# BLEEDING DISORDERS—LECTURE 2

## Disorders of Primary Hemostasis

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**OUTLINE:**

- Primary hemostasis
  - Vascular abnormalities
    - HHT
    - Ehlers-Danlos
    - Vasculitis
  - Platelet defects
    - Quantitative defects (Inherited and Acquired)
    - Qualitative defects (Inherited and Acquired)
    - Combined defects (Inherited and Acquired)
  - Von Willebrand Disease

**OBJECTIVES:**

- Be aware of the various vascular abnormalities that my present with abnormal bleeding
- Be able to recognize the various inherited and acquired platelet disorders, both inherited and acquired
- Understand the pathophysiology of von Willebrand Disease (vWD)
- Be able to recognize the signs and symptoms of vWD and use appropriate diagnostic procedures to diagnose this disorder

**REFERENCE:**

- The current pathology test has very little information on Bleeding Disorders, therefore extensive NOTES have been provided to supplement information on this topic

# Bleeding Disorders

*LECTURE 2*

# Primary Hemostasis

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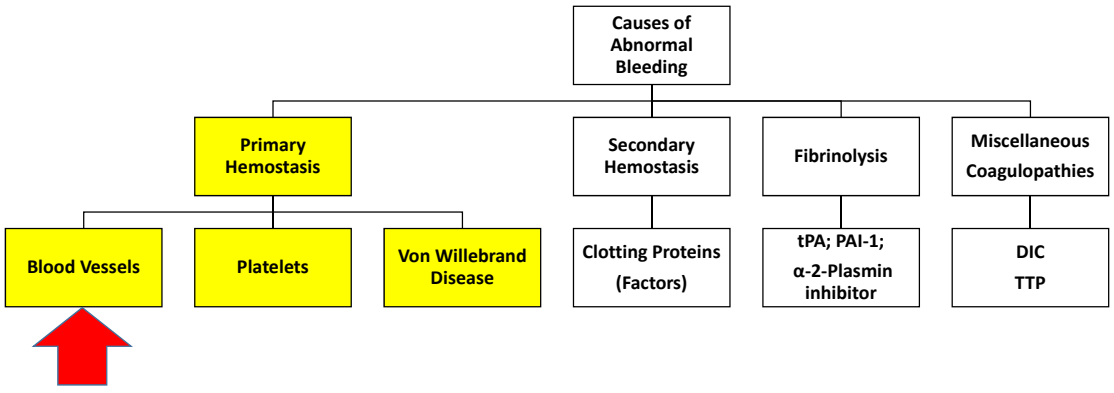
## Bleeding Disorders



# Bleeding Disorders
## Vascular Disorders

- There are several hereditary and acquired disorders that are associated with abnormal bleeding
- The bleeding manifestations of these disorders are generally suggestive of defects in primary hemostasis:
  - Petechiae
  - Bruising
  - Mucocutaneous bleeding
  - *BUT*: normal platelet counts and normal platelet function studies
- The bleeding is accompanied by various other symptoms associated with the specific disease/syndrome
- **The most important point is that there are vascular abnormalities that can present as defects in primary hemostasis.**

| | |
|---|---|
| **Hereditary** | Ehlers-Danlos syndrome |
| | Hereditary hemorrhagic telangiectasia |
| | Marfan syndrome |
| | Pseudoxanthoma elasticum |
| | Amyloidosis |
| **Acquired** | Scurvy |
| | Amyloidosis |
| | Cushing's syndrome |
| | Arteriovenous malformations |
| | Infections (Septic Vasculitis) |
| | Aseptic vasculitis (Henoch-Scholein) |

# Bleeding Disorders
## Vascular Disorders

- **Ehlers Danlos syndrome** is an inherited (autosomal either dominant or recessive) condition caused by abnormal collagen in the blood vessels and subcutaneous tissue
- While there are various manifestations, and levels of severity, of this syndrome, the primary manifestation of this syndrome include:
  - "stretchy" skin
  - Overly flexible joints
  - "translucent" skin
  - Easy bruising

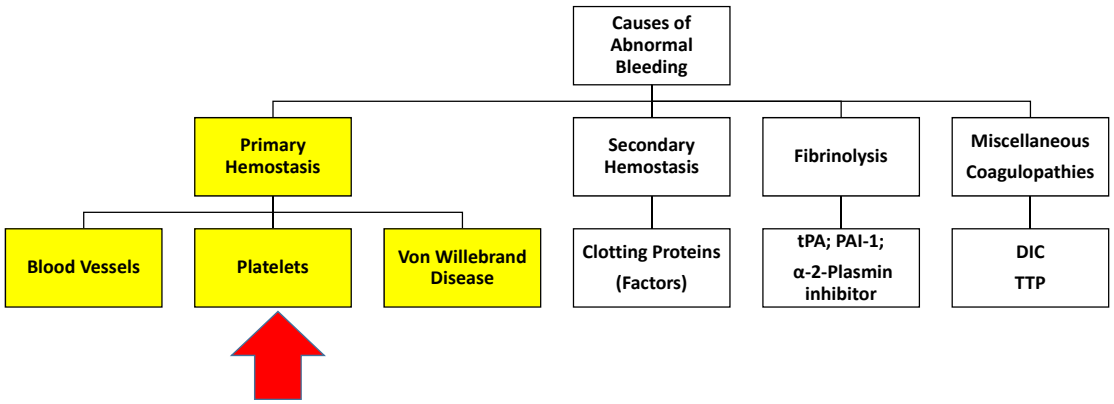
# Bleeding Disorders
## *Vascular Disorders*

