Basics of Platelet Disorders
An "Odyssey" from Birth to Adulthood

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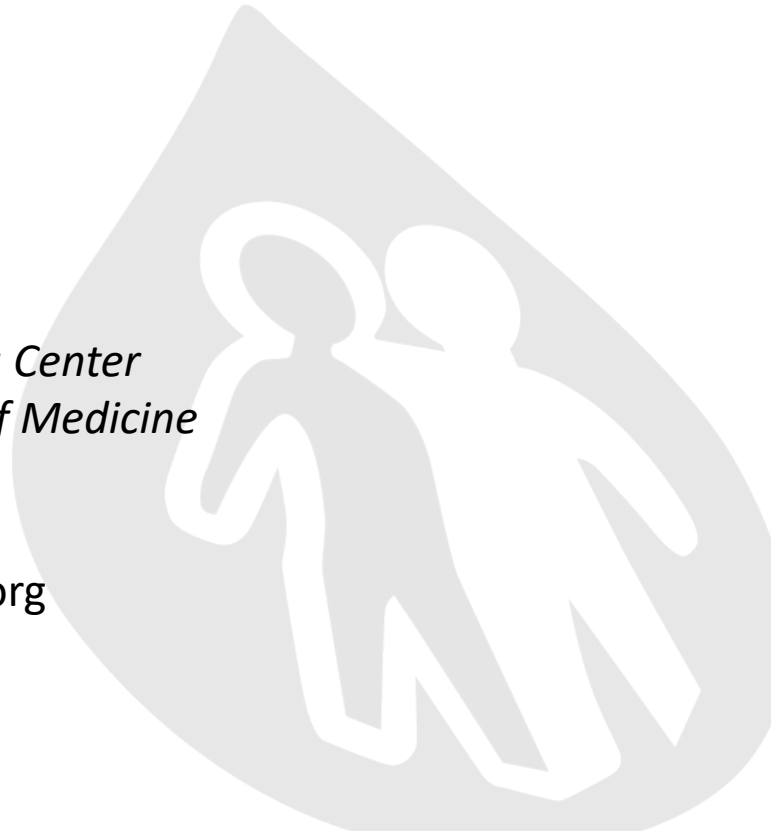

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The two steps involved in forming a clot

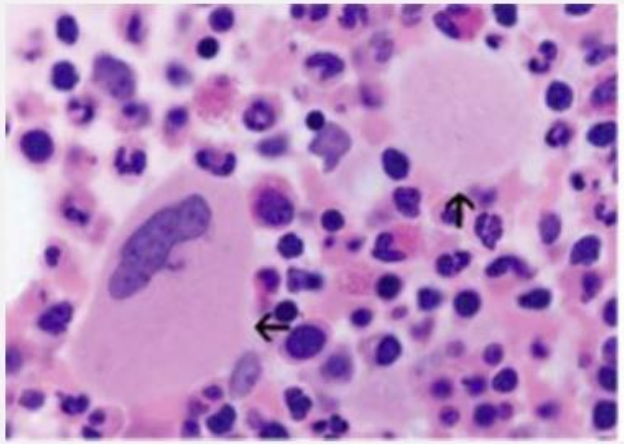
...And how a deficiency in a clotting protein or cell can lead to bleeding

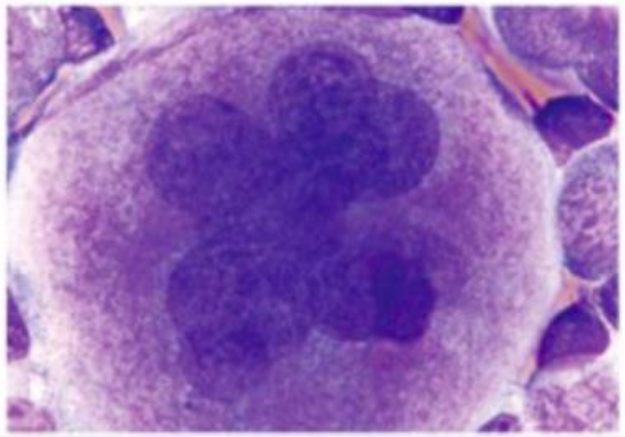
- Step 1: Formation of Platelet "Plug"
  - exposed collagen + von Willebrand factor (VWF) + platelets

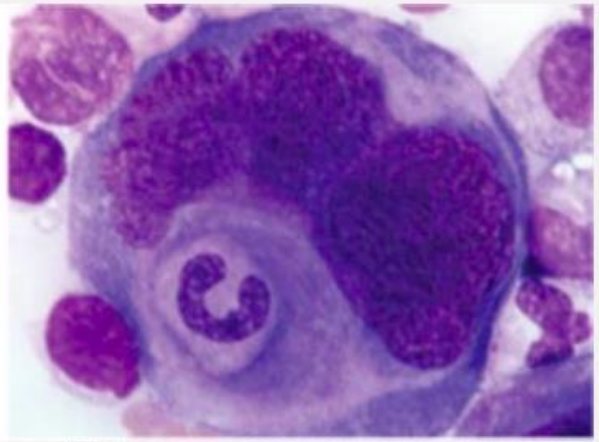
Deficiency of platelets or decreased function will lead to bleeding

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

About platelets







Normal human platelets are:

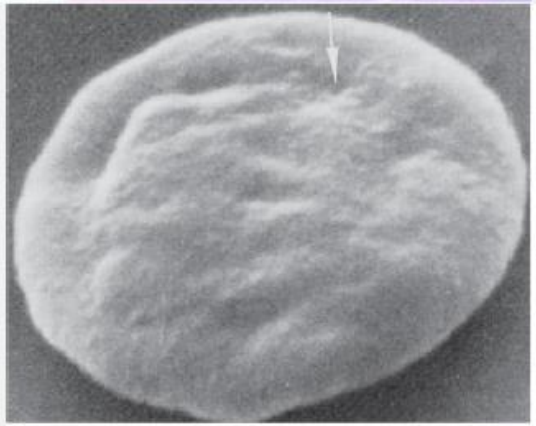
Size: Small in size (0.5 x 3.0 µm)

Shape:

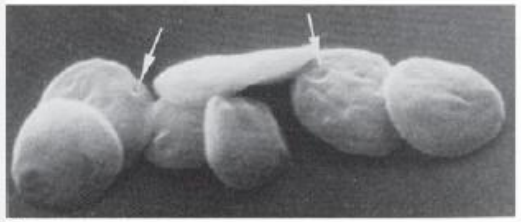
- Discoid in shape have a mean volume of 7–11 fL.
- Anucleated.

Number: They circulate in relatively high numbers (between 150 and 400 x 10^9 /L).

Life span: Their lifespan is approximately 10 days (9 – 12 days).

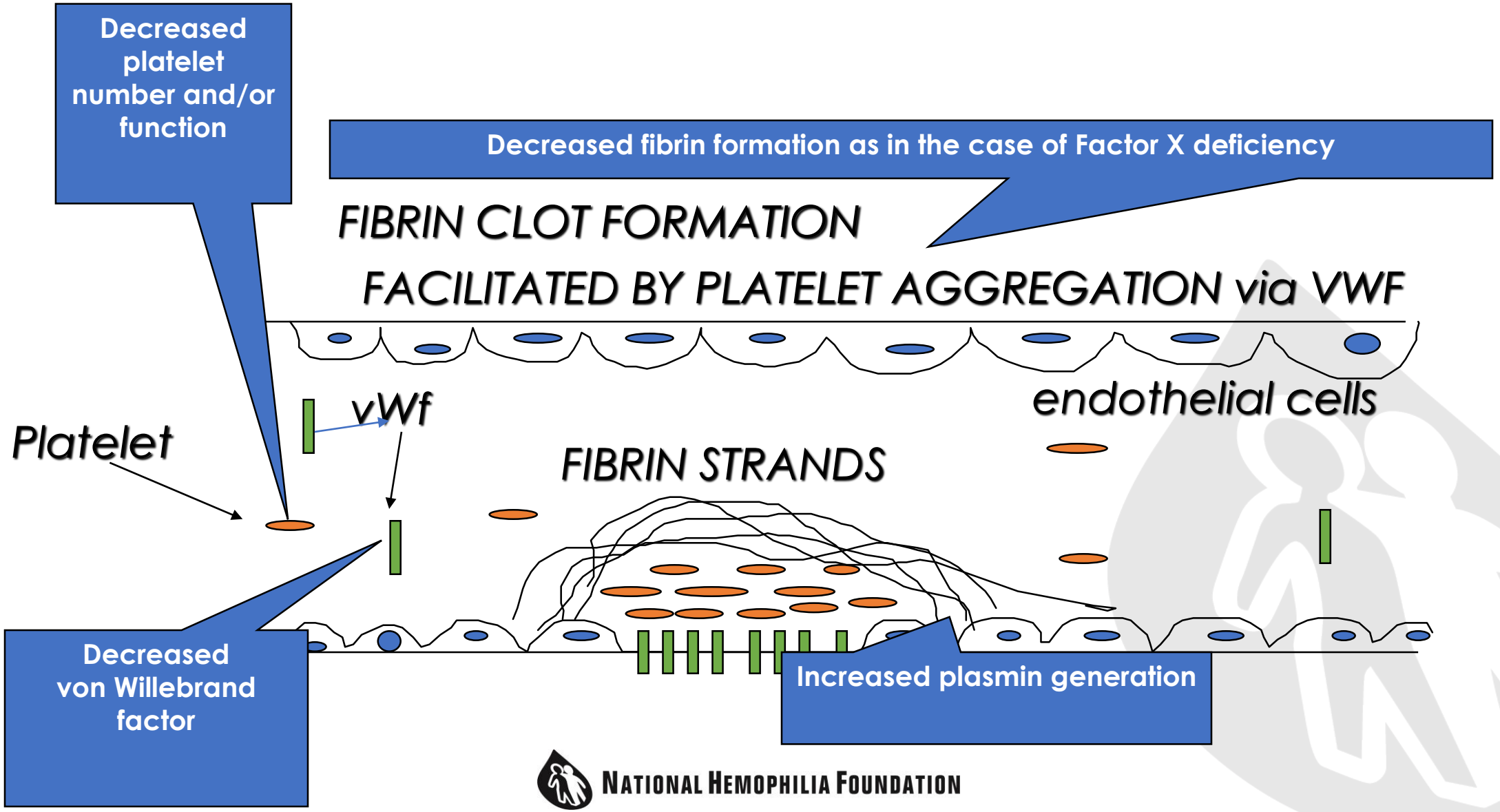


A



B

Where/why someone bleeds



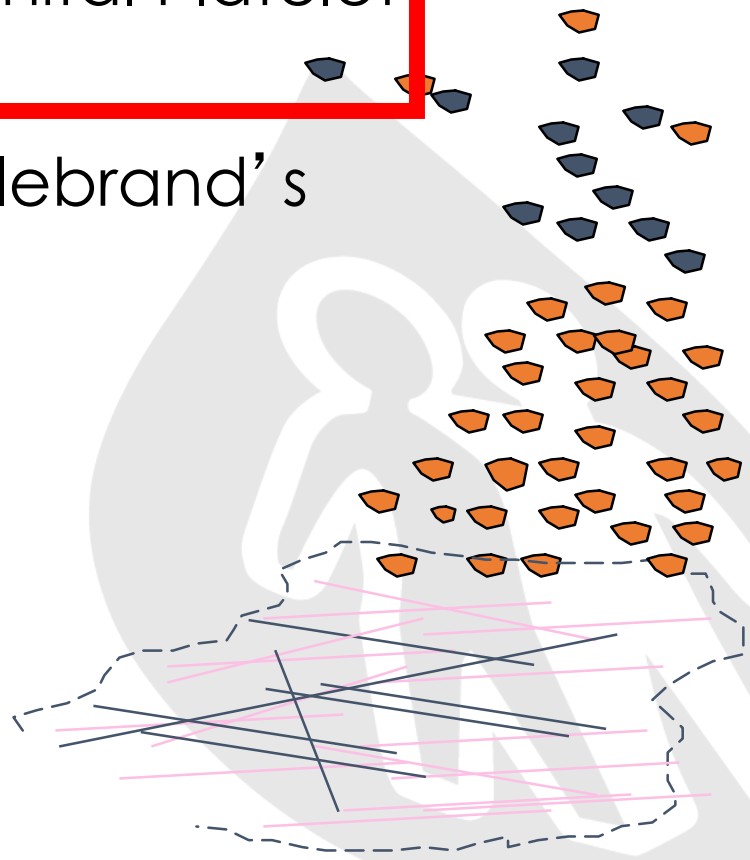
Where inherited disorders of bleeding can arise-

