# Coagulopathy Case - 3

Andy Nguyen, M.D.

2009

# CLINICAL HISTORY

- A 21 year-old male seen in the emergency room with a swollen, tender right knee. Patient is an electrician who had fallen to the ground an hour ago while working on a power line.
- Patient had a history of prolonged bleeding after dental extractions. The patient had not previously been hospitalized or received blood transfusions.
- There was no family history of bleeding problems.
- The patient was taking no medication at the time of the accident.

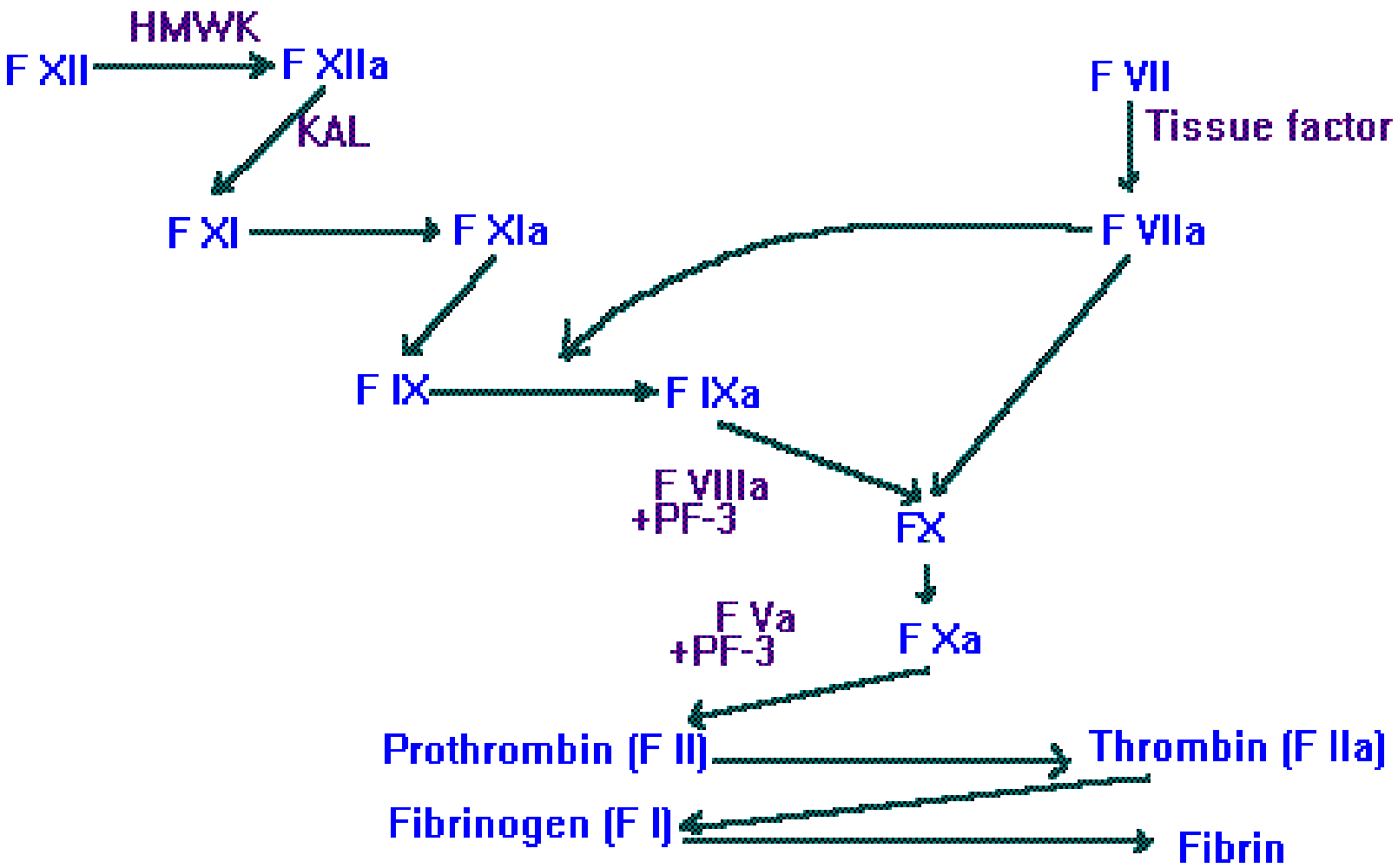
# PHYSICAL EXAMINATION

- Physical examination showed a swollen, tender right knee.