- Hereditary Hemorrhagic Telangiectasia (HHT)
  - Also known as *Osler-Weber-Rendu* disease
  - HHT is an uncommon autosomal dominant condition causing degeneration of the blood vessel wall
  - Characterized by the presence of angiomatous lesions resembling "blood blisters" on mucocutaneous membranes (e.g. lips and GI tract) and skin
  - The breakdown of these lesions results in epistaxis and gastrointestinal hemorrhage
  - These lesions tend to become more numerous with age

# Bleeding Disorders
## Vascular Disorders

- Vasculitis:
  - Septic Vasculitis:
    - Certain bacterial infections, especially meningococcemia, can cause vasculitis (inflammation of the blood vessel wall) resulting in raised (palpable) hemorrhagic lesions in the skin
  - Henoch-Schonlein purpura:
    - One type of ***aseptic*** vasculitis is Henoch-Schonlein purpura which most often occurs in children and young adults (occasionally adults)
    - This syndrome often occurs after a viral illness and appears to be caused by an IgA hypersensitivity reaction
    - This vasculitis often involves GI tract, kidneys and skin—generally legs—where raised purpuric lesions are characteristic
    - Usually spontaneously clears in 1-2 months


# Bleeding Disorders




# Bleeding Disorders
## Platelets

- **Intrinsic platelet disorders** associated with an increased risk of bleeding can be placed into 6 categories as shown in the table below:

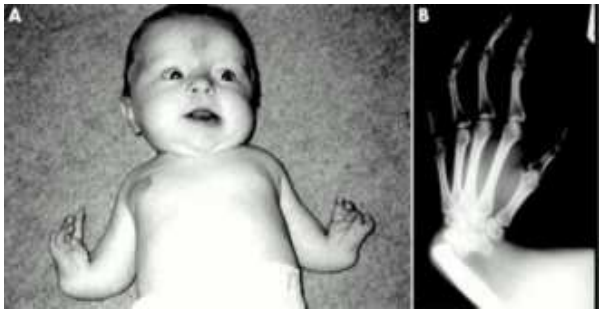
| **Quantitative Defects** (Abnormalities in platelet number--Thrombocytopenia) | **Qualitative Defects** *(Abnormalities in platelet function)* | **Combined Defects** |
|---|---|---|
| **Inherited:**<br>Thrombocytopenia with absent radii (TAR) | **Inherited:**<br>Glanzmann's thrombasthenia<br>Storage pool deficiencies<br>Gray platelet synd.<br>Chediak-Higashi synd.<br>Hemansky-Pudlak synd. | **Inherited:**<br>MYH 9 mutations<br>Bernard-Soulier syndrome<br>Wiskott-Aldrich syndrome |
| **Acquired:**<br>Immune thrombocytopenic purpura (ITP)<br>Bone marrow damage<br>Medications (including HIT)<br>Splenomegaly<br>Disease associations (HIV; SLE) | **Acquired:**<br>Uremia | **Acquired:**<br>Cirrhosis |

# Intrinsic Platelet Defects Quantitative / Inherited

Thrombocytopenia with Absent Radii (TAR)

## Intrinsic Platelet Defects Quantitative / Inherited

- Thrombocytopenia with Absent Radii (TAR)
  - Inherited as autosomal recessive
  - Diagnostic features:
    - No radii
    - Thrombocytopenia (15,000-30,000/μL) that is most severe in neonatal period but improves with age
    - Cardiac and other skeletal abnormalities often present
  - Patients who survive first 1-2 years of life can have a normal lifespan



# Intrinsic Platelet Defects Quantitative / Acquired

Immune thrombocytopenic purpura (ITP)

Bone marrow damage

## Quantitative Platelet Defects Acquired

- ITP presents in two distinct ways:
  - Chronic ITP is generally seen in adults with a 3:1 female predominance and has a frequency of approximately 2 cases/100,000
  - Acute ITP is usually seen in children between 1-6 years of age. Acute ITP has an equal presence in males and females and the overall frequency is approximately 5 cases/100,000
- The chart in the next slide compares these two manifestations of ITP

