Objectives

• Objectives on page 257
  – Hemostasis Theory #16
  – Laboratory Evaluation of Hemostasis #18c-e, 20b-f, 22c
  – Disorders of Hemostasis #5, 6, 8, 9, 11, 12, 14, 15

• NOTE…you are responsible for information as designated in lecture and/or covered on discussion questions, cases or worksheet with an emphasis on vWD, Hemophilia A & B, DIC
Coagulation & Fibrinolysis Tests

• Tests for secondary hemostasis
  – PT and APTT tests
  – *Thrombin time* and Fibrinogen level
  – Mixing study and Factor assays
  – 5M Urea test

• Tests for fibrinolysis
  – FDP and Dimer tests
  – *Thrombin time*
INJURY
COLLAGEN CONTACT

PLATELET ADHESION
PLATELET RELEASE & AGGREGATION

TEMPORARY PLATELET PLUG (1°)

PTT Test

INTRINSIC
PK XII XI IX VIII

EXTRINSIC

COMMON
X V

PROTHROMBIN
THROMBIN
FIBRIN GEN
SOLUBLE FIBRIN
STABLE FIBRIN CLOT (2°)

THROMBIN time & Fibrinogen Level

PTT Test

TT Test

Fibrinogen Level

PT Reagents:
- PLT phospholipid substitute with surface activator
- Calcium

PT Reagent:
- Tissue thromboplastin with calcium

Thrombin
Thrombin Time and Fibrinogen Level

• Thrombin time (qualitative test), TT
  – Measures the time required for the reagent thrombin to convert fibrinogen to fibrin, in seconds
    • Only factor I (fibrinogen) is measured
  – Prolonged by a low fibrinogen level (<100 mg/dl) and the presence of heparin or increased levels of FDPs

• Fibrinogen level (quantitative test)
  – Adaptation of the thrombin time; plasma diluted 1:10
  – Thrombin clotting time (seconds) is converted to fibrinogen concentration in mg/dl
    • Standard curve uses calibration standards of known fibrinogen concentration
    • Normal fibrinogen level 150-450 mg/dl
Fibrinogen Standard Curve

The fibrinogen standard curve is set up using dilutions of the calibration standard plasma with a known fibrinogen concentration.

The thrombin time in seconds obtained for each dilution vs the fibrinogen concentration in mg/dL is plotted.
Mixing Study

- Mixing Study
  - Performed to differentiate a factor deficiency from a circulating inhibitor
    - Done when in vitro PT or APTT results are abnormal and patient is on no anticoagulant therapy
    - Mixing study (1:1 mix) = PT or APTT repeated using part patient plasma and part normal plasma (contains all factors)

- Significance
  - Correction = factor deficiency
  - No correction = inhibitor
    - Causes are heparin (#1), Lupus inhibitor (#2), factor VIII inhibitor (#3) or factor IX (#4) inhibitor
Factor Assay and 5M Urea Test

• Specific Factor assays
  – Measures ability of patient plasma to correct PT or APTT results obtained with plasma known to be factor deficient
    • Done to verify a suspected factor deficiency or to monitor
  – Normal reference range is 50-150% factor activity

• Urea Solubility/5M Urea Test
  – Done to detect Factor XIII deficiency, only test available
    • Screening tests are normal, do NOT measure stable clot
  – Normal, takes >24 hours for clot to dissolve in 5M urea
  – If clot dissolves in a few hours, a factor XIII deficiency is indicated
Patient Examples:

Normal PT & PTT and factor activity levels; no bleeding

<table>
<thead>
<tr>
<th>AGE: 3M</th>
<th>SEX: F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT &amp; PTT</strong></td>
<td></td>
</tr>
<tr>
<td>INTER NORMAL RATIO</td>
<td>1.0</td>
</tr>
<tr>
<td>PTT</td>
<td>29.2</td>
</tr>
<tr>
<td>FACTOR V (5) ASSAY</td>
<td>89</td>
</tr>
<tr>
<td>FACTOR VII (7) ASSAY</td>
<td>100</td>
</tr>
</tbody>
</table>

