I. INTRODUCTION

Thrombotic and bleeding disorders can result from abnormalities of platelets and vascular endothelial function. Both acquired and congenital factors contribute to these disorders.

PATHOLOGY OF PLATELETS

Both quantitative and qualitative disorders of platelets result in bleeding and thrombotic disorders. These disorders may be acquired or congenital.

A. QUANTITATIVE DISORDERS

Several diseases result in a decrease or increase in the number of platelets. A decreased platelet count results in bleeding and is known as thrombocytopenia. An increased platelet count is known as thrombocytosis when it is benign and thrombocythemia when it is a clonal proliferation (neoplastic). Both bleeding and thrombosis may occur.

1. THROMBOCYTOPENIA (Decreased number of circulating platelets)

   a. Marrow hypoplasia, aplasia, replacement by neoplastic cells.
      Marrow fibrosis, radiation injury, leukemia, paroxysmal nocturnal hemoglobinuria (PNH)
   b. Hereditary thrombocytopenia
      May Hegglín anomaly (autosomal dominant), Wiskott-Aldrich syndrome, absent radius syndrome, Fanconi’s anemia
   c. Abnormal hematopoiesis (acquired)
      B12/folate deficiency, pre-leukemia
   d. Drug induced thrombocytopenia
      Heparin, gold, quinine, quinidine, sulfonamides, GP IIb/IIIa inhibitors
   e. Dilutional
      hemodialysis, heart lung machine
   f. ITP and TTP

     ITP: Immune thrombocytopenic purpura (IgG mediated)
TTP: Thrombotic thrombocytopenic purpura (abnormal vWF multimers), arterial thrombi (platelet-rich)

g. HUS: Hemolytic Uremic Syndrome

2. **THROMBOCYTOSIS** (Increased number of circulating platelets)

a. Splenectomy
   platelets normal in function.

b. Thrombocytosis – reactive
due to cancer, infection, drugs.

c. Autonomous thrombocytosis (thrombocytemia)
clonal disorder
Platelets $\uparrow$ (>1,000,000/µl): clusters of platelets in circulation. May occlude small vessels. Bleeding may occur.

B. **QUALITATIVE DISORDERS**

Platelet numbers are usually normal, however, platelet function is impaired.

1. **Disease induced platelet defects**
   Liver disorders, paraproteinemia

2. **Drug induced platelet defects**
   Aspirin, NSAID (non-steroidal anti-inflammatory drugs)

3. **Diet induced platelet defects**
   Omega 3 fatty acids (ocean fish)

C. **INHERITED DISORDERS OF PLATELETS**

Congenital disorders resulting mostly in bleeding diathesis.

1. **Glanzmann's thrombasthenia**
   Autosomal recessive, GPIIb/IIIa defect, aggregation defect, bleeding time $\uparrow$

2. **Bernard-Soulier disease**
   Autosomal recessive, GP Ib defect, adhesion defect, bleeding time $\uparrow$

3. **Storage pool disease**
   decreases dense granule content, no aggregation

4. **Other disorders**
   Purpura of unknown origin – gray platelet syndrome. Lack
of alpha granules.

D. OTHER ACQUIRED DISORDERS OF PLATELETS

1. Metabolic disorders – uremia (bleeding)

II. VASCULAR DISORDERS

These disorders are usually called non-thrombocytopenic purpuras. Although common, these disorders do not result in severe bleeding diathesis.

Platelet function and coagulation are normal. Easy bruising, bleeding from mucosa, purpura, vasculitis.

A. SUBENDOTHELIAL DISORDERS

1. **Congenital** - Ehler Danlos Syndrome - Hypermobile joints
   Hyper flexible skin, osteogenesis imperfecta, drugs, infections, amyloidosis

2. **Acquired** - Purpura simplex, amyloids, drugs, steroid purpura (prednisone), Cushing’s syndrome (steroid excess), Henoch-Schonlin purpura (usually drug induced).