# Quantitative Platelet Defects: Acquired (ITP)

| Clinical Feature | Acute ITP | Chronic ITP |
|---|---|---|
| Age of patient | Children (1-6 years) | Adults (20-40 years) |
| Sex predilection | M= F | F > M (3:1) |
| Antecedent Infection? | Common (1-3 weeks; viral) | Unusual |
| Onset of bleeding | Abrupt | Insidious |
| Typical Platelet Count | <20,000 | 30,000-60,000 |
| Type of bleeding | Skin: petechiae, bruising<br>Mucosa: epistaxis, gingival, GI/GU | |
| Duration | 2-6 weeks (longer is rare) | Months to years |
| Spontaneous remission | Occurs in 80% of cases | Uncommon |
| Intracranial hemorrhage | Rare | Rare |

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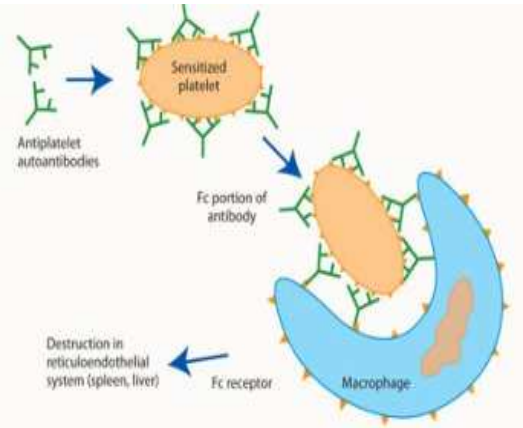
Initially these 2 syndromes seem distinctly different other than the fact that both present with some degree of thrombocytopenia, so why do we discuss these together?

**Comes down to PATHOPHYSIOLOGY**

# Quantitative Platelet Defects: Acquired (ITP)

- Pathophysiology
  - The pathogenesis of ITP is presumed to be accelerated platelet destruction due to the presence of specific **autoantibodies** most often to platelet glycoproteins such as GPIIb/IIIa (fibrinogen receptor) and GPIb/IX (vWF receptor)
  - Recently, there has been some evidence suggesting that in some patients these autoantibodies also inhibit platelet production as well (in about 2/3 of patients)
  - It should be noted that *not all* patients with ITP actually demonstrate anti-platelet or anti-megakaryocyte autoantibodies




# Quantitative Platelet Defects: Acquired (ITP)

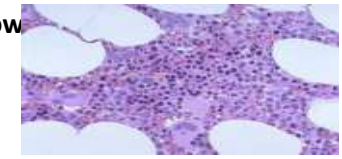
- Diagnosis
  - The diagnosis of ITP is based on the finding of an *isolated thrombocytopenia and the elimination of "other" causes of decreased platelet counts* (e.g. DIC, TTP, myelodysplastic syndrome, etc.)
  - Occasionally, patients with a diagnosis of CLL will present with ITP
  - Additionally, *Evans syndrome* is the association of thrombocytopenia and severe anemia

- Treatment—multiple modalities:
  - Oral prednisone
    - Standard initial therapy in adults
    - 50-75% respond, but most have a recurrence when prednisone is tapered
  - Intravenous anti-D (Rh Immune globulin)
    - This therapy has a response rate of up to 70%, but is effective ONLY in patients who are Rh positive and have a functioning spleen (*causes macrophage Fc receptor blockade*)
  - Intravenous immune globulin
    - IVIG can be tried in patients who fail to respond to prednisone
  - Splenectomy
    - Failure to respond to the above therapies for 3-6 months
    - While this therapy is often successful, it increases the risk of sepsis for the patient

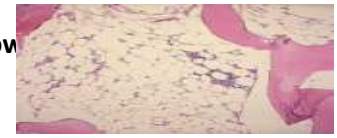
# Quantitative Platelet Defects: Acquired—Marrow Damage

- **Marrow Damage** leading to thrombocytopenia can occur in:
  - Aplastic anemia
    - Toxic chemicals (e.g. benzene),insecticides, autoimmune disorders, viral infections (parvo B19, CMV), idiopathic
  - Chemotherapy
  - Radiation therapy
  - Malignancy / leukemia / lymphoma