Child with severe liver disease; bleeding expected

<table>
<thead>
<tr>
<th>AGE: 6M</th>
<th>SEX: M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT &amp; PTT</strong></td>
<td></td>
</tr>
<tr>
<td>PROTIME</td>
<td>94.4*</td>
</tr>
<tr>
<td>INTER NORMAL RATIO</td>
<td>&gt;14.0</td>
</tr>
<tr>
<td>PTT</td>
<td>72.9*</td>
</tr>
<tr>
<td>Results called @ 1615</td>
<td></td>
</tr>
<tr>
<td>FACTOR V (5) ASSAY</td>
<td>16*</td>
</tr>
<tr>
<td>FACTOR VII (7) ASSAY</td>
<td>1*</td>
</tr>
</tbody>
</table>
## Differential Diagnosis using Tests for Secondary Hemostasis

<table>
<thead>
<tr>
<th>Defect</th>
<th>PT</th>
<th>PTT</th>
<th>PT 1:1 Mix</th>
<th>PTT 1:1 Mix</th>
<th>Thrombin Time</th>
<th>Fibrinogen Level</th>
<th>5M Urea test</th>
</tr>
</thead>
<tbody>
<tr>
<td>XII</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XI</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMWK</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td>Abn^^</td>
<td>Abn^^</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIII</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abn^^</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Var</td>
<td>Abn</td>
<td>NC</td>
<td>NC</td>
<td>Abn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII inhibitor</td>
<td></td>
<td>Abn</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX inhibitor</td>
<td></td>
<td>Abn</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus inhibitor</td>
<td>Var</td>
<td>Abn</td>
<td>Var</td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumadin</td>
<td></td>
<td>Abn</td>
<td></td>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abn** Abnormal  
--- Test not indicated or factor not measured by test  
C Mixing study with normal plasma corrects  
NC Mixing study with normal plasma does not correct  
Var Results are variable  
\^\^ ONLY factor measured by test
FDP and Dimer Tests

• FDP detection and D-dimer tests (quantitative)
  – Immunoassays that use antibody coated latex particles to detect elevated plasma levels of degradation products
  – Normal is negative….normally, FDPs are undetectable
• FDP test, detects fibrin OR fibrinogen DPs
• D-dimer test, detects ONLY cross-linked fibrin DPs that contain D\text{XD}
Classification of Hemostatic Disorders

III. Coagulation & Fibrinolytic Disorders
   A. Hereditary defects
      1. vonWillebrand's disease (vWD)
      2. Factor VIII deficiency (Hemophilia A)
      3. Factor IX deficiency (Hemophilia B)
      4. Prekallikrein deficiency
      5. High Molecular Weight Kininogen deficiency
      6. Factor XII deficiency
      7. Factor XI deficiency (Hemophilia C)
      8. Factor X deficiency
      9. Factor V deficiency
     10. Factor II deficiency
     11. Factor I deficiency/defects
     12. Factor XIII deficiency
     13. Factor VII deficiency
   
   B. Acquired defects
      1. Disseminated Intravascular Coagulation (DIC)
      [2. Primary fibrinolysis]
      3. Vitamin K deficiency including hemorrhagic disease of the newborn
      4. Severe hepatic disease
      5. Acquired pathologic inhibitors – Lupus inhibitor, antibodies to factors VIII or IX
      6. Thromboembolic disorders - hereditary and acquired causes
      7. Anticoagulant therapy – heparin, coumarin
      8. Thrombolytic therapy - TPA
Disorders of Hemostasis
Coagulation & Fibrinolysis

• The clinical manifestation of hemostatic disorders can be hemorrhage and/or thrombosis
  – Patient evaluation should include age of onset, family history, prior bleeding or clotting episodes, medications

• Bleeding sites
  – Mucosal bleeding/petechiae only…vessel/platelet defect
    • Spontaneous bleeds may occur if PLT count is <20,000/ul
  – Deep bleeding/hematomas…factor defect
    • Spontaneous bleeding (severe factor deficiency) or post-injury bleeding (mild factor deficiency)
  – Multiple site bleeding…severe combined defects (DIC)
Bleeding Sites

- Superficial Bleeding Platelet/Vessel Defect
- Joint Bleeding - Hemophilia A
- Muscular Hematoma Factor Defect
- Diffuse Hemorrhage - DIC
Balance of the Coagulation & Fibrinolytic Systems

