Protective functions of blood Hemostasis system

Hemostatis

- **Hemostasis** or stoppage of bleeding (stasis = halting).
- No hemostasis → No sealing → bleed to death from minor wounds
- The hemostasis response is
  - fast
  - localized and
  - carefully controlled
- Involves many blood coagulation factors normally present in plasma as well as some substances that are released by platelets and injured tissue cells.
- During hemostasis, following steps occur:
  - Vascular spasms,
  - Platelet plug formation,
  - Coagulation, or blood clotting.
  - Growth of fibrous tissue in clot to close the hole in vessel.
- Blood loss at the site is permanently prevented when fibrous tissue grows into the clot and seals the hole in the blood vessel.

TABLE 17.3 Blood Clotting Factors (Procoagulants)

FACTOR NUMBER	FACTOR NAME	NATURE/ORIGIN	FUNCTION OR PATHWAY
I	Fibrinogen	Plasma protein; synthesized by liver	Common pathway; converted to fibrin, insoluble weblike substance of clot
II	Prothrombin	Plasma protein; synthesized by liver; formation requires vitamin K	Common pathway; converted to thrombin, which enzymatically converts fibrinogen to fibrin
III	Tissue factor (TF) or tissue thromboplastin	Glycoprotein in plasma membrane of cells underneath the endothelium	Activates extrinsic pathway
IV	Calcium ions (Ca^{2+})	Inorganic ion present in plasma; acquired from diet or released from bone	Needed for essentially all stages of coagulation process
V	Proaccelerin, labile factor, or platelet accelerator	Plasma protein; synthesized in liver; also released by platelets	Common pathway
VI	Number no longer used; substance now believed to be same as factor V		
VII	Proconvertin or convertin	Plasma protein; synthesized in liver in process that requires vitamin K	Both extrinsic and intrinsic mechanisms
VIII	Antihemophilic factor (AHF)	Plasma protein synthesized in liver; deficiency causes hemophilia A	Intrinsic mechanism
IX	Plasma thromboplastin component (PTC) or Christmas factor	Plasma protein; synthesized in liver; deficiency results in hemophilia B; synthesis requires vitamin K	Intrinsic mechanism
X	Stuart factor, Stuart-Prower factor, or thrombokinase	Plasma protein; synthesized in liver; synthesis requires vitamin K	Common pathway
XI	Plasma thromboplastin antecedent (PTA)	Plasma protein; synthesized in liver; deficiency results in hemophilia C	Intrinsic mechanism
XII	Hageman factor, glass factor	Plasma protein; synthesized in liver; activated by negatively charged surfaces (e.g., glass)	Intrinsic mechanism; activates plasmin; initiates clotting in vitro; activation initiates inflammation
XIII	Fibrin stabilizing factor (FSF)	Plasma protein; synthesized in liver and bone marrow	Cross-links fibrin, forming a strong, stable clot