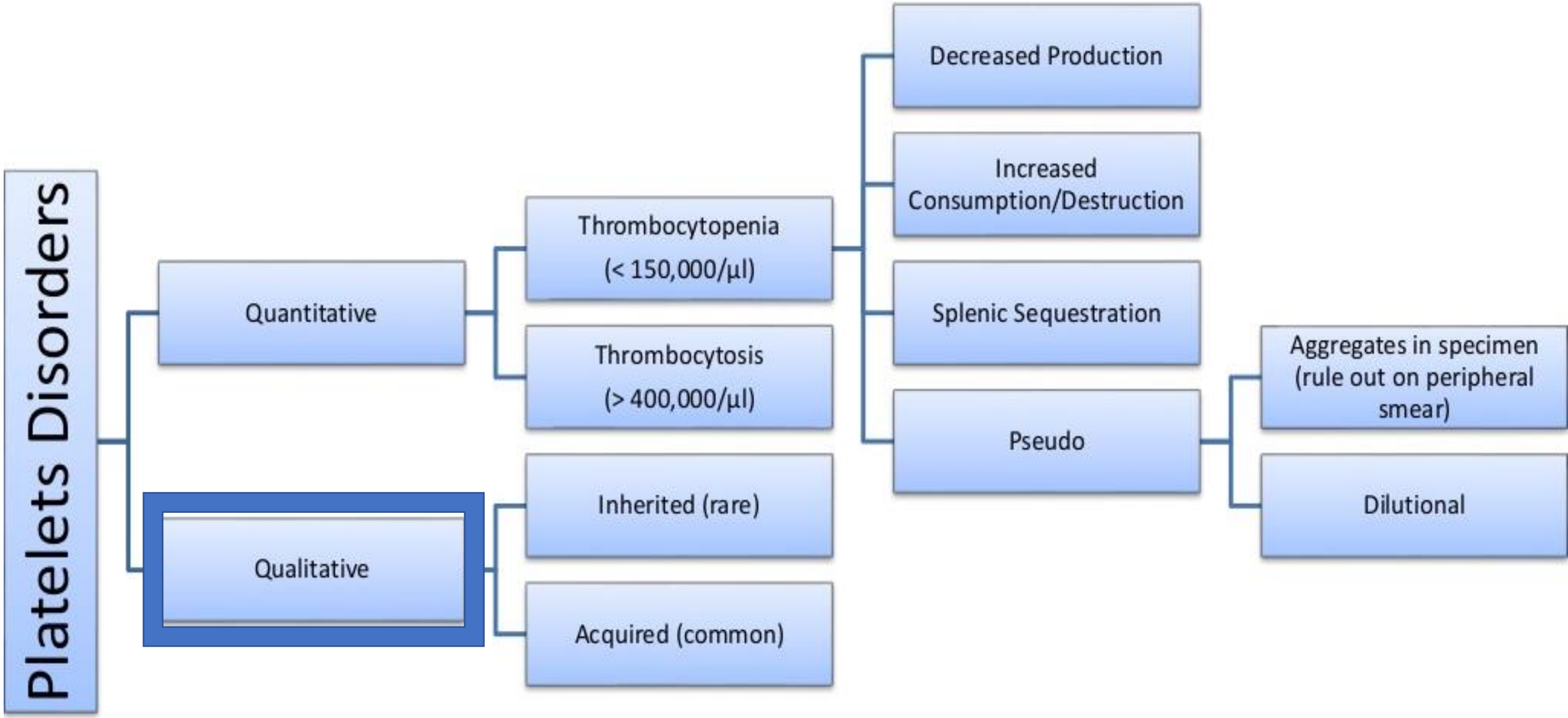
1. Unable to form platelet plug-

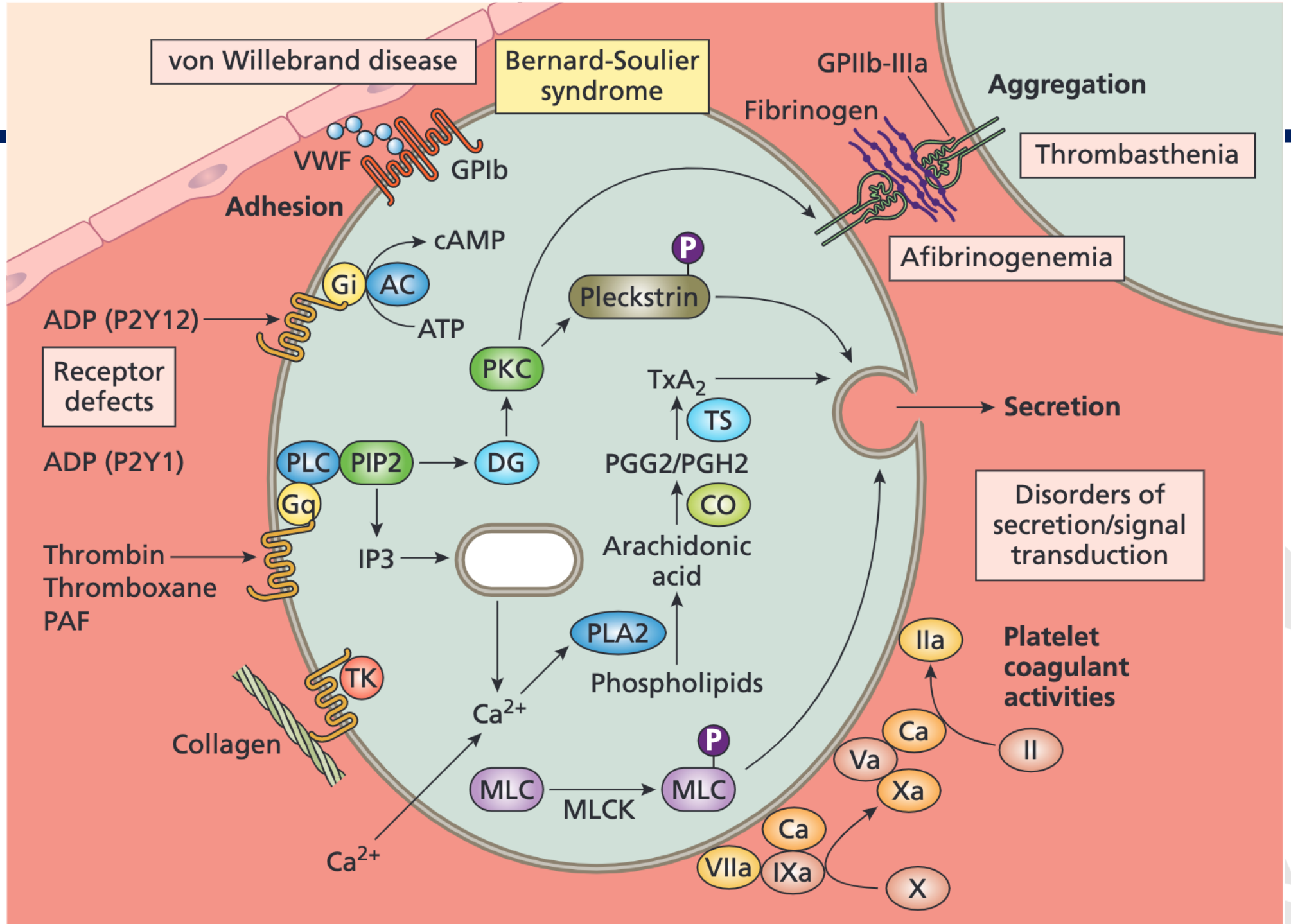
- Congenital Platelet Disorders
- Von Willebrand's Disease

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




Platelets Disorders
Quantitative
Qualitative
Thrombocytopenia (< 150,000/µl)
Thrombocytosis (> 400,000/µl)
Inherited (rare)
Acquired (common)
Decreased Production
Increased Consumption/Destruction
Splenic Sequestration
Pseudo
Aggregates in specimen (rule out on peripheral smear)
Dilutional


von Willebrand disease
Bernard-Soulier syndrome
GPIIb-IIIa
Aggregation
Fibrinogen
Thrombasthenia
VWF
GPIb
Adhesion
Afibrinogenemia
cAMP
Gi
AC
ATP
ADP (P2Y12)
Receptor defects
Pleckstrin
P
PKC
TxA2
TS
Secretion
ADP (P2Y1)
PLC
PIP2
DG
PGG2/PGH2
CO
Gq
Disorders of secretion/signal transduction
Thrombin
Thromboxane
PAF
IP3
Arachidonic acid
PLA2
Phospholipids
IIa
Platelet coagulant activities
TK
Collagen
Ca2+
Ca
Va
Xa
II
MLC
MLCK
MLC
P
Ca2+
Ca
VIIa
IXa
X

