naturally occurring inhibitors in blood. Thrombosis occurs as a result of abnormalities in blood vessels like atherosclerosis, stasis or pooling of blood, inflammation of blood vessels and abnormalities in blood flow due to viscosity, increased levels of fibrinogen, FVIII etc.

Notes

WHAT HAVE YOU LEARNT

- Haemostasis means arrest of bleeding
- Phases of Haemostasis are vascular phase, platelet phase, coagulation phase and fibrinolytic phase
- Blood vessel plays a major role in maintaining the blood in the liquid state
- The entire surface of the vessel is lined by Endothelial cells (EC)
- Endothelial cells secrete a major protein called Von Willebrand factor into plasma and sub-endothelium
- Platelets are formed from megakaryocytes in bone marrow and normal count is 150 – 450 X 10^{9}/L
- When endothelial cells is damaged platelets adhere to sub endothelial cells
- Platelet derived growth factor released from á granules promotes fibroblast proliferation and healing
- Blood coagulation takes place in a series of enzyme reactions each successive step being catalysed by active enzyme formed in previous step
- Coagulation phase has been divided into Intrinsic pathway, Extrinsic pathway and common pathway
- Extrinsic and common pathway is tested by Prothrombin Time (PT)
- Intrinsic and common pathway is tested by Activated Thromboplastin Time (APTT)
- Final conversion of FI to fibrin is tested by Thrombin time (TT)
- Hemophilia A or FVIII deficiency is a disorder of coagulation pathway due to single factor
- Abnormalities of haemostasis may result in Bleeding & Thrombosis
- Bleeding time measures platelet vessel wall interaction and is a poor predictor of abnormal surgical bleeding
- Prothrombin time (PT) is the time taken for citrated plasma to clot on the addition of tissue thromboplastin and calcium citrate
- Normal PT is 12-14 seconds and for patients on oral anticoagulants, PT is reported as INR or International Normalised Ratio and normal INR is 0.9 – 1.2
- Activated partial thromboplastin time (APTT) measures all coagulation factors except FVII and FXIII. Normal APTT is 30-35 seconds
- Thrombin time (TT) measures clottable fibrinogen and normal TT is 12 – 14 seconds



TERMINAL QUESTIONS

1. Draw and describe the coagulation pathway.
2. Short notes on:
   (a) Platelet function
   (b) Haemophilia
   (c) Prothrombin time

ANSWERS TO INTEXT QUESTIONS

24.1

1. Arrest of bleeding
2. Von Willebrand
3. Megakaryocytes
4. 150-450x10^9/l
5. Platelets
6. Calcium
7. Platelet derived growth
8. Scott

24.2

1. Prothrombin time
2. Activated thrombopastin time
3. Thrombin time
4. Bleeding and thrombosis

24.3

1. International Normalised Ratio
2. 0.9 – 1.2
3. 12-14 seconds
4. FVII & FXIII
5. 30 – 35 seconds
6. 12 – 14 seconds