Putting some hematology into Pediatric Hematology/Oncology:

a review of Hemophilia and Sickle Cell Disease in the Pediatric Patient

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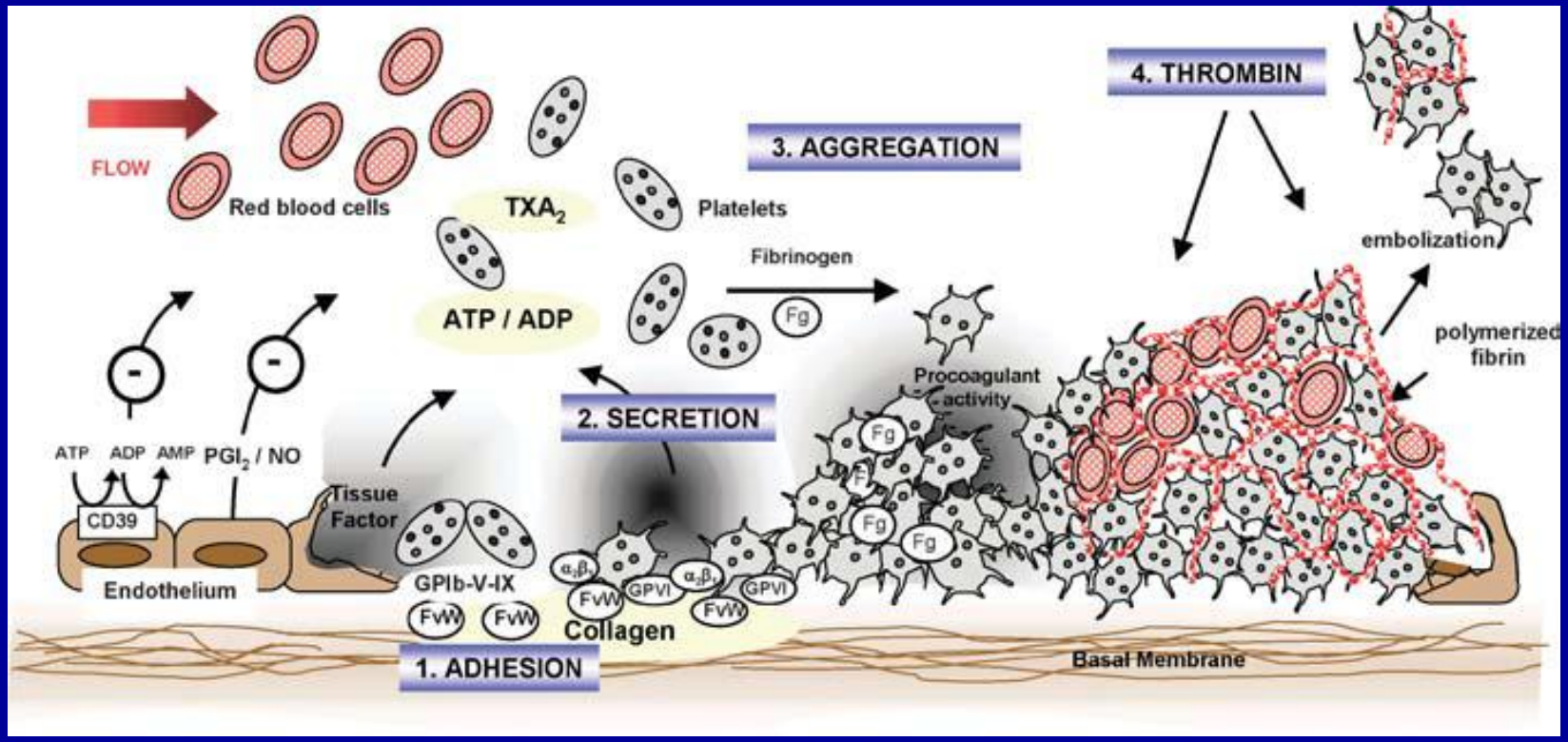
March 10, 2012