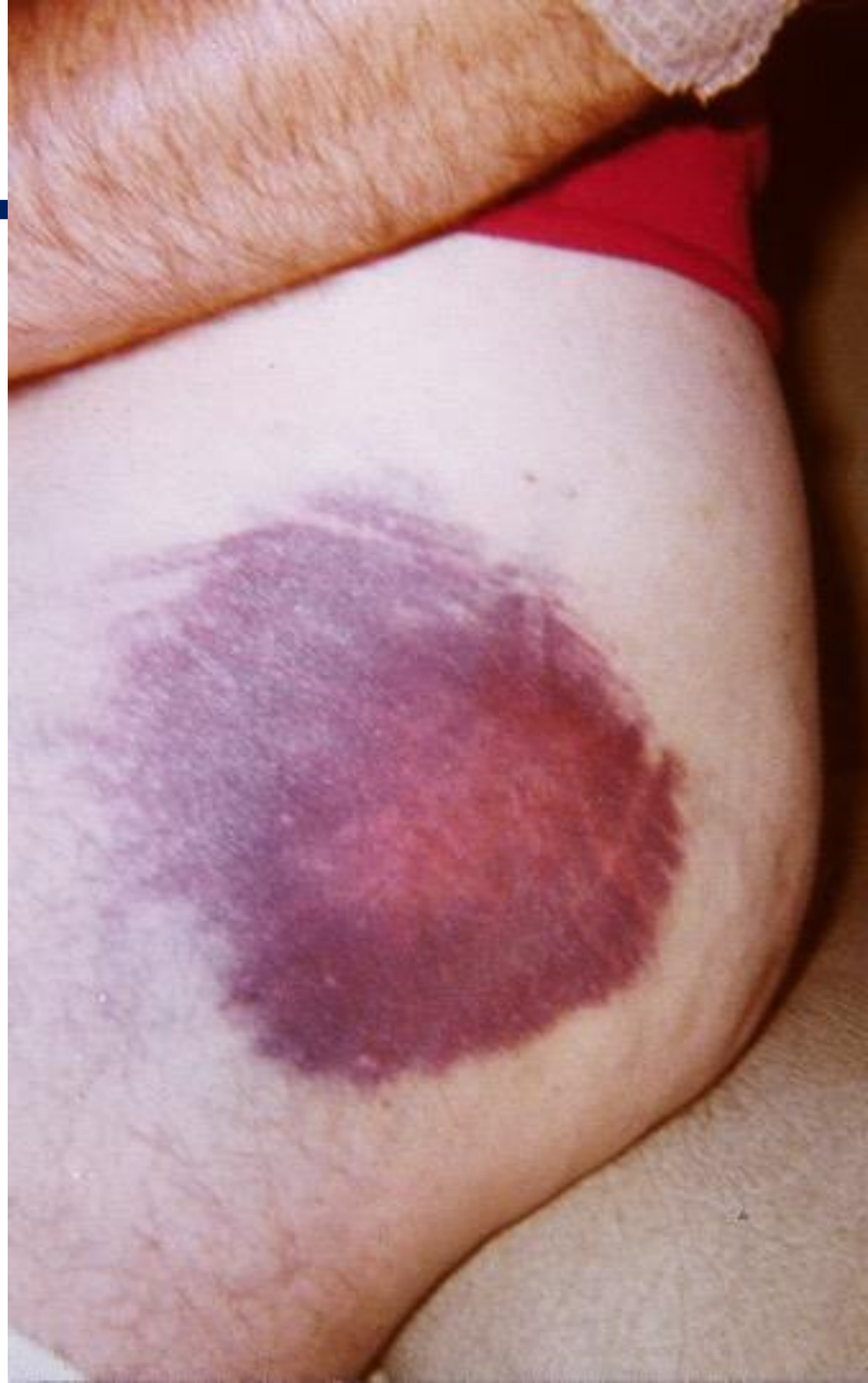
How common are platelet function disorders? And how is it genetically transmitted?

- Rarely X-linked as in hemophilia (males predominantly affected)
- Usually autosomal recessive from both parents
- Occasionally autosomal recessive- from both parents (who are usually "silent" carriers)

How do we make the diagnosis?

Bleeding patient MD:

This 14 y/o white male presented with an enlarging 8 cm. subcutaneous hematoma on his left thigh after being "speared" by a football helmet on an off tackle plunge. X-rays were negative for fracture. The hematoma resolved slowly with decreased activity and local application of iced compresses.



(Patient MD continued)

He had occasional small post-traumatic bruises and mild epistaxis but no other major bleeding. He had had no dental or other surgery. He denied the use of ASA or other nonsteroidal drugs. There was no known family history of a bleeding disorder. His older sister had had somewhat heavy menstrual periods since her menarche two years earlier.

Examination was unremarkable except for the resolving hematoma.

Bleeding Time Test

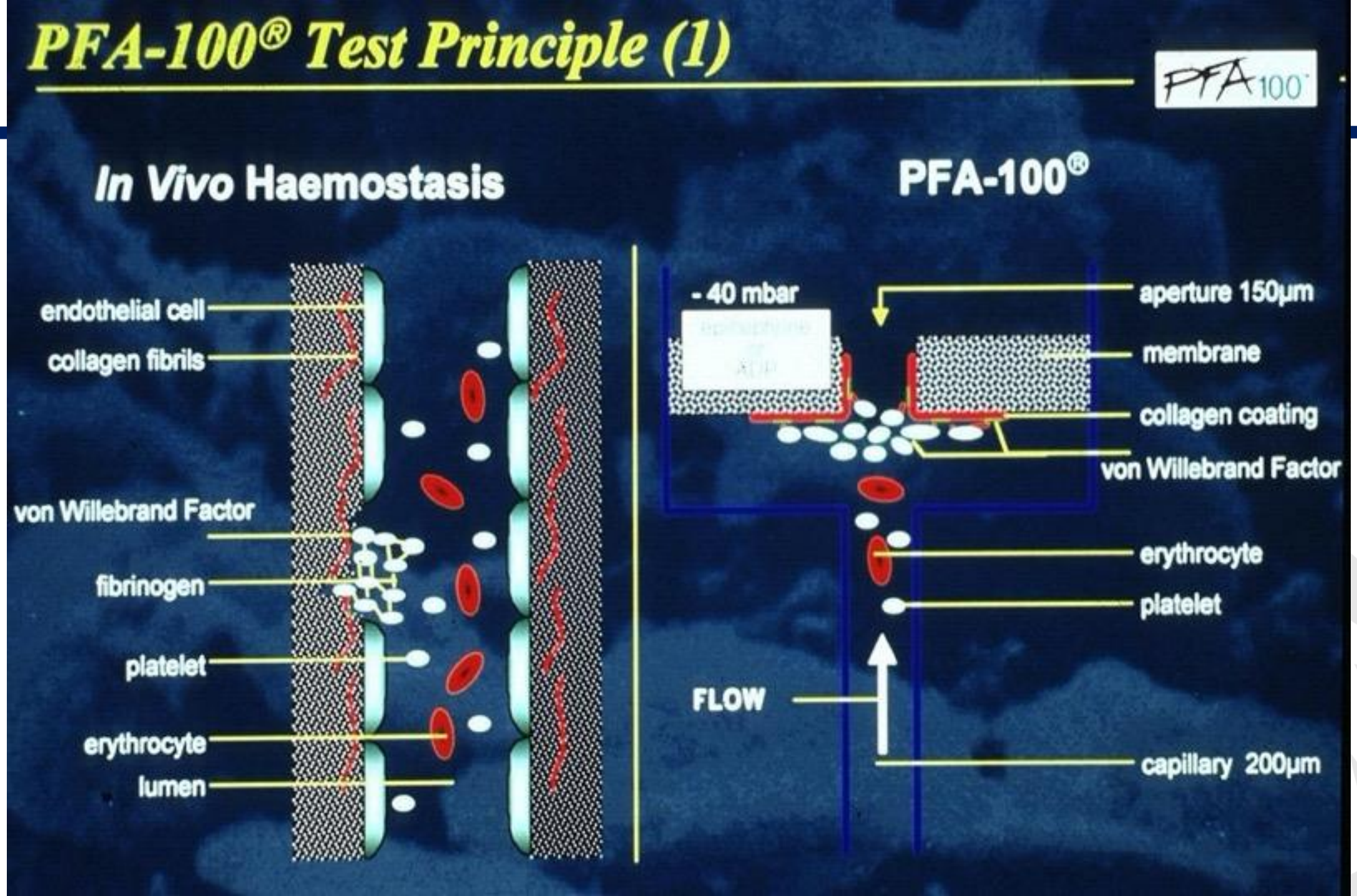
Historically screening test for platelet function disorders

Another alternative to the bleeding time: Platelet Function Analyzer-100

Platelet Function Screen

- Measurement of platelet plug formation in cartridges containing collagen and ADP or collagen and EPI, using whole blood under flow conditions
- Endpoint is closure of an aperture by platelet plug formation- “Closure Time” (CT)

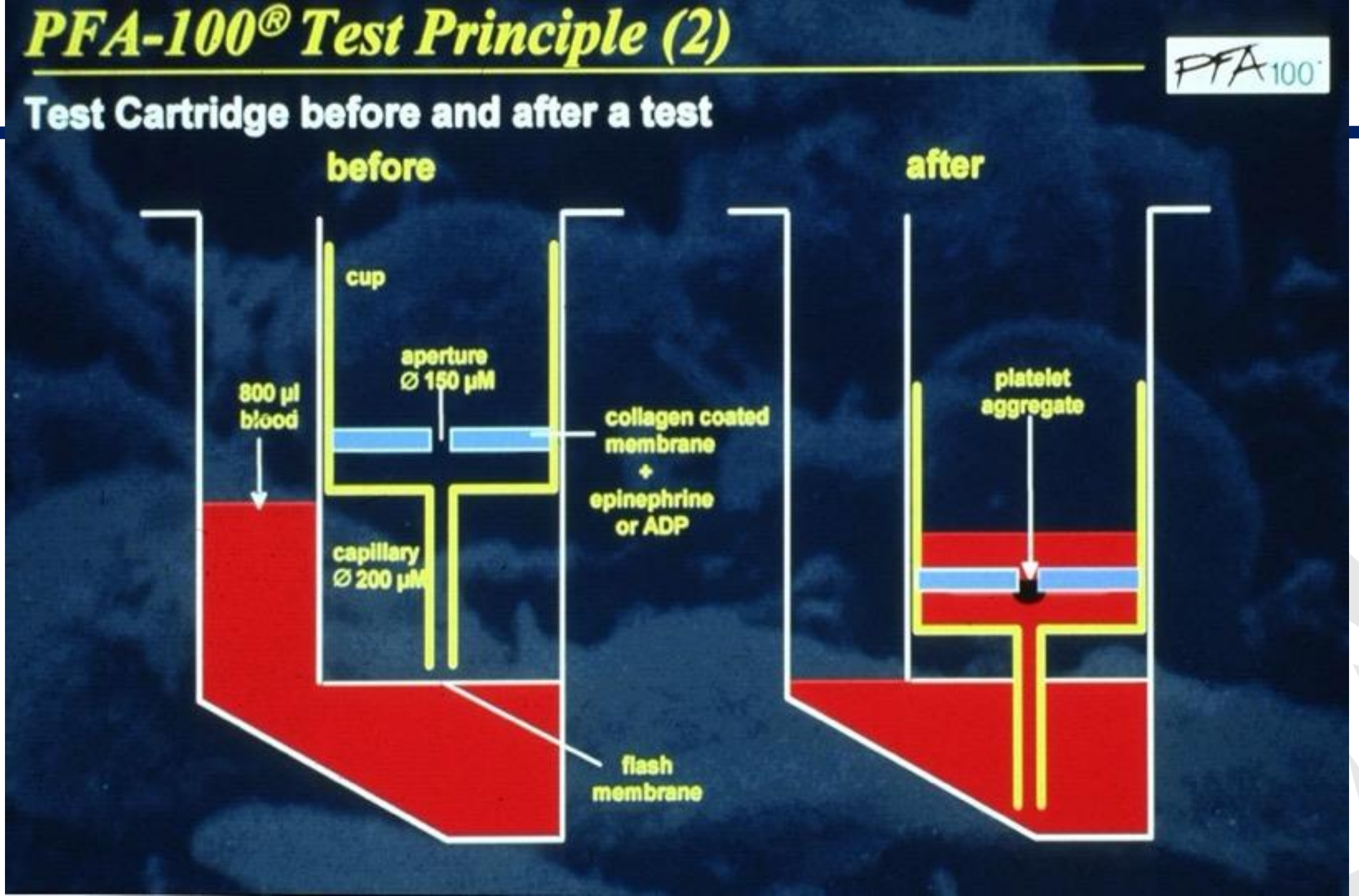
PFA-100® Test Principle (1)



