Common hematological disorder

There is only 6 slide which the doctor explained the rest are notes

Done by:

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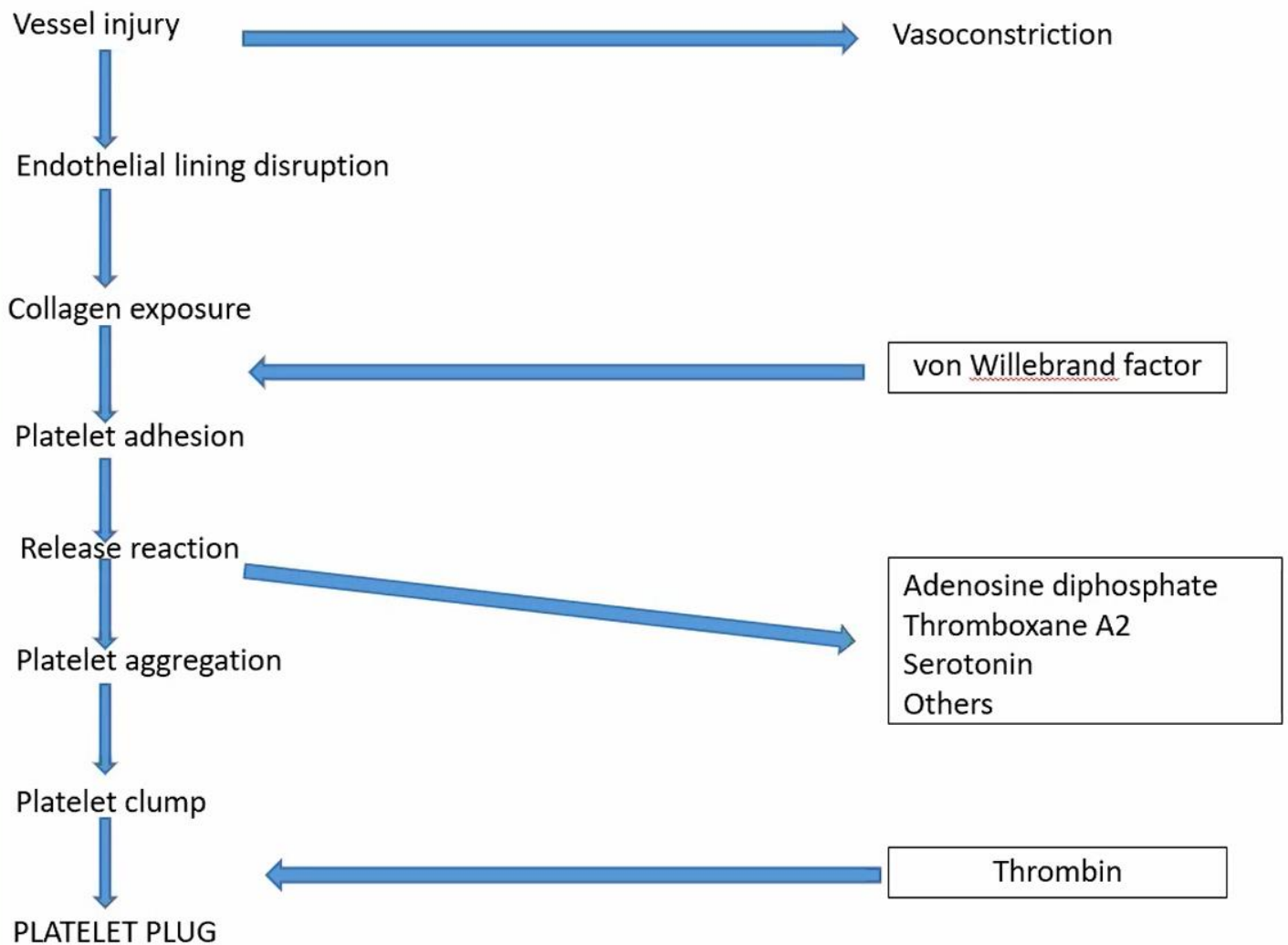

Vessel injury
Vasoconstriction
Endothelial lining disruption
Collagen exposure
von Willebrand factor
Platelet adhesion
Release reaction
Adenosine diphosphate
Thromboxane A2
Serotonin
Others
Platelet aggregation
Platelet clump
Thrombin
PLATELET PLUG

❑ 1-Normal bleeding:

-(6-8 min) to stop bleeding, max time to stop bleeding normally is 8 min .
-how children stop bleeding mechanism (normal child)?