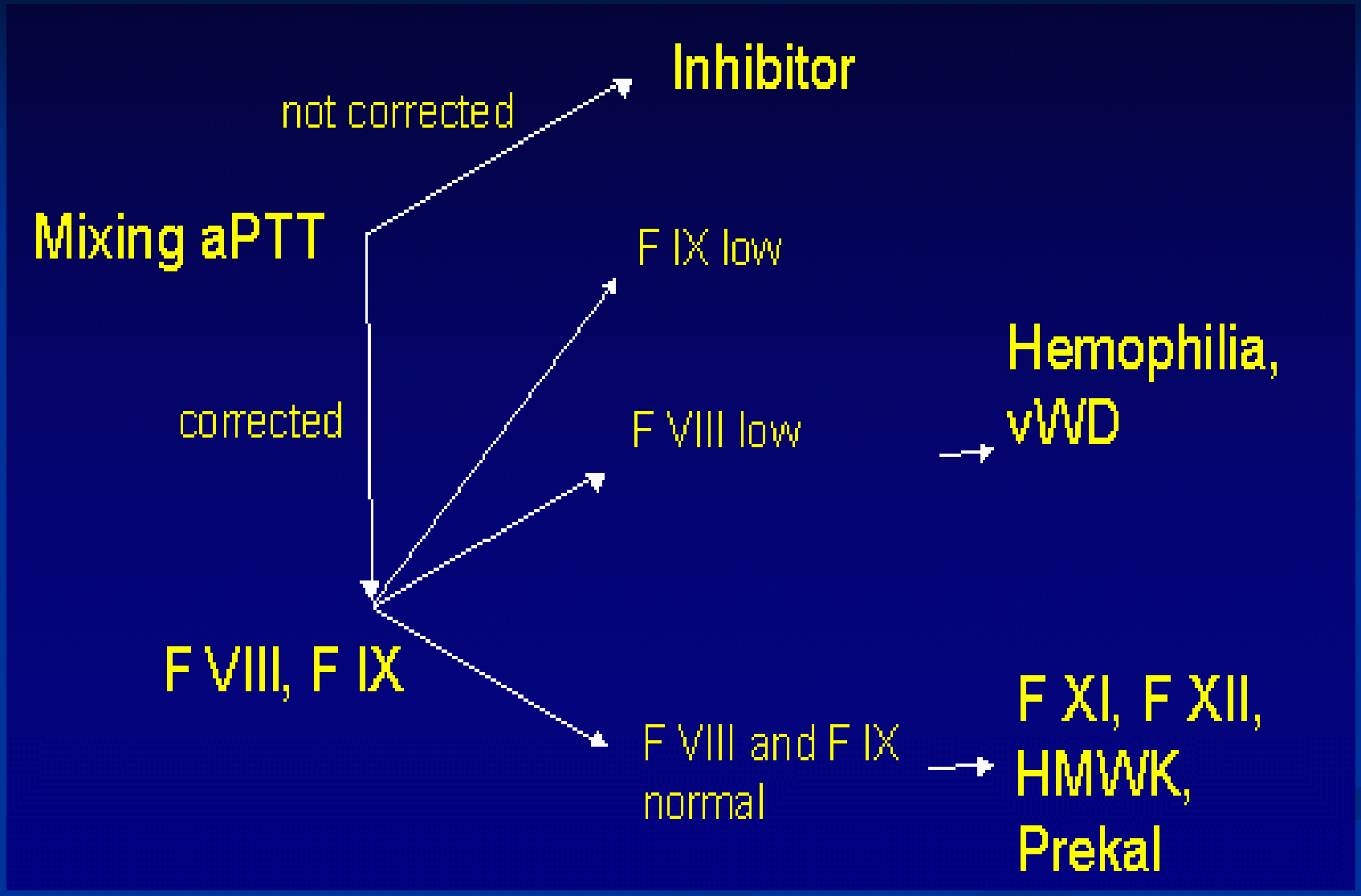
# SCREENING COAGULATION LABORATORY RESULTS

- PT= 10 sec (Normal 8-14.6)
- aPTT= 57 sec (Normal 24-36.5)
- Plt= 450,000 /μL (Normal 130,000-350,000)

