eding and
mbotic Disorders

Kristine Krafts, M.D.

Bleeding and Thrombotic Disorders

Bleeding disorders

- von Willebrand disease
- Hemophilia A and B
- DIC
- TTP/HUS
- ITP

Thrombotic disorders

- Factor V Leiden

Platelet bleeding

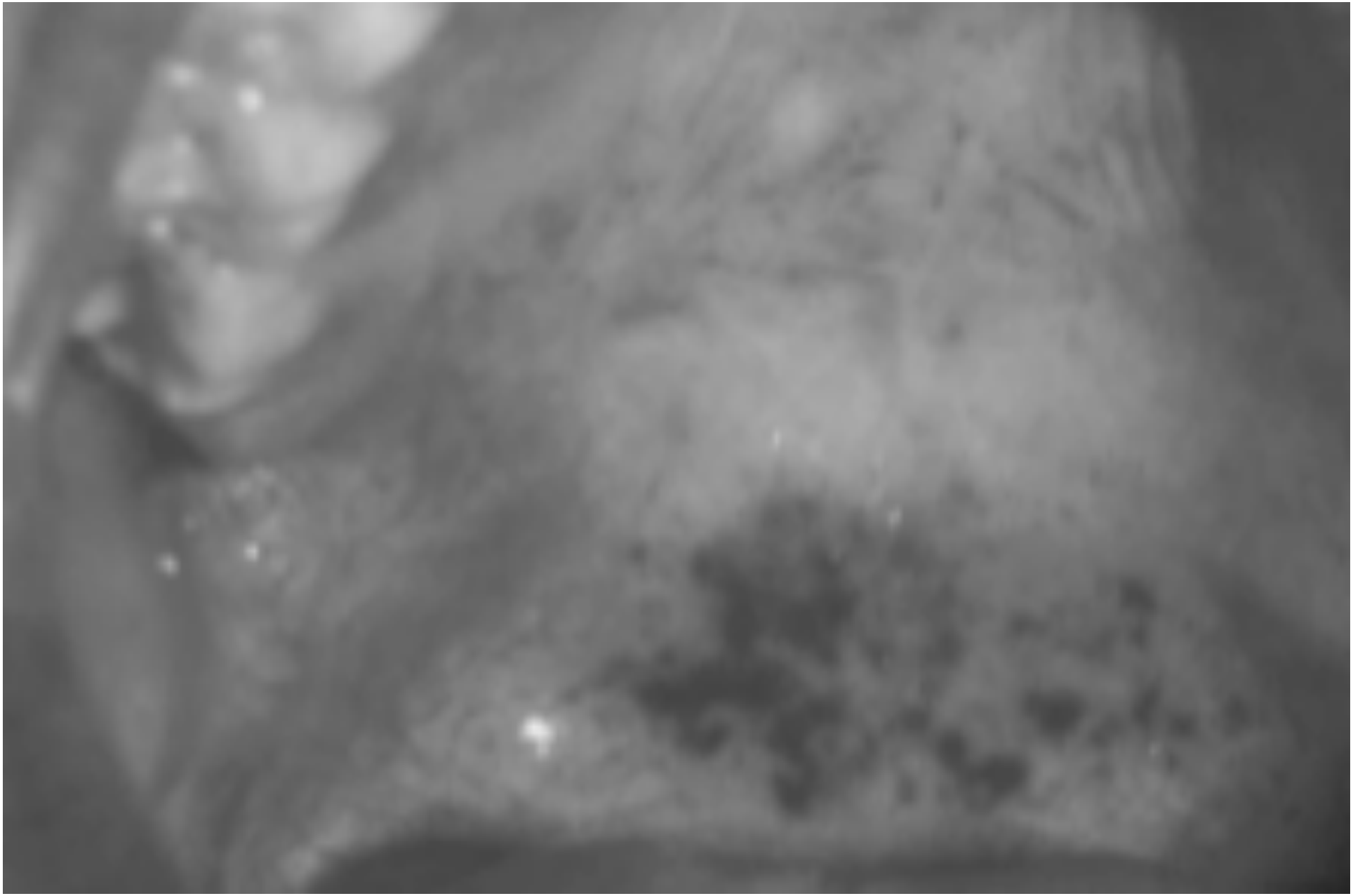
- Superficial (skin)
- Petechiae
- Spontaneous

