Basics of Factor X Deficiency
An "Odyssey" from Birth to Adulthood

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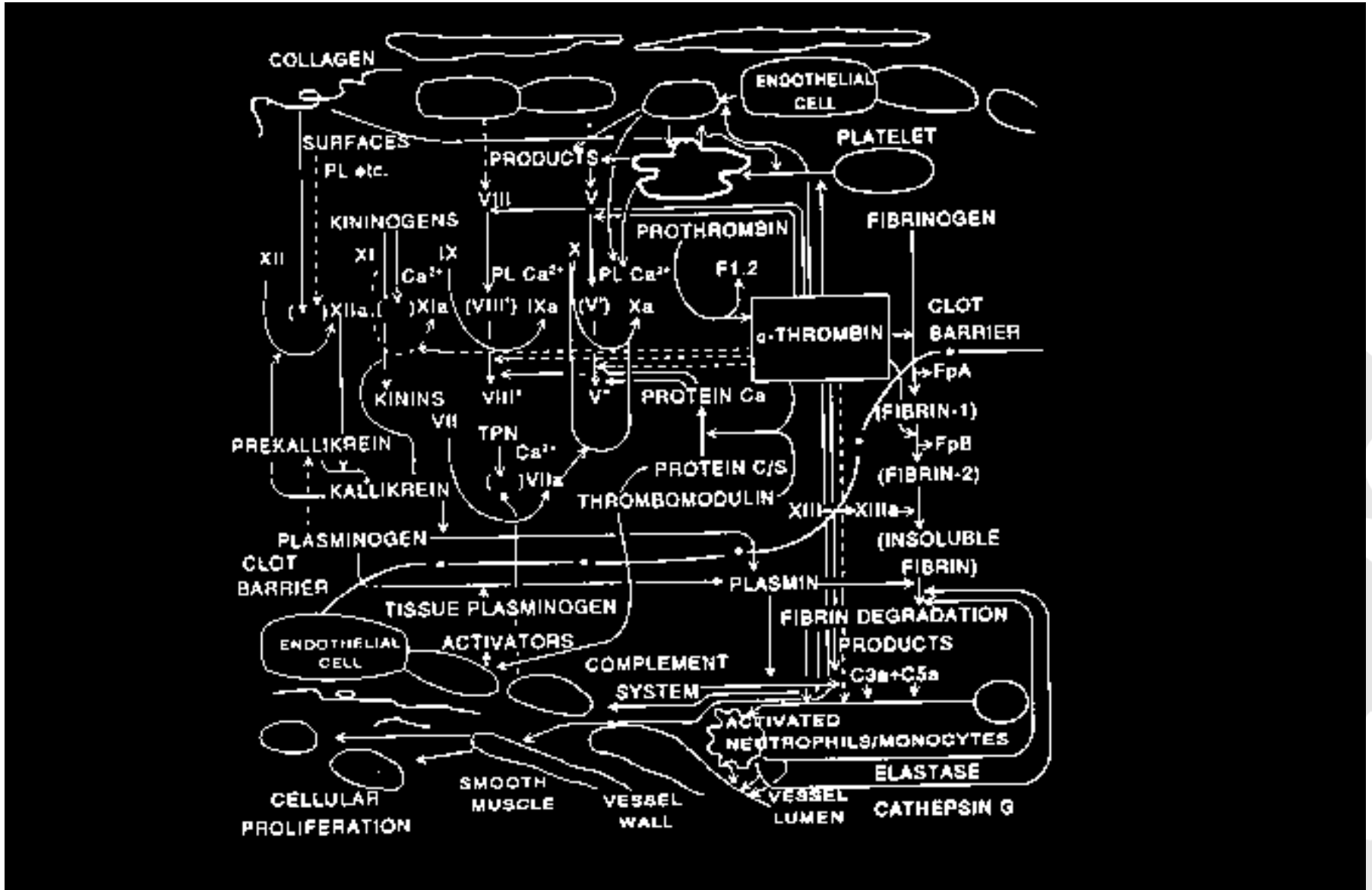
What's Factor X got to do with bleeding?



The two steps involved in forming a clot

...And how a deficiency in a clotting protein or cell can lead to bleeding

- Step 1: Formation of Platelet "Plug"
  - exposed collagen + von Willebrand factor (VWF) + platelets

Deficiency of VWF leads to poor platelet plug formation= von Willebrand Disease

- Step 2: Formation of fibrin clot over platelets
  - platelets + clotting factors I, I, V, VII, VIII, IX, XI and **Factor X**

