Lec(1) Hemostasis and blood coagulation

د لقاء محمد مجيد الشريفي

Objectives:

To classify and describe the etiology and pathogenesis of vascular and platelets disorders

Haemostasis: is the physiological arrest of hemorrhage at sites of vascular leakage.

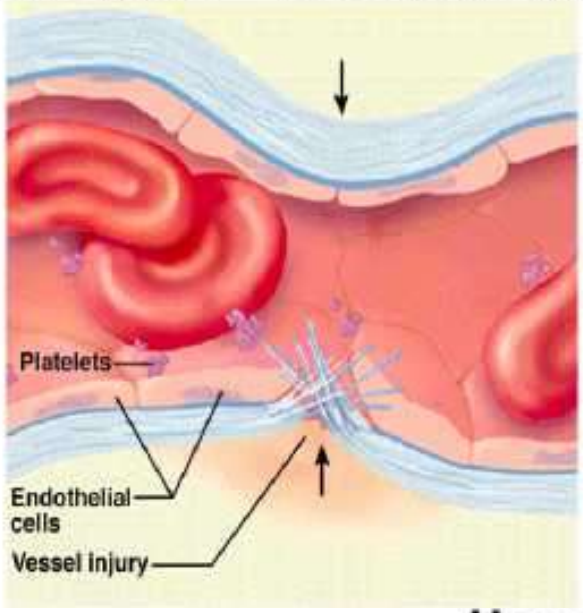
There are mainly **5 systems** which interact together to ensure hemostasis, namely:

1. Platelets.
2. Coagulation Factors.
3. Natural Coagulation inhibitors.
4. Fibrinolytic system.
5. Vascular factors.

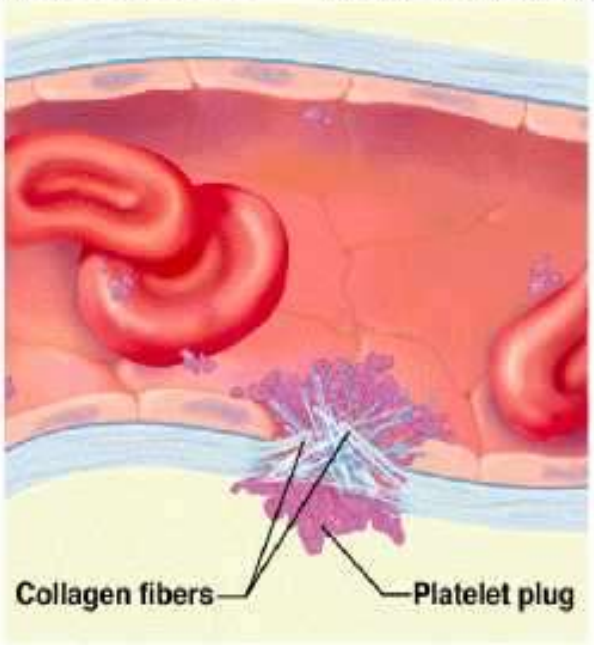
Response to vascular injury

- **Vasoconstriction.**
- **Primary hemostasis** (platelet reactions and primary hemostasis plug formation), unstable plug, within few first minute, temporal control.
- **Secondary hemostasis** (stabilization of platelets plug by fibrin) fibrin formation by coagulation factors, within several min.

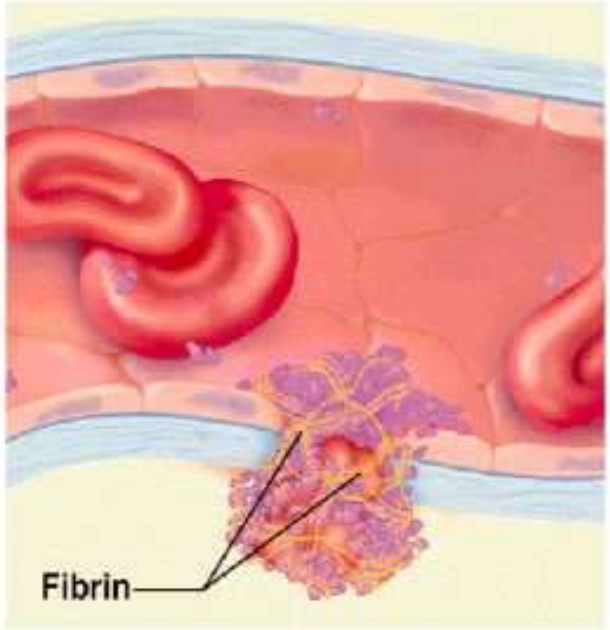
Hemostasis — Vasoconstriction



Hemostasis — Platelet Plug



Hemostasis — Blood Clot



Terms in bleeding tendency

Purpura is extravasation of RBC into skin and SCT.

Petechiae is purpura < 2mm , **ecchemosis** is purpura > 2mm.

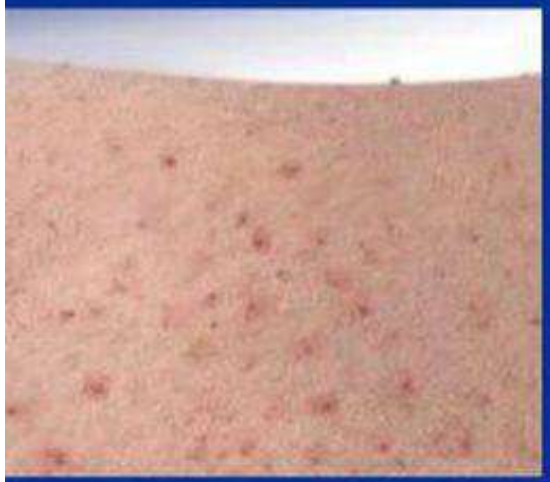
Dry purpura: cutaneous purpura (petechiae, ecchymosis, easy bruising).