Jovita Reyes Memorial Pediatric Hematology/Oncology Nursing Conference

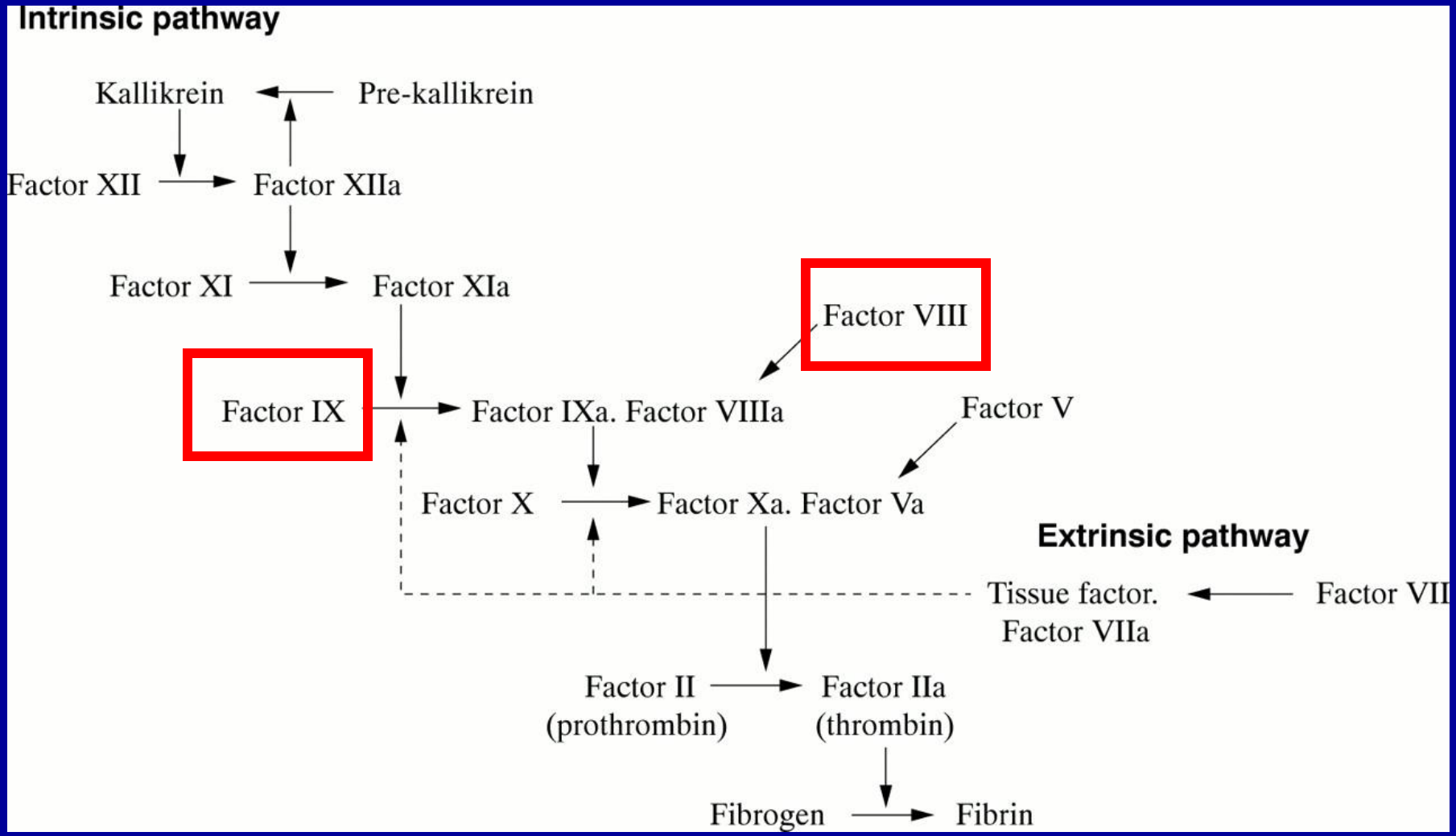
Objectives:

- Review Hemostasis and Hemoglobin production
- Discuss the pathophysiology of hemophilia and sickle cell anemia
- Describe the common reasons bringing these patients to medical attention
- Discuss treatment options for hemophilia and sickle cell disease
- Describe Future directions in the care of these patients