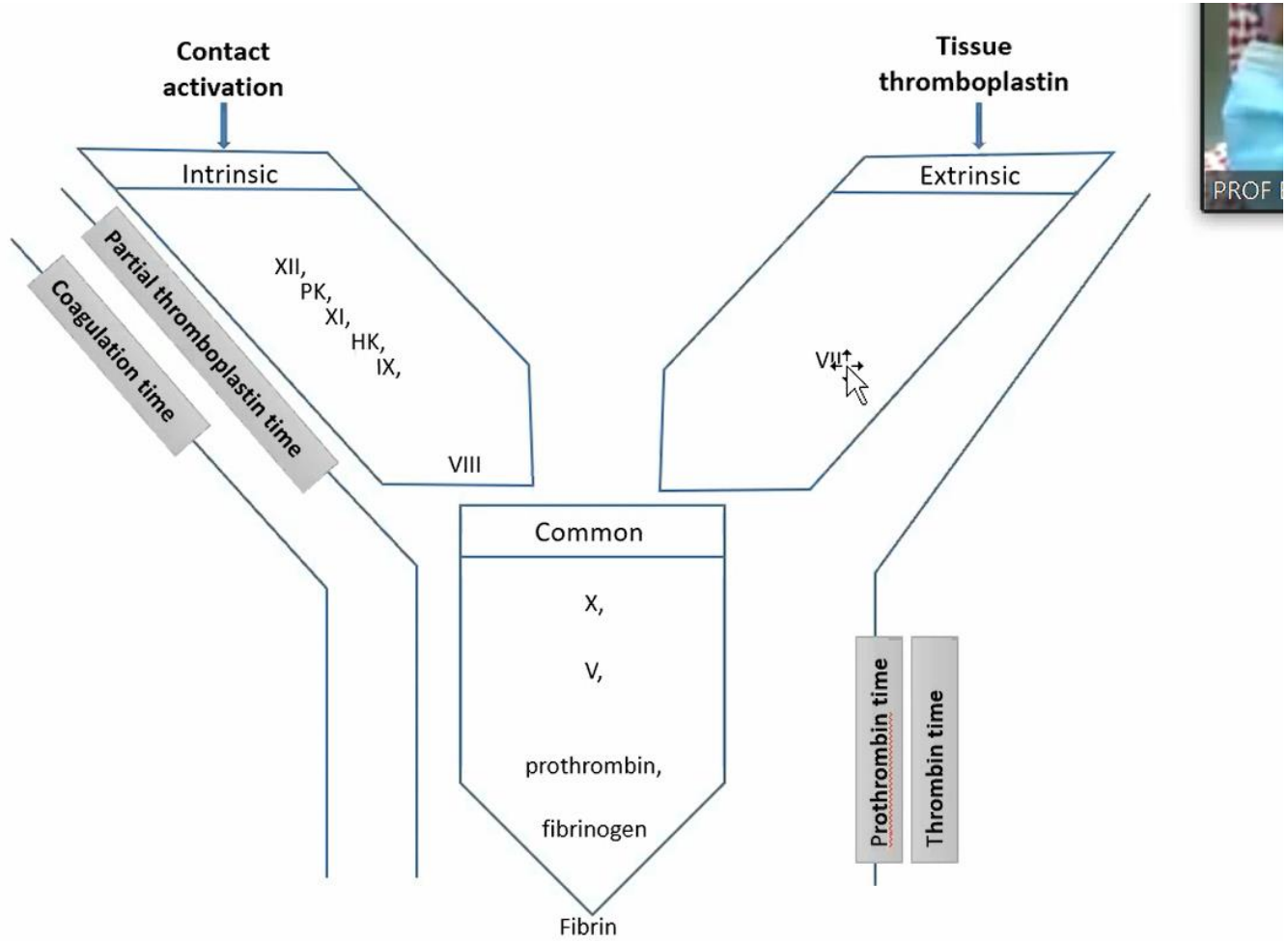
1. normal vessels and normal capillaries
2. normal platelets count and function
3. protein (coagulation factors) normal in amount and function

Physiology:

Children have clear smooth arteries Not like adults (ugly with lipids 😍 💔)

1. Injury in endothelial lining will get collagen to be exposed
2. Vasoconstriction (vessels will have immediately constriction)
3. platelet will adhere to the collagen(platelets need vonwillbrand to adhere)
4. start to release substance (ADP & Thromboxane A2) are the most imp* , they release these substance in order to aggregate
5. forming adhesive clout (platelet plug)
6. Bleeding will be stopped

If any step of these has disease (adhesion or aggregation affected) ,If the child continues oozing there is problem with the child within blood vessel , platelet or coagulation factor



Diagrammatic relationship among common screening tests of blood coagulation. The major pathways of coagulation are enclosed in the arrow-shaped boxes. The screening tests are indication at the side of the boxes in relation to the pathways and coagulation factors measures by each.

- 2-Coagulating cascade: (3 areas =intrinsic, extrinsic, common pathway)

1-Tissue thromboplastin pathway (factor 3) :

it will combine and activate factor 7 - we test this pathway by (PT and PTT) :

If PT is abnormal(prolonged) and PTT is normal —- factor 7 deficiency

Why not factor (3)? it's has never ever been inherited as deficient in animal or human

2- contact pathway

- If PTT is abnormal (prolonged) and PT is normal —- factor 12,11,8,9 def
- We approve the dx by hx if the child was a boy then — must be 8,9 def , If the child is a girl —something else
- Factor (12) called Hageman factor — if def it makes a prolonged PTT without prolonged bleeding
- Factor (11) causes bleeding only in jewish ashkenazi we don't have it in another nation ,so for the lab do (11.12)
- when you have a prolonged PTT alone then you are dealing with either factor (8,9)
- Both factor (8) (9) are x-linked but factor (8) is 100 times more common than (9)
- Factor (8) def called -hemophilia A
- Factor (9) def called -hemophilia B
- 8,9 are the only x-linked the others are autosomal dominant or autosomal recessive

- The acquired causes of prolong PTT are more common than the inherited causes so the lab will do mixing study— they add all the defect factors to the blood to see if it's corrected or not to rule out antiphospholipid antibodies' syndrome

- If child has prolonged PTT with no bleeding at all — ask for mixing study
- If child has real bleeding with family hx with epistaxis and ecchymosis — factor 8,9 if is a boy , if it's a girl she must have von willbrand factor

3- common pathway (factor1 = fibrinogen) (factor 2= prothrombin)

- Contain only 4 proteins = Factor 10,5,2,1
- Factor (7) from the extrinsic pathway comes to activate factor (10)
- Also factor 8,9 from the intrinsic pathway will activate factor 10 —- will activate 5 —and form factor 5,10 complex — then activated prothrombin to form thrombin —- then thrombin will cleave a huge molecule which is fibrinogen to form the fibrin (clot)

- Then how to know if its factor 10,5,2,1?
  - You have to ask for PT and PTT and fibrinogen
  - So when we have PT abnormal and PTT abnormal— it has to be either factor 10 or 5 or 2 or 1

  - If the fibrinogen is not deficient it is HIGH and there is a bleeding problem in a child —- the child may have dysfibrinogenemia (very rare) the amount is high and super normal , BUT is NOT FUNCTIONING

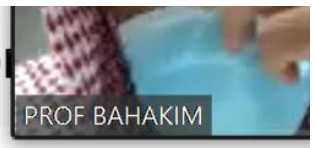
- Q: Child has bleeding, and he is normal with normal platelets in function and count, and normal PT and PTT = factor 13 def
  - factor 13 does not belong to the cascade, it is formed to solidified the fibrin – it is called clot stabilizing factor
  - Its function: it facilitate the crossing of fibrin on each other, so the clot will be solid and stable.
  - A clot Without factor 13 will not be solid and will lysed and turns to blood again

  - Clot dissolving test (screening test) for factor 13 done using : acetoacetic acid or 5 mol of urea , all other teats are normal.