table-17-03.jpg

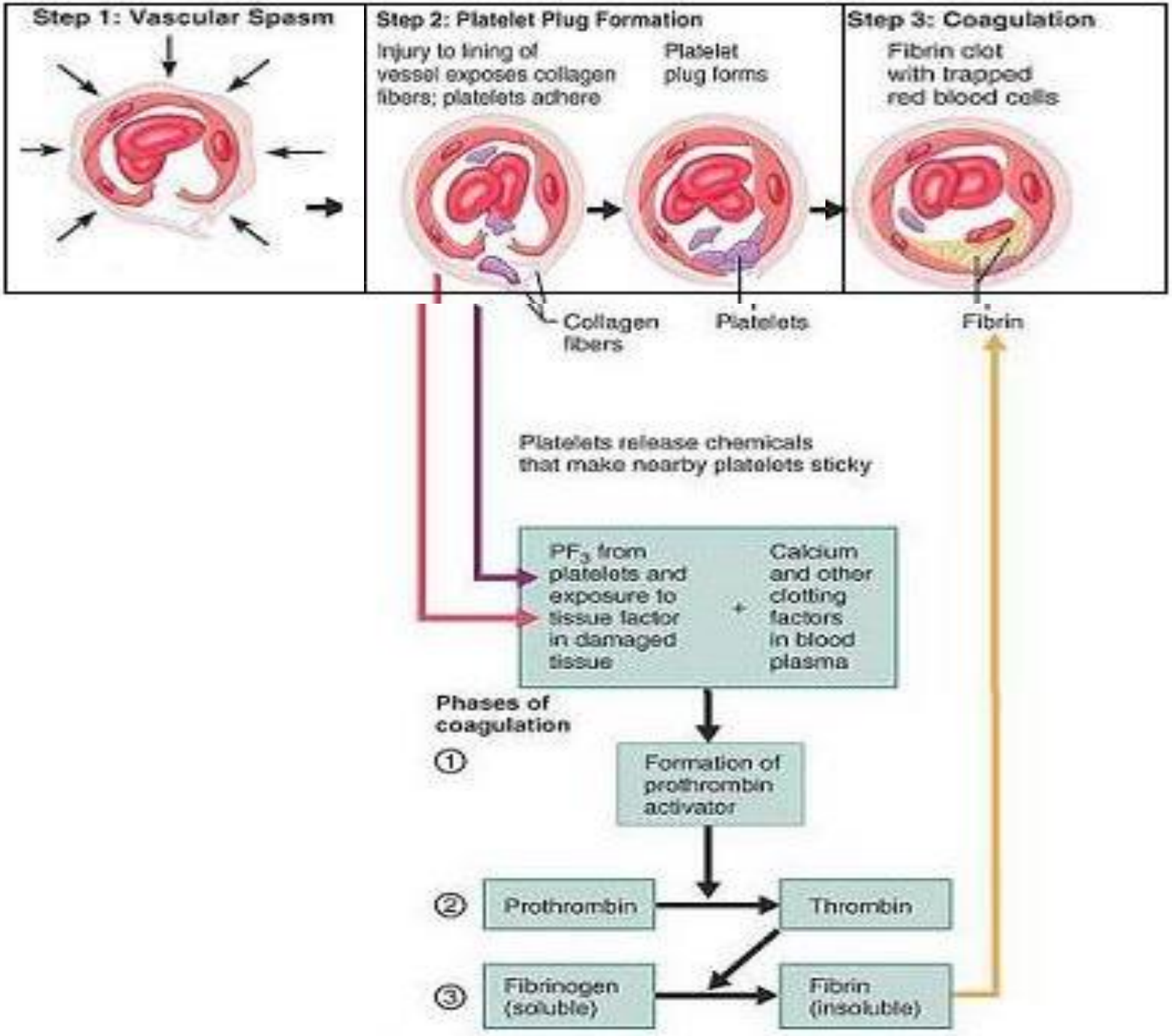
Table 27-8. System for naming blood-clotting factors.

Factor[1]	Names	Half-life (h)
I	Fibrogen	96
II[K]	Prothrombin	72
III	Thromboplastin or Tissue Factor	
IV	Calcium	
V	Proaccelerin, labile factor, accelerator globulin	20
VII[K]	Proconvertin, SPCA, stable factor	5
VIII	Antihemophilic factor (AHF), antihemophilic factor A, antihemophilic globulin (AHG)	12
IX[K]	Plasma thromboplastic component (PTC), Christmas factor, antihemophilic factor B	24
X[K]	Stuart-Prower factor	30
XI	Plasma thromboplastin antecedent (PTA), antihemophilic factor C	48
XII	Hageman factor, glass factor	50
XIII	Fibrin-stabilizing factor, Laki-Lorand factor	250
HMW-K	High-molecular-weight kininogen, Fitzgerald factor	
Pre-K_a	Prekallikrein, Fletcher factor	
Ka	Kallikrein	
PL	Platelet phospholipid	

[1] Factor VI is not a separate entity and has been dropped.