TF, tPA, Thrombin, Plasmin and FDPs are NOT normally present in the circulation

- Procoagulant forces = Regulatory/anticoagulant forces
Hemostatic Imbalance

- Imbalance may result in mild, moderate or life-threatening bleeding or clotting, depending on the component affected
  - Hemorrhage $\rightarrow$ deficient clotting or excessive clot lysis
  - Thrombosis $\rightarrow$ excessive clot formation or inadequate clot lysis
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

• Hereditary disorders occur as single clotting factor deficiencies
  – May be caused by:
    • Decreased synthesis of a factor (quantitative)
    • Synthesis of a factor with abnormal function (qualitative)

• Hereditary disorders are most often characterized by deep tissue hemorrhage or delayed bleeding
  – Bleeding symptoms are proportional to degree of factor deficiency, i.e., % activity
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

• vonWillebrand’s disease (vWD)
  – #1 hereditary bleeding disorder, males and females
    • Many types of vWD, mild to severe
  – Defect of the vWF portion of VIII/vWF complex
    • Decreased vWF:RCo
    • Decreased vWF:Ag
    • Decreased VIII:C
  – Clinical features
    • Mucocutaneous bleeding, nosebleeds, petechiae
  – BT/PFA  PT  APTT  1:1 mix
    • Abnormal platelet aggregation with ristocetin only
  – Treatment
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

• Hemophilia A (Classical hemophilia)
  – #2 hereditary bleeding disorder, males only
  – Defect of the Factor VIII portion of VIII/vWF complex
    • Decreased VIII:C
    • Normal vWF portion – platelets are normal in function
  – Types
    • Severe <1% factor VIII activity, moderate, mild, asymptomatic
  – Clinical features
    • Severe, often spontaneous bleeds, recurrent joint bleeding, intramuscular hematomas, abdominal or CNS bleeds common
  – BT/PFA  PT  APTT  1:1 mix
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

– Treatment, lifelong recombinant FVIII concentrates

– Complications
  • Inhibitors to factor VIII, AIDS, surgery to repair joints

• Hemophilia B (Christmas disease)
  – Deficiency of factor IX, males only
  – Clinical features
    • Spontaneous bleeding with mild trauma
  – BT/PFA  PT  APTT  1:1 mix
  – Treatment
  – Complications
    • Inhibitors to factor IX
## Comparision of vWD & Hemophilias

<table>
<thead>
<tr>
<th>Comparison of:</th>
<th>vonWillebrand’s disease</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bleeding sites</strong></td>
<td>Mucosal/Superficial</td>
<td>Deep</td>
<td>Deep</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Autosomal dominant, males &amp; females</td>
<td>Sex-linked, males only</td>
<td>Sex-linked, males only</td>
</tr>
<tr>
<td><strong>Defect</strong></td>
<td>vWF (vWF:RCo/VII:C)</td>
<td>VIII (VIII:C)</td>
<td>IX</td>
</tr>
<tr>
<td><strong>Bleeding time test</strong></td>
<td>Abn/prolonged</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Platelet function</strong></td>
<td>Abn platelet adhesion</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>PLT aggregation: ADP, Collagen</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>PLT aggregation: Ristocetin</strong></td>
<td>Abn, with ristocetin ONLY</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Protime (PT)</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>APTT</strong></td>
<td>Normal or Abn/Incr (VIII:C varies)</td>
<td>Abn/Incr</td>
<td>Abn/Incr</td>
</tr>
<tr>
<td><strong>VIII assay</strong></td>
<td>Decr or Normal</td>
<td>Decr</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>IX assay</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Decr</td>
</tr>
<tr>
<td><strong>vWF:Ag assay</strong></td>
<td>Decr</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

- Prekallikrein (Fletcher factor) and High Molecular Weight Kininogen (Fitzgerald factor) deficiencies
  - Clinical features
    - NO bleeding, may have problems with thrombosis

- Factor XII (Hageman) factor deficiency
  - Deficiency of factor XII
  - Clinical features
    - NO bleeding, thromboembolic disease (deficient fibrinolysis)
  - BT Nor  PT Nor  APTT Abn
  - Treatment
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

- Hemophilia C
  - Deficiency of factor XI
  - Only contact factor associated with bleeding problems