PFA-100® Test Principle (2)

PFA 100

Test Cartridge before and after a test



(Patient MD continued)

Laboratory Studies:

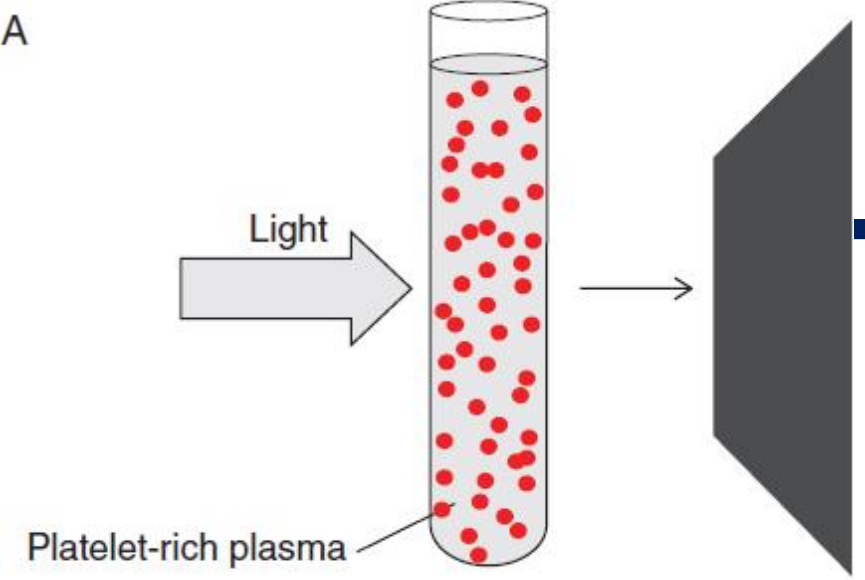
CBC and platelet count = normal

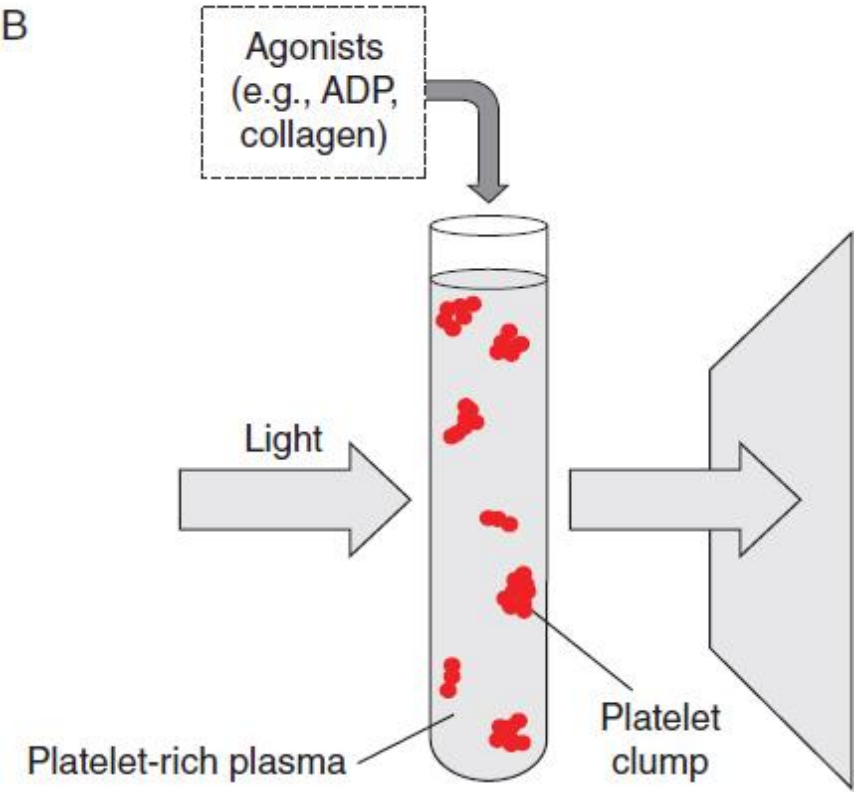
BT = 14, 16, an minutes

occasions (Normal-2-9 minutes)

PT, APTT = normal

Platelet Aggregation Study





According to the classical method, platelets in a suspension of *platelet-rich plasma* impede transmission of light. When any of a variety of agonists (collagen, thrombin, ADP, epinephrine) is added, aggregation occurs, consolidating the platelets and allowing the passage of light through the plasma

As the platelets aggregate (clump), the PRP becomes less cloudy, allowing more light to pass through (a fully aggregated sample of PRP will look like standard blood plasma).

The increase in light transmission as aggregation occurs is plotted as a function of time. Ideally, the waveform shows two physiologic processes

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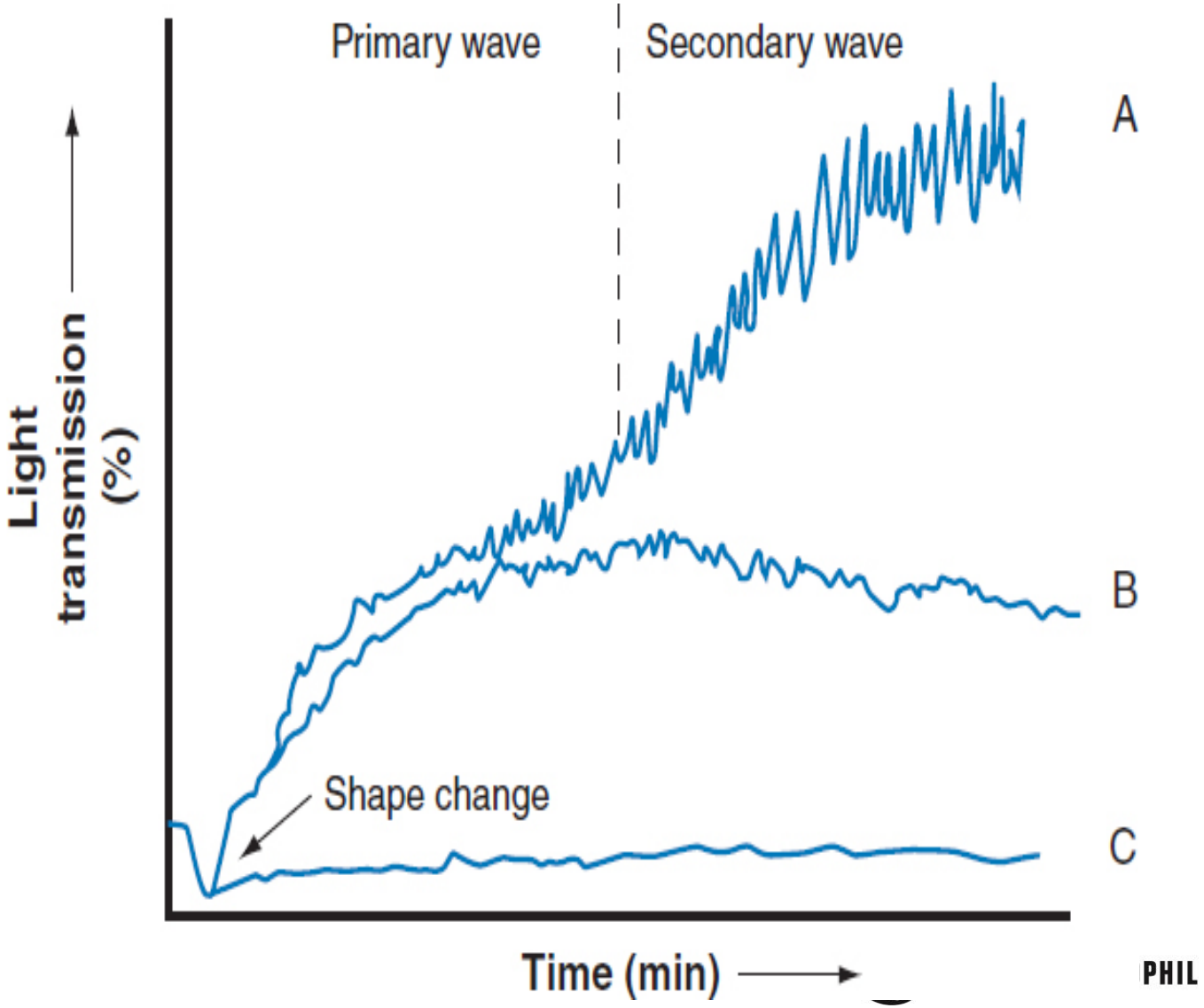
Platelet Aggregation Traces