B. ENDOTHELIAL DISORDERS

1. **Congenital** - Most common, hereditary hemorrhagic, telangiectasia (HHT), arteriovenous malformation; giant hemangioma (Kasaback-Merritt syndrome)

2. **Acquired** - Inflammation, vasculitis (drugs, viruses, Rickettsia)

C. MECHANICAL DISORDERS

1. Orthostatic purpura
2. Mechanical purpura
3. Increased transluminal pressure

D. NUTRITIONAL DISORDERS
1. Scurvy (vitamin C deficiency)

III. BLEEDING DISORDERS DUE TO COAGULATION FACTOR ABNORMALITIES

A. INTRODUCTION

1. Specific defects in clotting factors, -VIII (Hemophilia A), IX (Hemophilia B).

B. LABORATORY DIAGNOSIS

1. PT (extrinsic) II, V, VII, X and fibrinogen
2. APTT (intrinsic) VIII, IX, XI and XII (actually measures all factors but FVII, FXIII, protein C and S).

C. THE HEMOPHILIAS (HEMOPHILIA A & B)

1. Defects due to coagulation factors. Most result in bleeding.
2. Hemophilia A (Classical) VIII coagulant deficiency
   Hemophilia B (Christmas Disease) IX deficiency
   Both are transmitted as sex linked recessive; APTT is elevated, no effect on platelets.

D. VON WILLEBRAND'S DISEASE

Hemostatic defect due to von Willebrand factor (ristocetin co-factor, factor VIII antigen) defect. vWillebrand factor binds to platelet receptors (glycoprotein Ib, IIb, IIIa) and to collagen and subendothelium.

1. Type-1 and Type-3 von Willebrand’s diseases are characterized by a decrease in the circulating level of the factor.
2. Type-2 von Willebrand’s disease is characterized by a qualitative defect in the protein

E. HEMOPHILIAS VS. VON WILLEBRAND'S DISEASE

<table>
<thead>
<tr>
<th>HEMOPHILIAS</th>
<th>VON WILLEBRAND'S DISEASE</th>
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<tbody>
<tr>
<td>1. APTT elevated</td>
<td>1. APTT slightly elevated due to mild reduction in factor VIII:c.</td>
</tr>
<tr>
<td>2. Platelet function-normal</td>
<td>2. Hemostatic function impaired due</td>
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to impaired adhesion of platelets to collagen in-vivo.


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**Fig. 11-29: Robbins**

**IV. BLEEDING DISORDERS DUE TO ABNORMALITIES OF THE FIBRINOLYTIC SYSTEM**

**A. INTRODUCTION**

Excessive activation of the fibrinolytic system can cause bleeding.

Reduction in fibrinogen concentration and an increase in fibrinogen degradation products contribute to bleeding.

**B. PRIMARY FIBRINOLYSIS**

In primary fibrinolysis, fibrinogen is converted into fibrinogen degradation products.

This condition is seen in dead fetus syndrome (Abruptio Placenta).

\[
\text{plasmin} \quad \text{Fibrinogen} \rightarrow \text{Fibrinogen degradation products}
\]

Excessive fibrinolysis can result in bleeding due to decreased fibrinogen levels.
Fibrinogen degradation products can also produce anticoagulant effects.

Overdosage of thrombolytic agents can result in a primary fibrinolytic state and cause bleeding.

C. SECONDARY FIBRINOLYSIS (Disseminated intravascular coagulation)

In secondary fibrinolysis both fibrin and fibrinogen are digested by plasmin. This results in simultaneous digestion of clotting factors and consumption of platelets.

\[
\begin{align*}
\text{Thrombin} & \\
\text{Fibrinogen} & \longrightarrow \text{Fibrin} & \longrightarrow \text{Fibrin DP} \\
\downarrow & \downarrow & \downarrow \\
\downarrow & \downarrow & \downarrow \\
\text{Plasmin} & \leftarrow \text{Plasmin} & \\
\end{align*}
\]

Pathogenesis of Disseminated Intravascular Coagulation
D. DEFICIENCY OF $\alpha_2$-ANTIPLASMIN

Results in increased fibrinolysis (Bleeding). Excessive plasmin digests circulating fibrinogen.

V. DRUG INDUCED BLEEDING DISORDERS

A. Bleeding with thrombolytic drugs.

B. Bleeding with anticoagulants (Heparin)

C. Bleeding with drugs
   a. Antiplatelet drugs
   b. Thrombolytic drugs

D. Drug induced thrombocytopenia

E. Heparin Induced Thrombocytopenia (HIT)

VI. HIV ASSOCIATED BLEEDING DISORDERS

VII. DIAGNOSIS OF BLEEDING DISORDERS

A. Bleeding Time

B. Platelet Count
C. Platelet Function Studies
   a. Adhesion
   b. Aggregation
   c. Activation