Deficiency of Factor X leads to poor fibrin formation

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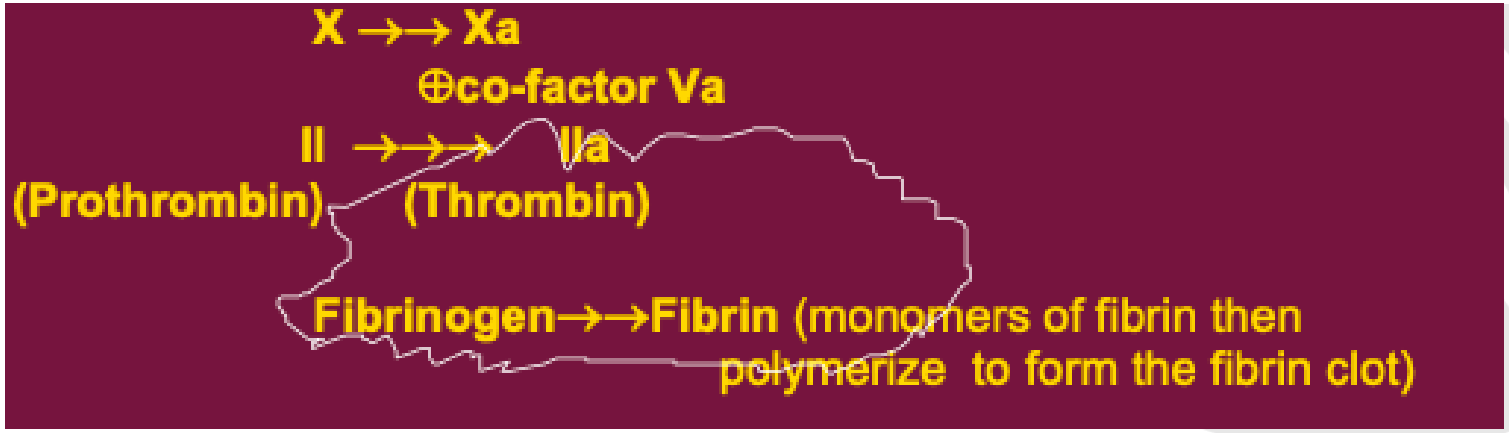
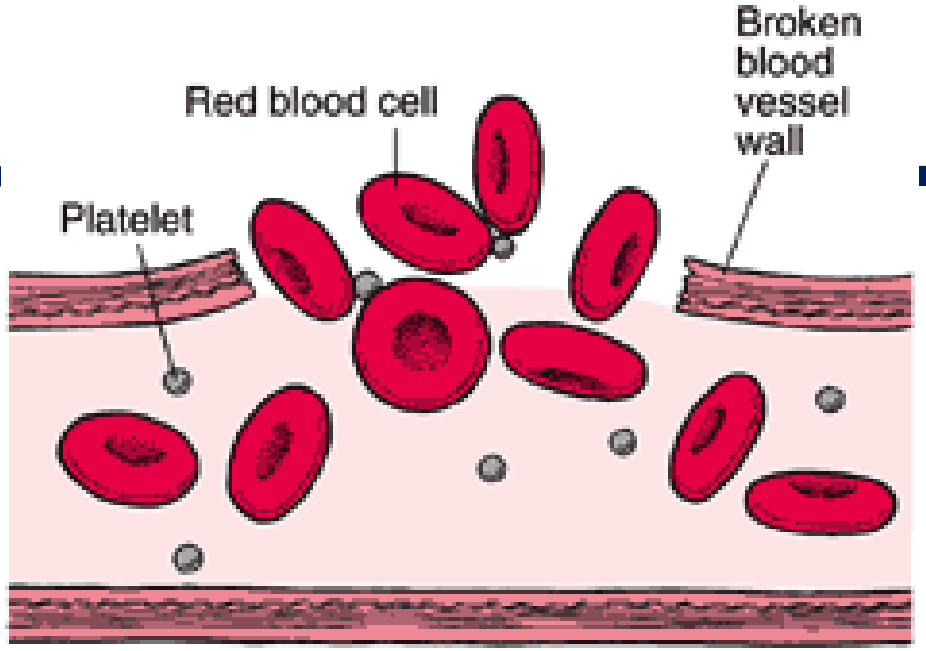
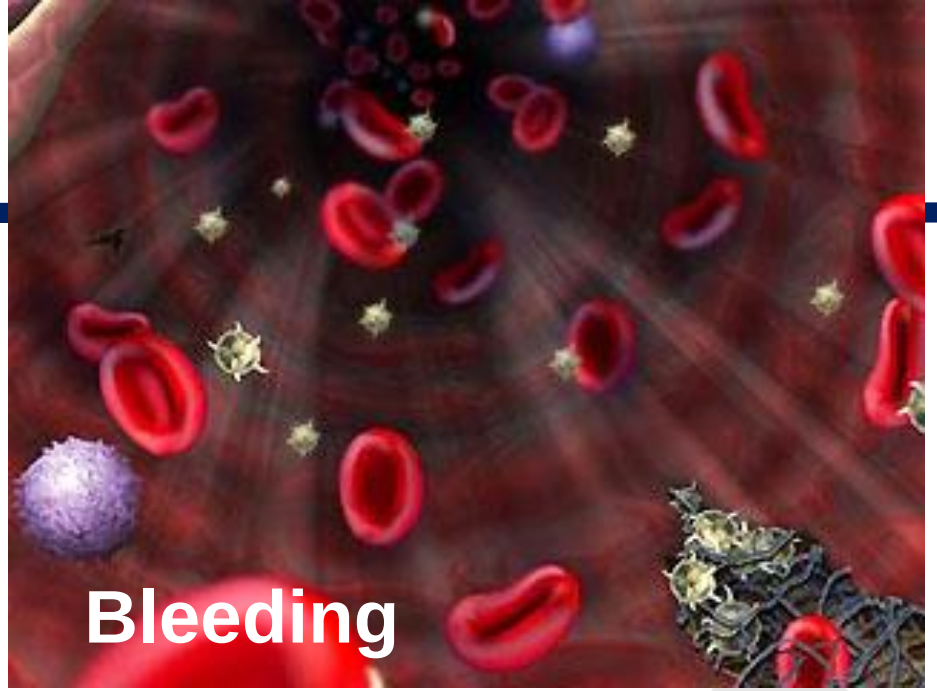
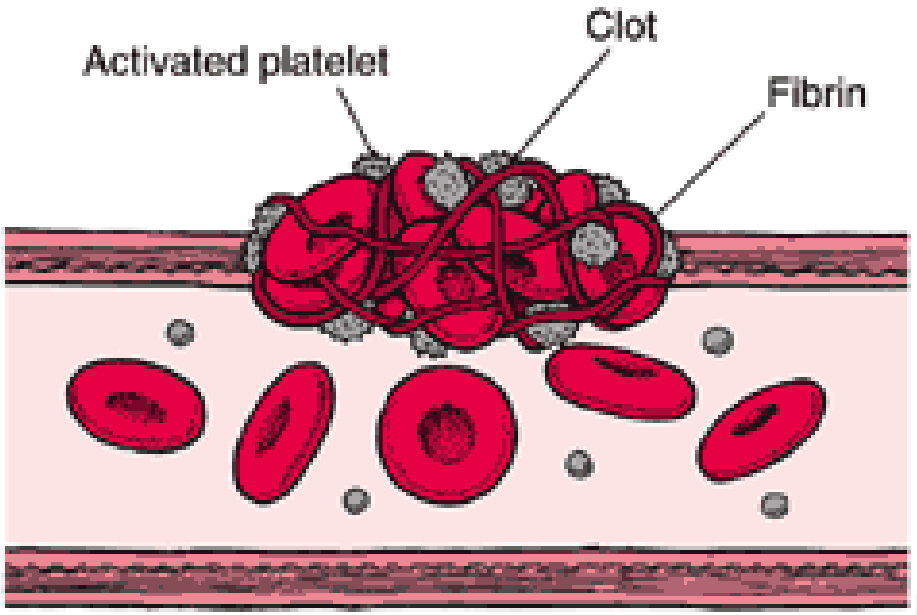
How does Factor X lead to formation of the fibrin-based clot?

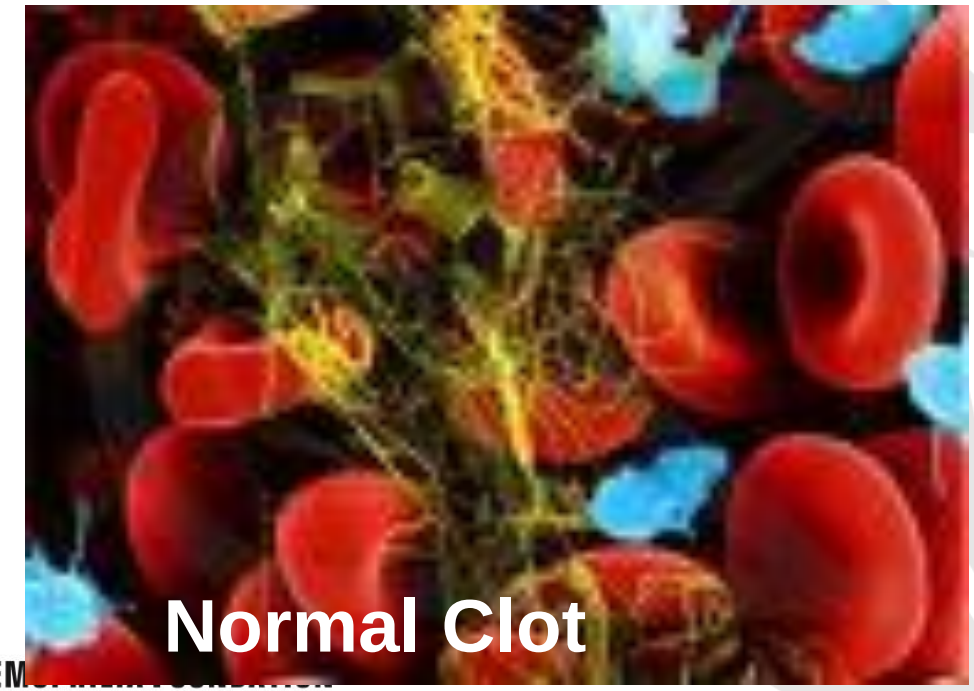
The "waterfall" hypothesis of one factor being activated by the previous one followed in turn by activating the next one…initially Factor X is converted to its active form Xa by the complex of tissue factor + Factor VIIa then Factor Xa inturn activated Factor to Factor Iia then in turn activates Factor I to Factor Ia which is fibrin that then self-polymerizes into this jelly like mesh clot to trap the blood from leaking out further