Hemophilia: a deficient hemostatic system



Hemophilia: a deficient hemostatic system



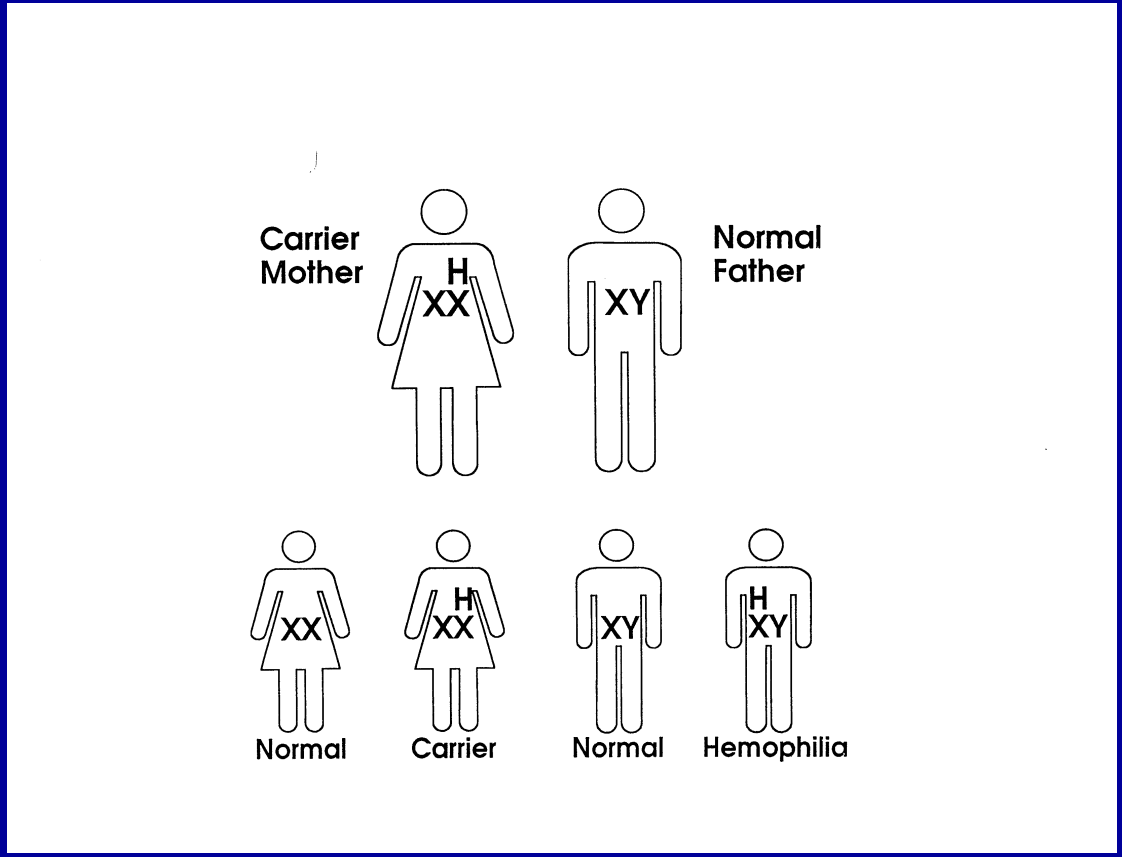
Hemophilia: the diagnosis

- Hemophilia A - factor VIII deficiency
  - 80% of those affected
- Hemophilia B - factor IX deficiency
  - 20% of those affected
- Amount of factor determines symptoms
  - Mild: 5-30%
  - Moderate: 1-5%
  - Severe: <1%