Factor bleeding

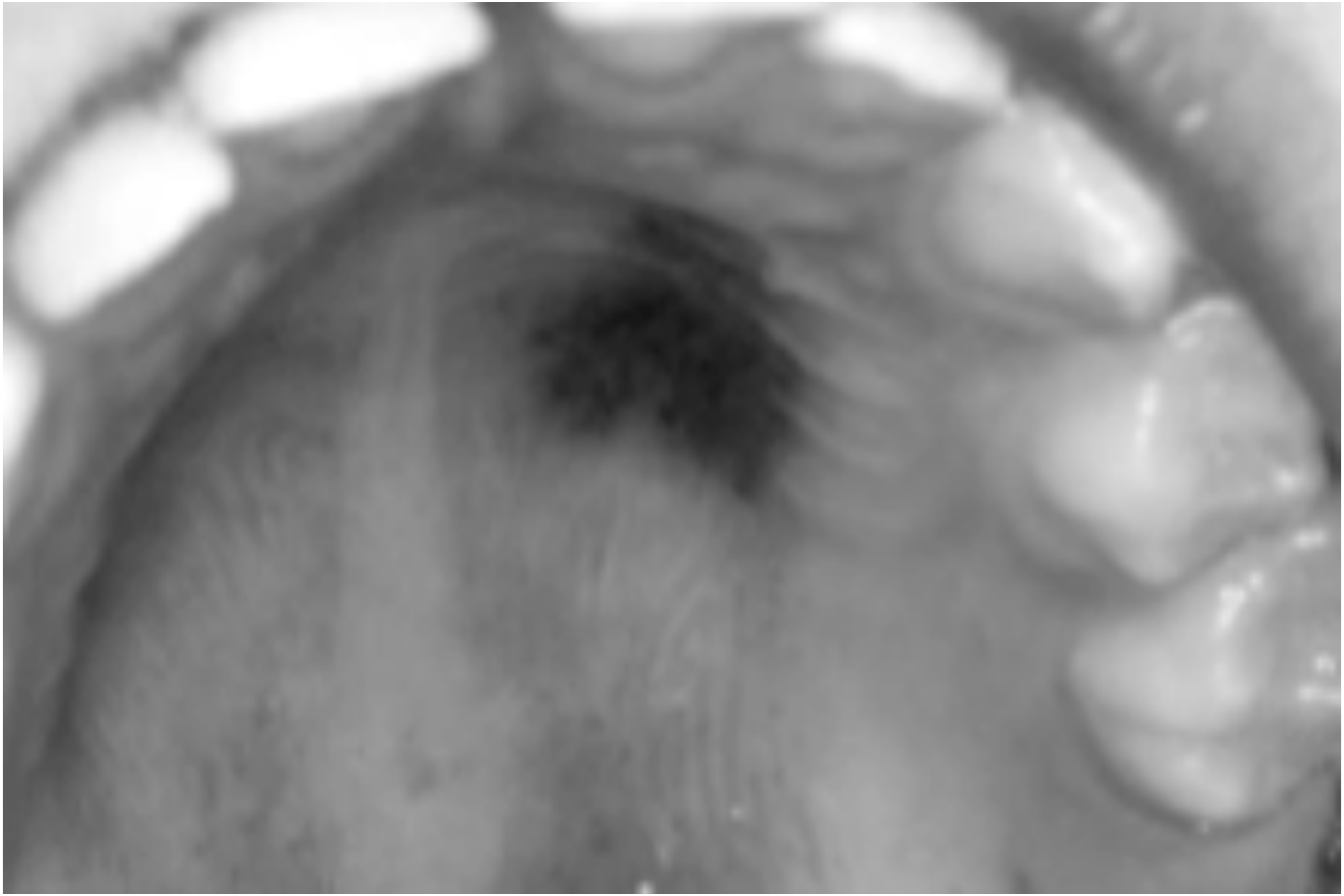
- Deep (joints)
- Big bleeds
- Trauma *

* Includes prolonged bleeding after dental work

Petechiae



Palatal petechiae



Palatal ecchymosis

Purpura

Bleeding after buttock injection in patient with hemophilia

Bleeding and Thrombotic Disorders

Bleeding disorders

- von Willebrand disease

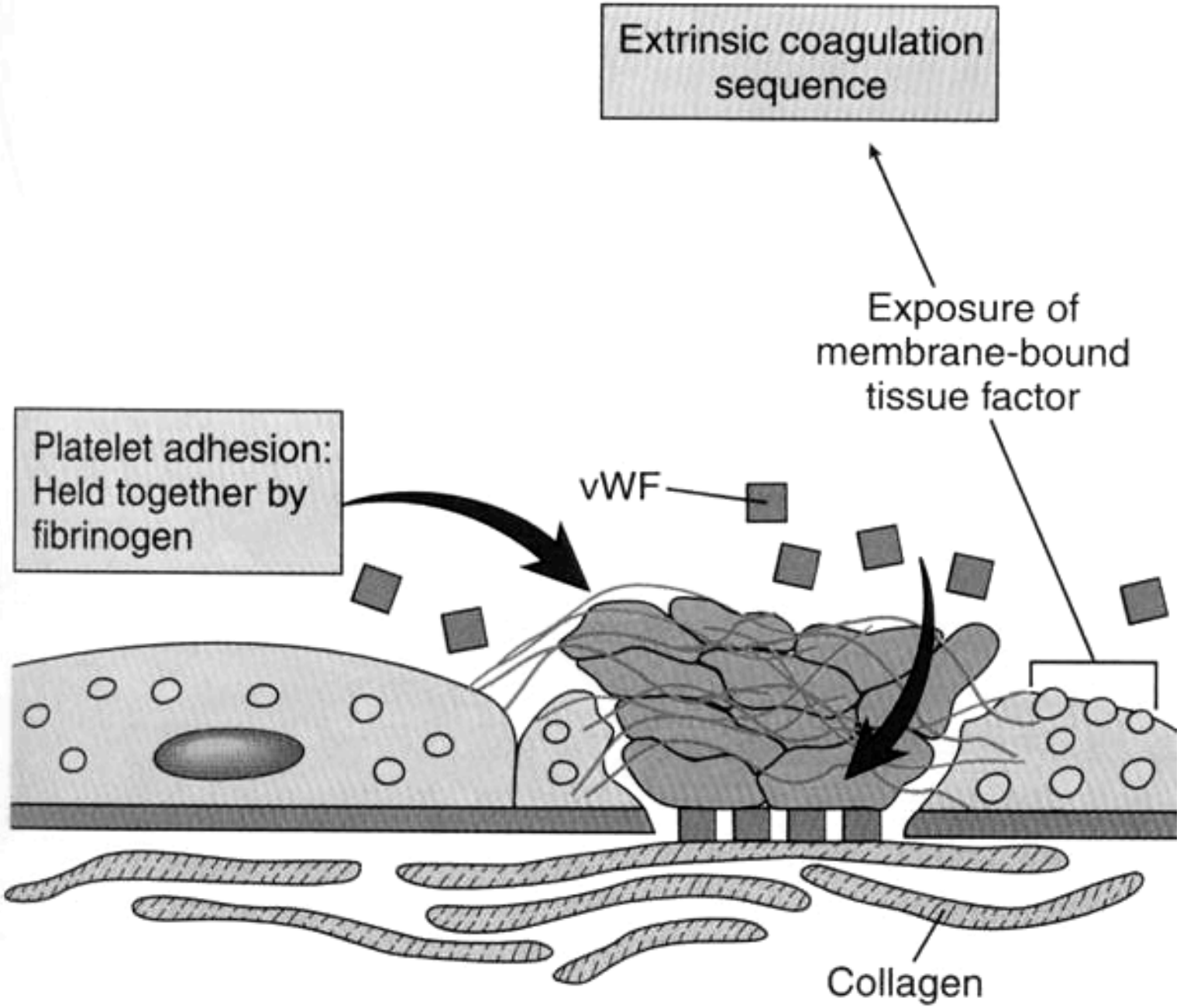
Von Willebrand Disease

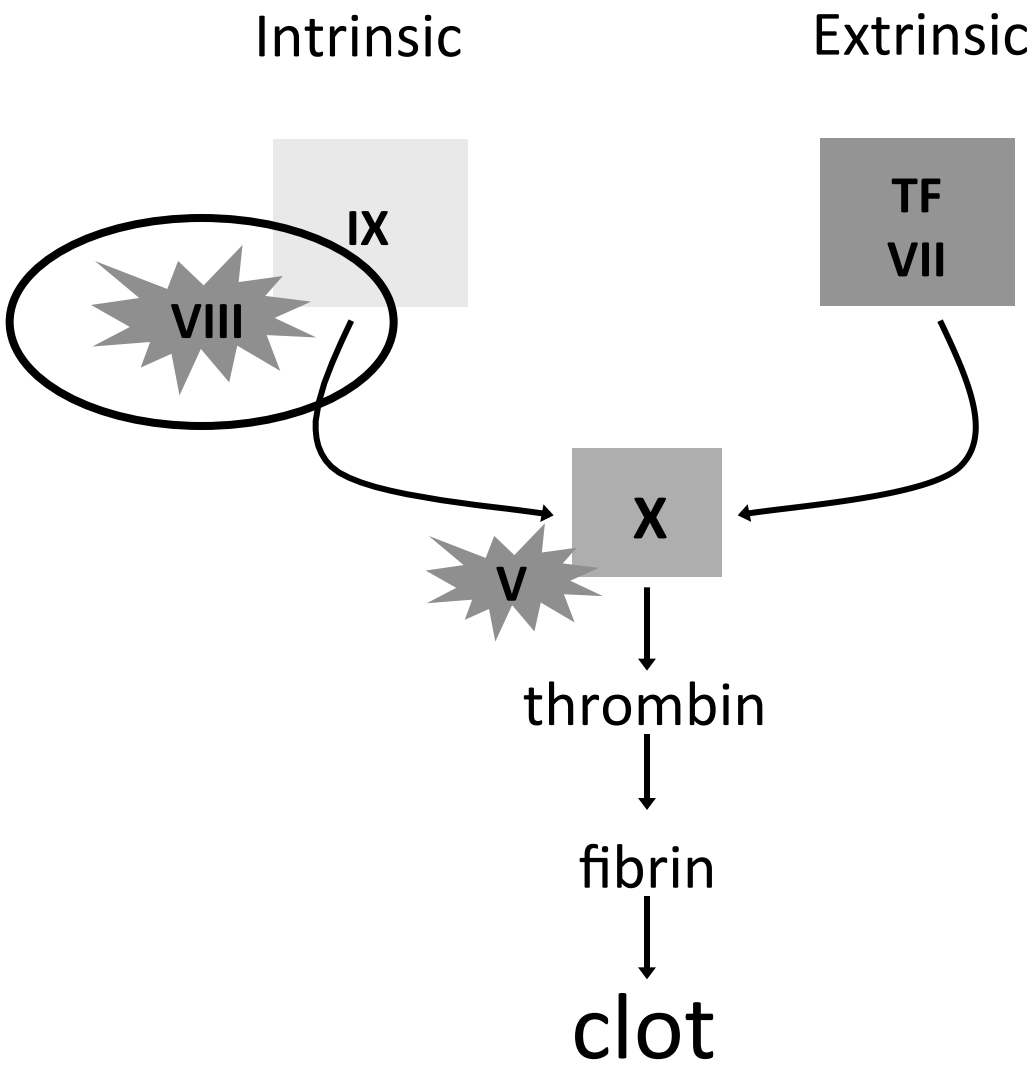
Things you must know

- Most common hereditary bleeding disorder
- Autosomal dominant
- vW factor decreased (or abnormal)
- Variable severity

What's von Willebrand Factor?

- Huge multimeric protein
- Made by megs and endothelial cells
- Glues platelets to endothelium
- Carries factor VIII
- Decreased or abnormal in vW disease


Extrinsic coagulation sequence
Exposure of membrane-bound tissue factor
Platelet adhesion: Held together by fibrinogen
vWF
Collagen


Intrinsic
Extrinsic
IX
VIII
TF
VII
X
V
thrombin
fibrin
clot

Symptoms of Von Willebrand Disease

- Mucosal bleeding in most patients
- Deep joint bleeding in severe cases

Lab Tests in Von Willebrand Disease

- Bleeding time: prolonged
- PTT: prolonged ("corrects" with mixing study)
- PT: normal

Treatment of Von Willebrand Disease

- DDAVP (raises VIII and vWF levels)
- Cryoprecipitate (contains vWF and VIII)
- Factor VIII