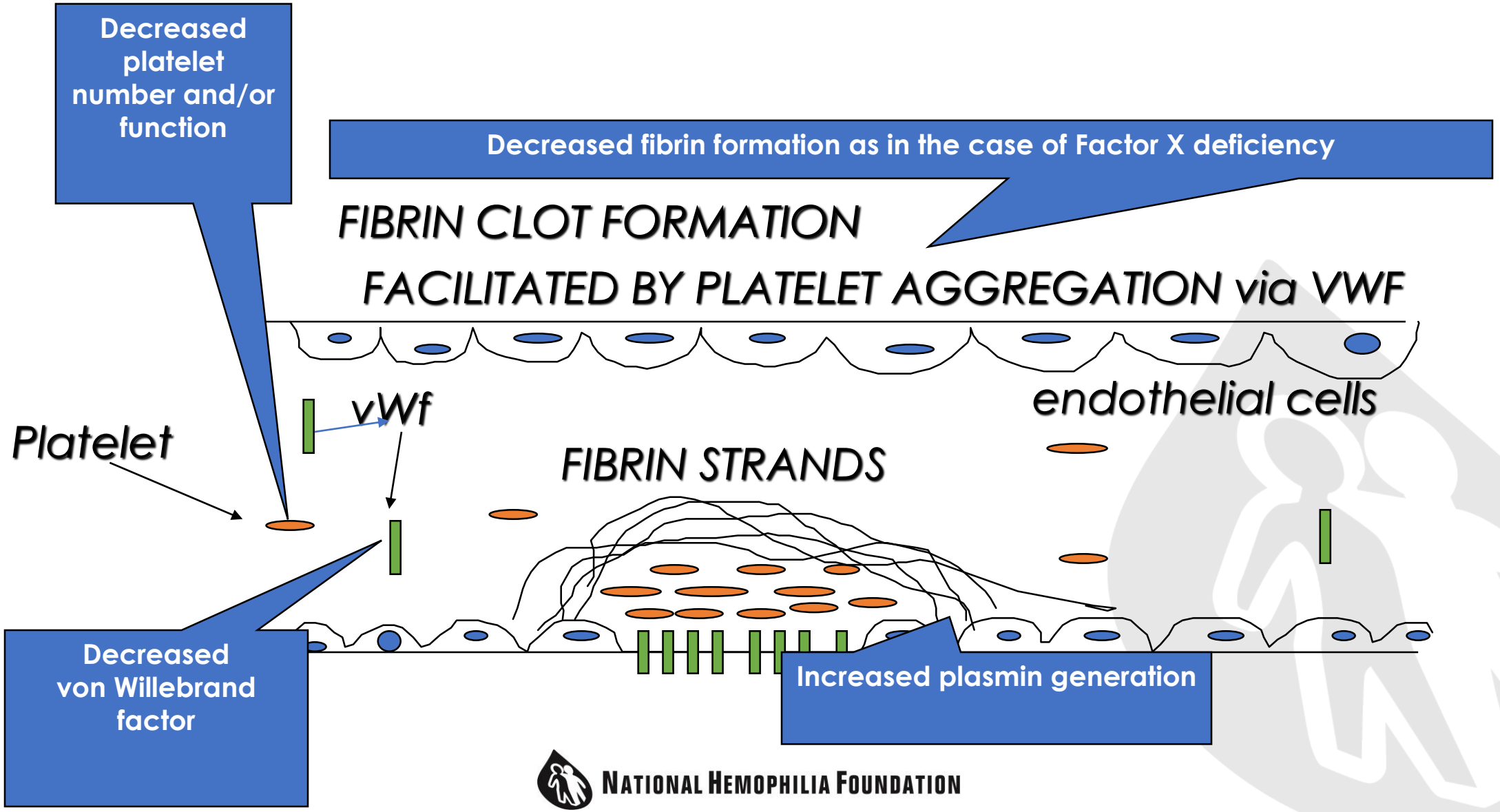

Red blood cell
Broken blood vessel wall
Platelet


Bleeding


Activated platelet
Clot
Fibrin


Normal Clot

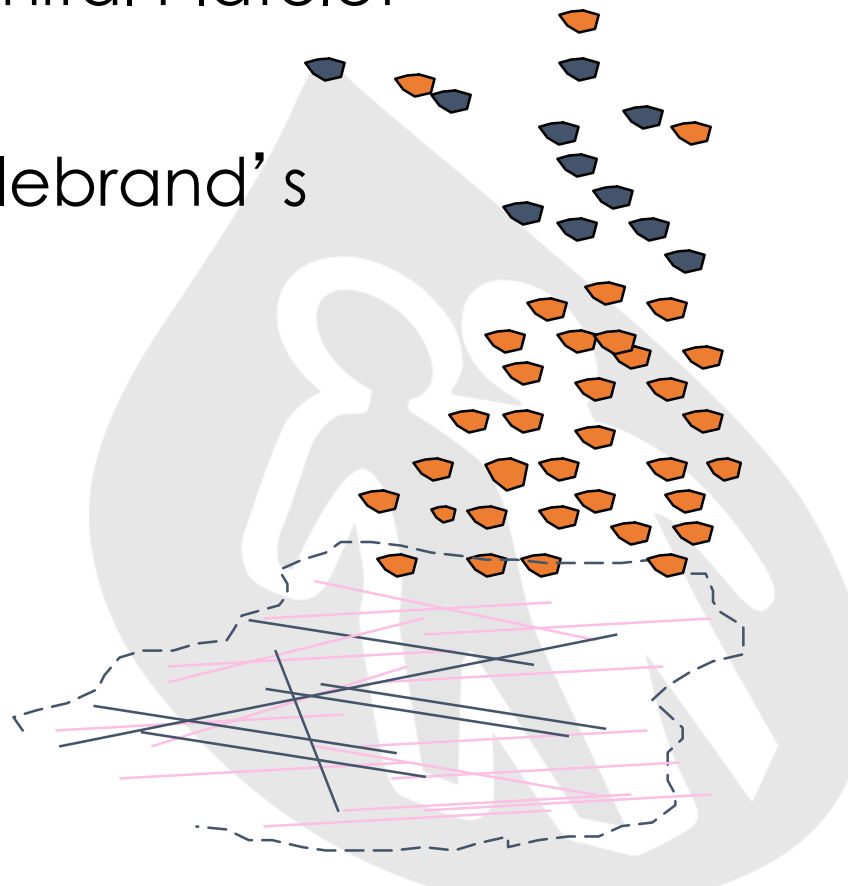
Where/why someone bleeds



Where inherited disorders of bleeding can arise-

1. Unable to form platelet plug-

- Congenital Platelet Disorders
- Von Willebrand's Disease



2. Unable to form fibrin clot on top of platelet plug because of deficiency of clotting factors-

- Factor VIII deficiency (Hemophilia A)
- Factor IX deficiency (Hemophilia B)
- Factor XI, II,V, VII, I deficiency
- Factor X deficiency

When was Factor X first discovered?

Patient AP- Diagnosed at age 22

Ms. Audrey Prower, an index patient with deficiency of factor X (Stuart-Prower factor), a disorder described in 1956 by Telfer, Denson, and Wright. (Photograph courtesy of Dr. Kenneth Denson.)

Mr. Rufus Stuart (seated), an index patient with deficiency of factor X (Stuart-Prower factor), a disorder described in 1957 by Drs. Cecil Hougie, Emily Barrow, and John Graham (standing left to right). *Photograph courtesy of Dr. Douglas Triplett.*

Patient RS- Had undetectable FX level- normal 50-125%

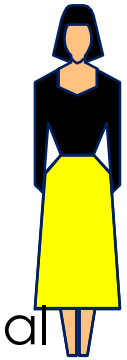
How common is FX deficiency? And how is it genetically transmitted?

- Estimated to occur in 1:1,000,000 individuals with up to 1:500 being carriers

- Mr. Rufus Stuart, case in point….

Factor X: Genetic Basis (we inherit one gene from each parent)