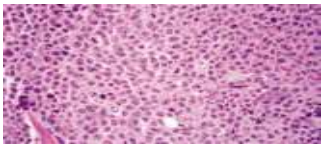
- **Normal Marrow**



- **Aplastic Marrow**



- **Malignancy**



# Quantitative Platelet Defects Acquired--Medications

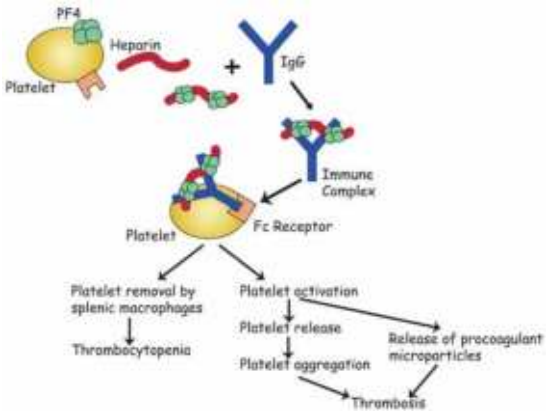
- Medications:
  - There is a long list of medications that have been associated with thrombocytopenia; among the most common are quinine and quinidine
  - Other medications include:
    - Antibiotics (penicillins, cephalosporins, vancomycin)
    - Antiepileptics and Antipsychotics (phenyltoin, carbamazepines)
    - Antihypertensives (diuretics, methyldopa, ACE-inhibitors)
    - Analygesics (naproxen, ibuprofen, acetaminophen)
    - Antiplatelet medications (acbiximab, tirofiban)
- Heparin-Induced Thrombocytopenia (HIT):
  - HIT represents a "*special case*" of medication-associated thrombocytopenia

# Quantitative Platelet Defects Acquired—Medications (HIT)

- Heparin-Induced Thrombocytopenia (HIT)
  - The diagnosis of HIT requires:
    - Patient currently being treated with heparin
    - Thrombocytopenia:
      - <150,000/µL or 50% lower than pre-heparin platelet count.
      - Profound thrombocytopenia is rare—most often platelet count is 60,000-80,000/µL
  - Thrombocytopenia generally develops 4-5 days after heparin therapy is initiated
  - Approximately 30% of patients with HIT develop **thromboses** (venous > arterial; particularly in legs) *rather than bleeding!!!*
  - ***WHY*** *thrombosis rather than bleeding???*
    - *The mechanism of HIT should explain this……*

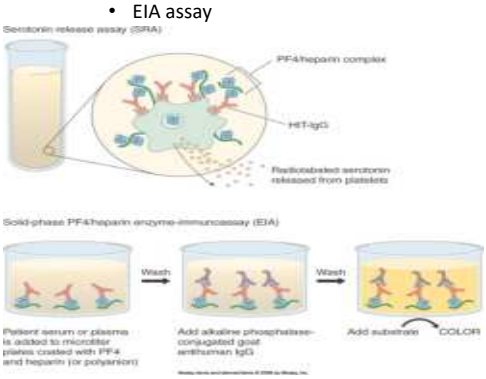
# Quantitative Platelet Defects Acquired (HIT)

- **HIT Mechanism:**
  - Platelet Factor-4 (PF-4) is a platelet-specific chemokine stored in the α-granules of the platelet
  - Heparin binds to PF-4 causing the formation of "neoepitopes" of PF-4 leading to the production of IgG antibodies
  - An immune complex of heparin, PF-4, and IgG antibody forms an immune complex that binds to platelet Fc receptors
  - This has 2 outcomes:
    - Removal of platelets from the circulation→↓ platelet count
    - Platelet activation→thrombosis



# Quantitative Platelet Defects Acquired (HIT)

- **Testing for HIT:**
  - Platelet activation assay
    - Serotonin-release assay
  - Antibody to heparin-PF-4
    - EIA assay




- **Therapy:**
  - Strictly eliminate all exposure to heparin and transition to another anticoagulant (even heparin used to irrigate lines!!!!!)
  - After the cessation of heparin the risk of thrombosis still exists:
    - 10% at 2 days
    - 30-40% at 10 days
    - 50% at 30 days

# Intrinsic Platelet Defects Qualitative / Inherited

Glanzmann's thrombasthenia

Storage pool disorders

# Qualitative Platelet Defects: Inherited

- Qualitative platelet abnormalities include **Glanzmann's thrombasthenia** and certain **Storage pool disorders**

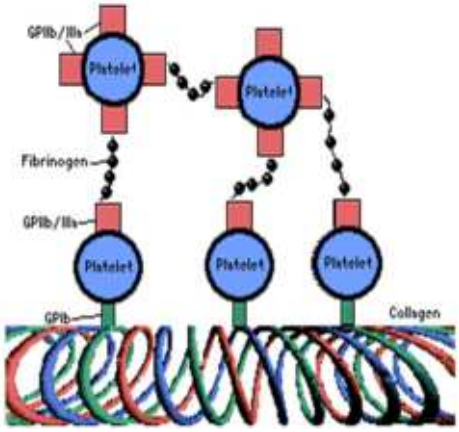
- Conceptually, platelet function can be subdivided into 3 categories:
  - Platelet aggregation (e.g. Glanzmann's)
  - Platelet secretion (e.g. Gray plt; CHS; HPS)
  - Platelet adhesion (e.g. Bernard-Soulier—*discussed in "Combined defects"*)
- In general, the *inherited qualitative platelet defects* that we will discuss fall into one of these categories.