Wet purpura: mucosal bleeding (oozing gums, blood blisters in mouth, epistaxis, hematuria, menorrhagia, melena, bleeding per rectum), fundal hemorrhages and joint hemorrhage (hemoarthrosis).

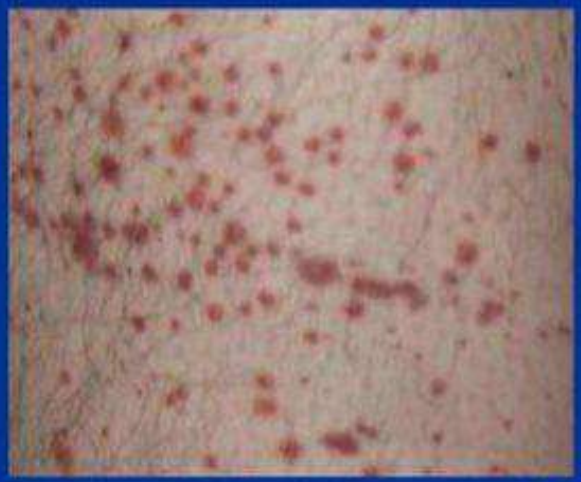
Erythema: mean redness of skin due to increase blood flow blanch with pressure.

Talengiectasia: dilated superficial capillaries blanch with pressure.

Petechiae
(1 – 2 mm)



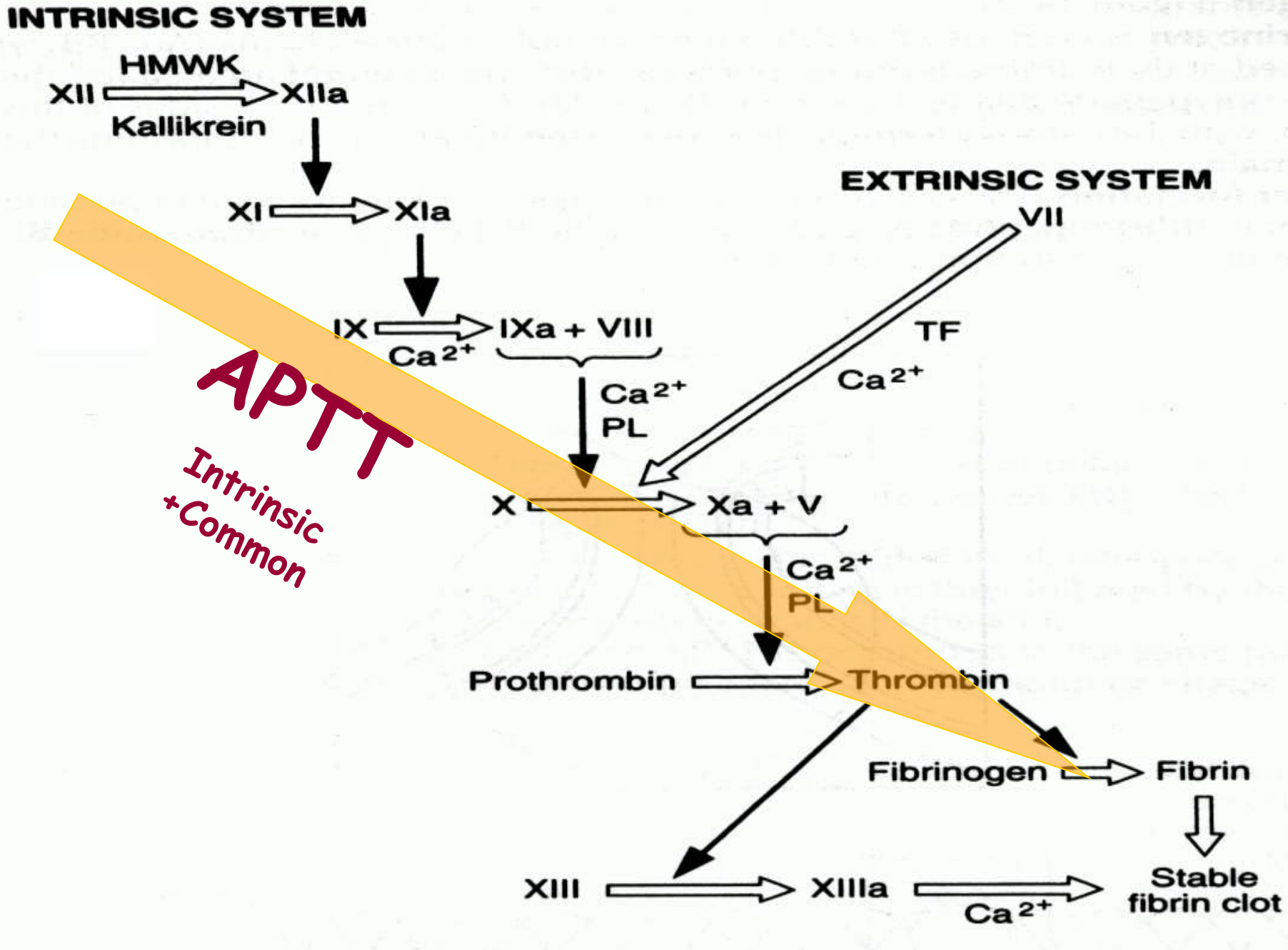
Purpura
(≥ 3 mm)