Coagulation

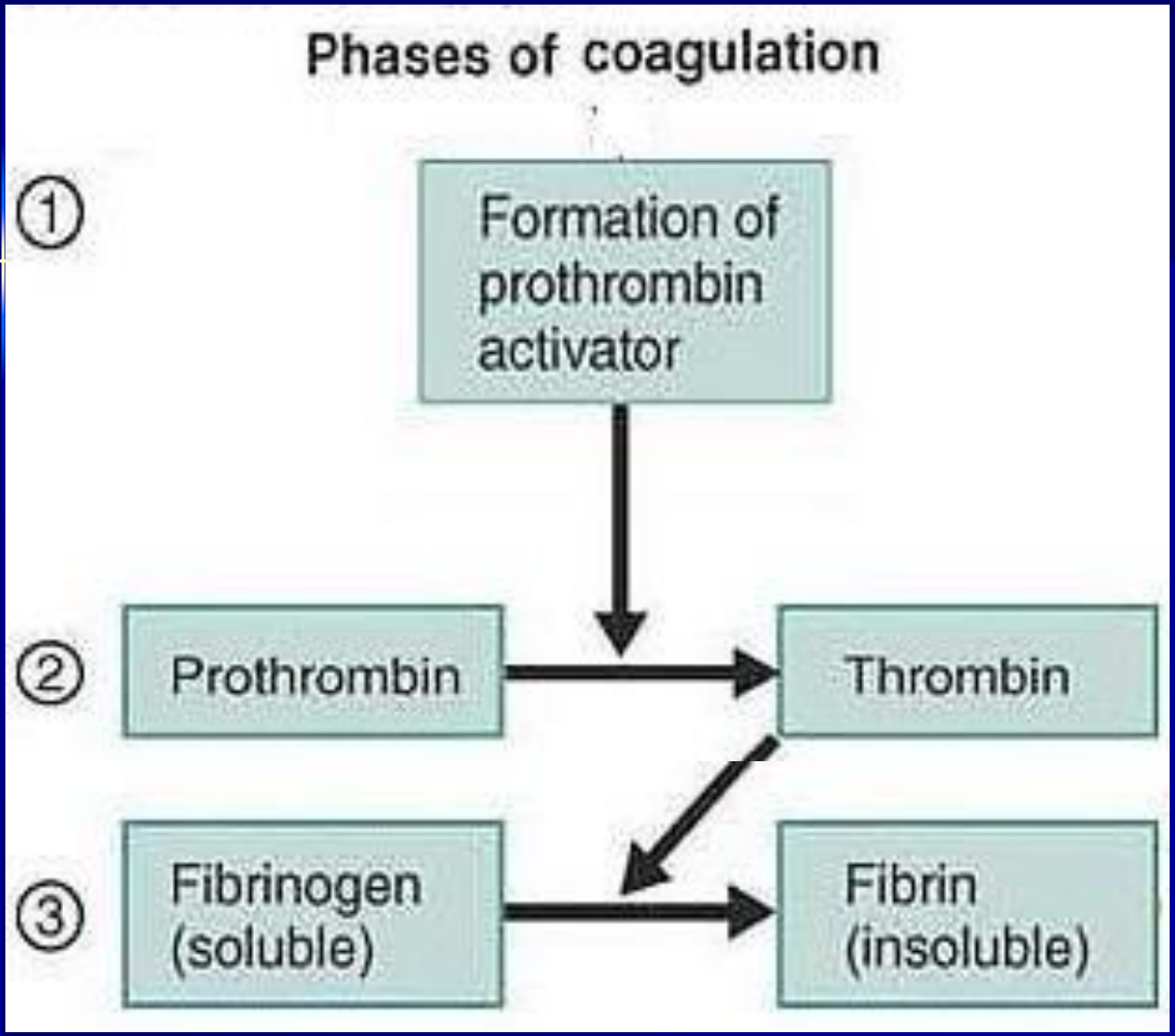
- **Coagulation** or blood clotting
  - Complicated process, Liquid Blood → becomes gel,
  - Over 50 Substances are involved
  - Factors that enhance clot formation are called *clotting factors* or *procoagulants*.
  - Factors that inhibit clotting are called *anticoagulants.*
  - Balance between these two groups of factors. Normally, anticoagulants dominate and clotting is prevented; but when a vessel is ruptured, procoagulant activity in that area increases dramatically and clot formation begins.
  - The procoagulants are numbered I to XIII according to the order of their discovery; hence the numerical order does not reflect the reaction sequence.
  - Most of these factors are plasma proteins made by the liver that circulate in an inactive form in blood until mobilized.


Step 1: Vascular Spasm
Step 2: Platelet Plug Formation
Injury to lining of vessel exposes collagen fibers; platelets adhere
Platelet plug forms
Step 3: Coagulation
Fibrin clot with trapped red blood cells
Collagen fibers
Platelets
Fibrin
Platelets release chemicals that make nearby platelets sticky
PF_3 from platelets and exposure to tissue factor in damaged tissue
+
Calcium and other clotting factors in blood plasma
Phases of coagulation
1
Formation of prothrombin activator
2
Prothrombin
Thrombin
3
Fibrinogen (soluble)
Fibrin (insoluble)

3-Coagulation

- Three Phases of Coagulation:
  - A complex substance called prothrombin activator is formed.
  - Prothrombin activator converts prothrombin (a plasma protein) into thrombin, (an enzyme).
  - Thrombin catalyzes the joining of fibrinogen molecules present in plasma to a fibrin mesh.
- Role of Vitamin K in coagulation.

  Vitamin K **not directly** involved in coagulation, this fat-soluble vitamin is required for the synthesis of four of the procoagulants made by the liver i.e (II, VII, IX and X).