# Qualitative Platelet Disorders: Inherited—Glanzmann Thrombasthenia

- **Glanzmann's Thrombasthenia** is an uncommon deficiency of the GIIb/IIIa receptor (**fibrinogen**) on the platelet membrane:

  ← Platelet GPIIb/IIIa receptor

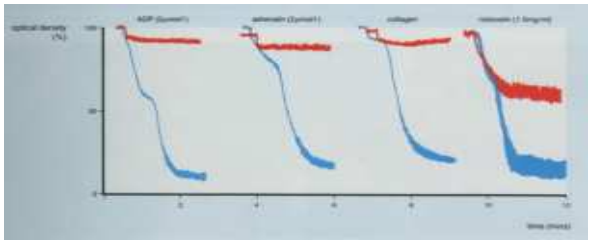
  and, therefore, is a disorder of ***platelet aggregation*** *("binding" one platelet to another)*
- Glanzmann's is inherited in an autosomal recessive manner
- Glanzmann's can be subcategorized based on the amount of GPIIb/IIIa receptor remaining on the platelet membrane



# Qualitative Platelet Disorders: Inherited—Glanzmann Thrombasthenia

- Symptoms:
  - Typically presents in neonatal period
  - Bleeding, which can be severe, usually occurs in those situations which would also cause bleeding in normal individuals and is often manifest by:
    - Mucocutaneous bleeding
    - Purpura
    - Epistaxis
    - Gingival bleeding
    - Menorrhagia
    - Childbirth, surgery, trauma can result in serious bleeding
- Treatment:
  - Platelet transfusion

- Laboratory Testing:
  - Plt count: Normal
  - PT: Normal
  - aPTT: Normal
  - Bleeding Time: Prolonged
  - Platelet Aggregation Testing
    - No aggregation to ADP, Epinephrine, Collagen; some (often NORMAL) aggregation to ristocetin:

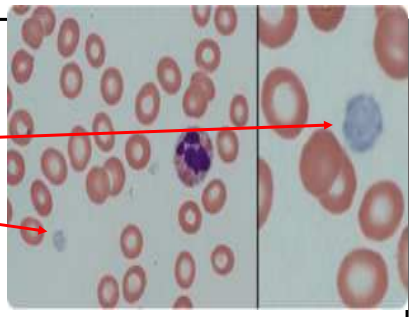


# Qualitative Platelet Defects Inherited (Storage Pool Disorders)

- Storage Pool Disorders
  - Platelets contain 4 types of granules:
    - Alpha (α) granules
      - ~50 granules per platelet; contain multiple proteins such as platelet factor 4, β-thromboglobulin, vWF, coag. Factor V)
    - Dense (δ) granules
      - ~6 granules per platelet; contain ADP, ATP, calcium, serotonin)
    - Lysosomes
    - Microperoxisomes
  - Deficiencies in α and δ granules lead to rare, but well-known, qualitative platelet abnormalities

# Qualitative Platelet Defects
## Inherited—Storage Pool Disorders

- **Gray Platelet Syndrome**
  - Caused by an absence of **α-granules** resulting in characteristic large, "gray" platelets



  - Symptoms include a slightly decreased platelet count and prolonged bleeding time
  - The syndrome is transmitted in an "autosomal" fashion
  - Clinical bleeding is mild to moderate; platelet transfusion is rarely required
  - While there may be a mild thrombocytopenia—this is *predominantly a qualitative defect* in platelet function

# Qualitative Platelet Defects
## Inherited—Storage Pool Disorders

- Dense (δ) Granule Deficiency
  - Dense granules in platelets are the storage sites for ADP, ATP, Calcium, and serotonin.
  - Dense granule deficiencies are a heterogeneous group of disorders including:
    - **Hermansky-Pudlak**: a rare disease, but with a 1:1800 in northwest Puerto Rico. These patients also suffer from Albinism, poor visual acuity, nystagmus, and pulmonary fibrosis
    - **Chediak-Higashi**: Partial albinism, frequent pyogenic infections, giant lysosomal granules in cytoplasm of hematologic and non-hematologic cells

  - Mucocutaneous bleeding in these disorders tends to be mild to moderate; platelet transfusion is rarely needed; DDAVP can often be used to control bleeding

# Intrinsic Platelet Disorders Qualitative / Acquired

Medications

## Qualitative Platelet Defects Acquired--Medications

- A large number of medications can affect platelet function; only a few will be mentioned:

| Medication | Risk of Bleeding | Mechanism |
|---|---|---|
| Aspirin (ASA) | In normal individuals the effect of ASA ion normal individuals is slight; impact on surgical bleeding is uncertain | Inactivation of cyclooxygenase-1 |
| Thienopyridines (e.g.: clopidogrel) | Inhibit ADP-related platelet responses. The effect of these drugs can persist for 4-10 days after drug is discontinued | Bind irreversibly to ADP receptor P2Y |

# Intrinsic Platelet Disorders Combined / Inherited

MYH 9 mutations

Bernard-Soulier syndrome

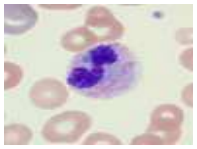
Wiskott-Aldrich

## Combined Platelet Defects (Qual. + Quant.) Inherited

- The inherited platelet defects that have ***both*** qualitative and quantitative abnormalities include **MYH 9 mutations, Wiskott-Aldrich syndrome, and Bernard Soulier syndrome**.