- In the hx there is leading Q for suspecting and diagnosing factor 13 def : Ask the mother about the umbilical cord stump when child was born when if fall off ? (it should fall off within week or 10 days)
  - if it took time more than that and it was wet not dry .= factor 13 def
  - Ask that Q even if the child is 4 y.o. And you suspecting factor 13 def

- Child who doesn't have any bleeding he was tested routinely for surgery, family hx is negative platelet count is normal everything was fine, but now he has a prolonged PTT (so child is not bleeding but he has a prolong PTT) —- the lab did mixing study (to see if its APLS) nothing was found what is the diagnosis? it must be factor 12 def —- so they screen for factor 12 and high molecular weight kininogen (this molecule also gives a prolonged PTT with no bleeding)

Relationship of factor Levels to Severity of Clinical Manifestation Hemophilia A and B



Type	Percentage factor VIII/IX	Type of Hemorrahge
Severe	< 1	Spontaneous; hemarthroses and deep tissue hemorrhages
Moderate	1 – 5	Gross bleeding following mild to moderate trauma; some hemarthrosis; seldom spontaneous hemorrhage
Mild	5 – 25	Severe hemorrhage only following moderate to severe trauma or surgery
High-risk carrier females	30 – 50	Gynecologic and obstetric hemorrhage

3-hemophilia :

- X linked disease and the mother is the carrier.

Severity of disease:

- normally we have 100% of factor 8 and 9 and that means normally you have 1 unit of factor 8 in each ml of plasma.
- if factor 8 or 9 is less than 1%= almost 0 —they will have massive GI or brain bleeding, and spontaneous bleeding with no documented trauma and they usually bleed deep into tissue, muscles and joint (hemarthrosis)
- if factor 8 between 1-5% - they still bleed deep into tissue but upon trauma (ecchymoses) , and bleed heavily upon surgery, and might develop hemarthrosis because 1-5% is noy enough
- More than 5% in mild
- The mother will not have ecchymosis because she has between 60-40% factors the only compline will be menorrhagia
- family Hx is very important in Hemophilia
- not only the mother is responsible for hemophilia, 20% of hemophiliac boys they have a spontaneous mutation of gene in utro.
- Genetic study is the definitive way to know if the mother is a carrier or not.

Difference between von Willebrand Disease and Hemoph

	Von Willebrand Disease	Hemophilia A
Symptoms	Bruising and epistaxis Menorrhagia or mucosal bleeding	Joint bleeding Muscle bleeding
Sexual distribution	Male = females	Males
Frequency	1:200 to 1:500	1:6000 males
Abnormal protein	vWF	Factor VIII
Molecular weight	0.6-20x10 Da	280 kDa
Function	Platelet adhesion	Clotting cofactor
Site of synthesis	Endothelial cell or megakaryocytes	??
Chromosome	Chromosome 12	X Chromosome
Inhibitor frequency	Rare	14 – 25% of patients
History	Abnormal	Abnormal
aPTT	Normal or prolonged	Prolonged
Factor VIII activity	Borderline or decreased	Decreased or absent
-vWF Ag	Decreased or absent	Normal or increased

From: Montgomery RR, Gill JC, Scott JP. Hemophilia and von Willebrand disease. In: Nathan D, Orkin S, editors. Nathan and Oski's Hematology of Infancy and Childhood, 5th ed. Philadelphia: Saunders.

❑ 4- The Schedule of VWD vs Hemophilia :

- Type 1 von willbrand — the commonest 95% of all VWB deficiency cases , easy to diagnose autosomal dominant that means one of the parents should have it, hematuria . Gi bleeding .***epistaxisis*** **bilateral.**
- Type 3 von willbrand is the severe type -autosomal recessive - the parents are cousins—have epistaxis all the time -Similar to hemophilia they have joint bleeding, deep tissue bleeding.
- If the child is girl with a manifestation that resembles severe hemophilia = type 3 vwd until proven Otherwise
- Girls can have Hemophilia but only if the father is affected and the mother is carrier(2 x gens must be affected)
- In von willbrand disease the amount and the function(aggregation & adhesion) of the platelets are all affected
- Von willbrand is responsible for factor 8 if its def, then factor 8 will also be defect, so if you have aggregation problem in that girl – that means she does not have hemophilia at all – and platelet function will come to be abnormal because VWF is deficient .
- If there is a problem with the factors it is either in amount or function, for instance; in hemophilia the amount in normal , but the function is affected . on the other hand , in vWd both are low amount and function(but the ratio between amount and function is 1:1)while in hemophilia the ratio is very bad 1:100 (the amount is normal but only 1% is functioning)