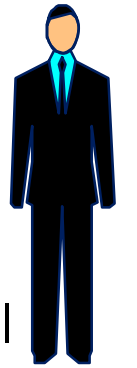
Rufus' mother



FX normal

FX gene abnormal

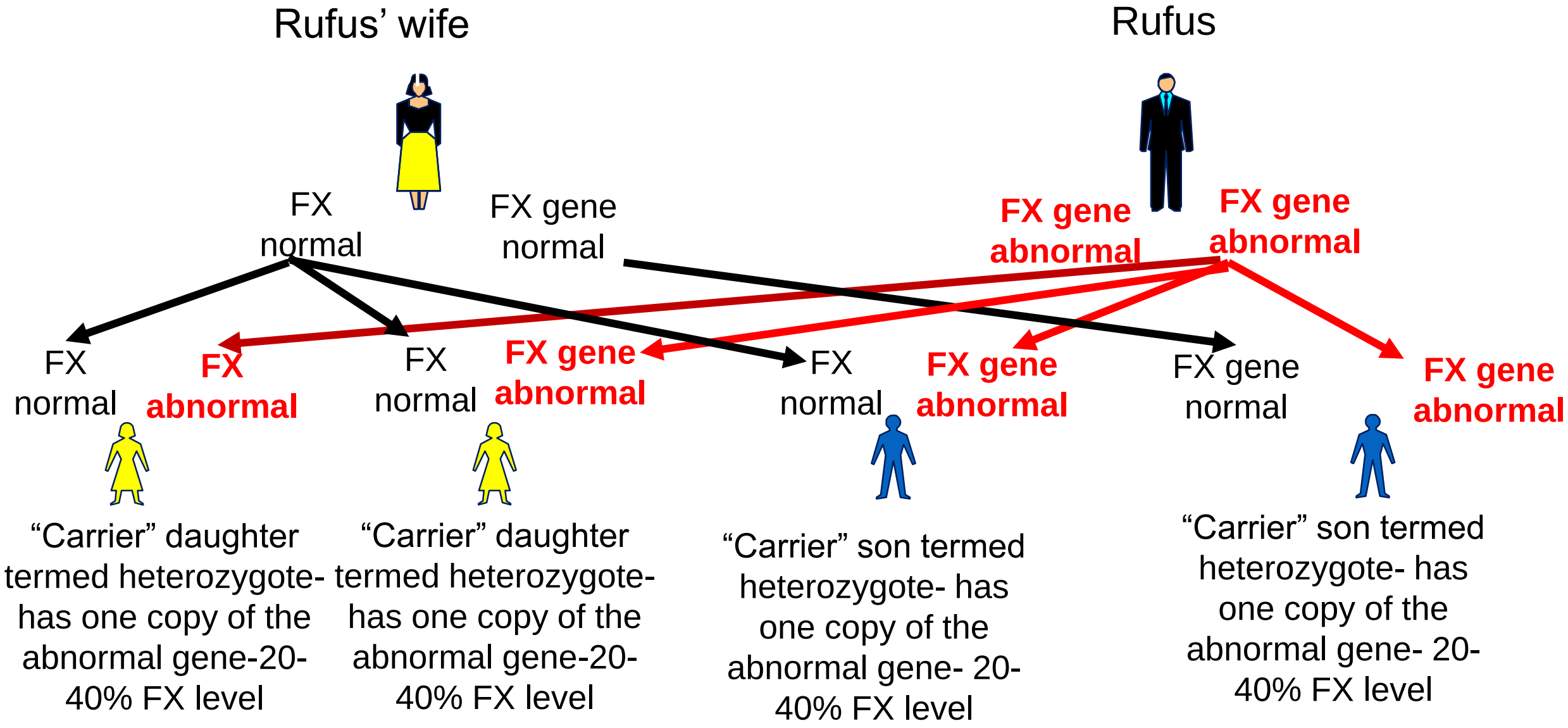
Rufus' Dad Man



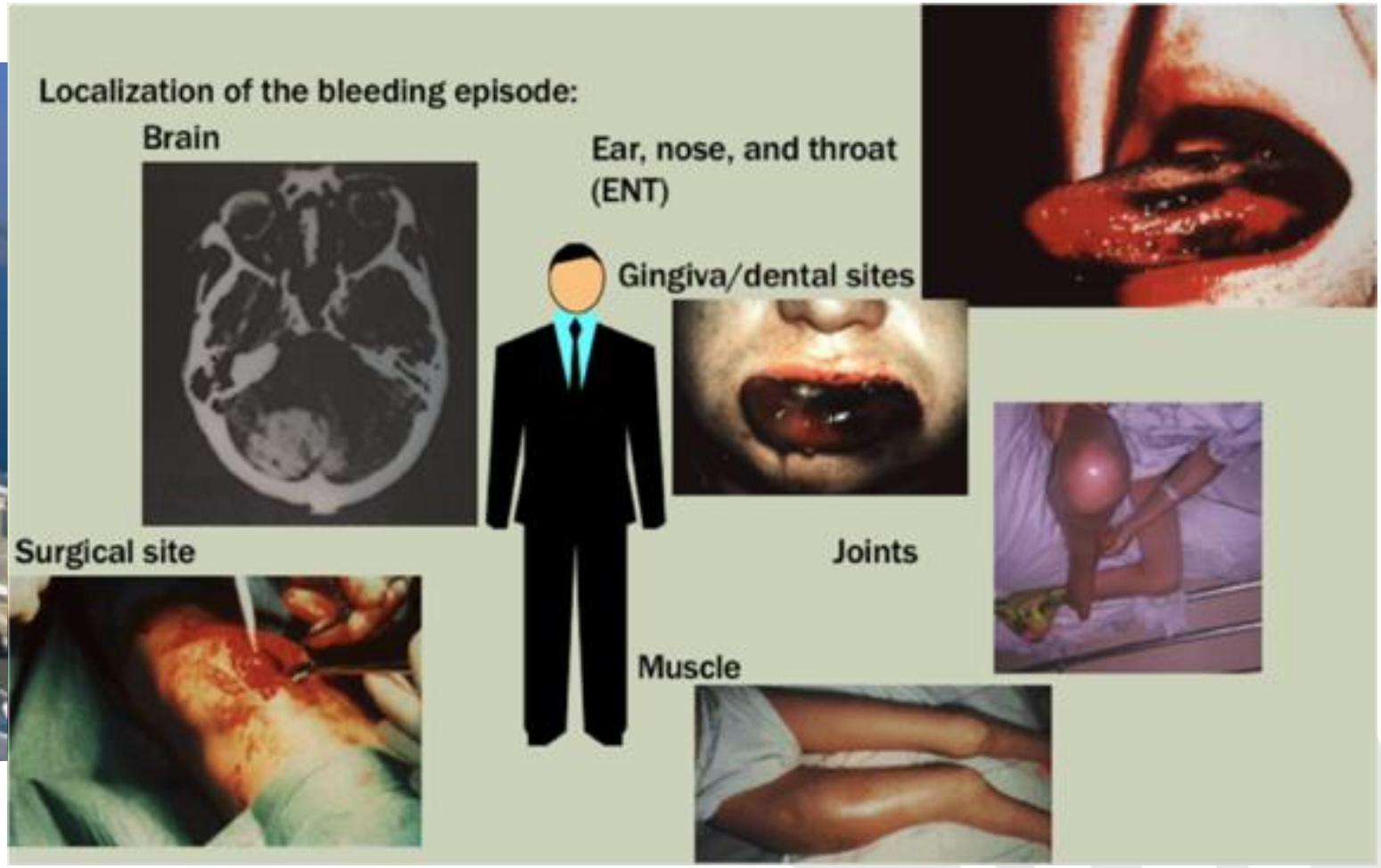
FX normal

FX gene abnormal

