INTRODUCTION

Hemostasis is the process of forming clots in the walls of damaged blood vessels and preventing blood loss while maintaining blood in a fluid state within the vascular system. A collection of complex interrelated systemic mechanisms operates to maintain a balance between coagulation and anticoagulation. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms: (Figure 1) (1) vascular constriction, (2) formation of a platelet plug, (3) formation of a blood clot as a result of blood coagulation, and

Figure 1

1. Severed vessel
2. Platelets agglutinate
3. Fibrin appears
4. Fibrin clot forms
5. Clot retraction occurs
Briefing the clinical distinction between disorders of vessels and platelets and disorders of blood coagulation in the table 1

<table>
<thead>
<tr>
<th>Finding</th>
<th>Disorders of coagulation</th>
<th>Disorders of platelets or vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petechiae</td>
<td>Rare</td>
<td>Characteristic</td>
</tr>
<tr>
<td>Deep dissecting hematomas</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Superficial ecchymoses</td>
<td>Common</td>
<td>Characteristic; usually small and multiple</td>
</tr>
<tr>
<td>Hemarthrosis</td>
<td>Characteristic</td>
<td>Rare</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding from superficial cuts and scratches</td>
<td>Minimal</td>
<td>Persistent</td>
</tr>
<tr>
<td>Sex of patient</td>
<td>80-90% of inherited forms occur only in male patients</td>
<td>Relatively more common in females</td>
</tr>
<tr>
<td>Positive family history</td>
<td>Common</td>
<td>Rare (except von Willebrand disease and hereditary hemorrhagic telangiectasia)</td>
</tr>
</tbody>
</table>

(4) eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

APPRAOCH TO BLEEDING DISORDERS

- Careful evaluation can provide valuable information as to whether the abnormality resides in the blood vessels, platelets or the process of blood coagulation.
- Meticulous history can establish whether the disease is inherited or acquired.
- Physical examination may provide additional clues (eg: characteristic skin lesions of hereditary hemorrhagic telangiectasia)

Disorders of hemostasis can be arbitrarily divided into two groups:
- Disorders of blood coagulation
- Disorders of vessels and platelets (also referred to as purpuric disorders)

POINTS FAVOURING INHERITED BLEEDING DISORDER

- Symptoms in infancy and childhood.
- Positive family history.
- Laboratory evidence of a single or isolated abnormality, most commonly deficiency of a single coagulation factor.

The emphasis of the study of the acquired bleeding disorders should be on the patient, not on the laboratory. A thorough history and the physical examination often reveal the cause of thrombocytopenia, such as a drug or acute leukemia.

In most vascular disorders, including senile purpura, allergic purpura, scurvy, and amyloidosis, the history and physical examination are of primary diagnostic importance, and the laboratory has little to offer.

POINTS FAVOURING ACQUIRED BLEEDING DISORDER

- Bleeding manifestations are less severe than inherited forms.
- Clinical picture is dominated by evidence of the underlying disorder rather than bleeding alone. (the neonate, for example, DIC usually is associated
with significant complications such as sepsis, hypoxia, acidosis, or problems related to prematurity).

- Multiple hemostatic defects commonly are present in patients with acquired hemorrhagic diseases, which often include thrombocytopenia and significant coagulation abnormalities. (in contrast functions individually.

Briefing the interpretation of common tests of hemostasis and blood coagulation in table 2

### PLATELET FUNCTION ASSAYS
Platelet aggregometry is the gold standard for platelet function testing.

<table>
<thead>
<tr>
<th>Test</th>
<th>Common causes of abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Thrombocytopenia, thrombocytosis</td>
</tr>
<tr>
<td>activated Partial Thromboplastin Time</td>
<td>Deficiencies or inhibitors of prekallikrein; high molecular weight kininogen; factors XII, XI, IX, VIII, X and V; prothrombin or fibrinogen</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Deficiencies or inhibitors of factors VII, X, and V; prothrombin or fibrinogen; dysfibrinogenemia; lupus inhibitors; heparin; warfarin</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Afibrinogenemia, dysfibrinogenemia, hypofibrinogenemia, and hyperfibrinogenemia; inhibitors of thrombin (heparin) or fibrin polymerization (fibrin degradation products, paraproteins)</td>
</tr>
<tr>
<td>Fibrinogen assay</td>
<td>Afibrinogenemia, dysfibrinogenemia, and hypofibrinogenemia; inhibitors of thrombin or fibrin polymerization</td>
</tr>
<tr>
<td>Factor VIII assay</td>
<td>Hemophilia A and von Willebrand disease; acquired antibodies to factor VIII</td>
</tr>
<tr>
<td>Fibrin degradation product assay</td>
<td>Disseminated intravascular coagulation; fibrinogenolysis; thrombolytic drugs, liver disease; dysfibrinogenemia</td>
</tr>
<tr>
<td>D-dimer assay</td>
<td>Disseminated intravascular coagulation; recent surgery; pregnancy</td>
</tr>
</tbody>
</table>

Table 2

to a single abnormality usually found in patients with inherited hemorrhagic disorders).