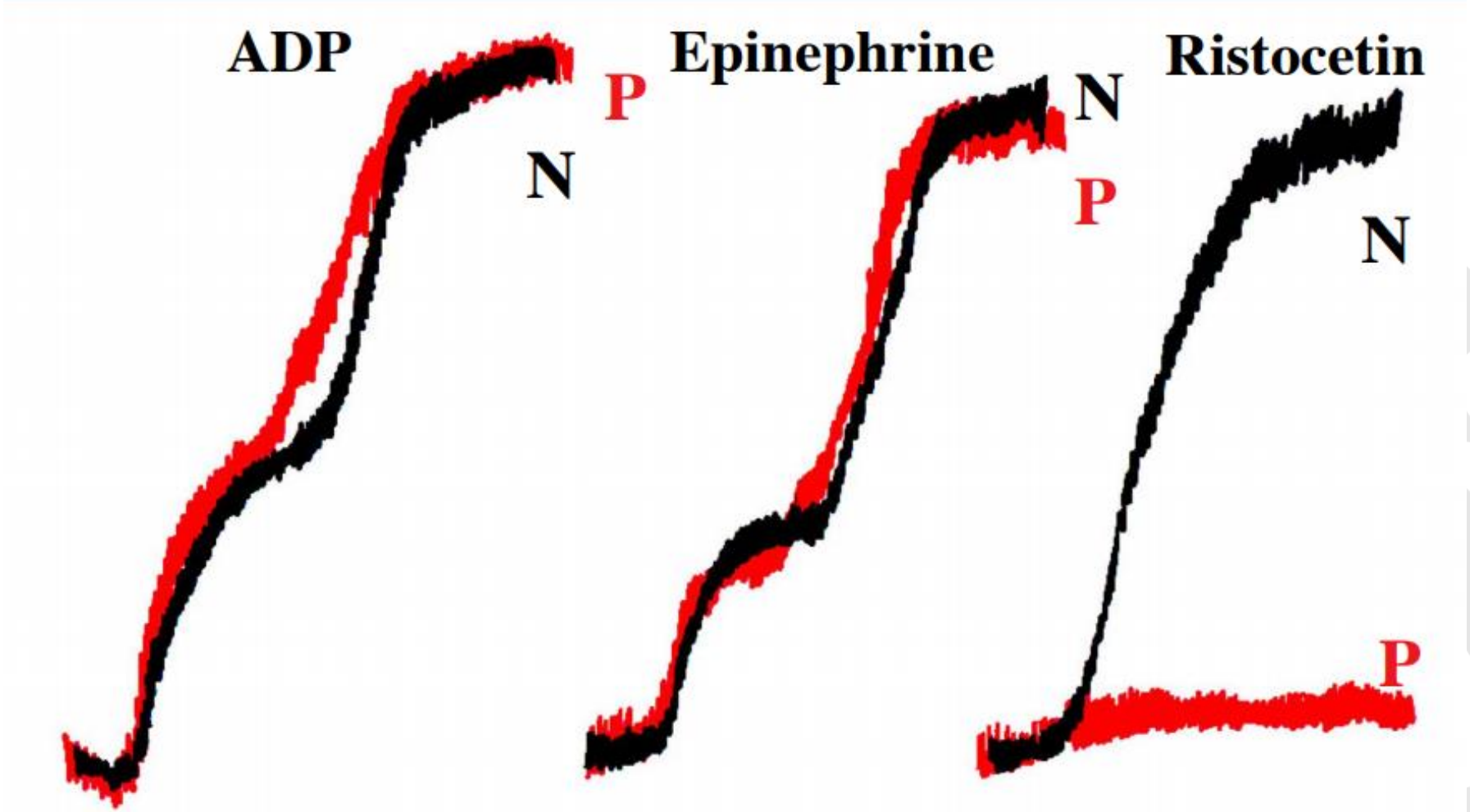
<u>There are two types of agonists:</u>

Strong Agonists e.g. Collagen, Thrombin, TxA2: These directly induce platelet aggregation, TxA2 synthesis and platelet granule secretion.

Weak Agonists e.g. ADP & Epinephrine: These induce platelet aggregation without inducing secretion.

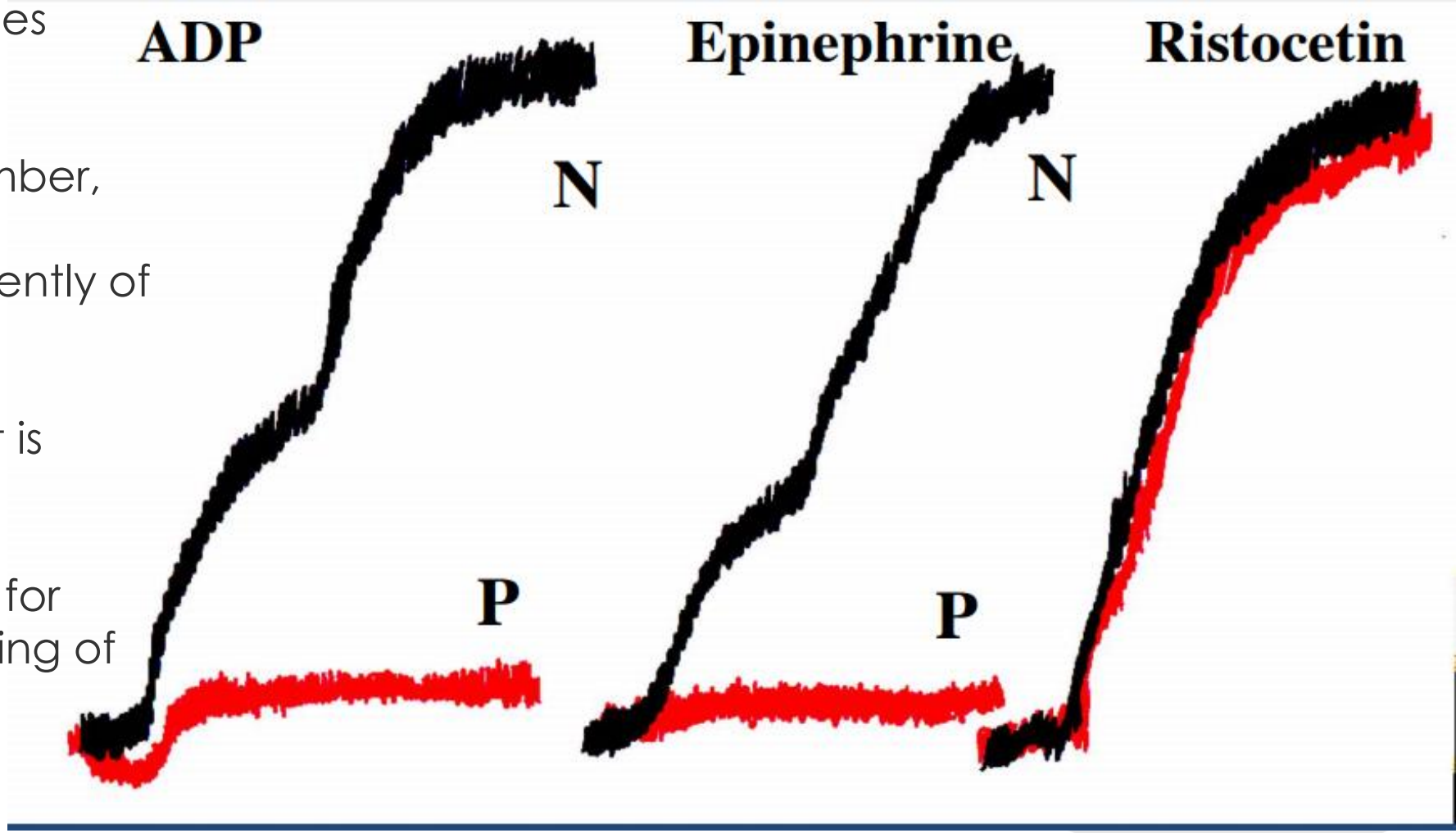
Ristocetin (but not generally in low dose i.e. 0.5 mg/mL) causes platelet agglutination (and not aggregation) through the VWF and GPIb-IX-V complex. [Platelet aggregation requires the binding of fibrinogen to the platelet via the GpIIb-IIIa complex.]

The only abnormality is a lack of agglutination with Ristocetin. Possible diagnoses are therefore, Von Willebrand Disease or Bernard Soulier Syndrome.

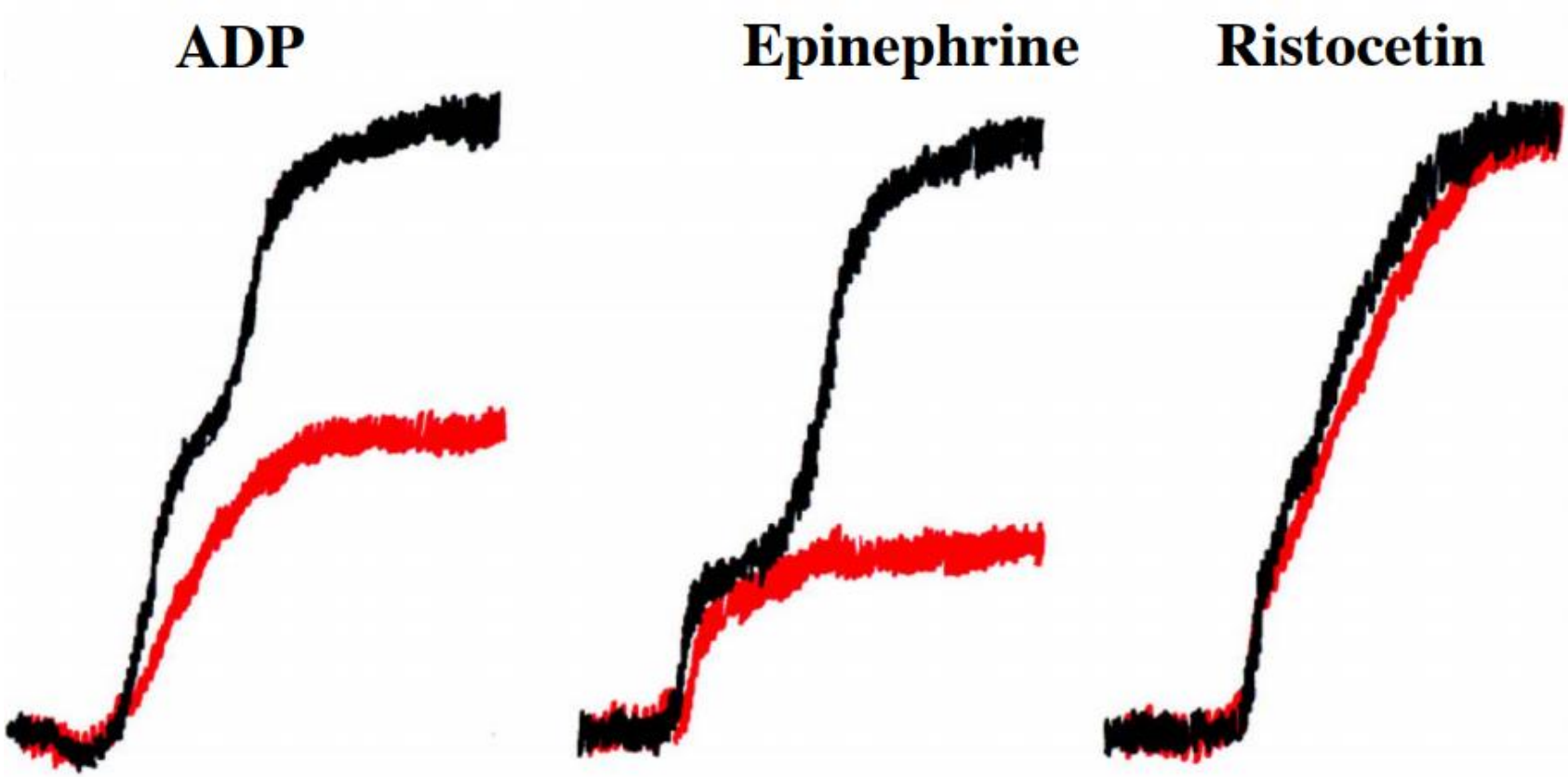


There is no aggregation with ADP, adrenaline , but only with Ristocetin . Possible diagnoses include Glanzmann's Thrombasthenia or Afibrinogenaemia. [Remember, platelet agglutination with Ristocetin occurs independently of Fibrinogen.]

In the traces shown below it is clear that only partial agglutination is seen with Ristocetin emphasising that for aggregation to occur, binding of Fibrinogen to the GpIIb/IIIa receptor is necessary.