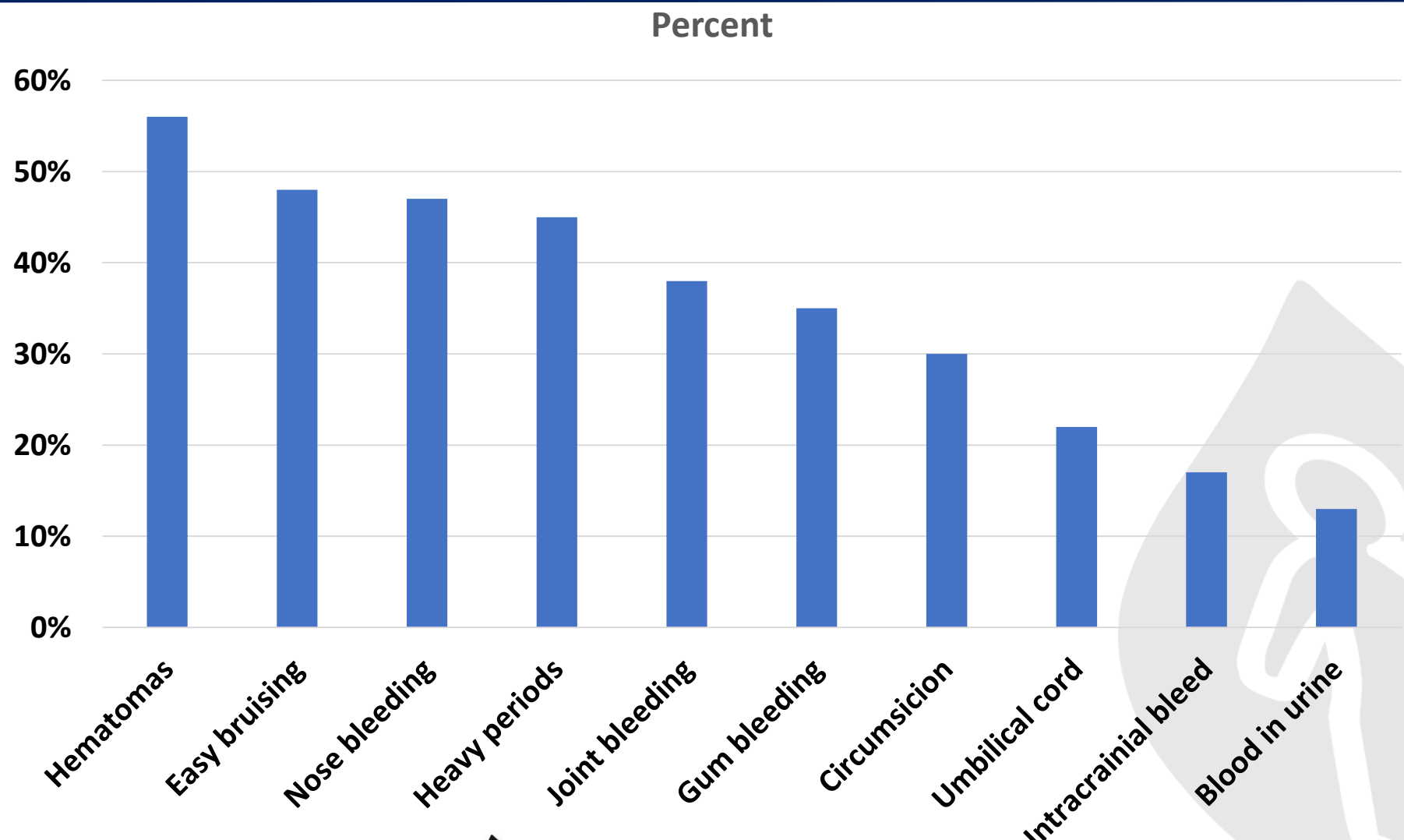
Factor X: Genetic Basis continued, next generation- (Autosomal recessive pattern of inheritance)



When Rufus was a newborn then a child, what type of bleeding could he have had?