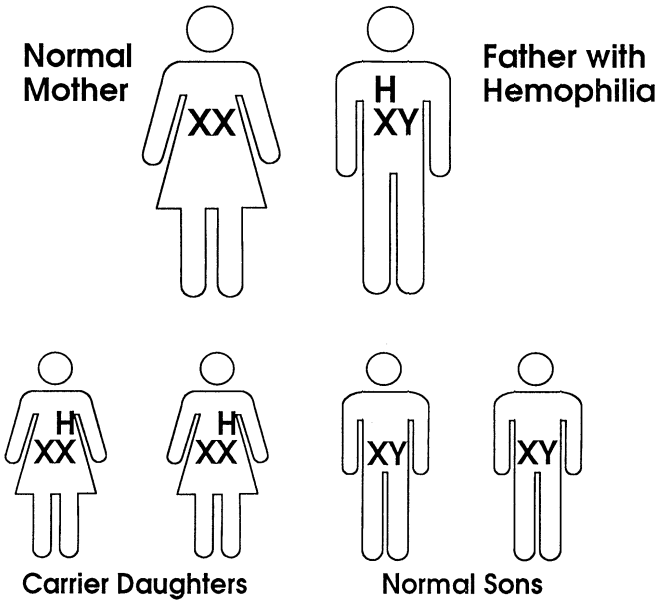
Hemophilia: genetics

- Life-long bleeding disorder
- X-linked inheritance
- New mutation in 30%

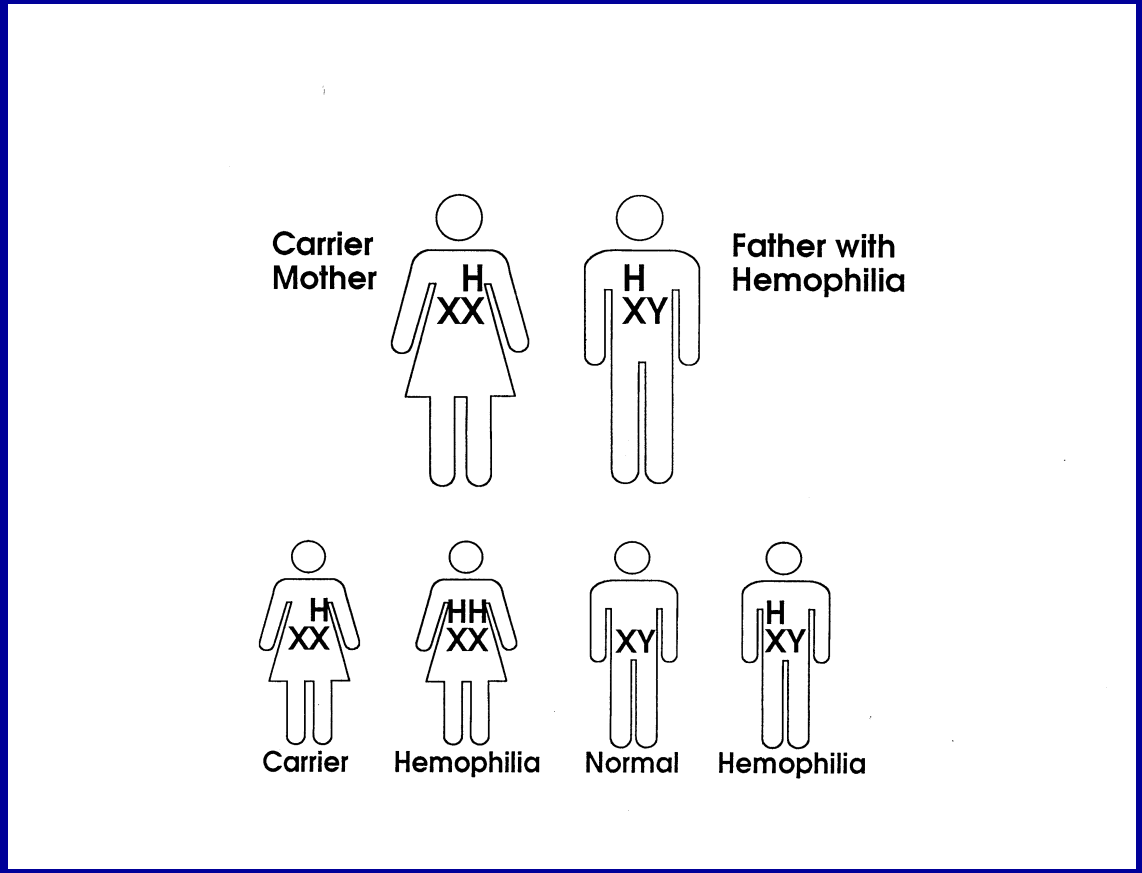
Family tree with carrier mother



Family tree with affected father



Family tree with carrier mother and affected father



Hemophilia clinical problems

- Bleeding characterized by joint and soft tissue hemorrhages
- Can also have mucosal, GI, CNS bleeds
- Symptoms of bleeding: swelling, redness, pain
- Recurrent bleeding can result in target joints

Hemophilia treatment in general

- Replace what's missing
- Recombinant factor products
  - Factor VIII 1U/kg of factor raises levels by 2%
  - Factor IX 1U/kg of factor raises levels by 1%
- Prophylaxis has become the mainstay of treatment for people with severe hemophilia or moderate hemophilia with frequent bleeding

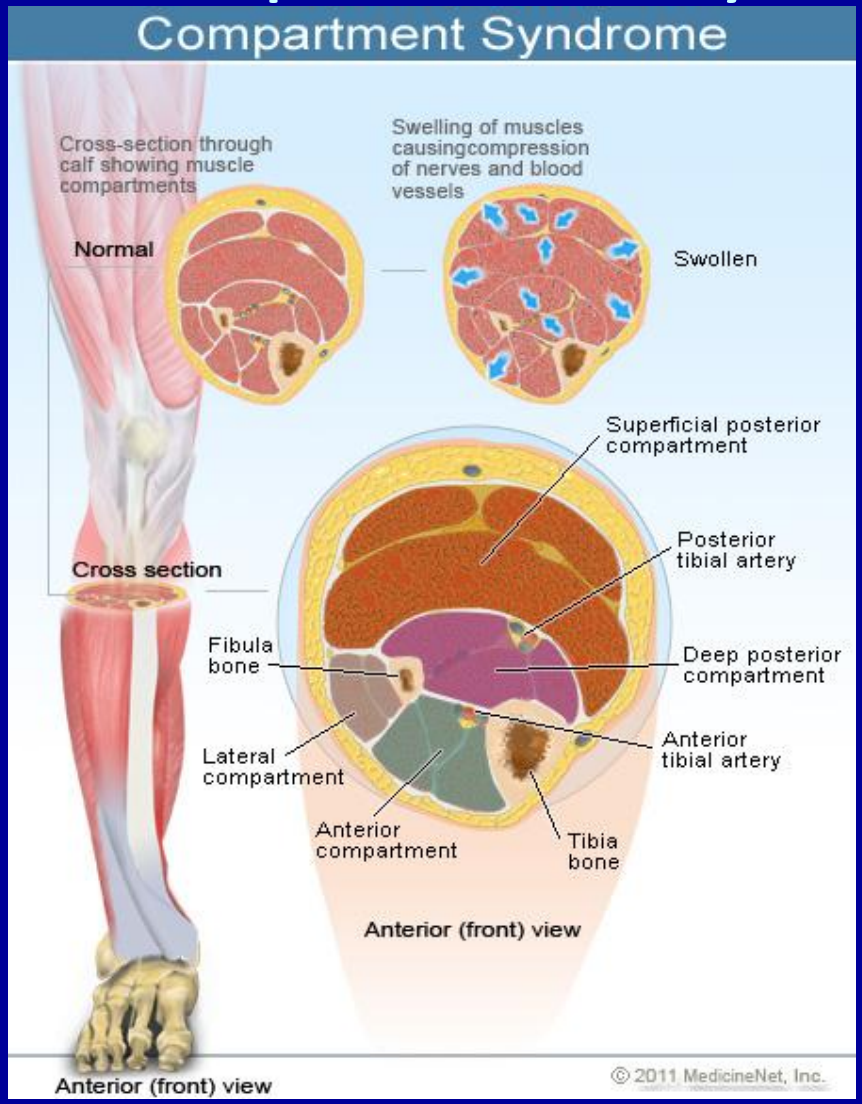
Prophylaxis

- Initiated at ~1 year of age, when child begins to walk
- Requires venous access device
- Designed to keep trough factor levels >2%
- Goal is to prevent joint damage and deterioration
- Schedule
    - Hemophilia A→3 times/wk
        - 50% on Mon and Wed
        - 100% on Fri
    - Hemophilia B→2 times/wk
        - 50% on Tues
        - 100% on Fri