## Combined (Quantitative and Qualitative)Platelet Defects:
### Inherited / Combined

- MYH9 Mutations:
  - Uncommon
  - MYH9 mutations include 4 related, named syndromes that might represent a "spectrum" rather than discrete entities:
    - May-Hegglin anomaly, Fechter syndrome, Sebastian syndrome, Epstein syndrome
  - These each of these entities have distinguishing features, but they share the following triad:
    - Thrombocytopenia
    - Giant platelets
    - Neutrophil inclusions called "Dohle-like" bodies (*remnants of RER*)



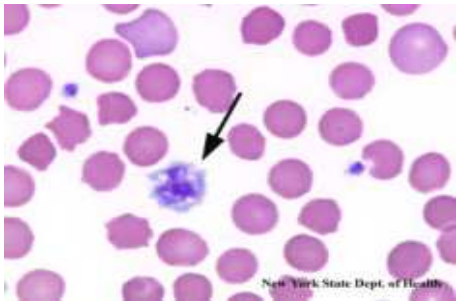
  - Bleeding risk is mild and platelet transfusion is not generally required

## Combined (Quantitative and Qualitative) Platelet Defects

- Wiskott-Aldrich
  - Rare X-linked inheritance
    - (4/1,000,000 males)
  - Variable clinical manifestations:
    - Microthrombocytopenia (<70,000/µL)
    - Eczema
    - Increased susceptibility to recurrent infections
      - ↓IgM; Normal IgG
    - Increased risk or autoimmune disorders and malignancy
    - Intestinal bleeding

# Combined Platelet Defects (Qual. + Quant.) Inherited—Bernard-Soulier Syndrome

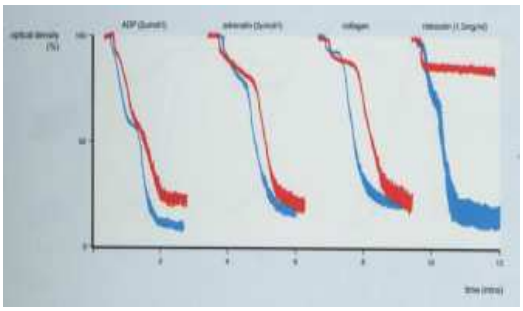
- **Bernard-Soulier** is a congenital deficiency of GP Ib/IX/X complex (vWF platelet receptor)
  - Autosomal recessive inheritance
  - Large ("giant") platelets




- Symptoms:
  - Presents in infancy or neonatal period with mucocutaneous bleeding
  - While bleeding can be severe when it occurs, most of these patients do NOT require therapy on a routine basis (preoperative therapy is prudent)
- Laboratory Testing
  - Plt count: **DECREASED**
    - 40,000-100,000/µL
  - PT / aPTT: Normal
  - Bleeding Time: Prolonged

# Combined Platelet Defects (Qual. + Quant.) Inherited

- Laboratory Testing (continued):
  - Platelet Aggregation Studies:
    - Normal aggregation to ADP, Epinephrine, and collagen; little or no aggregation to ristocetin:



- The platelet aggregation pattern for B-S looks like the pattern seen in VWD:
  - Both involve the GPIb receptor
    - B-S: deficiency of GPIb receptor
    - VWD: limited amounts of (or abnormality of) VWF to bind to GPIb receptor
- Treatment:
  - Platelet transfusion
  - DDAVP has also be used successfully

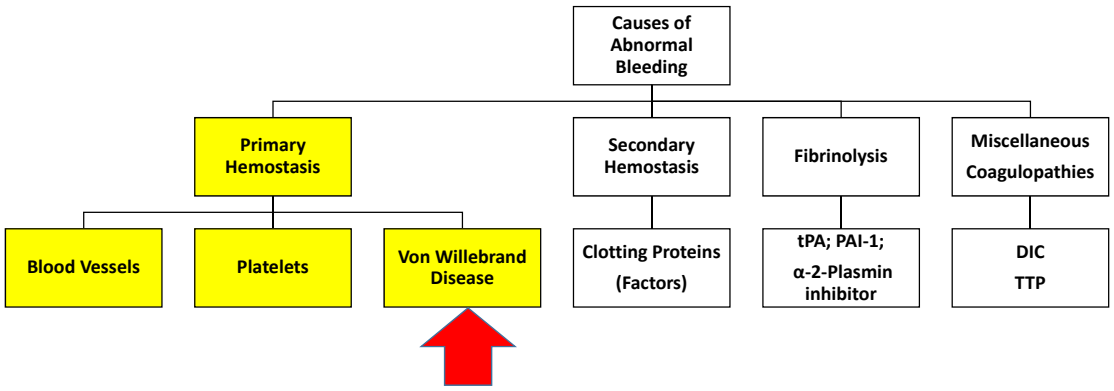
# Intrinsic Platelet Defects Combined / Acquired