busy
distracting
sinful

SIN

Intrinsic

thrombin

XI → XIa

IX → IXa

VIII → VIIIa

Extrinsic

exposed TF

TF
VIIa ← VII

X

V → Va

Xa

prothrombin → thrombin

fibrinogen → fibrin → clot

Bleeding and Thrombotic Disorders

Bleeding disorders

- von Willebrand disease
- Hemophilia A and B

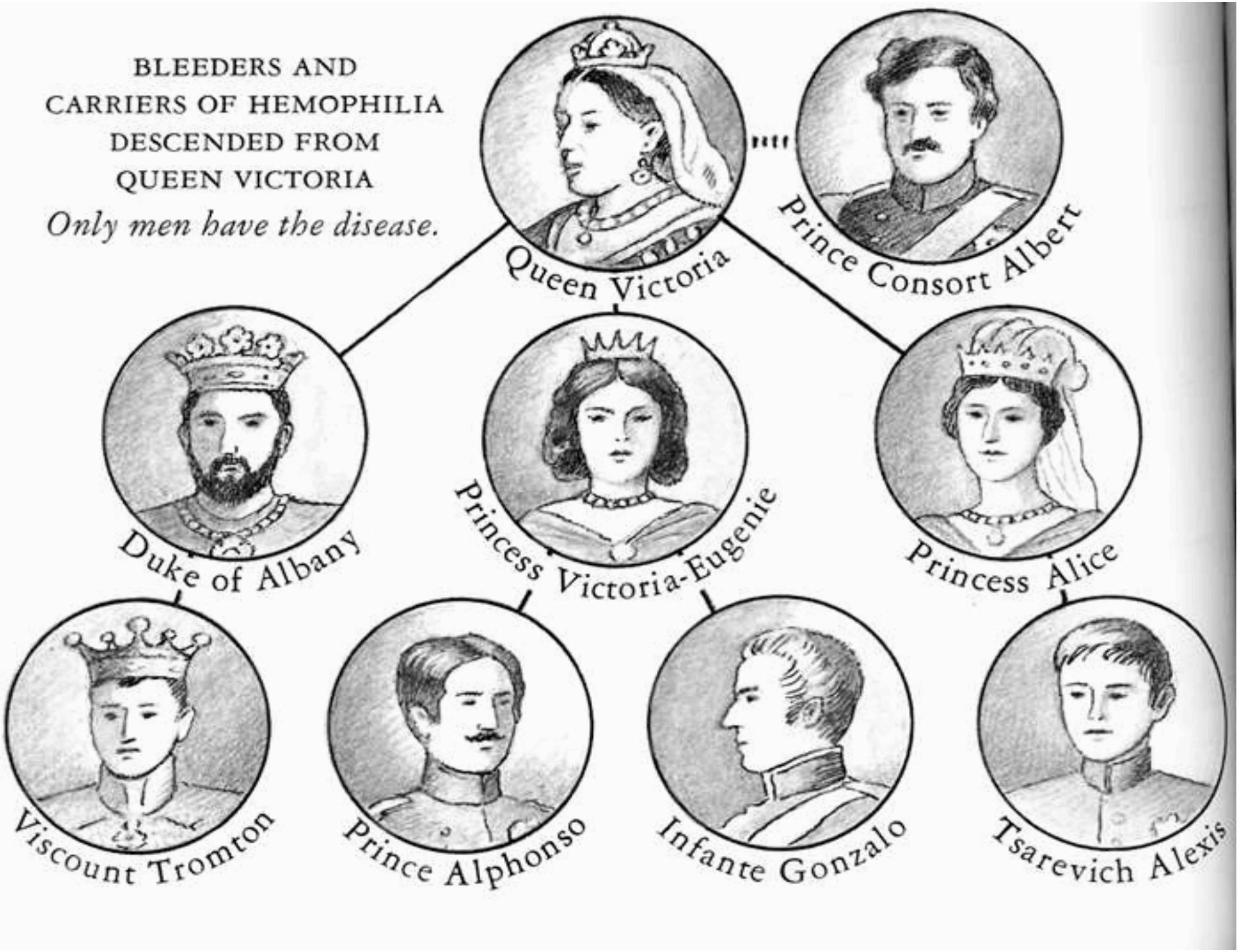
Hemophilia A

Things you must know

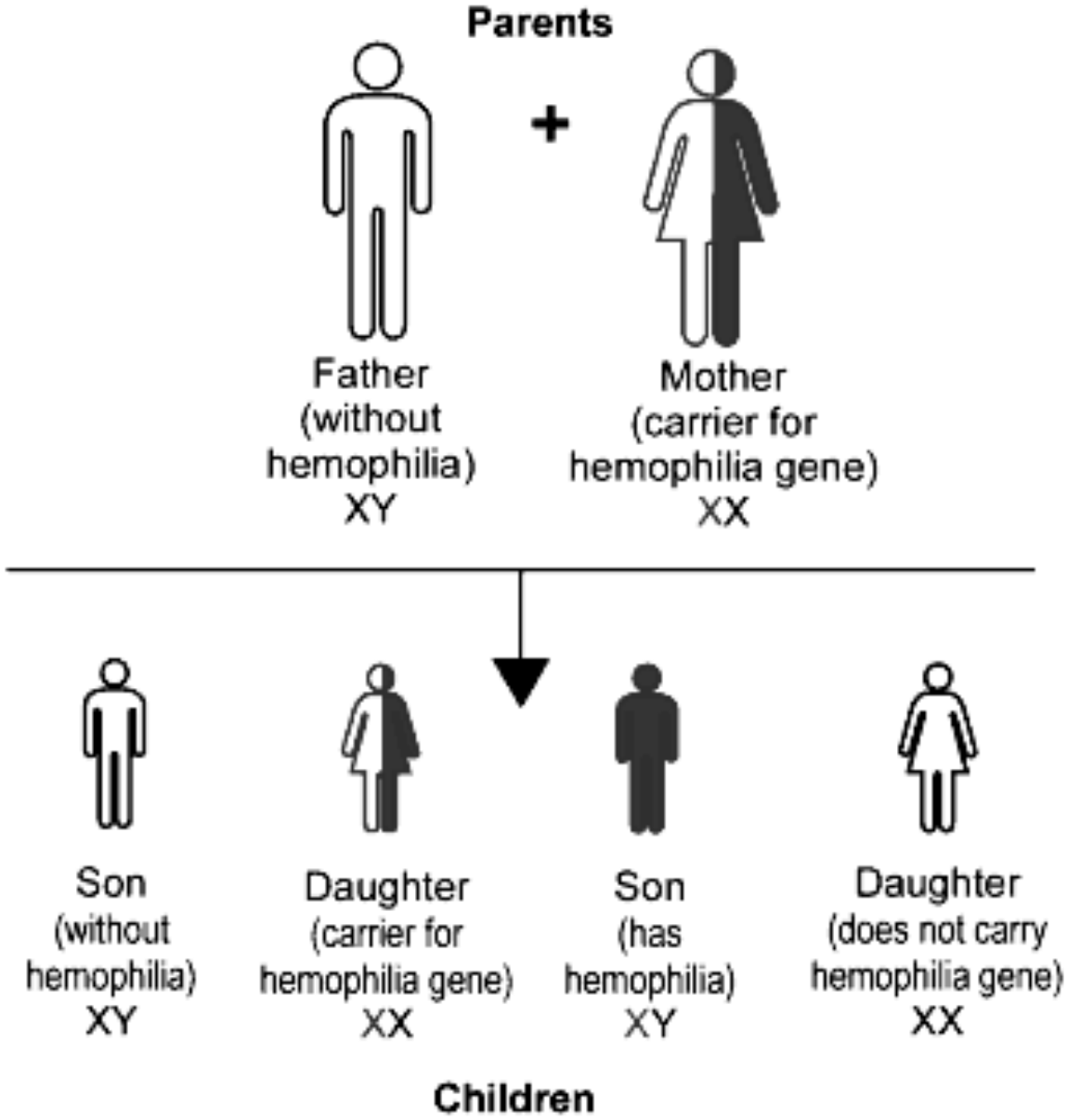
- Most common factor deficiency
- X-linked recessive in most cases (30% are spontaneous mutations)
- Factor VIII level decreased
- Variable amount of “factor” bleeding

BLEEDERS AND
CARRIERS OF HEMOPHILIA
DESCENDED FROM
QUEEN VICTORIA

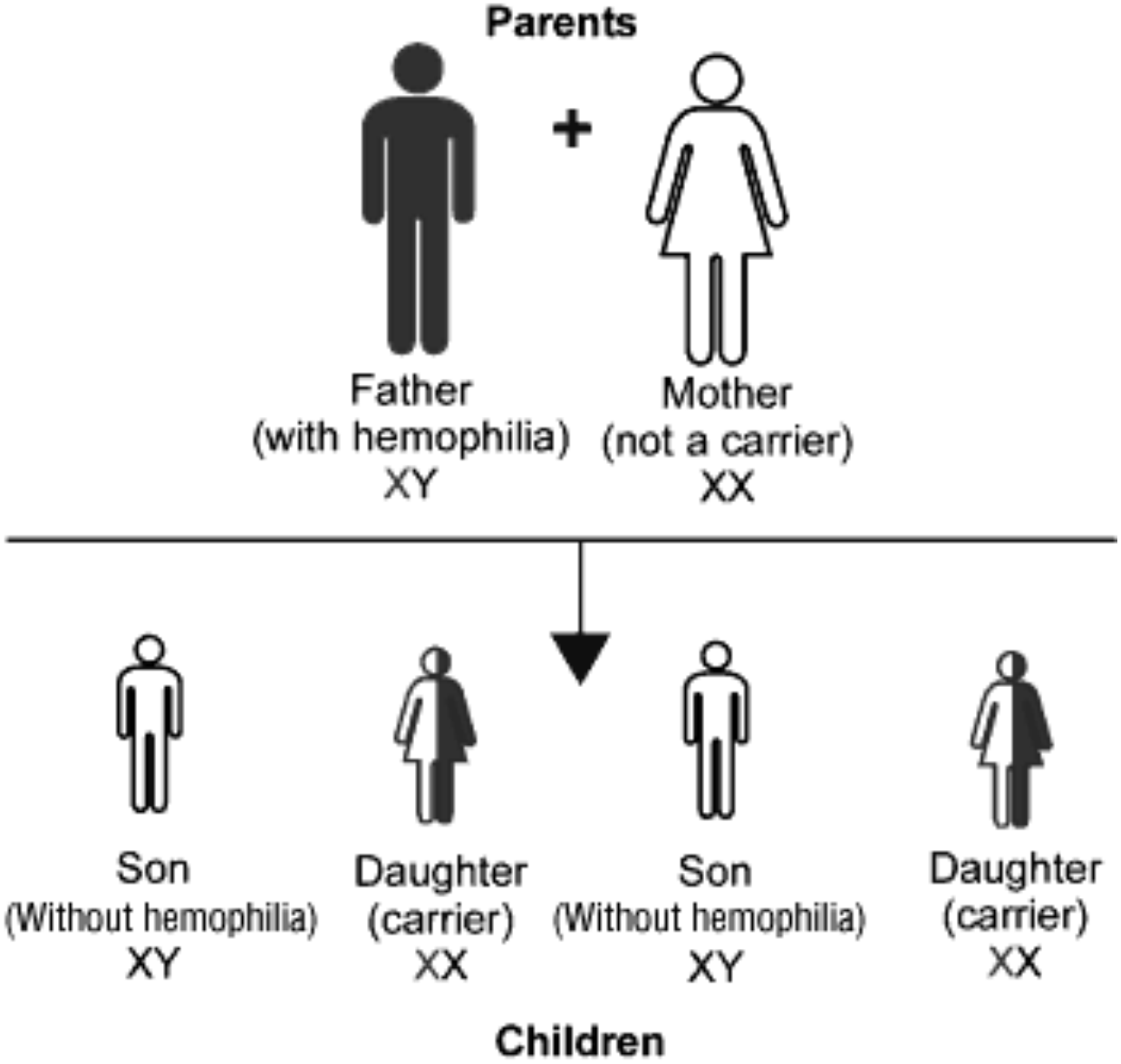
Only men have the disease.