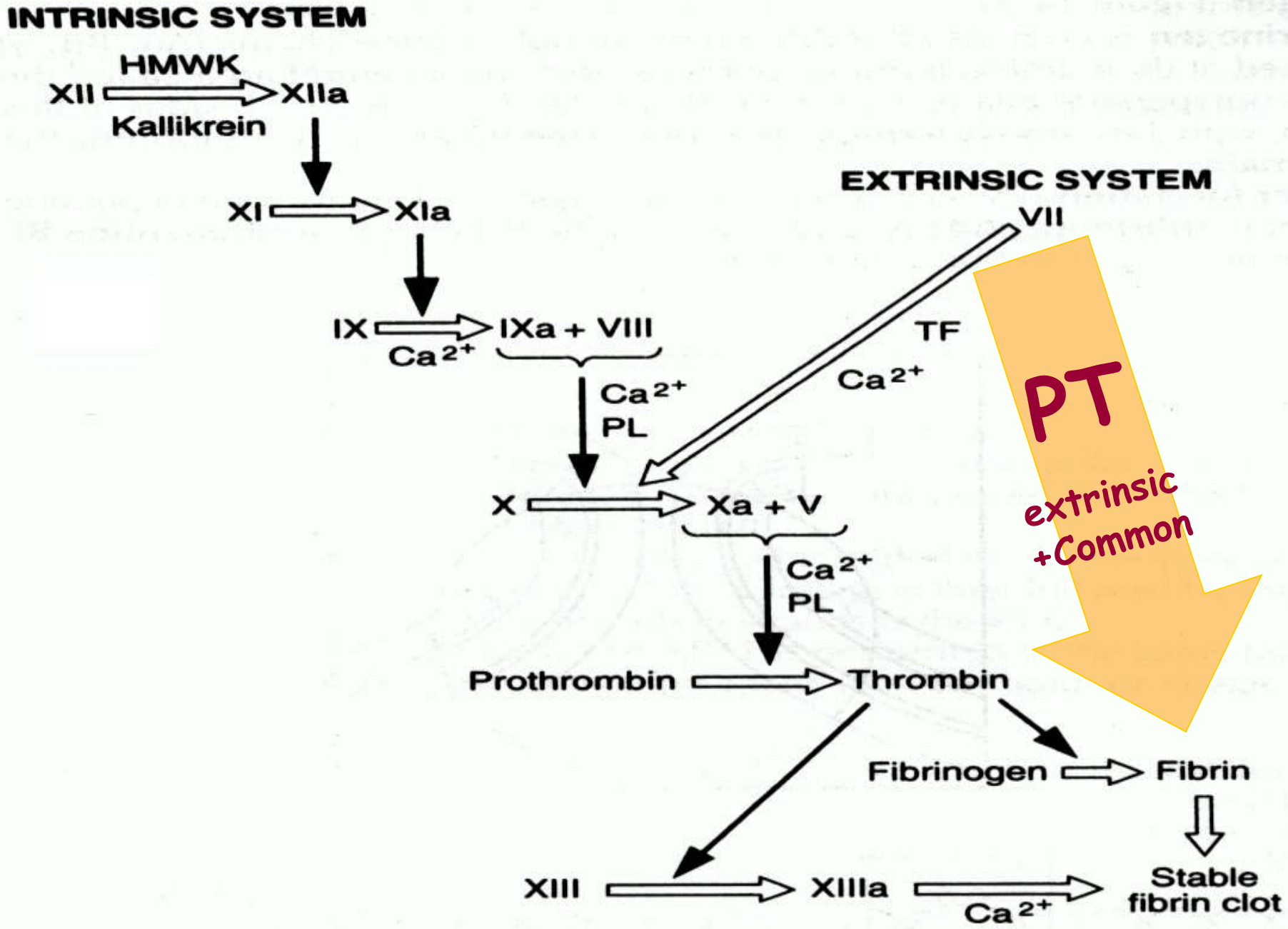


Ecchymosis
(> 1 – 2 cms)

Basic Screening tests for Haemostasis (1st line investigation)

1. Blood count and blood film examination
2. Platelets count (Normal range 150 000 – 450 000/cmm): a reduced platelets count is associated with increased liability to bleeding.
3. Bleeding time: is prolonged if there is reduced platelets count or platelets dysfunction, or if there is a vascular defect.
4. Prothrombin Time (PT): this is a test which tests the extrinsic and the common pathway of the coagulation.
5. Activated Partial Thromboplastine Time (APTT): This test is used to test for intrinsic and the common pathway.
6. Thrombin time: this tests the last step in the coagulation pathway i.e. the conversion of Fibrinogen (factor I) to fibrin.