- Factor X (Stuart-Prower) deficiency
  - Deficiency or abnormal function of factor X

- Factor V (Labile factor) deficiency
  - Deficiency of factor V

- Hereditary Prothrombin deficiencies
  - Factor II deficiency or types that yield abnormal amounts of thrombin
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

- Factor I (Fibrinogen) deficiency and defects
  - Group with decreased synthesis or synthesis of an abnormal fibrinogen molecule
  - Hereditary Afibrinogenemia
    - Marked decreased in fibrinogen production
  - Clinical features
    - Severe bleeding from birth, defective wound healing
  - BT  PT  APTT
    - Critical low fibrinogen level, prolonged TT, decreased ESR
- Dsyfibrinogenemia
  - Abnormal functioning fibrinogen molecule
Coagulation & Fibrinolytic Disorders
Hereditary Disorders

• Factor XIII (Fibrin stabilizing factor) deficiency
  – Deficiency of factor XIII
  – Clinical features
    • Bleeding from umbilical cord, poor healing, severe delayed post-op bleeding, spontaneous abortions, cerebral bleeds
    – BT PT APTT
      • Abnormal 5M urea solubility test ONLY

• Factor VII (Stable factor) deficiency
  – Deficiency or abnormal function of factor VII
### Hemostatic Disorders

#### Hemostatic Disorders Characterized by Deficiencies or Dysfunction

<table>
<thead>
<tr>
<th>Factor or Protein Affected</th>
<th>Hereditary Disorders</th>
<th>Comments or Mechanism</th>
<th>Acquired Disorders</th>
<th>Comments or Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A fibrinogenemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Factor V deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>Factor VII deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td>Hemophilia A*</td>
<td>Sex-linked</td>
<td>DIC with 2™ fibrinolysis</td>
<td>Initially thrombotic</td>
</tr>
<tr>
<td></td>
<td>vonWillebrand disease*</td>
<td>Autosomal dominant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>Hemophilia B</td>
<td>Sex-linked</td>
<td></td>
<td>Warfarin therapy</td>
</tr>
<tr>
<td>X</td>
<td>Factor X deficiency</td>
<td></td>
<td></td>
<td>Warfarin therapy</td>
</tr>
<tr>
<td>XI</td>
<td>Hemophilia C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIII</td>
<td>Factor XIII deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Manifestation: Hemorrhage**

**Clinical Manifestation: Thrombosis**

DIC - Disseminated or diffuse intravascular coagulation

APCR - Activated Protein C resistance

* - #1 hereditary bleeding disorder & #1 hereditary clotting disorder

** - #2 hereditary bleeding disorder & #2 hereditary clotting disorder
Coagulation & Fibrinolytic Disorders
Acquired Disorders

• Usually more than one factor or hemostatic component is defective in the acquired disorders
  – May be caused by:
    • Decreased synthesis of factors or regulatory proteins
    • Production of structurally abnormal proteins
    • Increased use or increased destruction of factors
    • Acquired pathologic inhibitors that interfere with the function of normal factors

• Acquired disorders are characterized by a state of imbalance which may result in hemorrhage or thrombosis or both
Disseminated intravascular coagulation (DIC), a thrombotic-lytic-hemorrhagic disorder

- Secondary complication of conditions that trigger widespread clotting in microvessels
  - Sepsis, OB complications, AProL, tissue trauma, etc.

- Out of control clotting and lysis leads to bleeding
  - Platelets & coagulation factors are consumed in clots
  - Clotting activates fibrinolysis to remove fibrin clots → high levels of FDPs inhibit normal clotting

- Removal of activated factors/activators is overwhelmed
  - Antithrombin and antiplasmin are depleted
  - Uncontrolled thrombin and plasmin circulate
Coagulation & Fibrinolytic Disorders
Acquired Disorders

**Triggering Event**
- OB Trauma
- Sepsis
- AProL

**Disseminated Intravascular Coagulation**
DIC, a Thrombo-Hemorrhagic Disorder

**Activation**
- Platelets
- Coagulation
- ↑ Thrombin

**Widespread Clotting in microvessels**

**Fibrinolysis**
- ↑ Plasmin

**Platelets & clotting factors I, V, VIII, XIII consumed in clots**

**Widespread Lysis of fibrin clots & factors I, V, VIII**

**Platelets & clotting factors inhibited by high FDPs**

**AT & AP inhibitors used up**

**Bleeding**

**Laboratory Diagnosis:**
- Low platelet count & prolonged BT
- Schistocytes on smear (RBCs are fragmented by fibrin in vessels)
- Prolonged PT & PTT
- Low fibrinogen level & prolonged TT
- Abnormal Dimer test & FDP test
- Low AT level