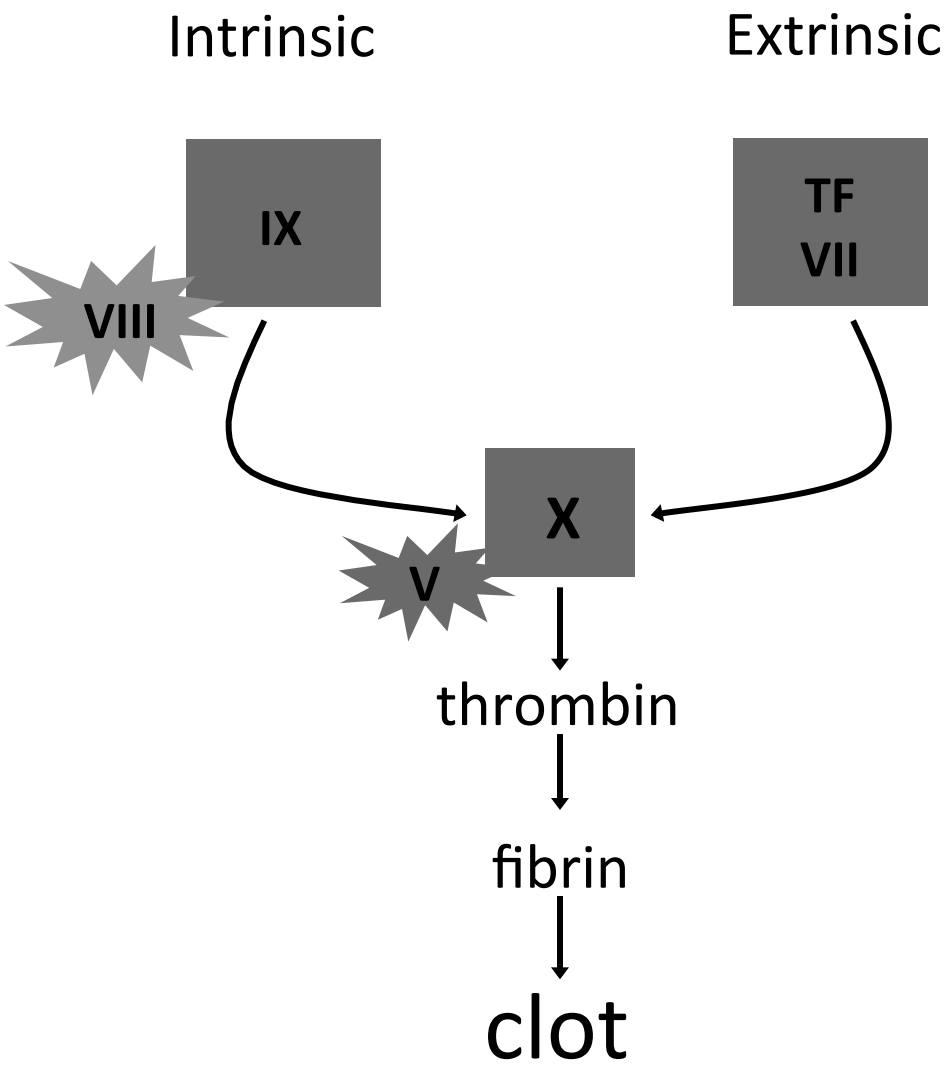


Inheritance of Hemophilia
"Carrier" Mother and Father Without Hemophilia



Inheritance of Hemophilia
Father With Hemophilia and Mother Who Is Not a Carrier

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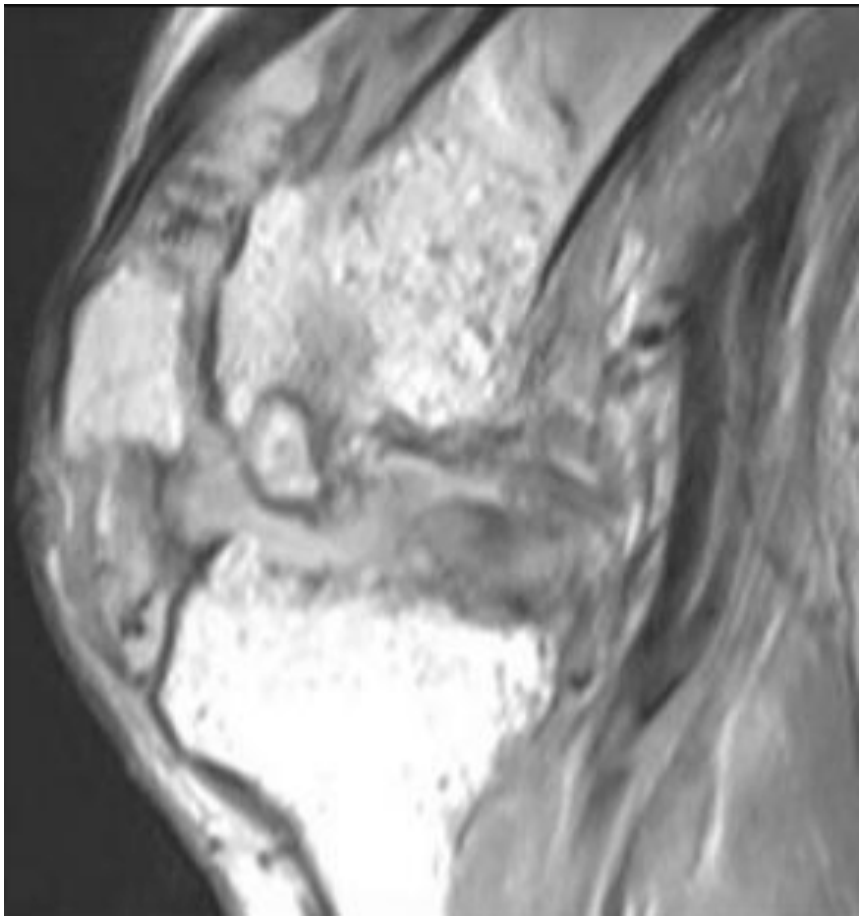
Deep joint bleeding in patient with hemophilia