Cirrhosis

## Combined Platelet Defects Cirrhosis

- Thrombocytopenia is a very common finding in patients with cirrhosis
  - 70-90% of patients with severe liver disease have platelet counts less than 150,000/μL
  - The decreased platelet count is probably multifactorial with potential causes such as ↓platelet survival, ↓platelet production, and splenic sequestration
- Some studies have also shown mild platelet dysfunction

# Bleeding Disorders



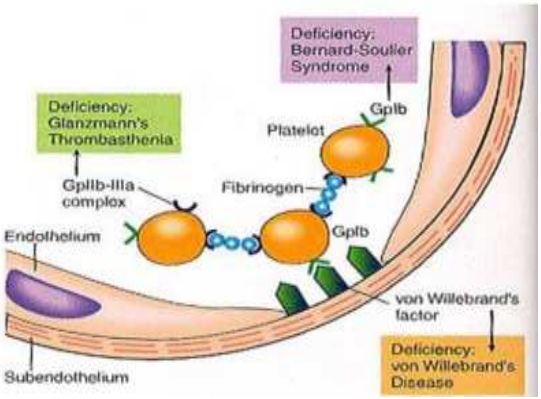

# Bleeding Disorders
## Primary Hemostasis—von Willebrand Dis.

- Von Willebrand Disease (vWD) gets a "special category" among disorders of primary hemostasis for a couple of reasons:
  - In spite of the fact that this disorders presents as a defect in primary hemostasis, it is **not** caused by an *intrinsic* abnormality in platelet function or quantity
  - vWD is the most common inherited coagulation disorder that you will encounter in the general population (~1.3/1000)

# Bleeding Disorders

## von Willebrand Factor—*What does it do?*

- **Von Willebrand Factor has 2 principal functions:**
  - VWF protein acts as a binding molecule between platelet ***GP Ib receptor*** and collagen in the subendothelial tissues at the site of a vascular injury
    - **Thus, either a quantitative or a qualitative abnormality in VWF can result in defective platelet adhesion causing a prolonged bleeding time and the typical appearance of platelet-related bleeding.**
  - VWF also acts as a carrier protein for Factor VIII significantly prolonging the half-life of that molecule—**This is why Factor VIII can be deficient in vWD causing a ↑PTT**




# Bleeding Disorders

## von Willebrand Disease

- **Von Willebrand Disease** is a disorder characterized by a deficiency (or abnormality) of von Willebrand Factor (VWF)
- There are 3 general types of VWD (*outlined in the next slide*) arising from either:
  - **Quantitative defects** in the amount of VWF produced (Types 1 and 3)
    - Type 1 = ~75% of vWD cases; Type 3 = ~5% of vWD cases
  - **Qualitative defects** in VWF leading to abnormal platelet-VWF binding or, in some cases, to a loss in certain high molecular weight multimers of VWF (Types 2A, 2B, 2M, 2N)
    - Type 2 = ~20% of vWD cases
- The disease is inherited as an *autosomal dominant* (except for type 3 VWD and type 2N VWD , which are inherited as autosomal recessives)

# von Willebrand Disease: SUBTYPES

| Lab Test | Von Willebrand Disease--Subtypes | | | | | |
|---|---|---|---|---|---|---|
| | 1 Partial Quantitative Defect | 2A Qualitative Defect | 2B Qualitative Defect | 2M Qualitative Defect | 2N Qualitative Defect | 3 Severe Quantitative Defect |
| PT | Normal | Normal | Normal | Normal | Normal | Normal |
| aPTT | Normal or ↑ | Normal or ↑ | Normal or ↑ | Normal to ↑ | ↑ | ↑↑↑ |
| Factor VIII | Low | Low | Normal to Low | Normal to Low | Very Low | < 10% |
| vWF Antigen (functional + nonfunctional vWF | Low | Low | Normal to Low | Low | Normal | Undetectable |
| Ristocetin Cofactor (Functional vWF) | Low | Very Low | Very Low | Very Low | Normal | Undetectable |
| Ristocetin-Induced plt aggregation | Low to Normal | Low | ↑ | Normal to Low | Normal | Very Low |
| Plt Count | Normal | Normal | Low | Normal | Normal | Normal |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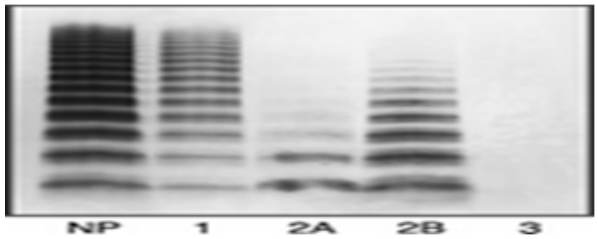
# Bleeding Disorders
## von Willebrand Disease CLINICAL PRESENTATION