Hemophilia- in the hospital

- Scheduled surgeries: port placement
  - Pre-op infusion of factor
  - Scheduled factor post-op
- Breakthrough/traumatic bleeding
  - Infuse first, then image
  - Continue infusions until symptoms resolve
  - Risk for compartment syndrome

Compartment syndrome



Complications/comorbidities

- Target joints
- ADHD
- Port infections
- Infections associated with factor
- Osteoporosis
- Development of inhibitors

Factor inhibitors

- Inhibitors are antibodies that block the function of coagulation proteins
- Develop in 25-30% of children with Hemophilia A
- Develop in 1-3% of children with Hemophilia B
- Complicates treatment

Treatment in the face of inhibitors

- Overcome the inhibitor
  - Increase the dose of factor replacement-
- Bypassing agents
  - FEIBA
  - Novo 7
- Plasmapheresis
- Immune tolerance

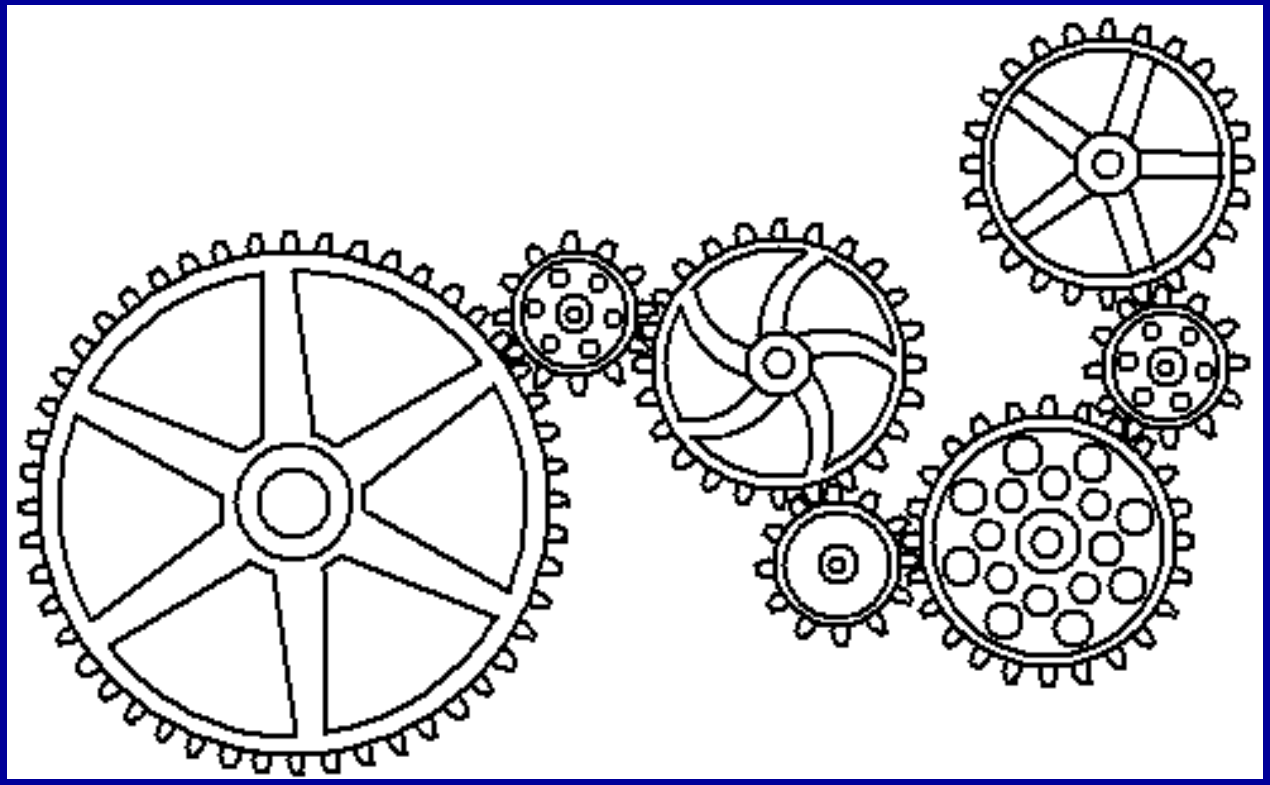
Future directions

- Open studies at OHSU:
  - Gait study
  - Use of ankle braces for pain control
  - ADHD and risk of injury
  - New factor replacements
  - Universal data collection
- Gene therapy??

Summary- hemophilia

- Hemophilia is secondary to a genetic defect resulting in decreased levels of factor VIII or XI
- Treatment is factor replacement- prophylaxis and on demand
- Can be complicated by inhibitor development
- Bleeding can lead to development of compartment syndrome- a medical emergency