Normal knee



Knee of patient with hemophilia

Hemophilic arthropathy of knee

Joint Deformity in Hemophilia

Hemophilia A

Lab tests

- PTT prolonged
- Factor VIII level low
- DNA studies abnormal

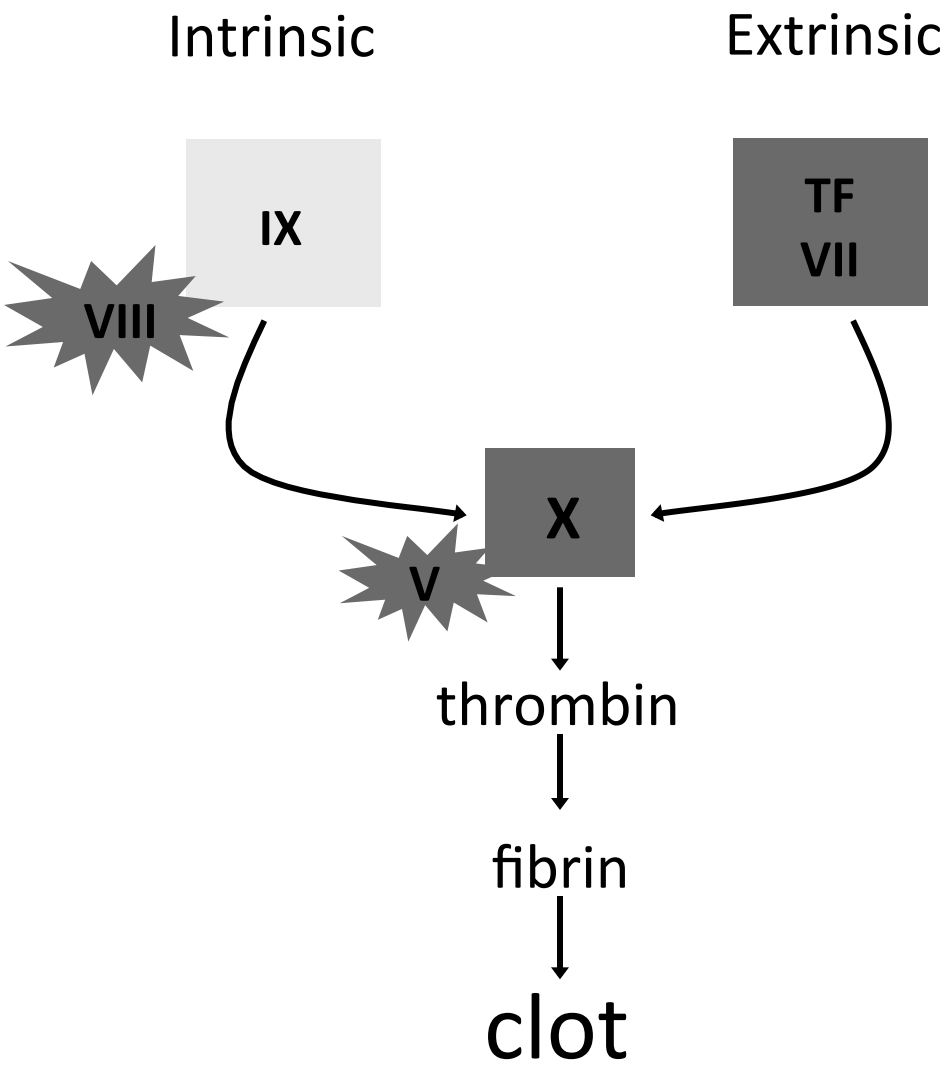
Treatment

- DDAVP
- Factor VIII

Hemophilia B

Things you must know

- Factor IX level decreased
- Much less common than hemophilia A
- Same inheritance pattern
- Same clinical and laboratory findings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Bleeding and Thrombotic Disorders

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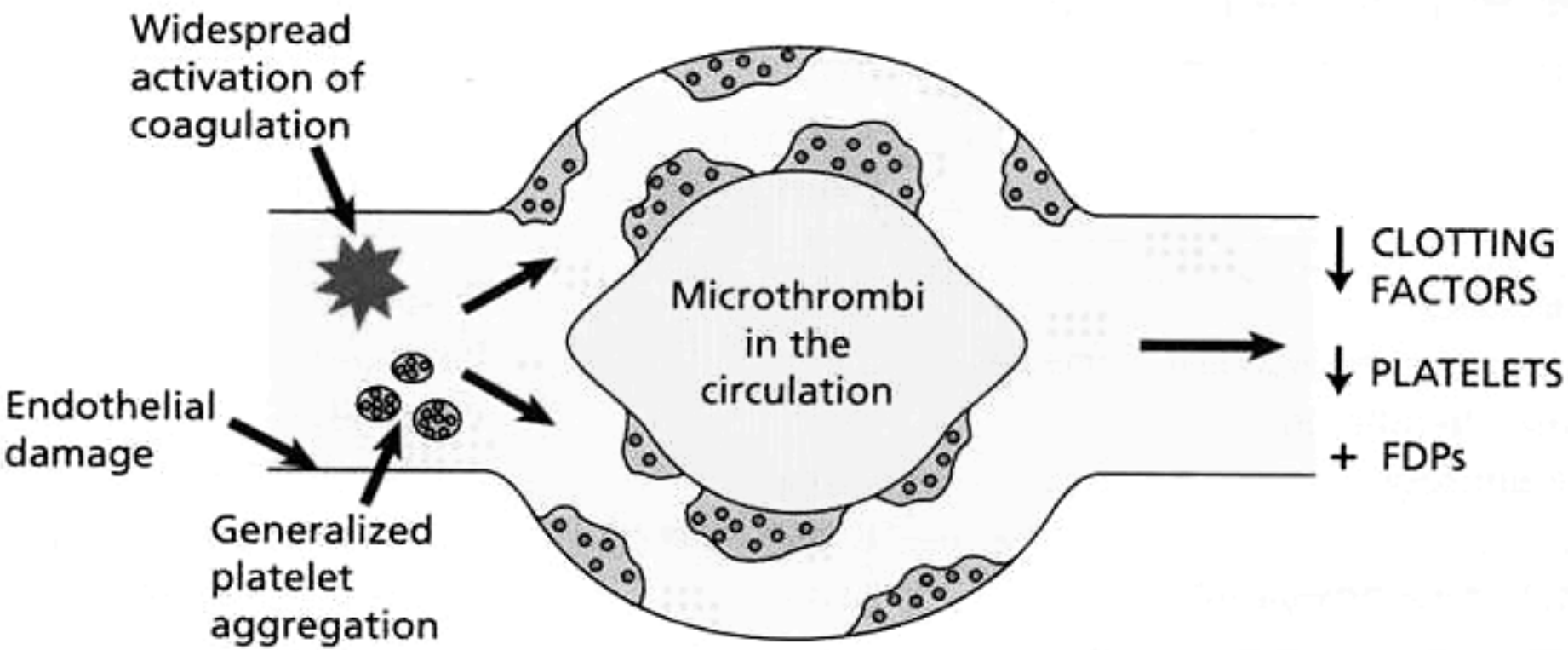
Widespread activation of coagulation
Endothelial damage
Generalized platelet aggregation
Microthrombi in the circulation
↓ CLOTTING FACTORS
↓ PLATELETS
+ FDPs

Thrombosis

Hemorrhage

Remember these for sure:

- Malignancy
- OB complications
- Sepsis
- Trauma

Bleeding and Thrombotic Disorders

Bleeding disorders

- von Willebrand disease
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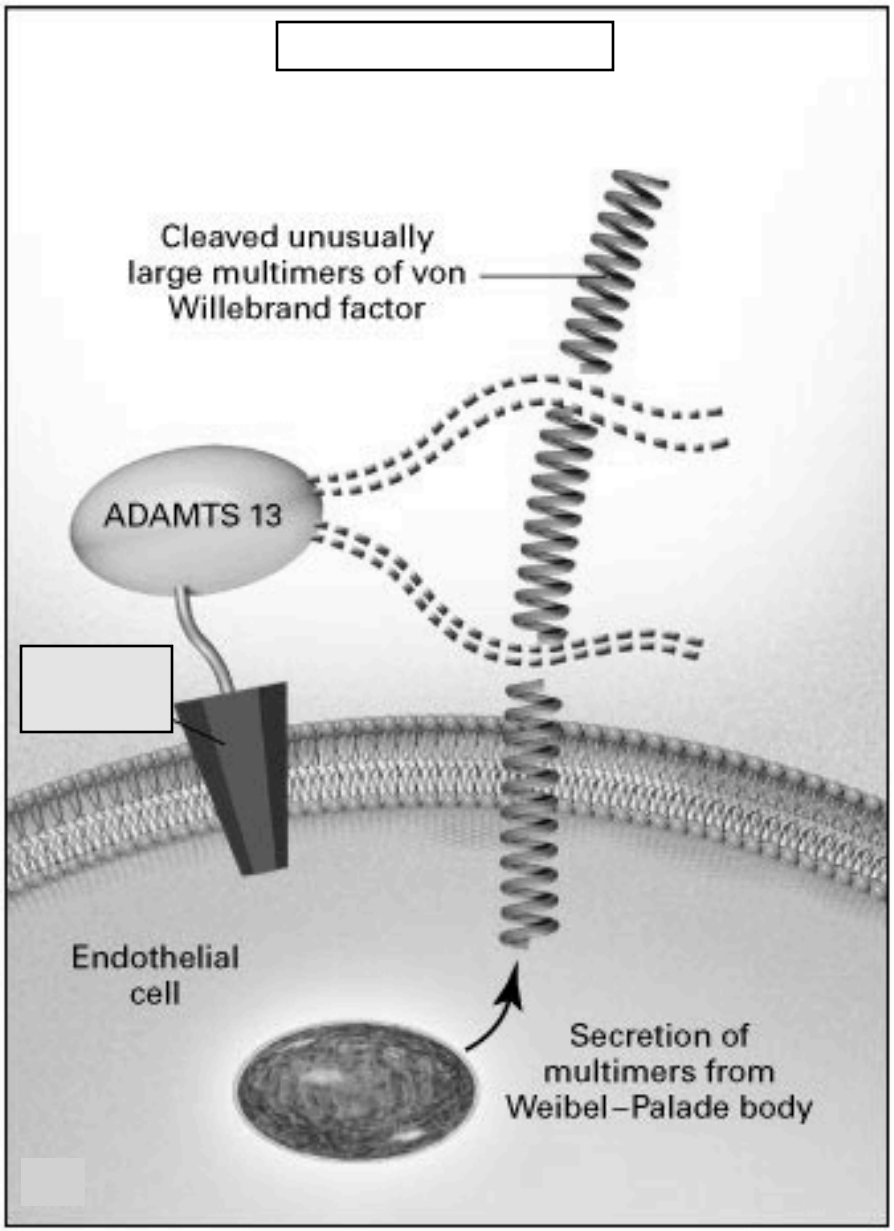
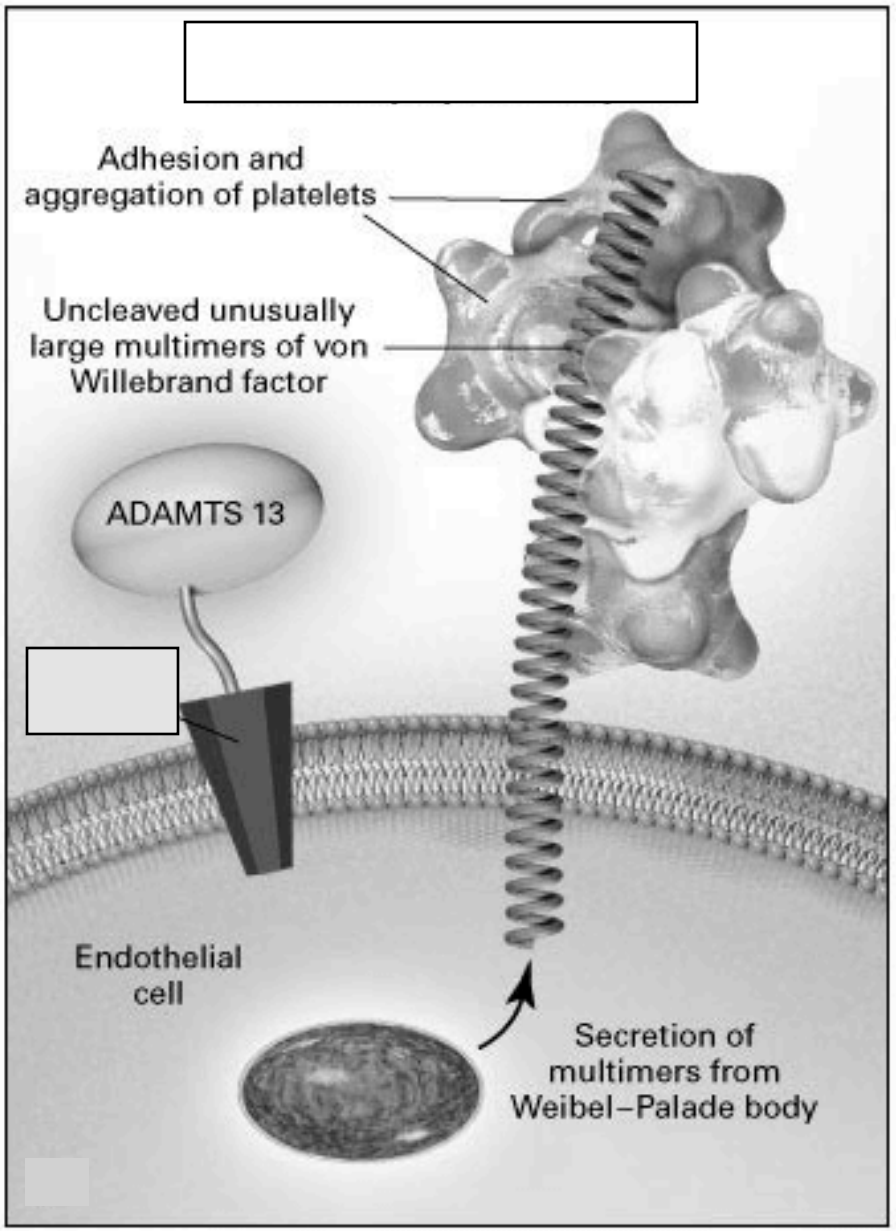
Thrombotic Thrombocytopenic Purpura

Things you must know

- Pentad: MAHA, thrombocytopenia, fever, neurologic defects, renal failure
- Deficiency of ADAMTS13
- Big vWF multimers trap platelets
- Plasmapheresis or plasma infusions

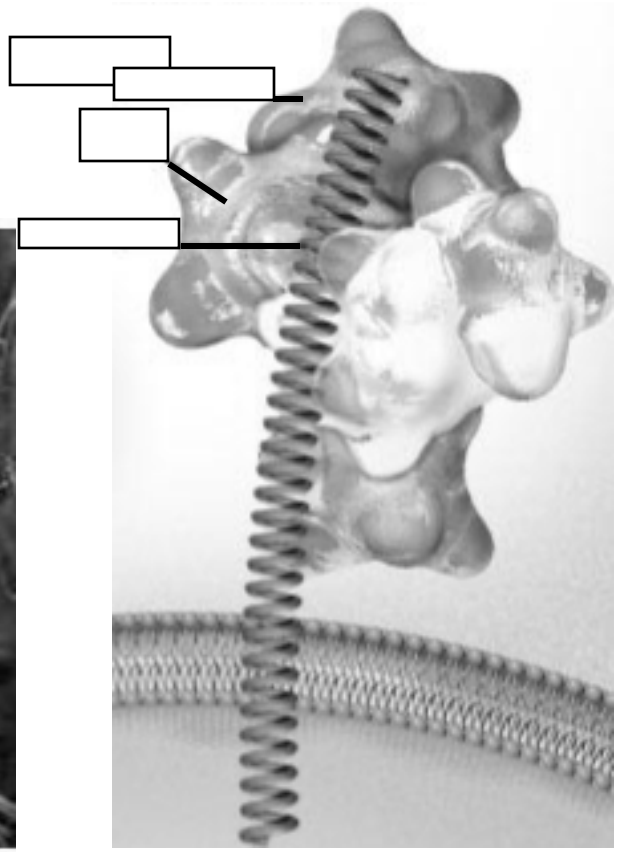

Cleaved unusually large multimers of von Willebrand factor
ADAMTS 13
Endothelial cell
Secretion of multimers from Weibel–Palade body


Adhesion and aggregation of platelets
Uncleaved unusually large multimers of von Willebrand factor
ADAMTS 13
Endothelial cell
Secretion of multimers from Weibel–Palade body

Nasty creatures

Rodent of unusual size (ROUS)

-*The Princess Bride*, 1987



Von Willebrand multimer of unusual size (MOUS)

- *NEJM,* 1982

Thrombotic Thrombocytopenic Purpura

Clinical pentad

- Hematuria/jaundice (MAHA)
- Bleeding/bruising (thrombocytopenia)
- Fever
- Bizarre behavior (thrombi in CNS)
- Renal failure (thrombi in kidney)

Treatment

- Plasmapheresis (in acquired TTP)
- Plasma infusions (in hereditary TTP)

Hemolytic Uremic Syndrome

Things you must know

- MAHA and thrombocytopenia
- Most are related to E. coli infection
- Toxin damages endothelium
- Treat supportively

Bleeding and Thrombotic Disorders

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- ITP

Idiopathic Thrombocytopenic Purpura

Things you must know

- Antiplatelet antibodies coat platelets
- Splenic macrophages eat platelets
- Diagnosis of exclusion
- Steroids or splenectomy