Distribution of symptoms in Factor X deficiency



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Distribution of symptoms in relation to the factor level

Severity	FX level	Bleeding symptoms
Severe- **i.e. Rufus**	< 1%	Nose bleeding, heavy periods, joint bleeding, bleeding into brain, GI bleeding
Moderate	1-5%	Nose bleeding, heavy periods, joint bleeding, bleeding into brain, GI bleeding
Mild- **i.e. Rufus' sibs and parents**	6-20%	Infrequently associated with bleeding; carriers usually without bleeding

Bleeding by stage of life

Childhood

- Bleeding at time of circumcision
- Bleeding when umbilical stump falls off
- Nose bleeds > 5/yr and/or > 10 min needing packing/cautery
- Prolonged bleeding > 10 min from simple cuts
- Risk of bleeding into brain with trauma

Adolescence

- Heavy periods changing tampon or pad or both every 2 hrs or less
- Gum bleeding with flossing, dental cleaning
- Oozing > 3 hrs after wisdom teeth extracted
- Large hematomas into skin/muscle with trauma

Adulthood

- Bleeding after childbirth- may need blood transfusion
- Bleeding with surgeries- may need blood transfusion
- Continued risk for nose bleeding, prolonged bleeding from cuts, hematomas

Bruising

- Often develop without known trauma- patient wakes up with bruise and not sure where it came from
- Distribution: usually lower extremities, trunk, not face
- Frequency: 1-4 x/ mo.
- Size: > 2 inches diameter or > 5 in toto ≥ 1 half inch

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Nose bleeding (Epistaxis)

- Duration
  - usually > 10 min
- Frequency
  - usually > > 5 /year
- Severity
  - Often cautery/packing needed
- Spontaneous
  - Often unrelated to hypertension, dryness, aspirin
    - though curiously level of evidence of each of these risk factors is quite weak
    - Evidence stronger with nasal steroid spray being causative for nose bleeding
- Sub-location- typically can be from either nostril, if localized to one nostril have ENT examine for any small blood vessel malformation ("AVM"-arteriovenous malformation) from that nostril

Gum/Dental-related

- Bleeding with flossing or dental cleaning
  - Usually unrelated to gingivitis

- Excess bleeding with wisdom teeth removal-
  - “dry” socket
  - Often Tea bag needed
  - May need Packing/cautery needed
  - Bleeding/oozing > 3 hrs

Heavy menses, termed Menorrhagia

- Menses perceived as heavy since menarche (age at start of first period)
- Changes every 30-120‘ on the heaviest day
- Uses one tampon + one pad or 2 pads/time
- Uses super absorbent brand
- Passes clots size of a quarter
- Frequently stains underclothes
- Loses time from work/school
- History of anemia/Low iron

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of pads you used that match each illustration.

Pad	1	2	3	4	5	6	7	8
								
								
Clots (Yes/No)								

Tampon	1	2	3	4	5	6	7	8
								
								
								
Clots (Yes/No)								

The numbers 1-8 represent the consecutive days of your menstrual period. Please record for each day, the number of tampons you used that match each illustration.

Tampons/pads with >80 cc blood loss.
(Image courtesy of Prof. Rezan Kadir)

Bleeding after childbirth (termed Post partum Hemorrhage)

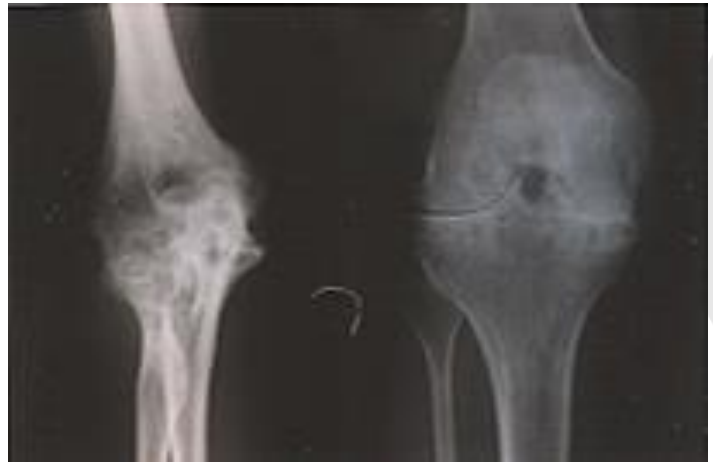
- > 1000 ml after delivery
- May need red cell transfusions for severe bleeding
- Worst case scenario is hysterectomy to stop the bleeding!

Joint bleeding episodes - Hemarthroses

- weight-bearing joints (ankles, knees, hips)
- elbows and shoulders
- synovial membrane

The Progression of Disabling Joint bleeding

Rheumatoid Arthritis-like



Osteo-arthritis-like

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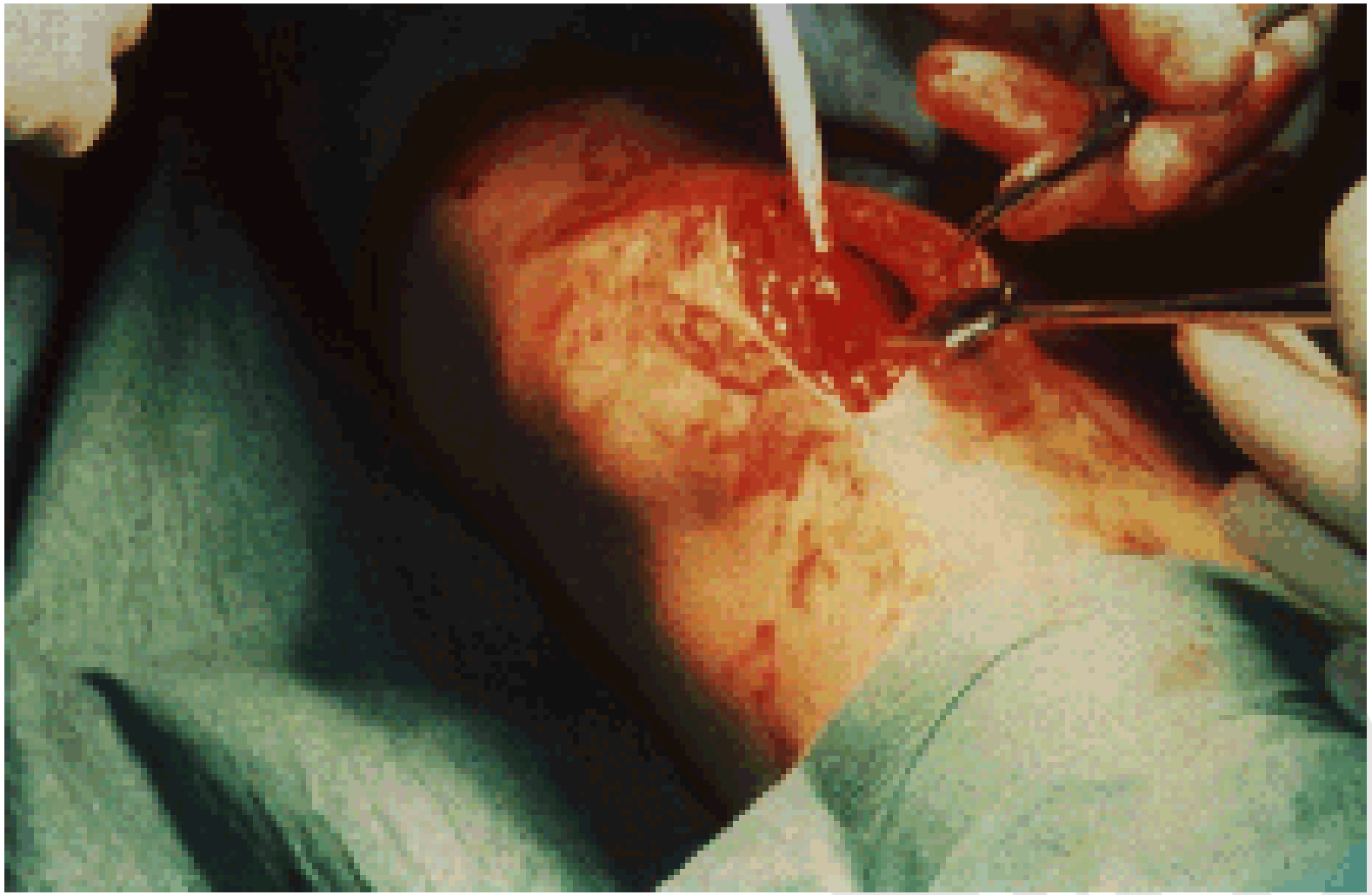
What to do to prevent recurrent bleeding into the knee or ankle in a severe Factor X deficient patient