INTRINSIC SYSTEM
HMWK
XII
XIIa
Kallikrein
XI
XIa
IX
Ca2+
IXa + VIII
Ca2+
PL
EXTRINSIC SYSTEM
VII
TF
Ca2+
APTT
Intrinsic
+Common
X
Xa + V
Ca2+
PL
Prothrombin
Thrombin
Fibrinogen
Fibrin
XIII
XIIIa
Ca2+
Stable
fibrin clot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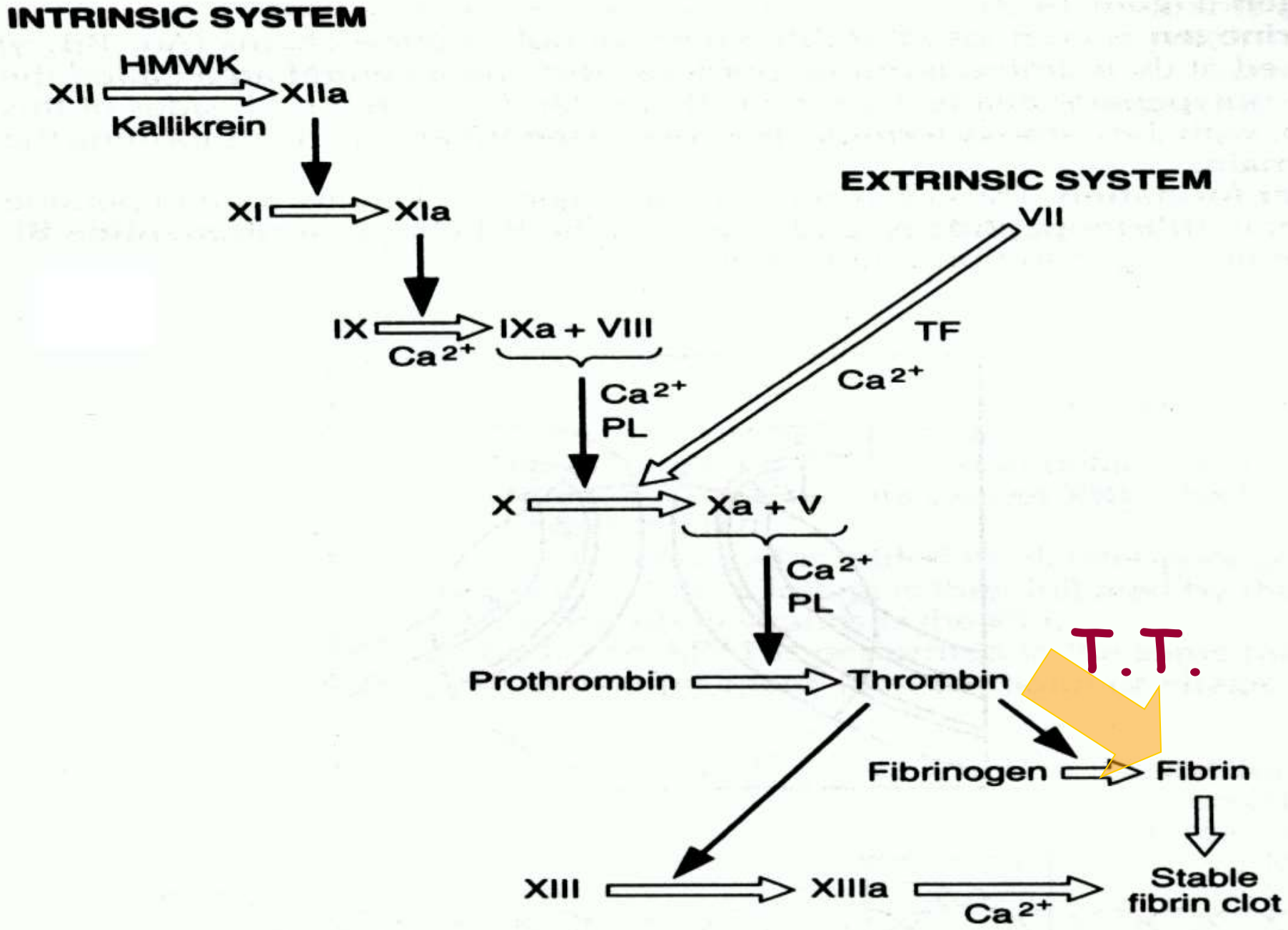
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Xa + V
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Thrombin
T.T.
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Ca2+
Stable
fibrin clot

Classification of bleeding disorders

(1) Platelets disorders: reduction in platelets count (TCP) or dysfunction.

(2) Coagulation factors disorders: inherited or acquired coagulation factors def. or dysfunction.

(3) Vascular Purpura: Inherited or acquired.

Platelets disorders

- Abnormal bleeding associated with platelets disorders is characterize by bleeding from skin, mucous membrane, post-traumatic.

- Platelets disorders include:
  1- Thromocytopenias (TCP).
  2- Thrombocytopathies.

Thromocytopenias

(I) Reduced production of platelets:

- Congenital TCP: e.g. TAR (TCP with absent radius) syndrome, CAMT(congenital amegakaryocyticTCP) syndrome.
- Acquired TCP secondary to drugs, chemicals, viral infections.

Acquired TCP as part of BM failure: acute leukaemia, Aplastic anemia, Cytotoxic drugs, Marrow infiltration by malignant disease, Myelofibrosis.

(II) Increased platelets consumption:

- Immune mediated:
  - Autoimmune Thrombocytopenic Purpura (AITP).
  - Alloimmune thrombocytopenia (NAIT, PTP).
  - Drug induced.
  - Infection induce.
- Non immune: DIC, TTP,HUS, Pre-eclampsia, HELLP syndrome

(III) Abnormal distribution: Hypersplenism.