In this patient the first wave shows a **partial** aggregation is seen with ADP, adrenaline **and only agglutination with Ristocetin.** The results suggest a failure of granule release and is consistent with either platelet : **Storage Pool Disorder or a defect in secretion release.**



Platelet Aggregation Disease State Summary	ADP		Epinephrine		Arachidonic Acid	Collagen	Thrombin	Ristocetin
	1°	2°	1°	2°				
Bernard-Soulier Syndrome	N	N	N	N	N	N	N or ↓	↓
von Willebrand Disease	N	N	N	N	N	N	N	↓*
Glanzmann's Thrombasthenia	↓	↓	↓	↓	↓	N/A	↓	N/A
Storage Pool Disorder	↓	↓ or ↓↓	↓	↓	N or ↓	↓	N/A	N/A
Aspirin Like Disorder or Aspirin Ingestion	↓	↓	↓	↓	↓	↓	N/A	N/A

N = Normal ↓ = Decreased ↓↓ = Substantially Decreased 1° = Primary Response 2° = Secondary Response

* Corrected by cryoprecipitate, Factor VIII concentrate or normal plasma; type IIB exhibits increased sensitivity to low concentrations

https://www.helena-biosciences.com/en/news/2015/why-perform-platelet-aggregation/

(Patient MD continued)

Factor VIII = normal

VWF antigen and activity (ristocetin cofactor) = normal

Additional labs:

Platelet aggregation delayed and reduced following exposure to collagen and ADP

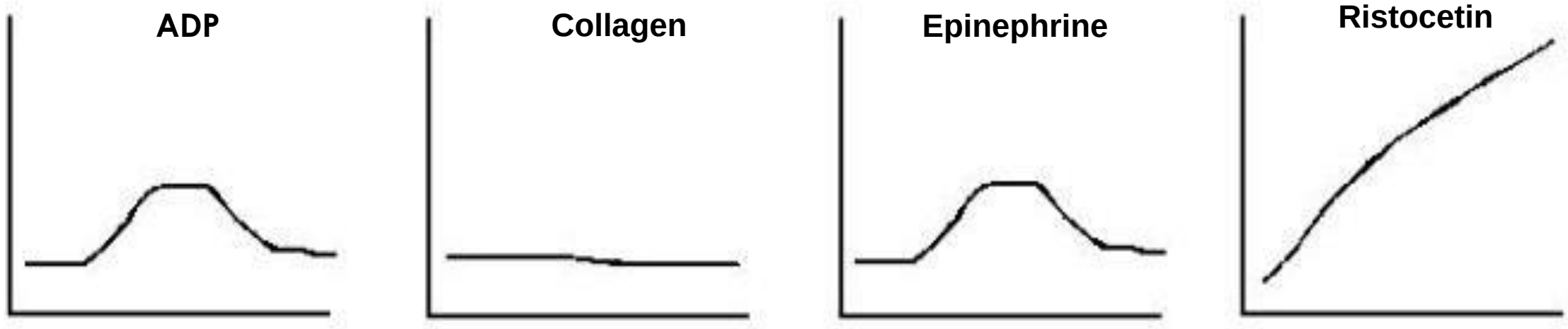
(Patient MD continued)

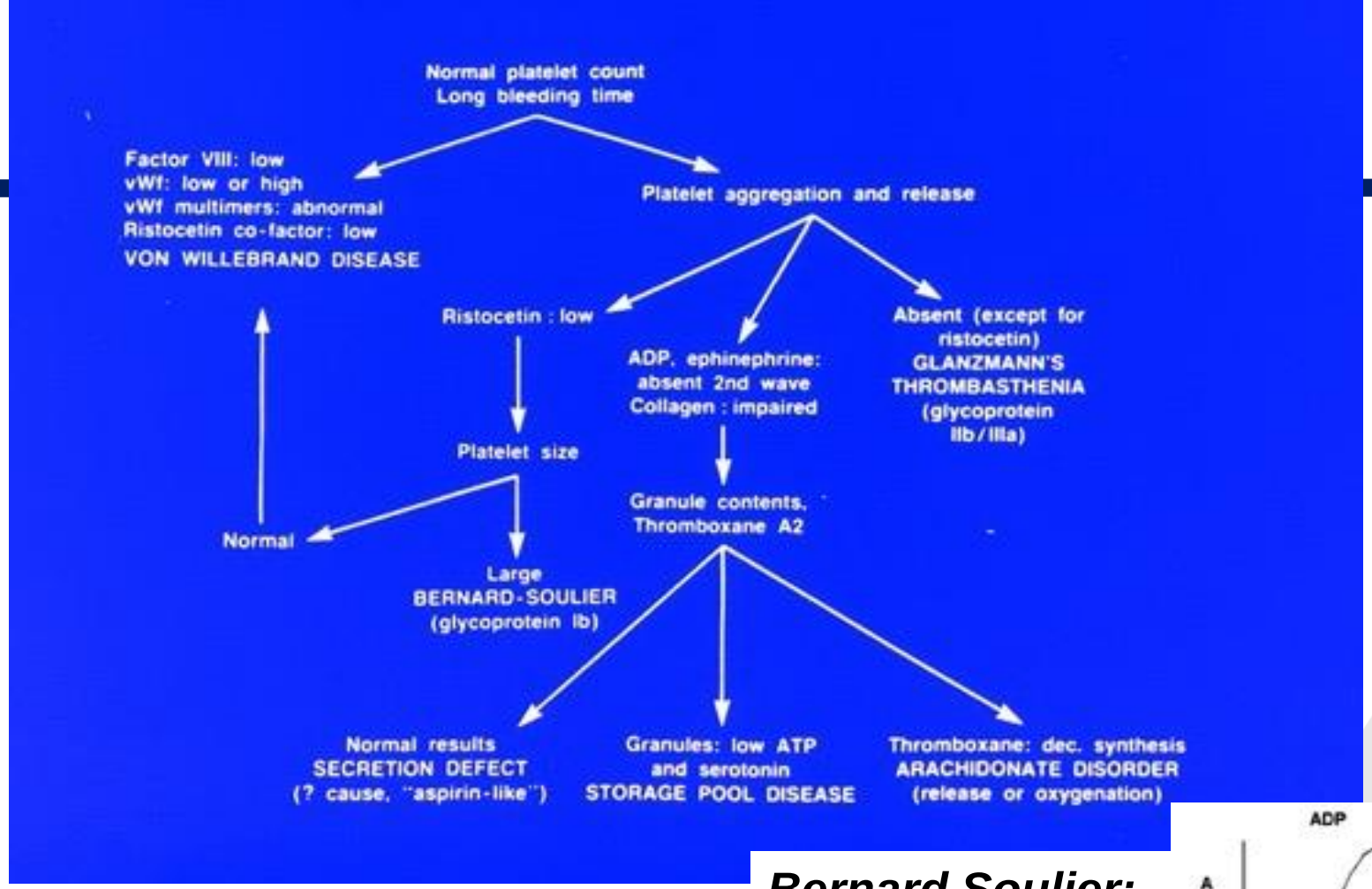
Factor VIII = normal

VWF antigen and activity (ristocetin cofactor) = normal

Additional labs:

Platelet aggregation delayed and reduced following exposure to collagen and ADP



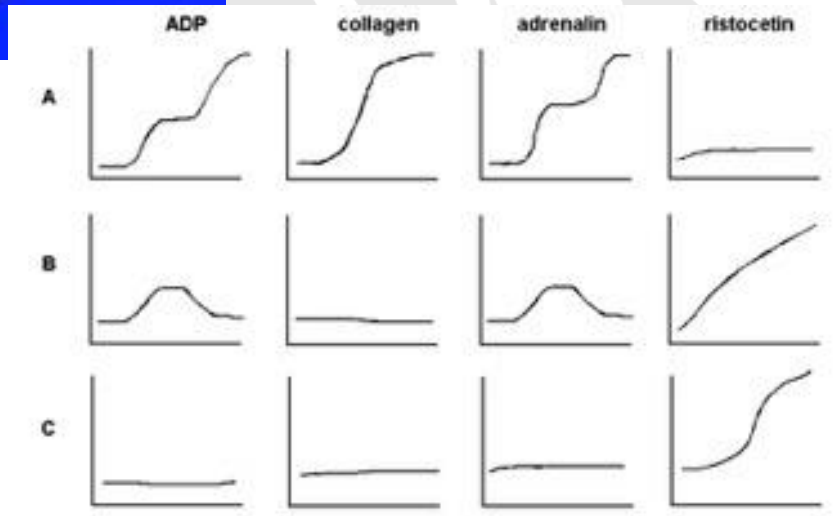


Patient M.D. >>>>
(had electron Micorscopy showing Dense granule Deficiency)

Bernard Soulier:

Storage Pool or Secretion Defect:

Glanzmann's Thrombasthenia:



Distribution of symptoms in relation to severity of the platelet function disorder

Severity	Bleeding symptoms
Severe i.e Bernard Soulier or Glanzmanns	Nose bleeding, heavy periods, joint bleeding, bleeding into brain, GI bleeding, childbirth related bleeding
Moderate	Nose bleeding, easy bruising, prolonged bleeds from cuts, heavy periods, GI bleeding, childbirth related bleeding
Mild	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

Adolescence

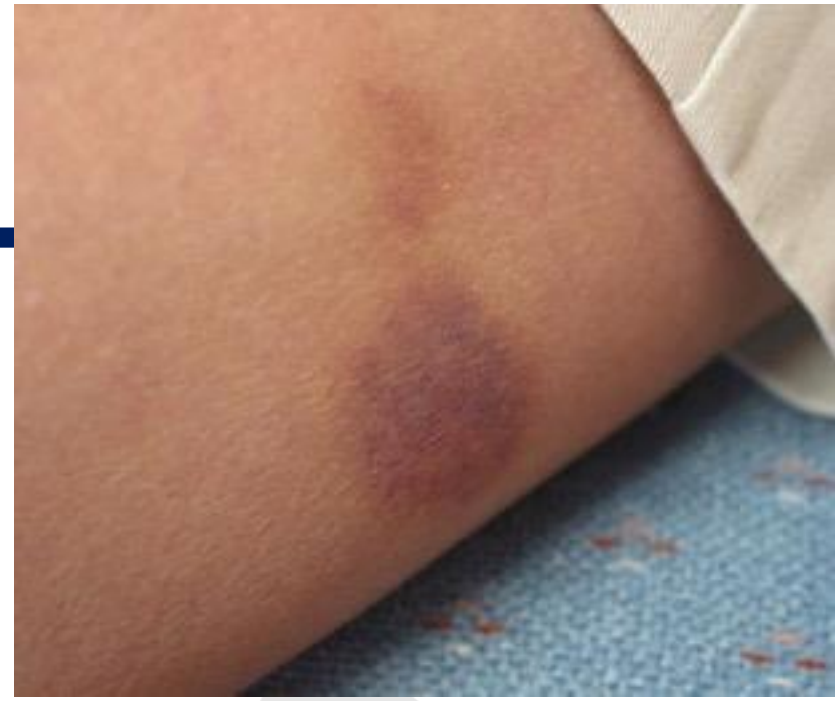
- Heavy periods changing tampon or pad or both every 2 hrs or less
- Gum bleeding with flossing, dental cleaning
- Oozing > 3 hrs after wisdom teeth extracted
- Large hematomas into skin/muscle with trauma