- As in severe hemophilia could give factor X concentrate 1-2 x week, termed "prophylaxis"

- We often encourage the child to go to camp to learn from their peers…

Complications due to surgery

- continued bleeding and oozing
- hematoma
- impaired wound healing



What to do if Rufus bled at time of circumcision?

- Replace the missing factor
- Historically fresh frozen plasma-

What to do for bleeding after surgery nowadays

- Plasma "concentrated" in Factor X termed Profilnine but has other factors (II, IX)
- Ideally "best" factor replacement product is a pure Factor X product termed Coagadex
  - However, need to make insurance coverage is adequate as it costs $6.50/unit- for major bleed if severe Factor X deficiency 30 u/kg x 70 kg =2,100 units = $13,650 daily

Muscular bleeding episodes - Hematomas

- calf, thigh, forearm
- iliopsoas
- compartment syndrome

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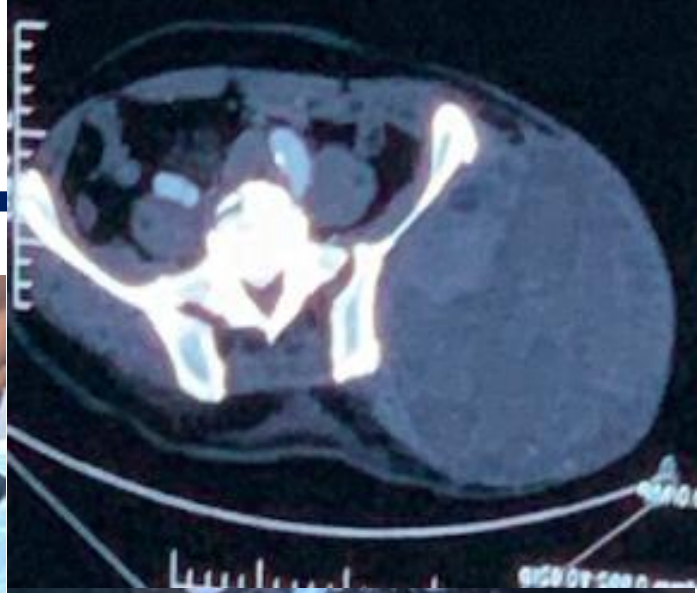
What about major surgery in a severe Factor deficient patient with a massive hematoma?

A large chronic collection of a hematoma is termed a pseudotumor

- 58 year old Nepalese severe Factor X deficient patient with pseudotumor

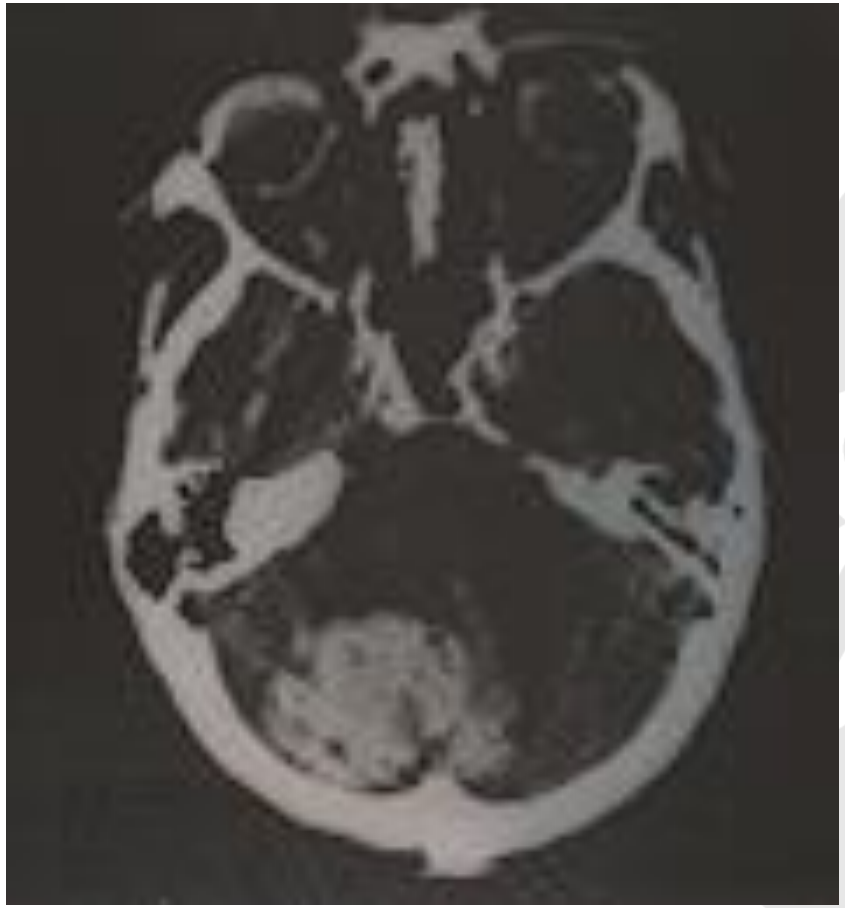
- Underwent successful excision with the Factor X concentrate "Coagadex" 30 u/kg daily x 3 days then every other day x 10 days