Type 1	Types 3
the commonest 95% of all VWB deficiency cases	rarest
autosomal dominant , one of the parent have it	autosomal recessive , parents are normal
Mucosal bleeding such as hematuria . Gi bleeding .epistaxisis bilateral	joint bleeding, deep tissue bleeding , very bad ecchymoses , and bleeding usually require blood transfusion
Very mild , factor 8 is almost normal	Factor 8 is only 2-3%
Tx: desmopressin	Tx: factor 8

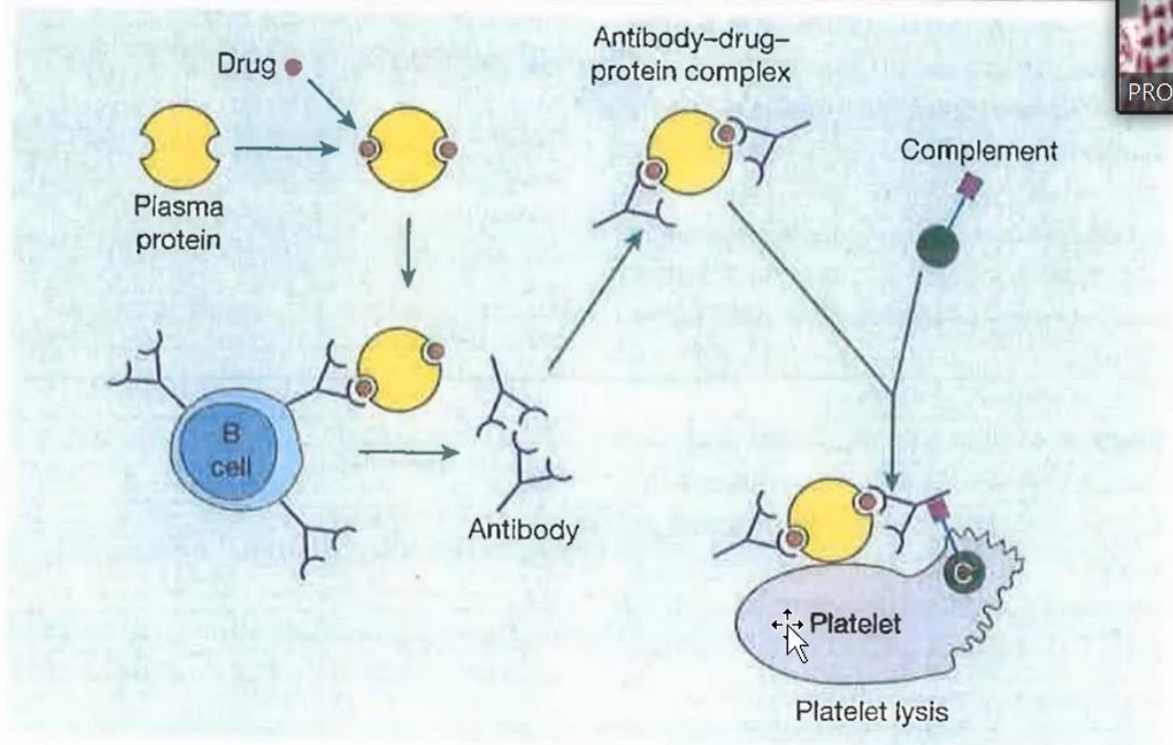


Figure 25.6 Usual type of platelet damage caused by drugs in which an antibody–drug–protein complex is deposited on the platelet surface. If complement is attached and the sequence goes to completion, the platelet may be lysed directly. Otherwise it is removed by reticuloendothelial cells because of opsonization with immunoglobulin and/or the C3 component of complement.

5-Thrombocytopenia:

- platelet problems : thrombocytopenia = in 92% of cases patient have ITP.
- mechanism : post viral infection or taking a drug , the immune system develop immunoglobulin, but they were not specific to that virus , and those immunoglobulin has coted the platelet after that monocyte will take the platelet right away and carry them to spleen where they will be degraded by macrophages as a result platelet will be low in circulation .
- **immune thrombocytopenia purpura** : common MCQ topic

1. child has viral infection 2-3 weeks ago with no history of autoimmune disease, and now complain of petechia hemorrhage (DDX: thrombocytopenia or vasculitis) , Systematic review should be negative for any active problem at that stage, the complain is only pinpoint bleeding into skin or mucous membrane 1st criteria no active problem at all specially fever , common cold or sore throat or minor disease.+ no history of bleeding disorder in family
2. physical exam : child is completely normal (no palpable spleen) (petechial hemorrhage with palpable spleen = leukemia),
3. CBC: all normal except low platelet

To summarize ITP :History of viral infection +negative history for autoimmune disease + normal physical examination + normal CBC except for low platelet = ITP until proven otherwise .