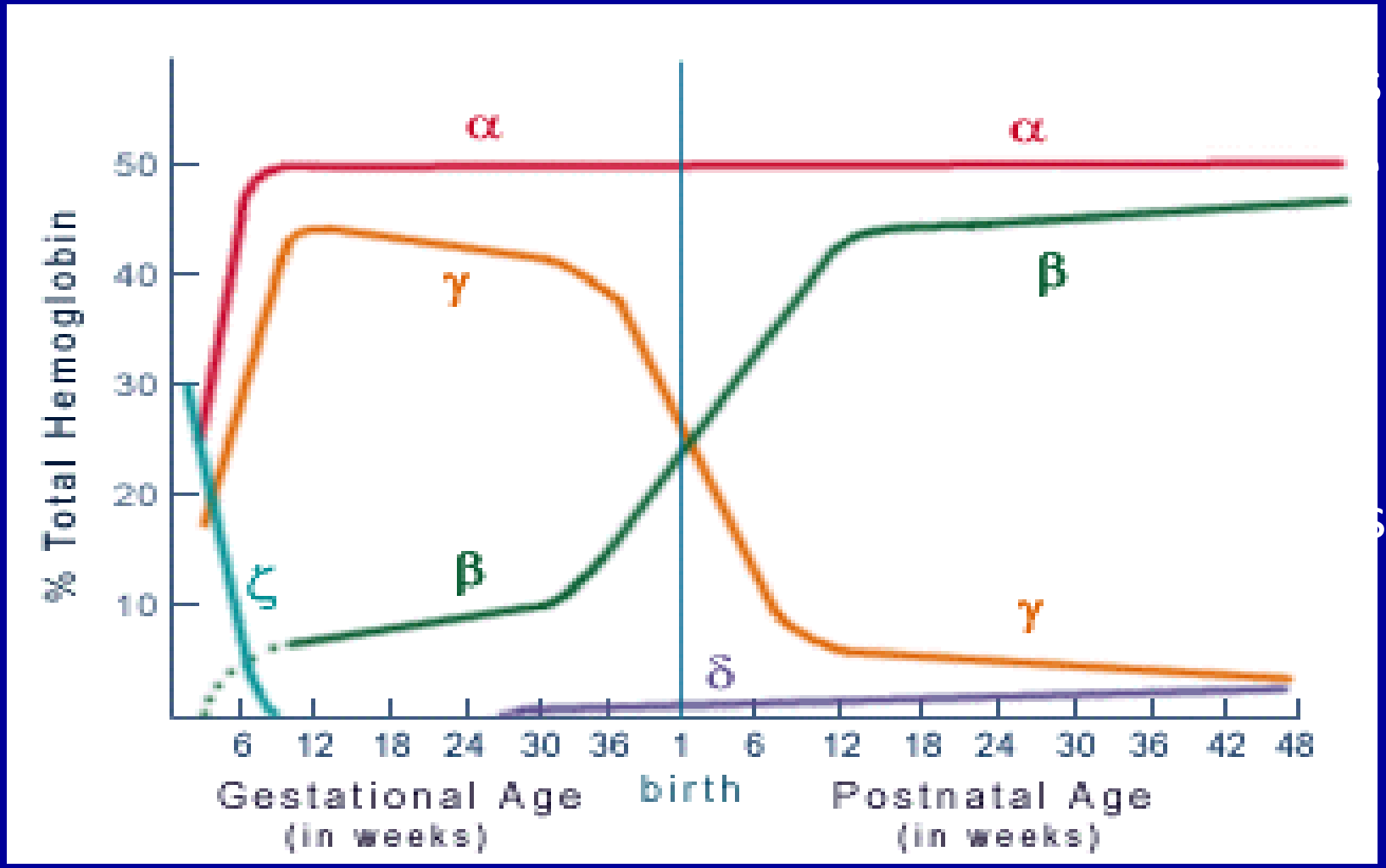
Questions?



Red cells and normal hemoglobin

- Each red cell contains ~640 million hemoglobin molecules
- Hemoglobin is responsible for oxygen delivery
- The red cell has to be deformable to get into close contact with tissues
  - The red cell is 8 micrometers and has to pass through 3.5 micrometer sized vessels