- The bleeding manifestations of VWD vary in severity based on the subtype with Type 1 often being so mild as to go undiagnosed. Type 3 generally has the most severe symptoms, often mimicking hemophilia. The various type 2 VWD tend to be intermediate in severity.
- The most common bleeding symptoms are:
  - Easy bruising
  - Epistaxis
  - Bleeding after dental extractions
  - Menorrhagia
  - Excessive bleeding after trauma or surgery
  - Postpartum bleeding
  - *Hemarthroses (bleeding into joint spaces) are **RARE***

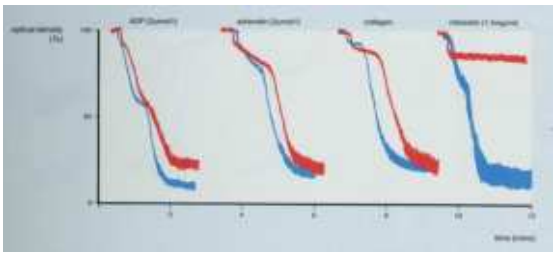
# Bleeding Disorders
## von Willebrand Disease LABORATORY TESTING

- There are several specific tests that can be used to confirm the diagnosis of VWD and to help to classify the disease into types 1, 2, or 3.
  - **VWF Antigen**
    - This test measures the ***quantity of VWF antigen*** whether functional or not
  - **Ristocetin Cofactor**
    - This test assesses the amount ***functional VWF*** by measuring the ristocetin-mediated binding of VWF to platelet GPIb
  - **Multimer Analysis**
    - This test involves the separation of the various multimers of VWF by size using an agarose gel electrophoresis. This test can help to discriminate the various subtypes of VWD.



# Bleeding Disorders
## von Willebrand Disease LABORATORY TESTING

- Platelet Function Testing: **Light Transmission Aggregometry**
- Characteristic pattern for vWD:
  - Platelet aggregation appears normal (red=patient preparation; blue= normal control) with ADP, adrenalin (epinephrine) and collagen.
  - Patient's platelets do ***NOT*** aggregate in response to ***ristocetin (looks like the aggregation pattern for B-S)***



- The pattern of platelet aggregation, coupled with the patient's:
  - Medical history
    - Mucocutaneous bleeding
  - Laboratory testing
    - Normal Plt count, PT
    - aPTT normal to prolonged
    - Abnormal plt function test: little or no aggregation to Ristocetin, but normal aggregation to ADP, Epinephrine, collagen
- Suggests a diagnosis of ***von Willebrand Disease***
  - *Why NOT Bernard-Soulier with this aggregation pattern which has exactly the same aggregomety pattern*

# von Willebrand Disease:
## TREATMENT

- The treatment of vWD is dependent upon the subtype:

| Von Willebrand Disease Subtype | Treatment(s) |
|---|---|
| **Type 1** | 80% of patients will respond to DDAVP (Desmopressin) which elevates plasma levels of Factor VIII and vWF by 80%. This increase occurs within 30 minutes and lasts 6-12 hours |
| **Type 2** | Type 2 has a variable response to DDAVP according to the specific subtype. Cryoprecipitate which contains vWF may be required to treat some of these patients |
| **Type 3** | DDAVP is NOT effective in type 3; cryoprecipitate is generally required. Also some Factor VIII concentrates (e.g. *Humate* or *Alphanate*) may be effective since these concentrates contain both Factor VIII and vWF |

# Quantitative Platelet Defects Acquired--Miscellaneous

- Miscellaneous Causes
  - Splenomegaly
  - The normal sized spleen sequesters 30-40% of the platelets in the peripheral blood
  - Splenomegaly, of any cause, can sequester larger numbers of platelets
  - Thrombocytopenia due to an enlarged spleen is usually mild to moderate with platelet counts ***rarely*** < 20,000/µL

  - Diseases associated with thrombocytopenia:
    - **HIV**
      - Common finding in patients with HIV infection
      - Etiology is probably multi-factorial, but increased immune destruction and possibly ineffective platelet production have been suggested
    - **SLE**
      - Multiple autoantibodies have been identified in the thrombocytopenia seen in some SLE patients

# REVIEW AND FOCUS

- Vascular Disorders:
  - The most important issue in this section is simply to know that there are a number of intrinsic vascular abnormalities that can present with symptoms suggestive of primary hemostatic disorders
  - Be familiar with the symptoms of HHT and Ehlers-Danlos that are suggestive of abnormal hemostasis
- Platelet Disorders
  - There are a large number of quantitative and qualitative platelet defects presenting as defects of primary hemostasis
  - While you should be familiar with each of the conditions discussed, FOCUS on ITP, bone marrow damage, HIT, Glanzmann's and Bernard-Spulier
- Von Willebrand Disease
  - vWD is the most common inherited bleeding disorder that you will encounter and, therefore, you should be very familiar with the information presented in the lecture including the "types" of vWD ***highlighted*** in the "slide" on vWD types