# Coagulation Cascade



# Differential diagnosis of prolonged PTT



# Further test results

- Mixing PTT: 32 sec (immediate),
  34 sec (2 hr incubation)
- F VIII=5% (ref 50-150%)
- F IX= 132%
- F XI = 112%

# DIAGNOSIS

- Factor VIII Deficiency (Hemophilia A)

# Early Observations

- 1828: The word "hemophilia" first appeared in a description of the condition written by German Physician Frederick Hopff at the University of Zurich
- 1840: First recorded case of hemophilia treatment by transfusion
- 1893: First documentation of abnormal prolongation of coagulation in capillary tube in hemophilia
- 1920-1930: Hemophilia treatments published; plasma for transfusions introduced
- 1937: IV administration of redissolved plasma precipitate (cryoprecipitate) shown to shorten blood clotting time

# New Discoveries

- 1952: Evolution of the definition of hemophilia: a blood clotting disorder affecting males with two possible major protein deficiencies: FVIII - Hemophilia A, FIX -Hemophilia B
- 1966: commercial availability of FVIII concentrates (plasma-derived)
- 1969: FIX concentrate licensed

# Hemophilia A

- X linked recessive
- 30% cases result from spontaneous mutation (patient in case study)
- Affects all races and ethnic groups equally
- Moderate & mild deficiencies are frequently under-diagnosed (patient in case study)
- Affected males
- All daughters are carriers
- No sons are affected

## Bleeding Pattern correlated with F VIII level

- Severe: <1% , spontaneous hemorrhage, ~1 per week
- Moderate: 1-5% , hemorrhage with incidental injury , ~ 4 –6 / year
- Mild: 5-30% , hemorrhage with injury or surgery, bleeding uncommon
- Subclinical: 30-50%, hemorrhage with major injury or surgery , bleeding very uncommon