Bruising after minor trauma in ITP

Bleeding and Thrombotic Disorders

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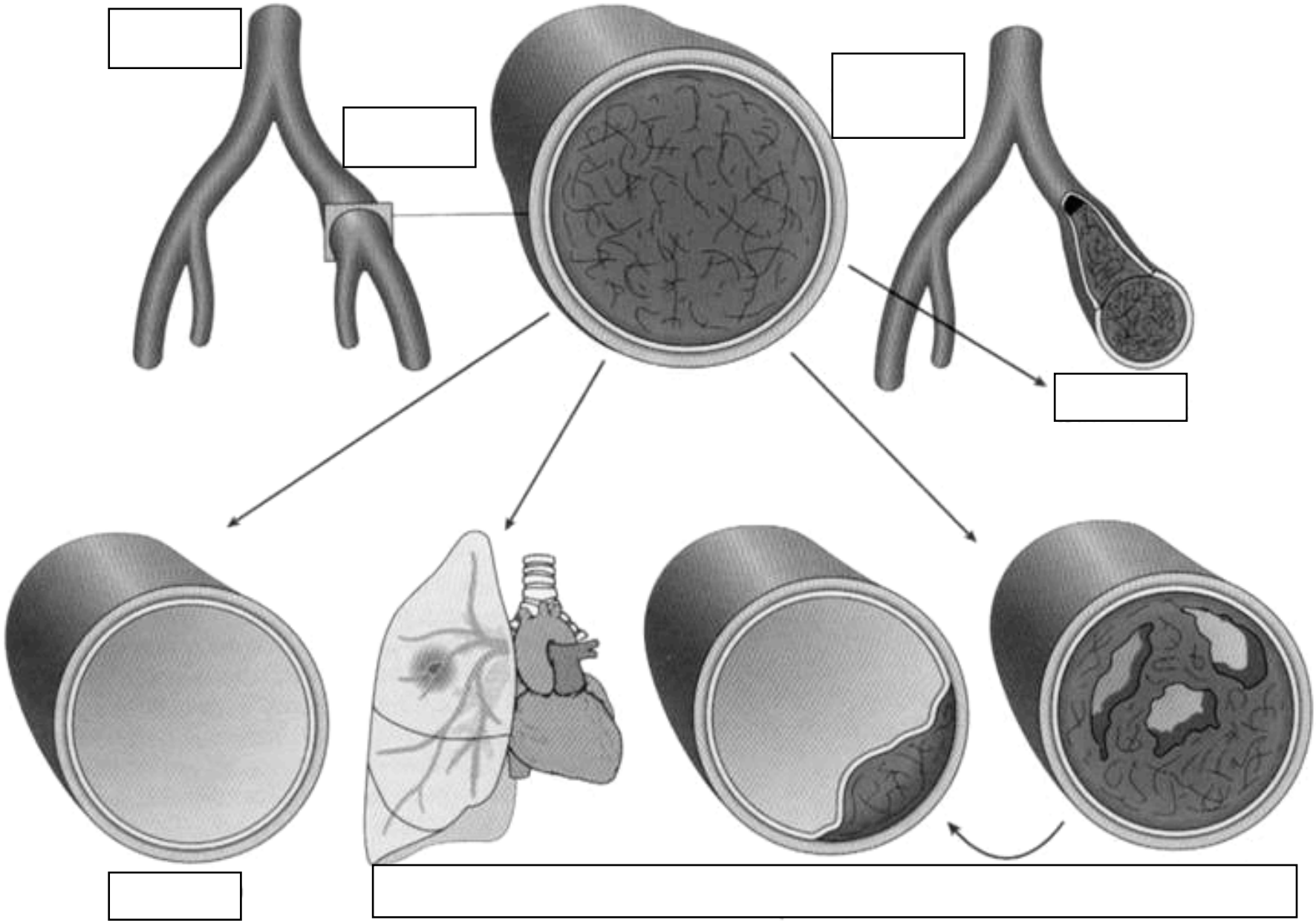
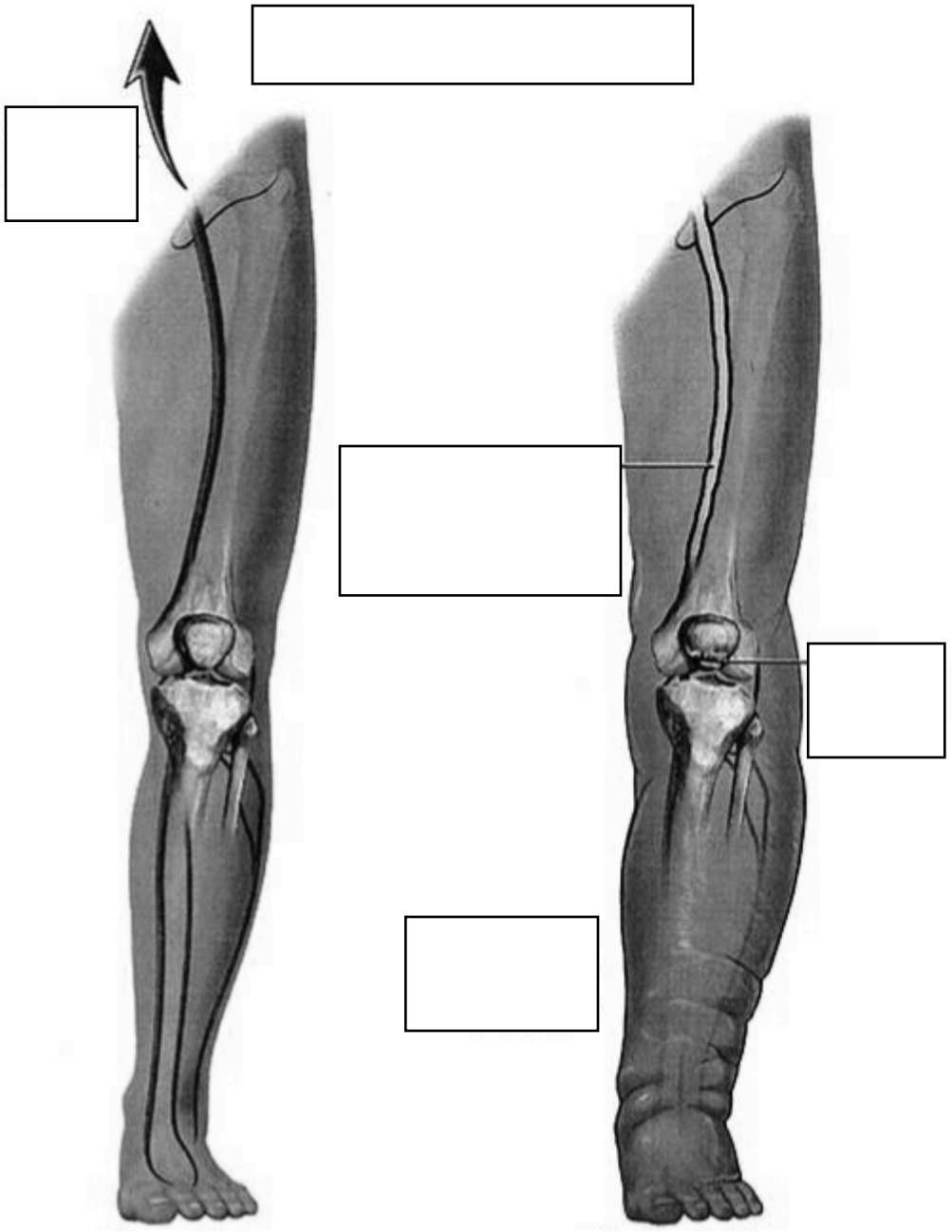
Thrombotic disorders

- Factor V Leiden

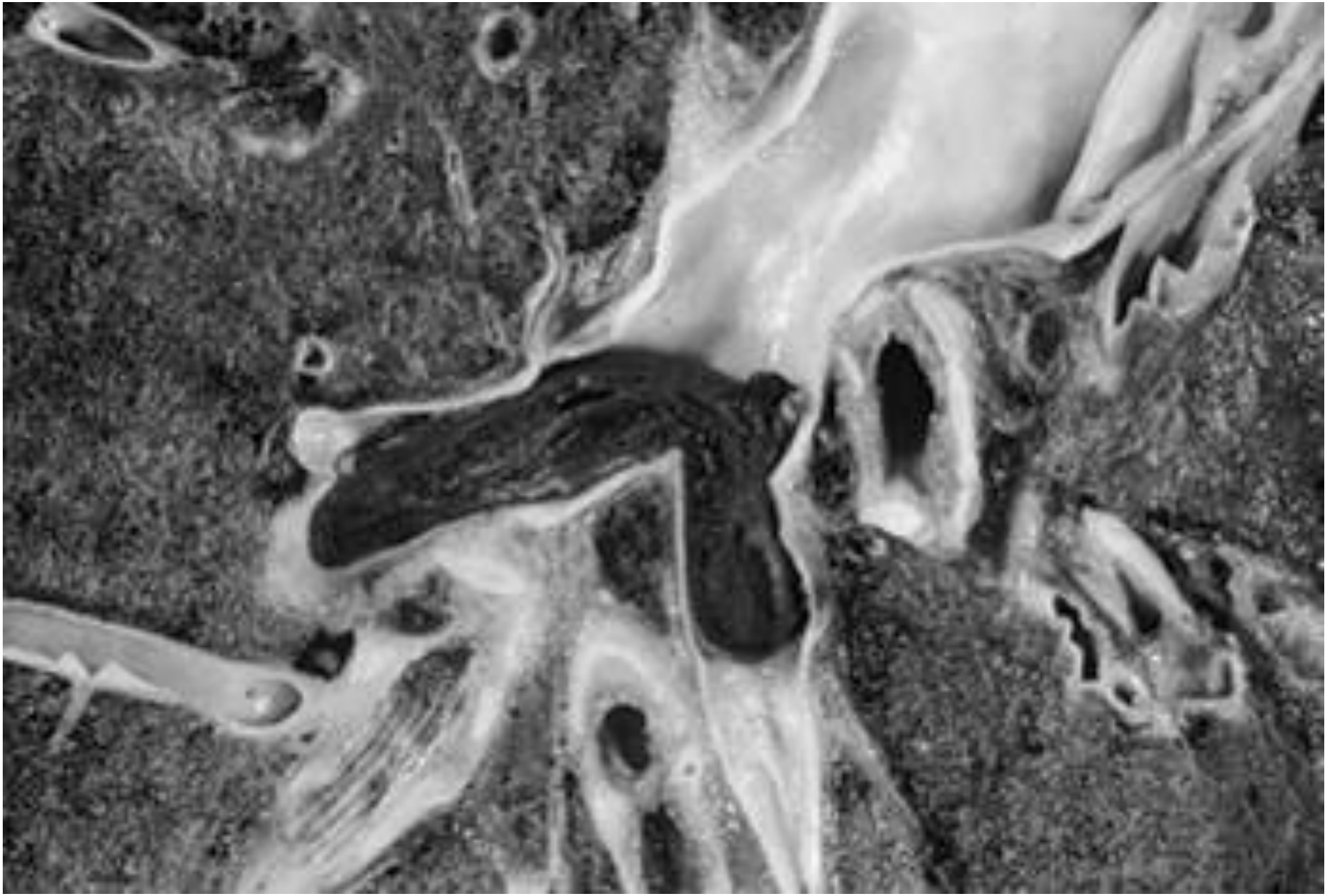


Blood clot sequelae



Deep venous thrombosis

Deep venous thrombosis



Pulmonary embolus

Thrombosis Risk Factors

Endothelial damage

- Atherosclerosis

Stasis

- Immobilization
- Varicose veins
- Cardiac dysfunction

Hypercoagulability

- Surgery
- Carcinoma
- Estrogen/postpartum
- Thrombotic disoders

When should you worry about a hereditary disorder?