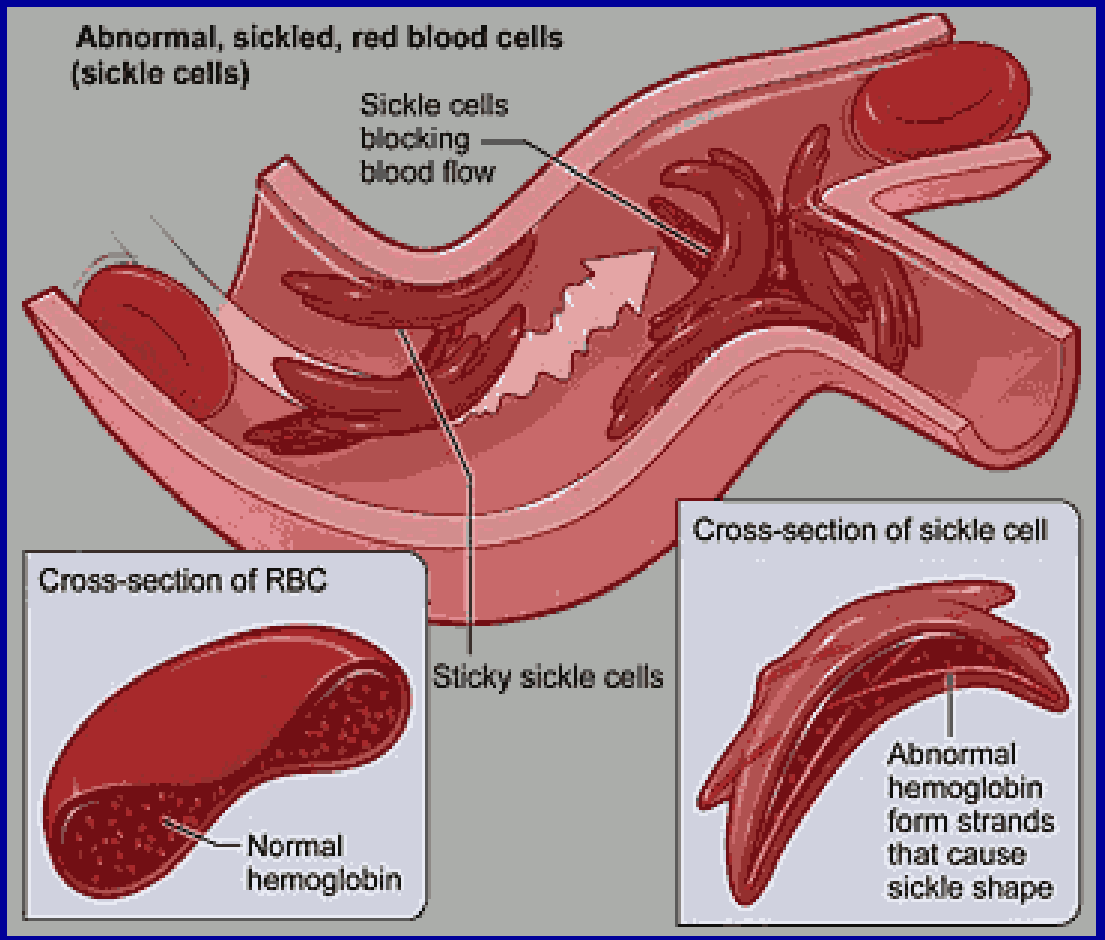
Normal hemoglobin production

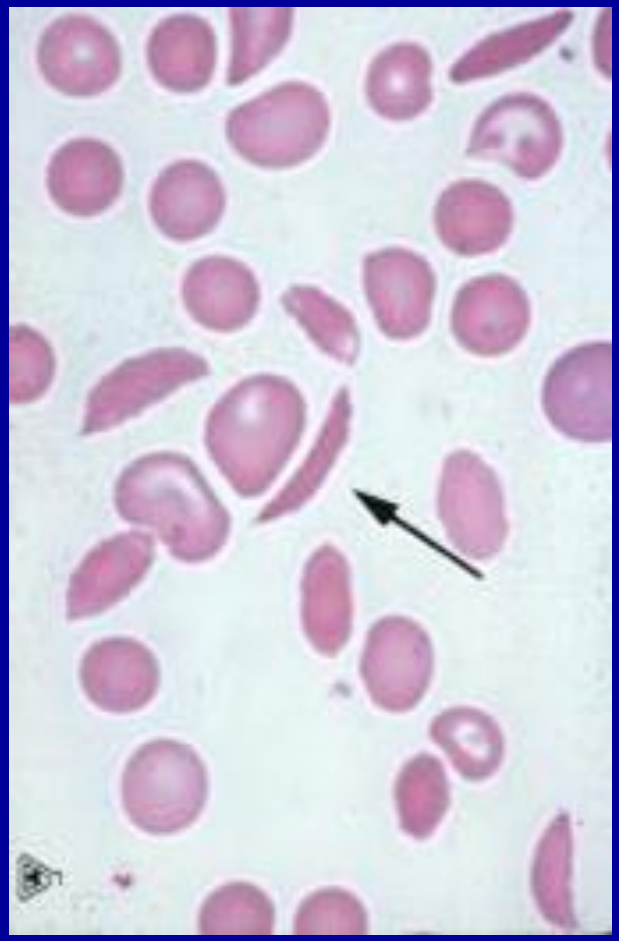


Sickle cell disease- qualitative hemoglobin problem

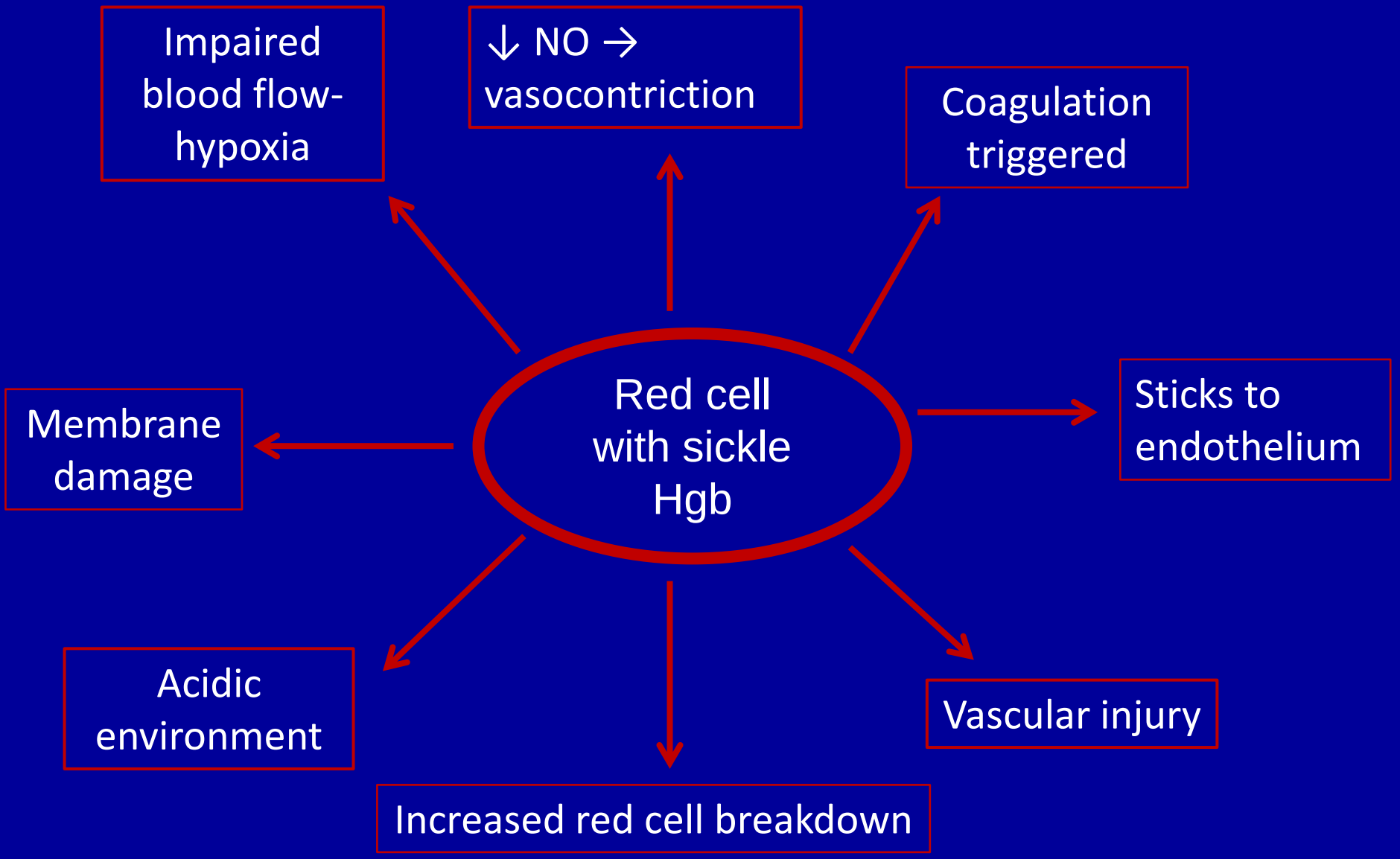
- Single change in the DNA coding for the β-globin results in the sickle β-globin
- Hemoglobin S ($\alpha_2\beta_2^s$) is insoluble and forms crystals when exposed to low oxygen
- The sickle hemoglobin polymerizes into long fibers which results in the red cell sickling

Sickled Cells- don’t deform





Sickle Cell pathophysiology



Sickle cell clinical problems

- Vaso-occlusive events: acute, painful episodes caused by intravascular sickling and tissue infarction
- Varied manifestations
  - Pain
  - Acute Chest Syndrome
  - Stroke

Painful events

- Acute onset of deep, gnawing, throbbing pain
- Secondary to bone marrow ischemia → infarction
- Common sites:
  - Lumbar spine
  - Knee
  - Shoulder
  - Elbow
  - Femur

Painful events

- Moderate-Severe events- managed in the hospital
  - Tailor treatment to patient and pain
  - Should be treated as medical emergency
  - Hydrate judiciously
  - Get pain under control quickly
  - Reassess frequently
  - NSAIDs help
  - No Oxygen needed
  - Transfusions don’t help

Acute Chest Syndrome

- Acute illness with lung injury – chest pain, fever, respiratory symptoms + new infiltrate on CXR
- May develop when in the hospital for pain
- High morbidity and mortality