(IV) Dilutional loss: massive transfusion.

Autoimmune Thrombocytopenic Purpura (ITP)

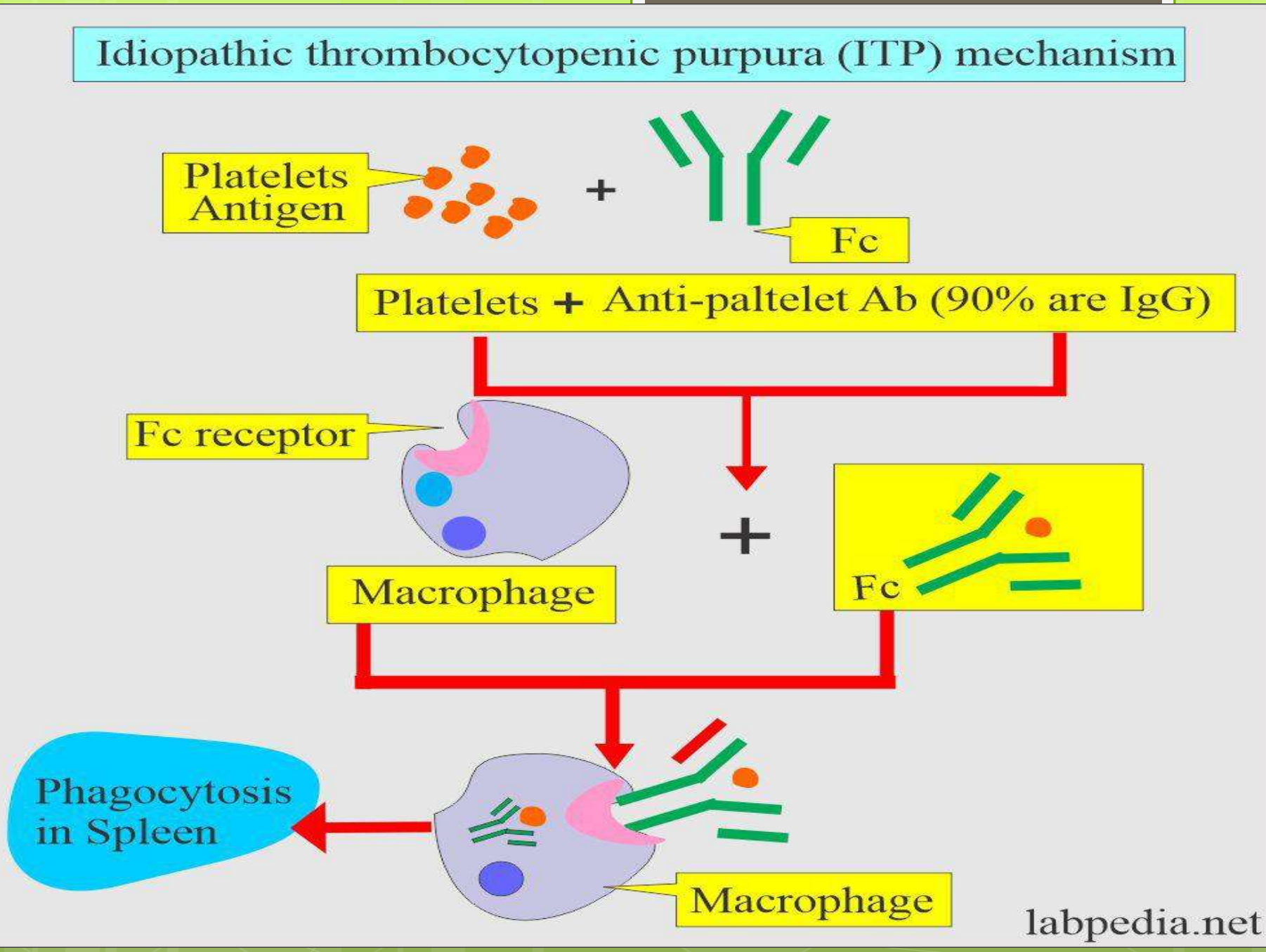
A relatively common hematological disorder, the main feature of which is bleeding tendency due to immune thrombocytopenia, and could be classified into:

1. **Idiopathic thrombocytopenic purpura:** a chronic autoimmune thrombocytopenia, young adults, without precedent or associated illness.
2. **Secondary autoimmune thrombocytopenia:** resembles ITP clinically, but associated autoimmune disorder, or malignancy.
3. **Acute Post-viral auto-immune thrombocytopenia:** acute usually self-limiting thrombocytopenic purpura, typically seen in children following acute viral infection or immunization.

Clinically: Patient is presented usually with purpura overall the body, may be dry or wet purpura. splenomegaly may be found, with feature of associated diseases.

Pathogenesis:

- Triggering factors induce autoAb production (usually IgG) against GP2b3a or 1b.
- Removal of platelets by macrophage of reticuloendothelial system mainly in the spleen.
- Life span of platelets reduce to few hrs.
- Spleen consider site of destruction and site of Ab production.
- In acute ITP in children Ab usually of IgM type.