# Main Sites of Bleeding

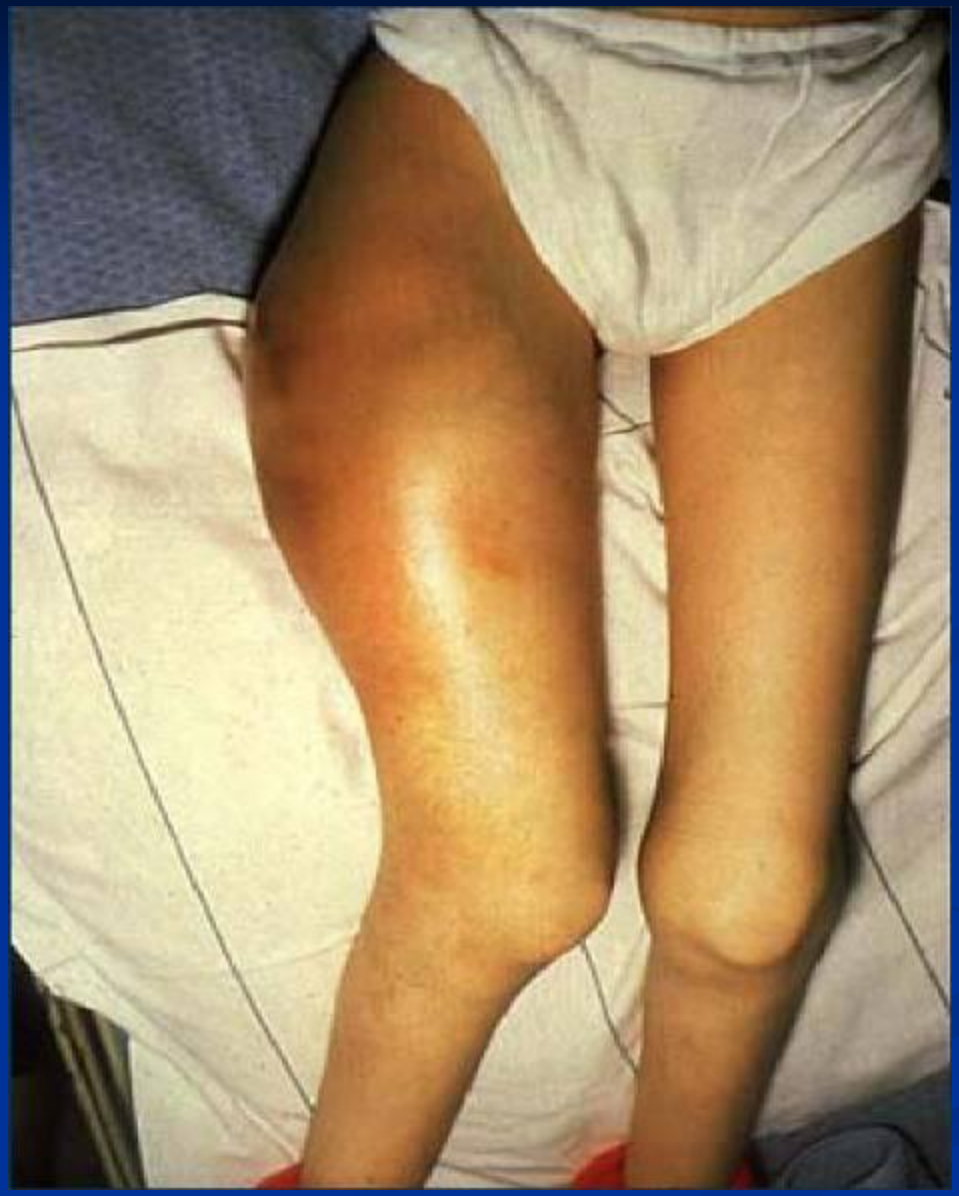
Joint:

- Acute: pain, swelling, interference with normal activities
- Chronic: synovial hypertrophy and synovitis leading to hemophilic arthropathy, disability

Muscle:

- Limb dysfunction
- Compartment syndrome due to nerve compression

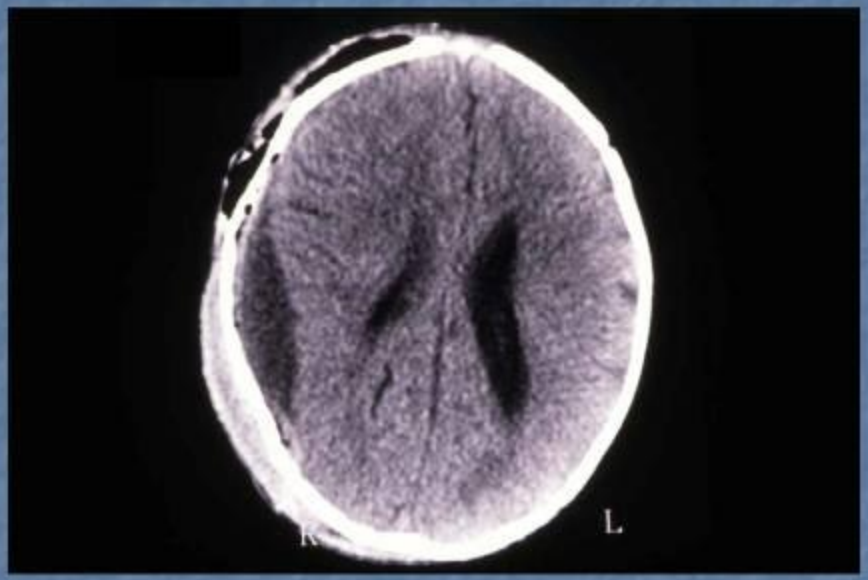
# Acute joint swelling due to bleeding

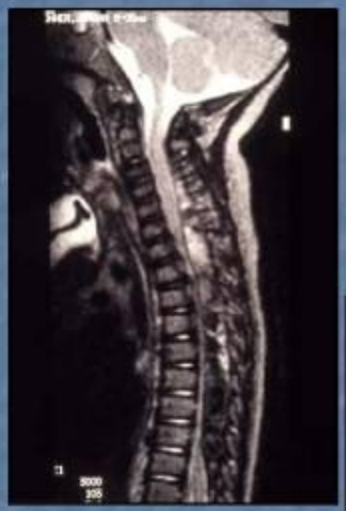


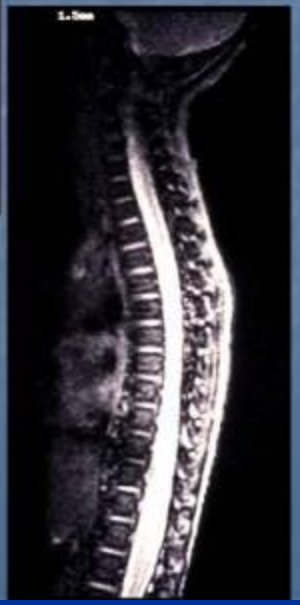
# Other Sites of Bleeding

- Gum
- Nose
- GU
- GI
- Retroperitoneal
- Retropharyngeal and sublingual
- CNS
- Others