- no obvious cause
- family history
- weird location
- recurrent
- patient is young
- miscarriages

Factor V Leiden

Things you must know

- Most common cause of unexplained thromboses
- Inherited point mutation in factor V gene
- Factor V can't be turned off
- High risk of thrombosis if homozygous

What is Factor V Leiden?

A mutated factor V gene

- Single point mutation
- Discovered in Leiden, Netherlands

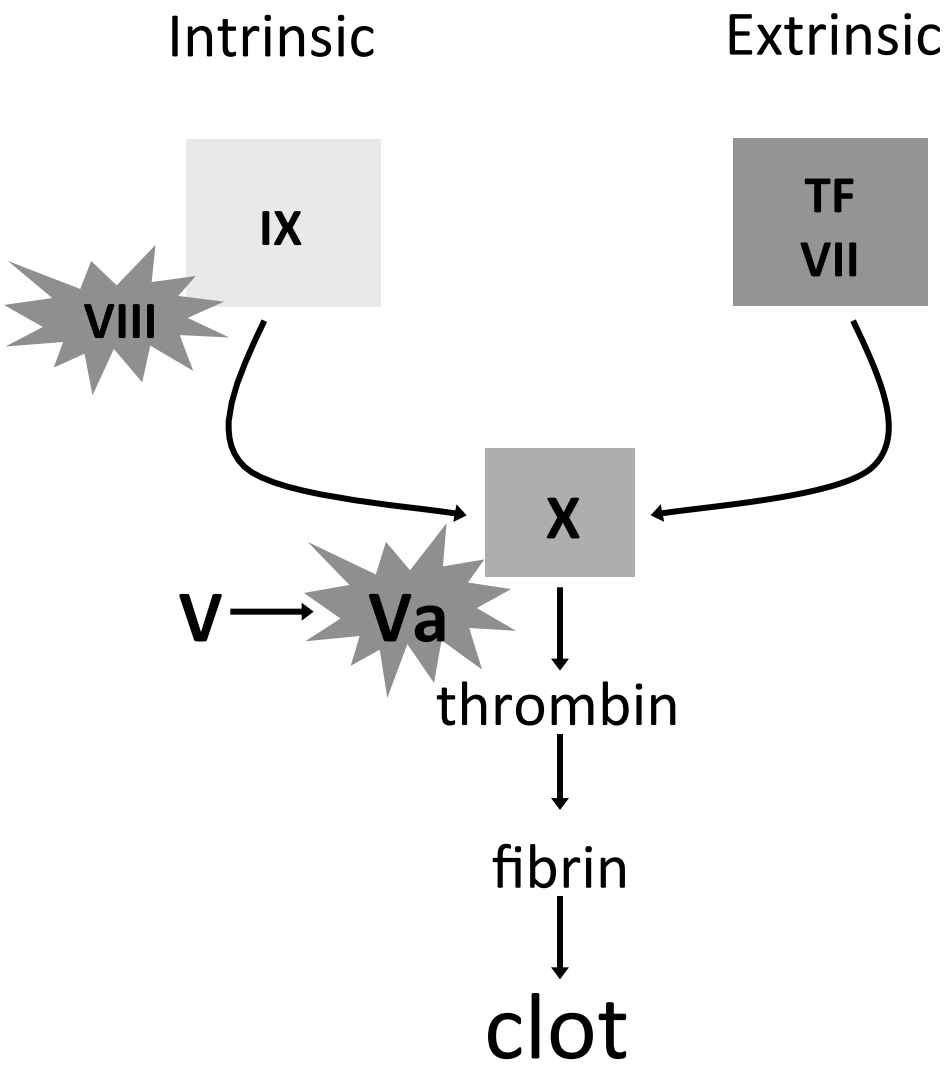
Produces abnormal factor V

- Participates in the cascade
- Can’t be cleaved by protein C

Yeah, so?

You can turn it on…

…but you can’t turn it off !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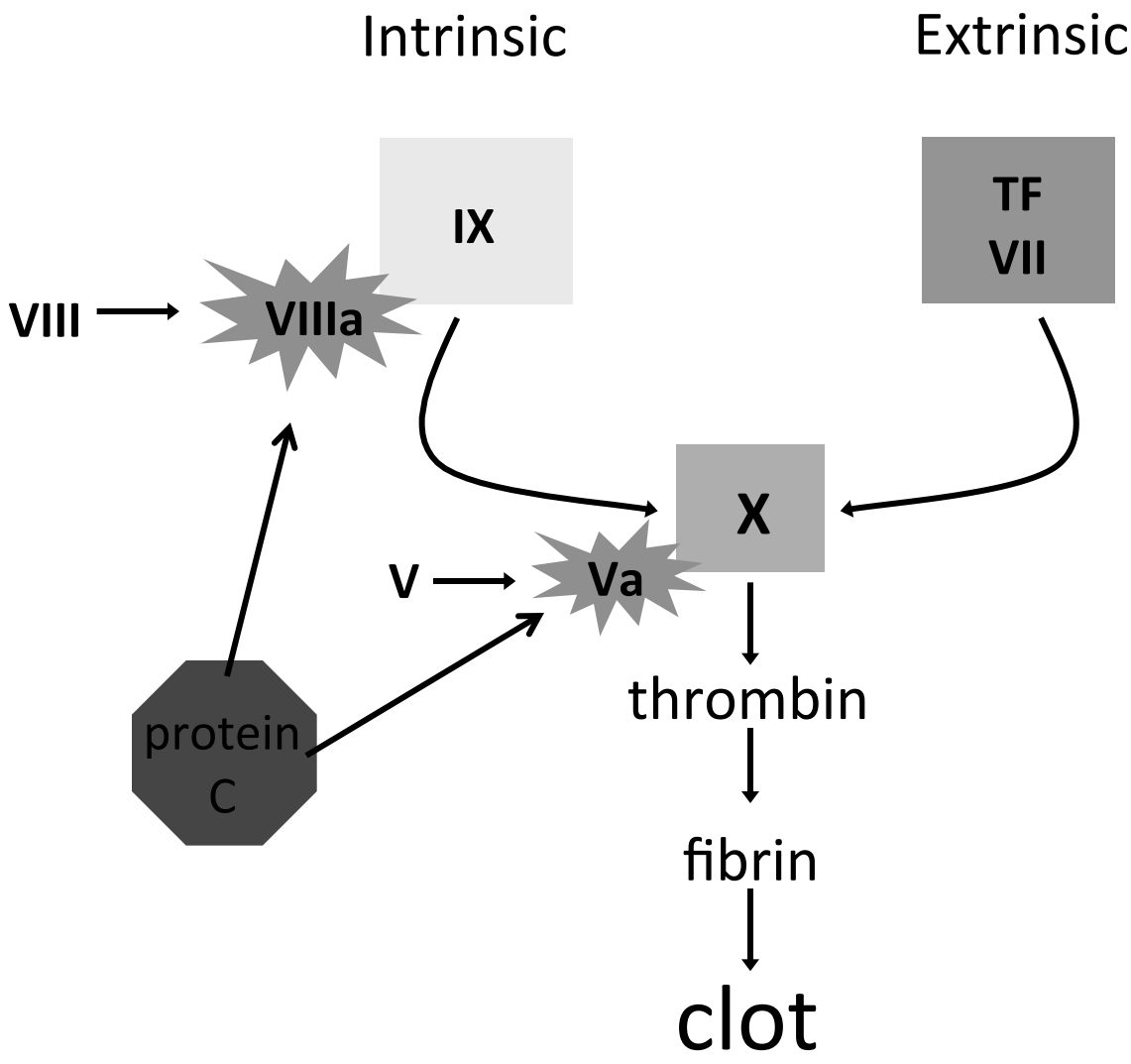
Intrinsic
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TF
VII
VIII
VIIIa
X
V
Va
protein
C
thrombin
fibrin
clot

What is the risk of getting a clot?

- Heterozygotes: 7 times normal
- Homozygotes: 80 times normal
- Normal risk = 5 per 100,000 person-years!

Factor V Leiden

Diagnosis

- PTT and INR not helpful
- Need genetic testing

Treatment

- Don't! Unless there is a thrombosis.
- Then give oral anticoagulants


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