Tests in [ ] are seldom performed
Coagulation & Fibrinolytic Disorders
Acquired Disorders

– Symptoms that suggest acute DIC
  • Diffuse bleeding from multiple sites, GI bleeds, petechiae, venipuncture site oozing, organ damage/failure due to vessel occlusion by fibrin clots…death

– Most DIC screens are done on bleeding OB patients or patients with sepsis or malignancy

– Treatment

Regarding 2° fibrinolysis associated with DIC…the increased fibrinolytic activity caused by DIC is a normal response to disseminated activation of clotting
**Patient Example:**

Patient died in DIC following traumatic delivery of stillborn

<table>
<thead>
<tr>
<th>AGE: 35Y</th>
<th>SEX: F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMOGLOBIN</strong></td>
<td>5.1*</td>
</tr>
<tr>
<td><strong>DIC SCREEN</strong></td>
<td></td>
</tr>
<tr>
<td>PROTIME</td>
<td>&gt;100.0*</td>
</tr>
<tr>
<td>PTT</td>
<td>&gt;200.0*</td>
</tr>
<tr>
<td>FIBRINOGEN</td>
<td>&lt;15*</td>
</tr>
<tr>
<td>D-DIMER</td>
<td>&gt;1000*</td>
</tr>
<tr>
<td>PLATELET COUNT</td>
<td>15*</td>
</tr>
<tr>
<td>SCHISTOCYTE SCAN</td>
<td>Several</td>
</tr>
<tr>
<td>ANTITHROMBIN III</td>
<td>28*</td>
</tr>
</tbody>
</table>

**Blood smear with presence of schistocytes and lack of platelets**
Coagulation & Fibrinolytic Disorders
Acquired Disorders

• Vitamin K deficiency
  – Causes synthesis of inactive factors II, VII, IX, X by liver
    • Antibiotics, liver disease, oral anticoagulants…Warfarin

• Severe hepatic disease
  – Decreased synthesis of coagulation, fibrinolytic & regulatory proteins and impaired liver clearance
    • Prolonged PT is first sign of worsening disease, ↓ FVII

• Pathologic inhibitors
  – Inhibit the clotting of normal blood, often antibodies
    • Mixing study shows no correction
    • **Heparin**, Lupus inhibitor, VIII inhibitor, IX inhibitor
Thrombotic Disorders

• Thromboembolic/Thrombotic disease
  – Inappropriate clotting response that is **NOT** a response to injury
    • Life-threatening if blood to a vital organ is cut off
    • No good screens to identify persons at risk
    • Suspect when person has a thrombotic event that reoccurs

– Hypercoagulable state due to an imbalance between procoagulant (clot promoting) and regulatory (clot inhibiting forces) that is caused by:
  • Structurally abnormal proteins
  • Low levels of an inhibitor to clotting
  • Reduced activation of fibrinolysis
**Thrombotic Disorders**

- Thrombi occur in areas of ↓ blood flow or are result of trauma to vessel interior
  - Thrombosis - formation of intravascular clot that blocks a vessel → DVT causes tissue necrosis
    - Redness, pain/swelling in leg, thigh
  - Embolism - Portions of thrombus break off and travel → PE occludes vessels in lungs
    - Shortness of breath, hyperventilation
  - Dimer test is used to exclude PE or DVT
Thrombotic Disorders

• Hereditary states associated with thrombosis
  – FV Leiden & FII 20210 are genetic mutations of factors V and II → the two most common hereditary causes
  – Antithrombin (AT) deficiency, lack of this coagulation inhibitor promotes clotting
  – Deficiency of FXII causes deficient fibrinolysis activation

• Acquired conditions
  – Low AT levels in DIC, pregnancy, liver disease

• Risk factors associated with thrombosis
  – Immobilized/post-surgical patients
  – Coronary artery or pulmonary disease
Treatment of Thrombotic Disorders