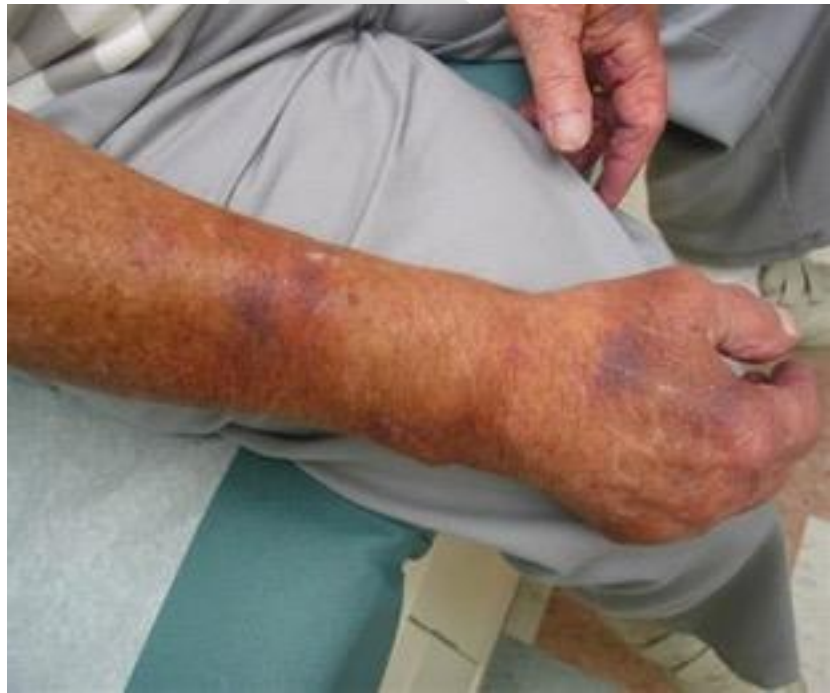
Adulthood

- 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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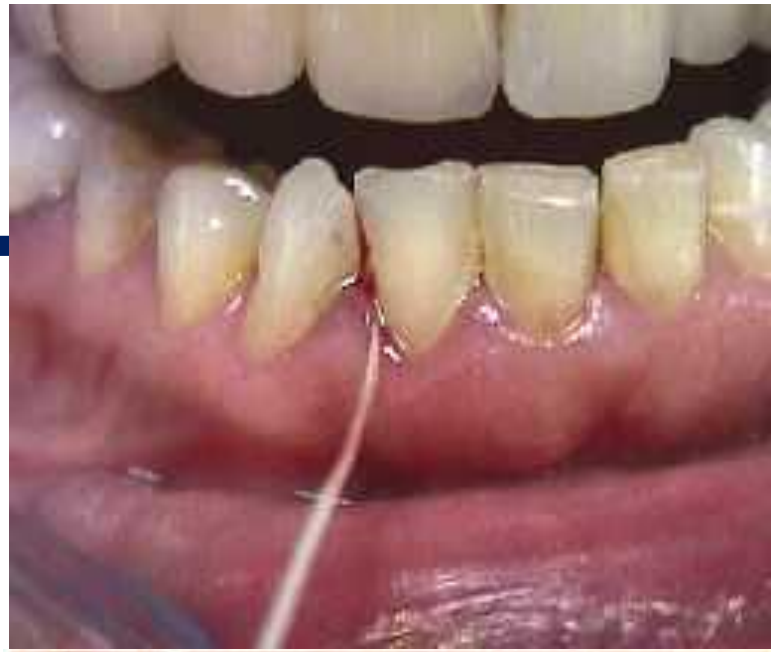
Nose bleeding (Epistaxis)

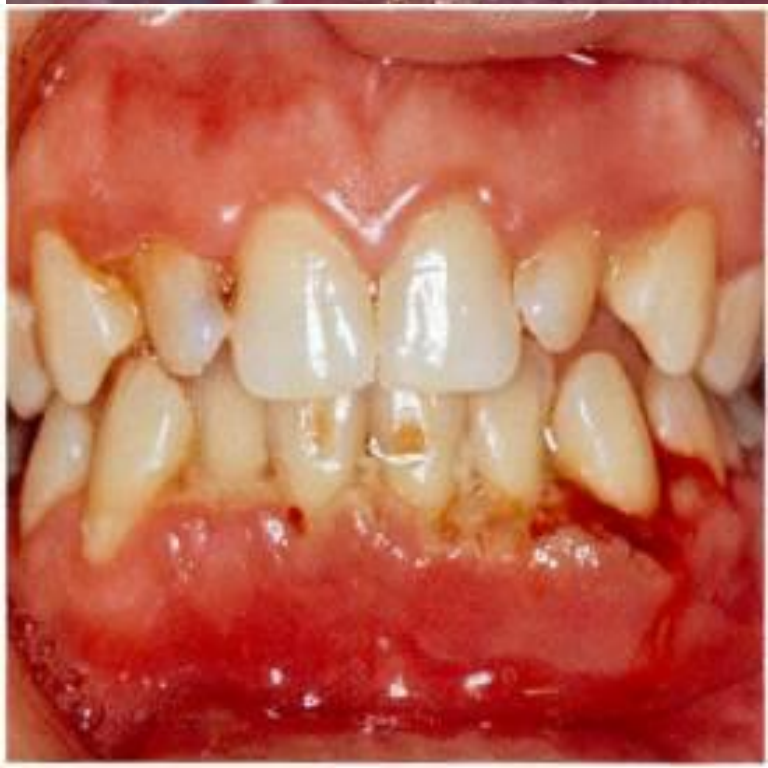
- Duration
  - usually > 10 min
- Frequency
  - usually > > 5 /year
- Severity
  - Often cautery/packing needed
- Spontaneous
  - Often unrelated to hypertension, dryness, aspirin
    - though curiously level of evidence of each of these risk factors is quite weak
    - Evidence stronger with nasal steroid 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!

Background: The Double Trouble of the Reproductive Cycle in Glanzmann's and Bernard Soulier

Heavy menstrual bleeding (HMB)

- defined by bleeding lasting more than 7 days and/or a blood loss of more than 80 ml per menstrual cycle
- Very common in patients with GT and often is serious and sometimes the presenting symptom.

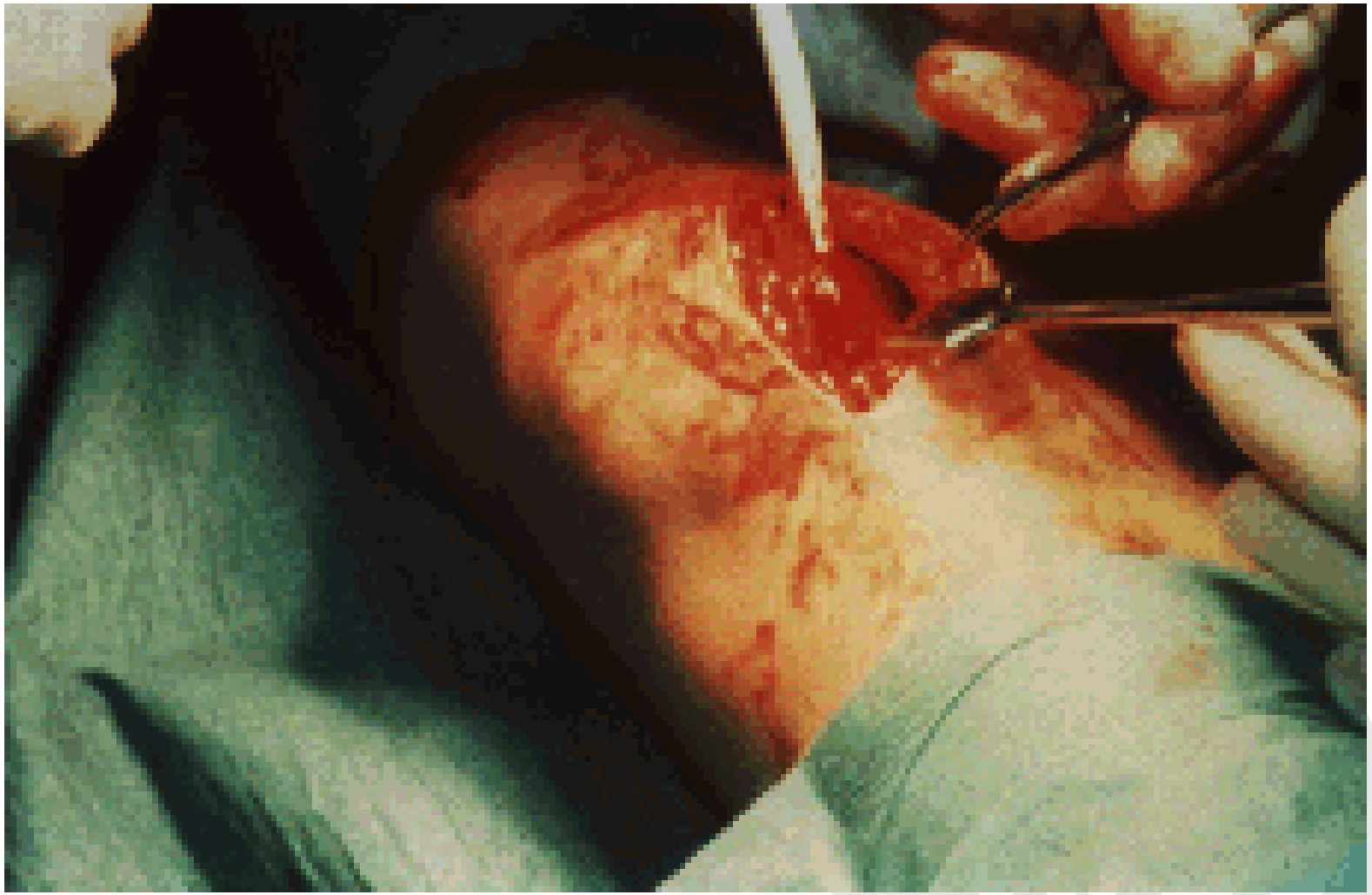
Post-partum Hemorrhage (PPH)

- Ante-partum: substantial risk of miscarriage, antepartum bleeding
- Post-partum: ≥ 40% risk of PPH!
- Pregnancies often complicated by antiplatelet antibodies (in 1/3rd) with increased risk of fetal death and neonatal thrombocytopenia and potential intracranial haemorrhage.