Idiopathic thrombocytopenic purpura (ITP) mechanism
Platelets Antigen
+
Fc
Platelets + Anti-paltelet Ab (90% are IgG)
Fc receptor
Macrophage
+
Fc
Phagocytosis in Spleen
Macrophage
labpedia.net

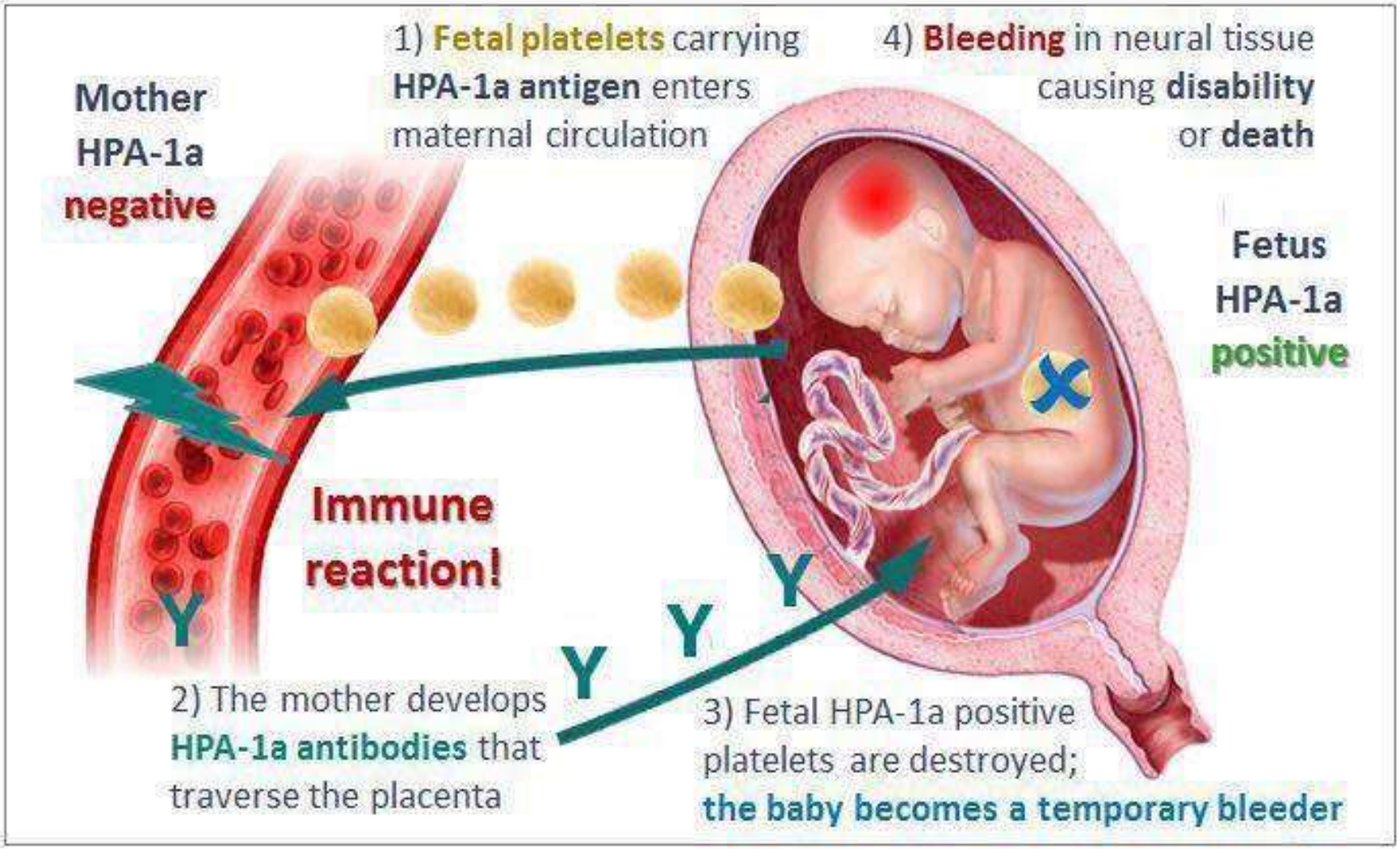
Haematological findings:

1. - Blood Picture showing isolated thrombocytopenia (10-50x10^9/L).
2.
3. - anemia may develop secondary to bleeding.
4. - Findings of associated disease.
5. - Bone marrow: usually normal cellularity. Increased or normal number of megakaryocytes.

Neonatal alloimmune TCP (NAITCP)

- Allo-Ab mainly Anti HPA-1a formed in mother due to incompatibility for HPA between mother and baby, leading to TCP in fetus.
- Affected 1st baby.
- Neonate showing isolated TCP with bleeding manifestation and normal well mother.
- Diagnosis made by demonstration of maternal platelets allo Ab and demonstrate incompatibility between mother and father for HPA-1a.

FNAIT: Fetal/neonatal alloimmune thrombocytopenia



Post transfusion purpura (PTP)

- Uncommon, serious, sever TCP, sudden, occur after 7-10 days of transfusion.
- Patient is HPA-1a negative and formed anti HPA1a Ab against transfused platelets HPA-1a, forming complex that adsorbed on patient platelets causing their destruction.