- Treatment
  - Oxygen
  - Antibiotics
  - Bronchodilators

- Pain meds
- Transfusion
- Judicious fluids

Stroke

- Ischemia and infarct secondary to damaged vessels
- Can also have hemorrhagic stroke
- Can be isolated or develop in the setting of acute chest, aplastic crisis, viral illness, painful event, dehydration
- Treat with exchange transfusion

Fever and infection

- Most common cause of death in sickle cell patients
- Splenic dysfunction increases risk of bacteremia
- Treat as emergency- fever in immunocompromised host
- Penicillin prophylaxis has decreased infections significantly
- Vaccinations are critical in these patients

If that wasn't enough…

- Sickle Cell patients are at risk for
  - Aplastic crisis
  - Splenic sequestration
  - Gallstones
  - Priapism
  - Renal dysfunction
  - Pulmonary hypertension
  - Leg ulcers

Current therapies & Future directions

- Increase the percentage of Hgb F- Hydroxyurea
- Folic acid
- Penicillin
- Chronic transfusions
- Bone marrow tranplants

Summary-Sickle Cell

- Genetic disease characterized by abnormal hemoglobin
- The change in hemoglobin results in increased red cell breakdown, vascular injury, and ischemia
- Patients are at risk for several life-threatening complications including infection, acute chest syndrome, and stroke
- Painful events should be managed promptly and with frequent reassessments

Questions?

Thank You!