One month post-op, July 2019

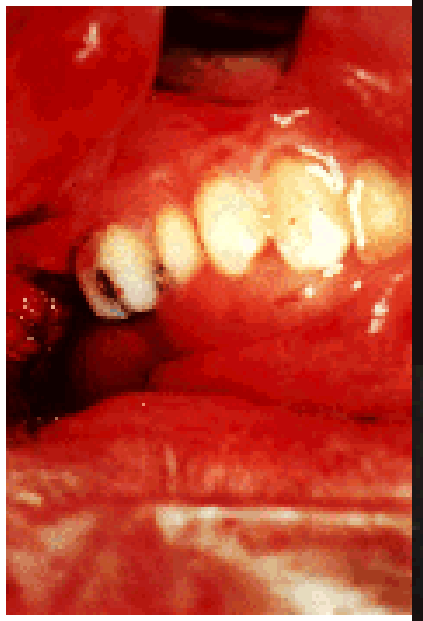
CNS bleeding episodes (termed intracranial hemorrhage)

- epidural
- subdural



ENT bleeding episodes

- nose, epistaxis
- mouth, dental
- throat, retropharyngeal
- ear



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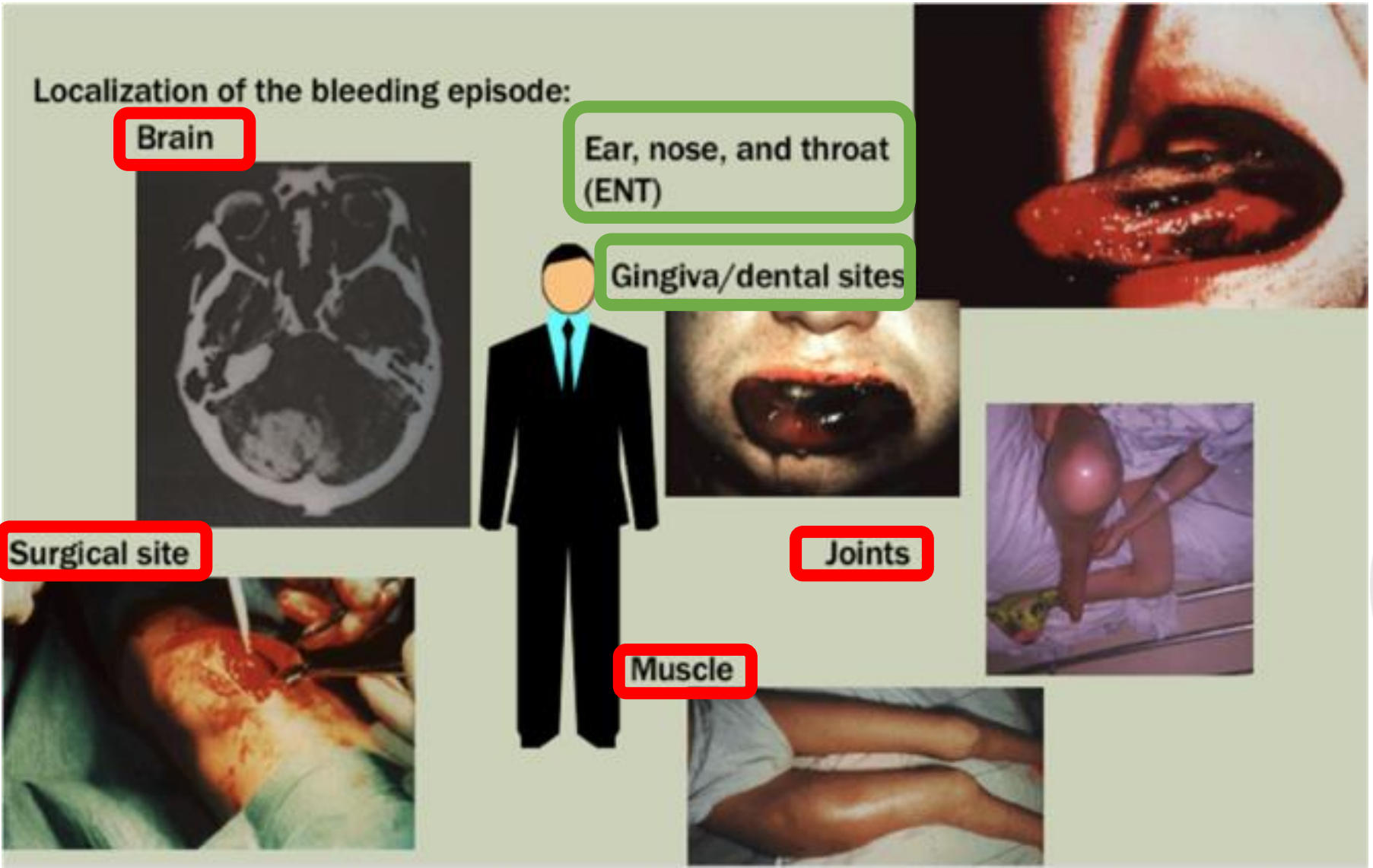
Managing specific bleeding situation besides infusing Factor



Infuse clotting factor concentrate containing Factor X to level at least > 70%

For bleeding from the mucus surfaces we use Lysteda or Amicar syrup and infuse FX containing concentrate if severe bleeding in the severely deficient patient

Managing dental work/dental issues

PRE-DENTAL WORK CHECK-LIST:

- **Extent of procedure?**
  - Dental cleaning- no pre-treatment even in severe Factor X deficiency unless poor hygiene or patient has an inhibitor
  - Tooth extraction, Nerve block
    - Depends on Factor level-

- **Severity of platelet disorder?**
  - severe(<1%)
  - moderate
  - Will need to pre-treat with clotting factor concentrate containing Factor X infusion 30-60 minutes prior
  - mild (> 20%)
  - Just use a medication called Amicar or Tranexamic acid (Lysteda)

Regardless of Factor level

- We prescribe Amicar 2.5 grams
  - 10 cc of Versapharm brand of syrup formulation (at 250 mg/5cc) po swish and swallow 1-2 hrs pre-procedure and 4 hours later
  - And depending on extent of procedure 4 cc (1 g) orally every 4-6 hrs for 3-5 days after the procedure

- But Amicar is costly ($1000/bottle) so most insurers don't cover it so we either-
  - Prescribe the generic oral anti-fibrinolytic Lysteda (tranexamic acid) 2 pills po 3 x a day beginning 24 hrs pre-procedure then for 4 days post-procedure (5 day supply #30)
  - If case in OR can transfer IV dose of Amicar into grape juice

How to manage heavy periods?

- If contraception also sought-
  - Start with oral contraceptive
- If not-
  - Try Lysteda 2 pills orally 3 x a day x 5 days

- If continued bleeding (usually in severe FX deficient patient)-
  - Infuse clotting factor concentrate containing Factor X

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How to prevent/manage childbirth related bleeding?

- Infuse clotting factor concentrate containing Factor X (usually if severe FX deficiency) at start of active labor and continue daily for several days

- Infuse post-delivery the IV form of Lysteda termed Tranexamic acid every 8 hours then can convert to the oral form Lysteda

Session Evaluation

Take a few minutes now to fill out the session evaluation:

Rate this session

- Meaningful?
- Learned new ideas/skills?
- Will implement new ideas/skills?

How could this session be improved?

Comments?