- Q: 10 y old girl with similar presentation what DDX? could be autoimmune disses + most common autoimmune disease associated with petechia is thyroiditis, SLE .
- Viral infection = very good prognosis, if platelet less than 200,000 we admit and treat with immunoglobulin, complication: spontaneous bleeding in brain , immunoglobulin are only used to raise platelet count
- If there is no improvement steroid is the drug of choice
- Can be used in combination: immunoglobulin to saturate the macrophages, steroid to kill B lymphocyte
- If chronic more than 1 year we use RITEXIMAB . Either to cure , remission for 1 y or 6 m + steroid must be stopped at 6 months in order to allow child to grow

- 6-thrombocytopenia due to splenomegaly

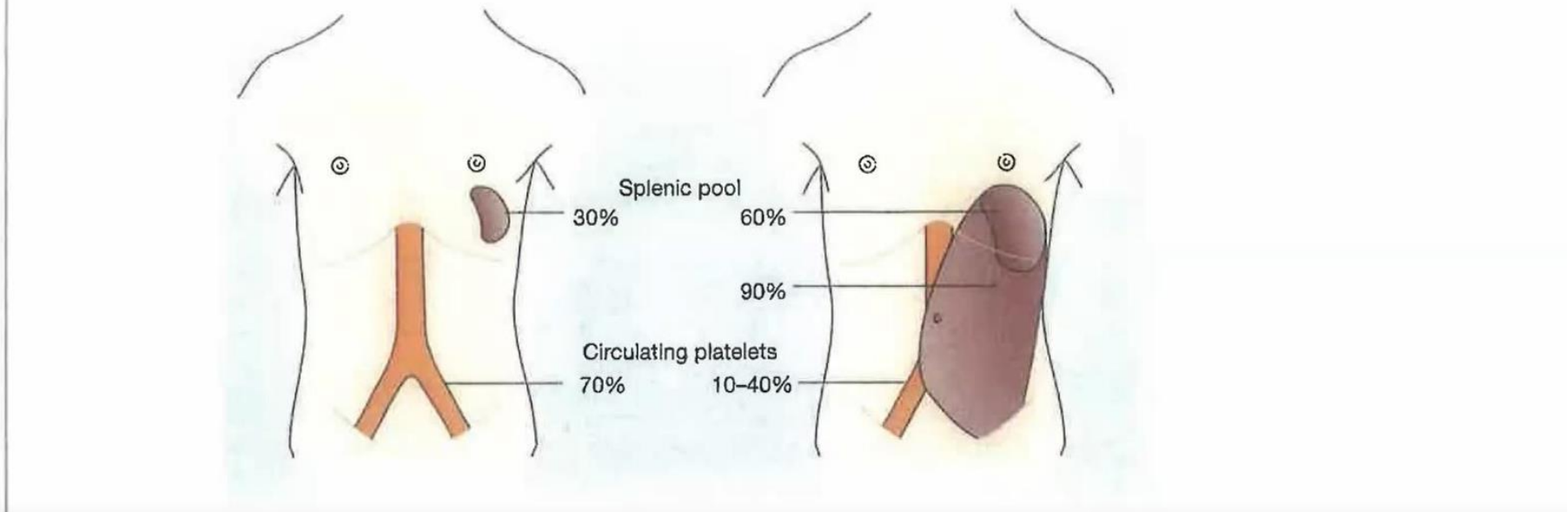


Figure 25.9 The platelet distribution between the circulation and spleen in normal individuals (left), and in patients with moderate or massive splenomegaly (right).

here the spleen is huge due to others disease , this spleen will take 90% of the platelets and patient end up with thrombocytopenia due to hypersplenism

- 7-Vit k deficiency:

- causes bleeding in newborn (factor 2,7,9,10 their function depend only on vit k which is synthesis in bowel, and the newborn bowel is sterile that we every newborn need 1mg IM injection of vit k)