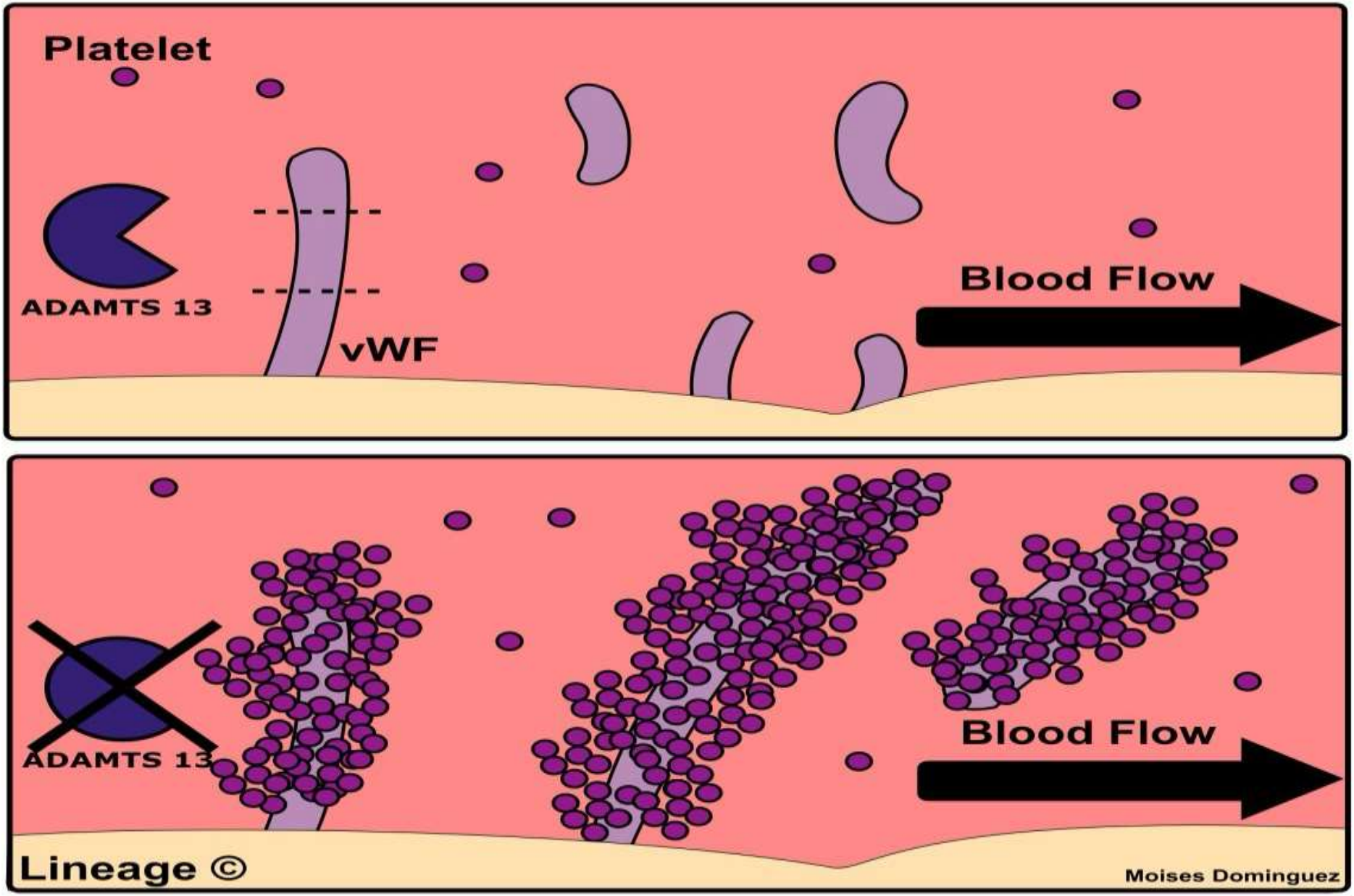
Drug induce TCP

- Many drugs can lead to TCP due to immune mechanism, with platelets usually < 10×109/L.
- e.g. Quinidine, Quinine, Heparin.

Thrombotic thrombocytopenic purpura (TTP)

- Pathogenesis: congenital or acquired deficiency or dysfunction of enzyme metalloprotease (ADAMTS-13) which responsible to breakdown HMW multimer of VWF resulting in microthrombous formation in small blood vessels.
- Characterize by disease of adult, TCP, Microangiopathic hemolytic anemia, neurological manifestation, fever, mild or no renal manifestation.
- Lab. findings include TCP, anemia, fragmented RBC, increase retic count, with normal coagulation tests.
- Treatment: plasma exchange using FFP or Cryoppt, steroid and immunosuppression in refractory cases.
- Mortality rate up to 90% in untreated cases.

Thrombotic Thrombocytopenic Purpura



Hemolytic uremic syndrome (HUS)