• Clot lysing drugs
  – Used to dissolve formed clots in patients with acute MI, DVT, pulmonary clots or stroke victims
    • Recombinant TPA, urokinase or streptokinase are thrombolytic agents that convert plasminogen to plasmin
    • Serious bleeding is a risk

• Therapeutic anticoagulants (heparin or coumadin)
  – Used to prevent the initiation and extension of clots
    • Cause defects in ability to form clots; do not lyse clots

• Anti-platelet agents
  – Aspirin or Plavix® are most often used to impair platelet aggregation in patients with cardiac disease
    • Cause prolonged BT but do not prolong the PT or PTT
CASE 1
A 20 year old woman, scheduled for wisdom teeth removal, has a history of epistaxis (nosebleeds) in childhood and severe bleeding following a tonsillectomy. Her pre-op coagulation tests show:

- Platelet count: 400,000/cmm
- Bleeding time: >15 mins (≤8.0)
- PT: normal
- APTT: abnormal but only slightly prolonged.
- Factor VIII assay: 26%
- Plt aggregation: Excellent aggregation was obtained with epinephrine and ADP, but NO aggregation was seen with ristocetin.

Most probable diagnosis:

Inheritance pattern:

Is this a defect of primary and/or secondary hemostasis?
CASE 2
A 4 year old boy was first noticed to bleed easily at the age of 2 years. At one time, he bled into subcutaneous tissues with hematoma formation. Family history revealed a maternal uncle had a bleeding tendency. On physical exam, there was a large bruise over his left elbow but no petechiae. Lab data:

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>200,000/cmm</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>normal</td>
</tr>
<tr>
<td>PT</td>
<td>normal</td>
</tr>
<tr>
<td>APTT</td>
<td>abnormal/prolonged</td>
</tr>
<tr>
<td>Mixing study</td>
<td>PTT performed with patient plasma + normal fresh plasma corrected to normal</td>
</tr>
<tr>
<td>Platelet aggregation</td>
<td>Normal aggregation with all agents</td>
</tr>
</tbody>
</table>

Most probable diagnosis:

Inheritance pattern:

Is this a defect of primary and/or secondary hemostasis?

Are the bleeding symptoms characteristic?
CASE 3
A patient was admitted in labor to the obstetrical floor at 1 a.m. Her bleeding history was negative. At the time of admission, she was having irregular contractions. In the delivery room, bleeding became extensive. A stat CBC, type and cross-match and a coagulation work-up was ordered. The lab data showed:

- HGB of 10.0 g/dl
- HCT of 29.0 %
- Platelet count 75,000/cmm with a few schistocytes noted on the smear.
- [Bleeding time 11 mins (<8.0) – for illustrative purposes only]
- PT 19.0 sec (11.0-13.4)
- APTT 65.0 sec (22.0-37.0)
- Fibrinogen level 90 mg/dl (150-450)
- D-dimer test Abnormal/positive
- FDP test Abnormal/positive
- AT level Decreased
- [Thrombin time Prolonged – for illustrative purposes only]

Most probable diagnosis:
CASE 4
A 50 year old male is admitted with frequent episodes of epistaxis and bleeding from the gums. The family history is negative. His own history reveals both a recent and past abuse of alcohol.

PE reveals an enlarged liver and spleen, and slight icterus. Lab data includes an elevated AST, LD, alkaline phosphatase, and bilirubin. Coagulation data:

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>12 mins (≤8.0)</td>
</tr>
<tr>
<td>Platelet count</td>
<td>58,000/cmm</td>
</tr>
<tr>
<td>PT</td>
<td>30.0 sec (11.0-13.4)</td>
</tr>
<tr>
<td>APTT</td>
<td>48.6 sec (22.0-37.0)</td>
</tr>
</tbody>
</table>

Does this patient have a defect of primary and/or secondary hemostasis?

Is this a hereditary or acquired defect?

Most probable diagnosis:
CASE 5
A 25 year old female is admitted to the hospital with a painful swelling of her left leg. She is a CLS student who sat in lecture for 6 hours and then was studying in the library for a Hematology exam for the last 8 hours. She was previously well. Her initial blood count and all coagulation screening tests were within normal limits.

What do you suspect?