### Laboratory Methods for Study of Hemostasis and Blood Coagulation

- No single test is suitable for the laboratory evaluation of the overall process of hemostasis and blood coagulation.
- Methods of varying complexity and use are available for assessing various components and
- Blood is centrifuged at sufficiently low force to obtain platelet-rich plasma (PRP), which is stirred in a tube at 37°C between a light source and a measuring photocell.
- Upon addition of an agonist, (such as ADP, epinephrine, ristocetin), platelets aggregate; the resultant increased transmission of light (reduced turbidity of the PRP) is detected and recorded as a function of time after addition of the reagent.
- The recorded response depends upon the normal
functioning of the platelet, the presence of inhibitors of platelet function, as well as the concentration of agonist, facilitating detection of classical platelet disorders based upon the pattern of aggregation.

Briefing the profiles of hemostasis screening tests in patients with bleeding disorders in table 3

<table>
<thead>
<tr>
<th>Prothrombin time</th>
<th>activated Partial Thromboplastin time</th>
<th>Platelet count</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td>NORMAL</td>
<td><strong>Common</strong> Acquired factor VII deficiency (early liver disease; early vitamin K deficiency; early warfarin therapy)</td>
</tr>
<tr>
<td>NORMAL</td>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td><strong>Rare</strong> Factor VII inhibitor; dysfibrinogenemia; some cases of DIC; inherited factor VII deficiency; certain factor X variants; superwarfarin ingestion</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td><strong>Common</strong> Deficiency or inhibitor of factors VIII, IX, or XI; vWD; heparin</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td><strong>Rare</strong> Lupus inhibitor with qualitative platelet defect; certain factor X variants</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td><strong>Common</strong> Vitamin K deficiency; liver disease; warfarin; heparin super warfarin</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>NORMAL</td>
<td><strong>Rare</strong> Deficiency or inhibitor of factors X or V, prothrombin, or fibrinogen; lupus inhibitor with hypoprothrombinemia; DIC; dysfibrinogenemia; primary fibrinolysis</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
<td><strong>Common</strong> DIC; liver disease</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
<td><strong>Rare</strong> Heparin therapy with associated thrombocytopenia</td>
</tr>
<tr>
<td>NORMAL</td>
<td>NORMAL</td>
<td>![Down Arrow]</td>
<td><strong>Common</strong> Increased platelet destruction; decreased platelet production; hypersplenism; hemodilution</td>
</tr>
<tr>
<td>![Up Arrow]</td>
<td>![Up Arrow]</td>
<td>![Down Arrow]</td>
<td><strong>Rare</strong> Certain inherited platelet disorders (Wiskott-Aldrich syndrome, Bernard-Soulier syndrome)</td>
</tr>
</tbody>
</table>
Bleeding disorders in which the results of primary screening tests may be normal are:

- von Willebrand Disease (vWD)
- Mild inherited coagulation disorders, particularly factor XI deficiency
- Heterozygous carriers of inherited coagulation disorders
- Factor XIII (fibrin-stabilizing factor) deficiency
- Some forms of dysfibrinogenemia
- Disordered platelet function, particularly deficient release reaction; Scott syndrome
- Hereditary hemorrhagic telangiectasia
- Allergic and other vascular purpuras
- Alpha 2-plasmin inhibitor deficiency
- Elevated levels of plasminogen activator

**LAB DIAGNOSIS OF vWD**
- Immunoassay of vWF antigen
- Bioassay of factor VIII
- Measurement of ristocetin cofactor activity
- Ristocetin is an antibiotic that induces platelet agglutination in the presence of von Willebrand factor (vWF).
- Patients deficient in vWF (vWD) or in the receptor for vWF (Bernard-Soulier syndrome) have an abnormal ristocetin response.

**TESTS FOR FACTOR XIII ACTIVITY**
- Principle of the factor XIII screening test is that clots cross-linked by factor XIII resist denaturation by high concentrations of urea or acid.
- Deficiency of factor XIII results in premature clot lysis.
- Patient plasma is recalcified to induce a clot; the clot is then suspended in 5 mol/L urea (or 1% monochloracetic acid) for 24 hours. Clot stability is examined visually after 24 hours of incubation.

**REFERENCES**
- Wintrobe’s Clinical Hematology 12th edition
- Harrison’s Principles of Internal Medicine 19th edition
- Indian Journal of Hematology and Blood Transfusion