# CNS Bleeding





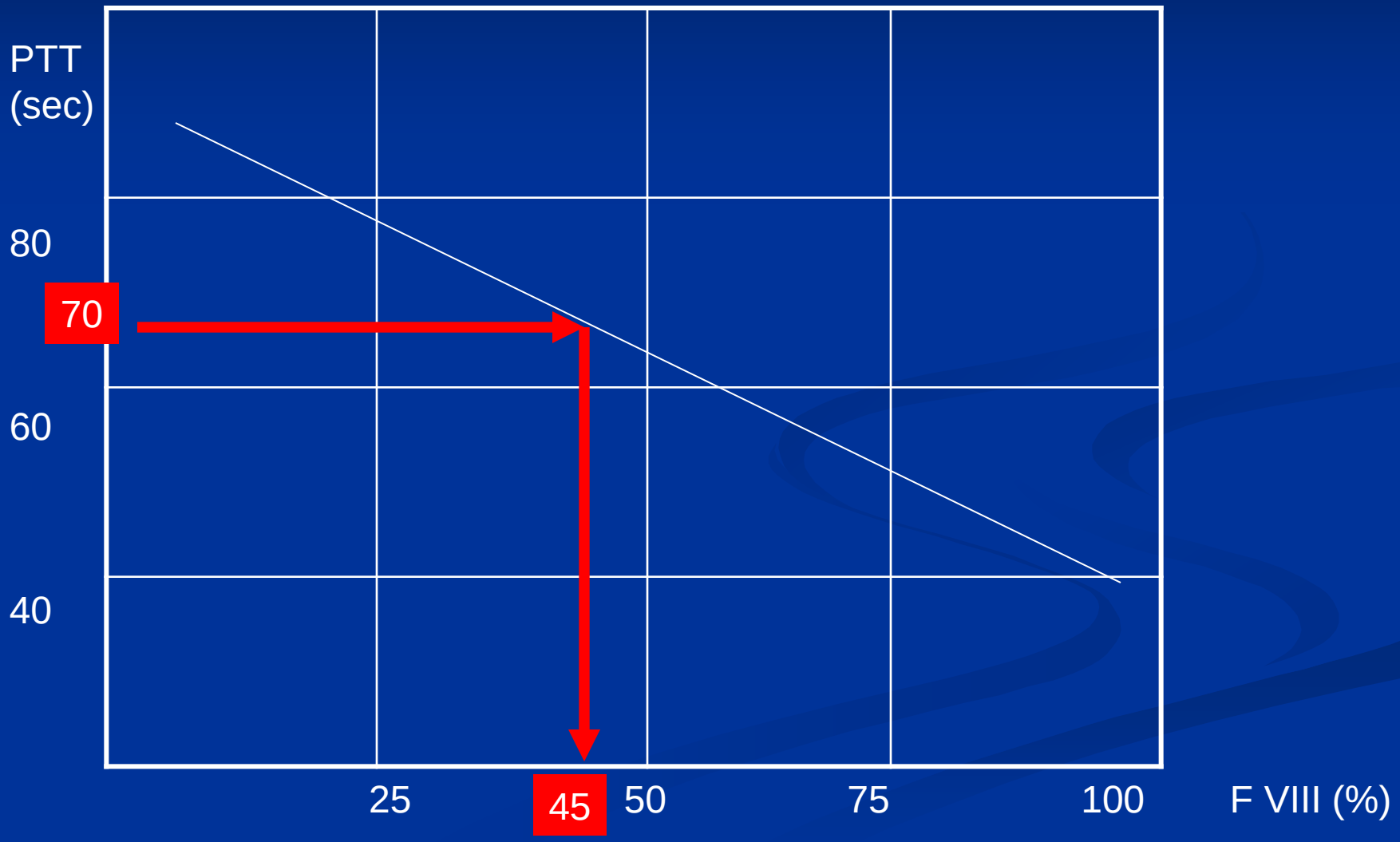
# Hemophilia A Carriers

- ~ 1/3 have low factor levels
- May experience bleeding symptoms seen in mild deficient states
- Bleeding after dental extraction, tonsillectomy, other surgery, delivery/post partum
- Treat carriers as potential bleeders

# Factor VIII assay

- Factor VIII level is inversely proportional to PTT
- A standard curve (PTT vs F VIII) is first set up using commercial assayed samples
- Mutiple dilutations of patient's sample (using F VIII-deficient substrate) are tested for PTT.
- These PTT's are plotted on the standard curve to intrapolate for F VIII
- Each F VIII is multiplied by the dilutation factor to obtain the actual F VIII before dilution
- F VIII level is the mean of F VIII's from multiple dilutions

# Factor VIII Standard Curve



# Treatment for Hemophilia A

- DDAVP (1-desamino-8-D-arginine vasopressin) for mild cases (2-10 fold increase in Factor VIII level)
- Factor VIII replacement, 1 unit/kg BW raises FVIII level by 2%, $T^{1/2}$=8hrs
- Factor VIII types: plasma-derived, recombinant, porcine

# Example for F VIII Dosage

- 1 IU/kg BW raises FVIII level by 2%
- Patient with 70 kg BW who needs to increase FVIII level from 0% to 100%:
  Dosage = 70 x (100 – 0) / 2 = 3,500 IU

(Note: for hemophilia B: 1 IU/kg BW raises FIX level by 1%)

# Target FVIII activity

- Surgery, CNS bleeding, GI and genitourinary bleeds -> 100%
- Bleeding into joints and muscle -> 40-80%

# F VIII Inhibitor Development

- Most serious complication of hemophilia A management
- Plasma-dervived FVIII and rFVIII carry similar inhibitor risk
- Inhibitor prevalence:
  - ~ 30% of severe population
  - ~3-13% in moderate deficiency

# Factor VIII Inhibitor Assay

- Measured in Bethesda Unit (BU)
- 1 BU = quantity of inhibitor in patient's plasma that results in loss of 50% factor activity in normal plasma sample (1:1 mix) after incubation for 2 hours at 37°C
- Positive for inhibitor: > 0.5 BU
- High responding inhibitor: titer > 5 BU
- Low responding inhibitor. titer < 5 BU despite repeated exposure

# Treatment for F VIII inhibitor

- More F VIII concentrates for mild case (double the dosage)
- For more severe cases:
  - Porcine F VIII (potential for development of inhibitor against porcine F VIII)
  - FEIBA (Factor eight inhibitor bypassing activity) consisting of F IIa, VIIa, IXa, Xa
  - Novo Seven (F VIIa)
- High risk of thrombophilia with FEIBA, Novo Seven