- Pathogenesis: usually associated with E.coli infection (verotoxin 0157) or other microoorganism as shigella. This toxin bind to specific renal cells receptors forming complex that lead to massive thrombosis in renal microvasculature. Little or no role of VWF and ADAMTS-13 in HUS. Familial forms without diarrhareal disease may occur.
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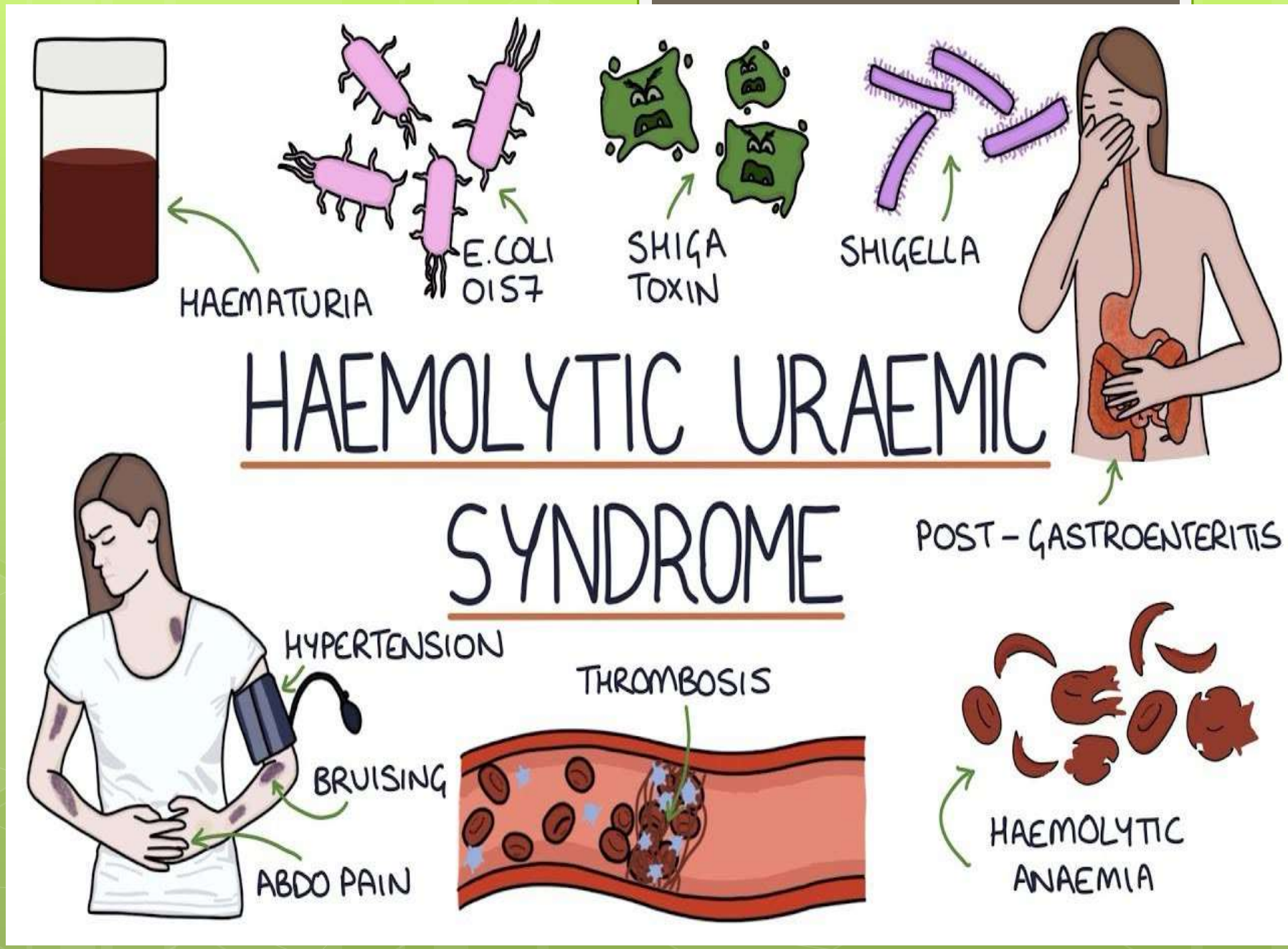
- Characterize by disease of children, TCP, Microangiopathic hemolytic anemia, renal impairment, mild or no neurological manifestation.
- Lab. findings include TCP, anemia, fragmented RBC, increase retic count, abnormal renal function, with normal coagulation. tests.
- Treatment: supportive management for renal function, control of HT and fit.
- Prognosis: usually self limiting, relapse is less, and residual renal dysfunction is common.


HAEMATURIA
E.COLI O157
SHIGA TOXIN
SHIGELLA
HAEMOLYTIC URAEMIC SYNDROME
POST - GASTROENTERITIS
HYPERTENSION
BRUISING
ABDO PAIN
THROMBOSIS
HAEMOLYTIC ANAEMIA

TCP in pregnancy

- Second most common hematological abnormality following anemia.
- Overall incidence is 8%, but decrease to 5.1% if exclude medical and obstetrical condition.

- Causes include:
  - Gestational TCP (75%)
  - Hypertensive disorder (21%)
  - ITP (3%)
  - Others (1%)

Thromocytopathies

Platelets dysfunction

- Characterize by superficial bleeding with normal platelets count and prolonged bleeding time.
- Definite diagnosis by platelets function study.
- Platelets dysfunction may occur at any phase of platelets function.

Classification:

1. Hereditary types
- defect in adhesion
- defect in aggregation
- defect in platelets granules

2. Acquired types
- Systemic disease as Ureamia, liver disease, DIC
- Antiplatelets drugs
- hematological disease as Myeloproliferative Disorders (MPD), aplastic anemia (AA), hyperglobulinemia, Myelodysplastic syndrome (MDS)

Anti-platelets drugs

- Aspirin is the most common type, it irreversibly inhibit cyclo-oxygenase with impair TXA2 formation.
- NSAID inhibi cyclo-oxygenase reversibly.
- Dipyridamole inhibit platelets aggregation by blocking reuptake of adenosine.
- Clopidogrel inhibit ADP binding to its receptor on platelets.
- Abciximab inhibit GP2b3a receptor
- Others as Antibiotecs, heparin, Dextran, B-blocker.