Multidisciplinary care is paramount for ensuring adequate control of menses and optimal fetal and maternal outcomes in females with GT

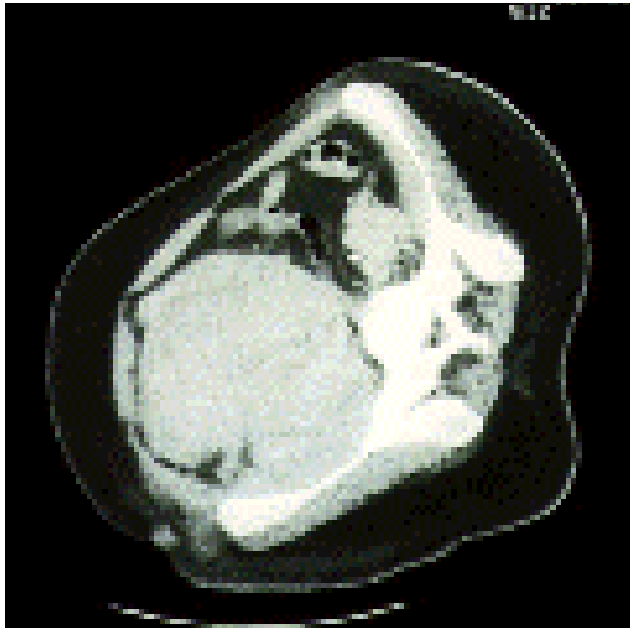
Complications due to surgery

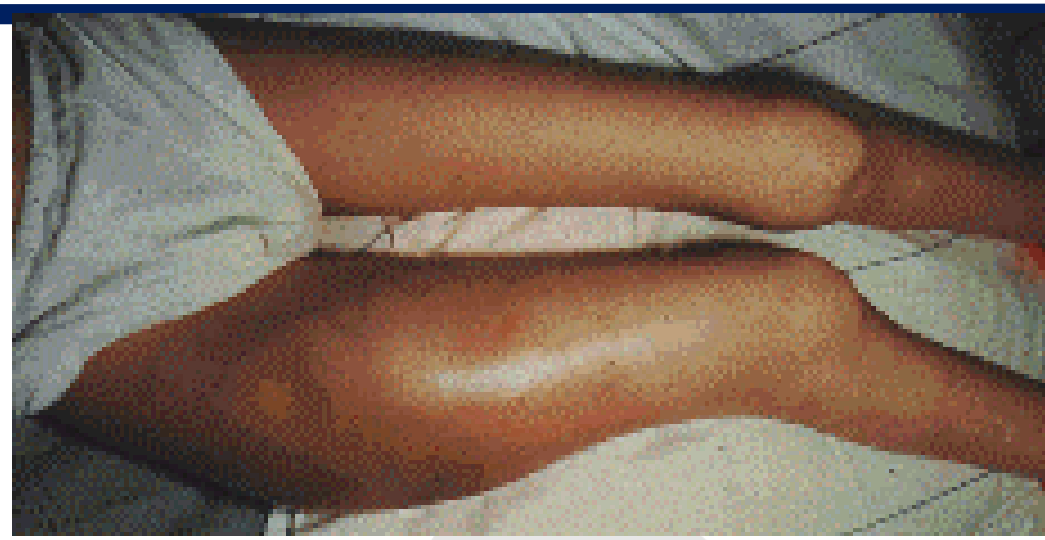
- continued bleeding and oozing
- hematoma
- impaired wound healing

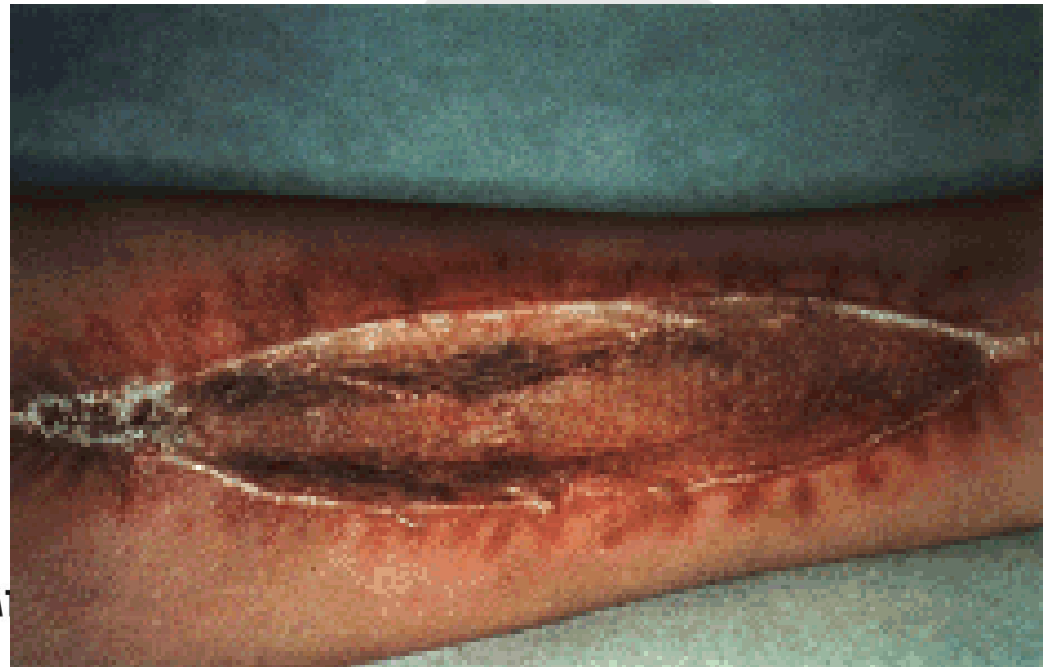


Muscular bleeding episodes - Hematomas

- calf, thigh, forearm
- iliopsoas
- compartment syndrome







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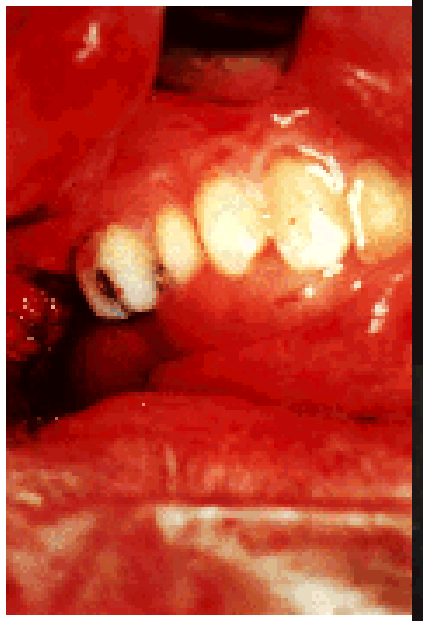
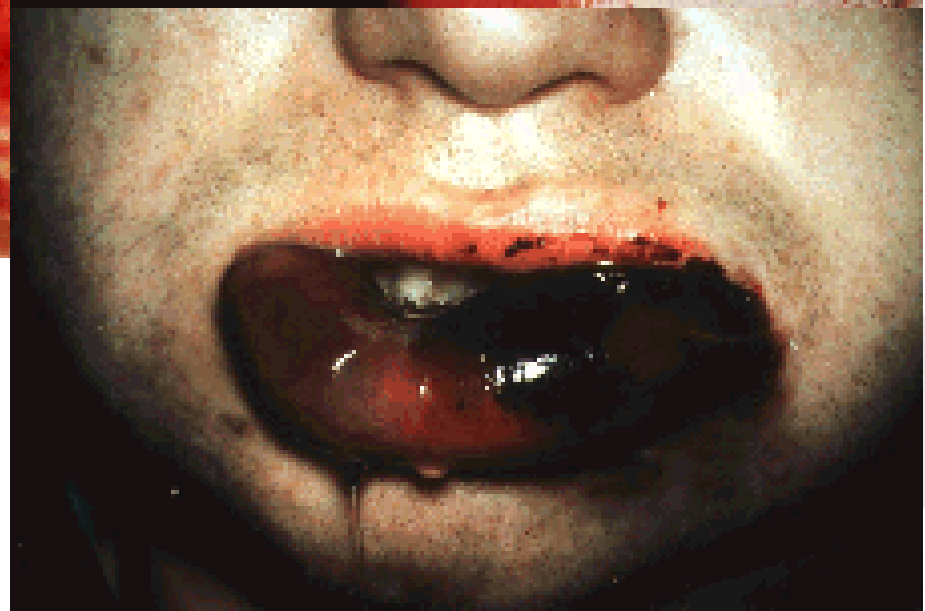
ENT bleeding episodes

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





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Treatment options in general for platelet function disorders

- **Anti-fibrinolytic therapy** (stabilizes the clot)- can be effective for mucus membrane related bleeding- mouth, GI tract uterus, bladder
  - Amicar, IV or oral in pill or syrup form- great for dental work
  - Lysteda (tranexamic or acid), IV or pill form (no syrup available)
- **Desmopressin**- effective treatment for another bleeding disorder called von Willebrand disease- sometimes can work in platelet function diosrders-
  - Give it IV, historically an intranasal form was also available- not available now due to recall
- **Recombinant VIIa** called Novoseven for severe bleeding, given IV
- **Platelet transfusion** for severe bleeding-
  - since there is a risk of being resistant we try to be conservation and use platelet transfusion only if major bleeidng

Managing dental work/dental issues

PRE-DENTAL WORK CHECK-LIST:

- **Extent of procedure?**
  - Dental cleaning- no pre-treatment unless poor hygiene
  - Tooth extraction, Nerve block
    - Depends on severity of platelet disorder

- **Severity of platelet disorder?**
  - severe–may need to give recombinant VIIa and if bleeding platelet transfusion

  - moderate to mild-Just use a medication called Amicar or Tranexamic acid (Lysteda)

Additional treatment

- 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

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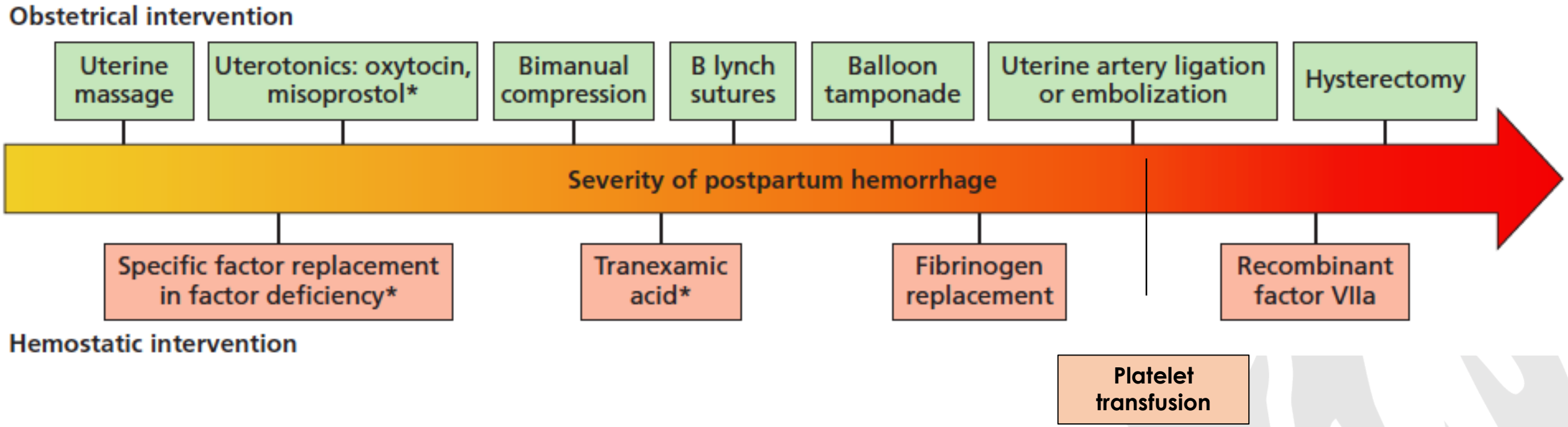
How to prevent/manage childbirth related bleeding?

- For Glanzmanns or Bernard Soulier- consider recombinant FVIIa and give platelet transfusion if bleeding
- Infuse post-delivery the IV form of Lysteda termed Tranexamic acid every 8 hours then can convert to the oral form Lysteda

Continuum of obstetrical and hemostatic interventions in the prevention and treatment of PPH



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Kouides PA, Blood Adv. 2017;1(11):699–702.

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?