Phases of coagulation
①
Formation of prothrombin activator
②
Prothrombin
Thrombin
③
Fibrinogen (soluble)
Fibrin (insoluble)

Phase 1- Formation of prothrombin Activator

- Clotting may be initiated by either the
  - Intrinsic Pathway
  - Extrinsic pathway
- Both pathways are usually triggered by the tissue-damaging events. Clotting of blood outside the body (such as in a test tube) is initiated only by the intrinsic mechanism.

  – Critical components in both mechanisms are negatively charged membranes, particularly those on platelets that contain phosphatidylserine (platelets phospholipids), also known as **PF_3** (platelet factor 3).

  – Many intermediates of both pathways can be activated only in the presence of **PF_3**.

Phase 1- Formation of prothrombin Activator

- **Intrinsic Pathway**

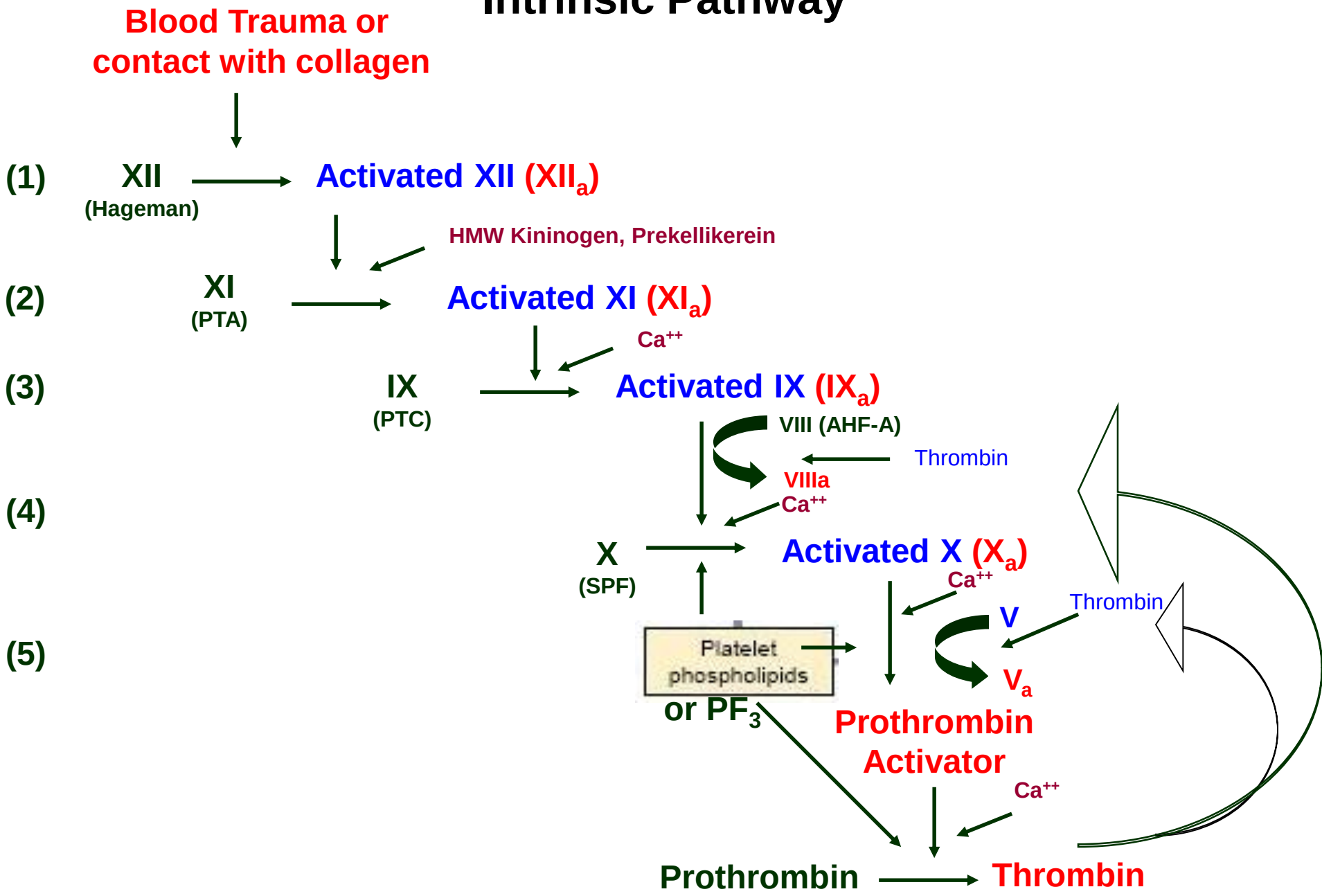
  In the slower intrinsic pathway, all factors needed for clotting are present in (intrinsic to) the blood.

- **Extrinsic Pathway**

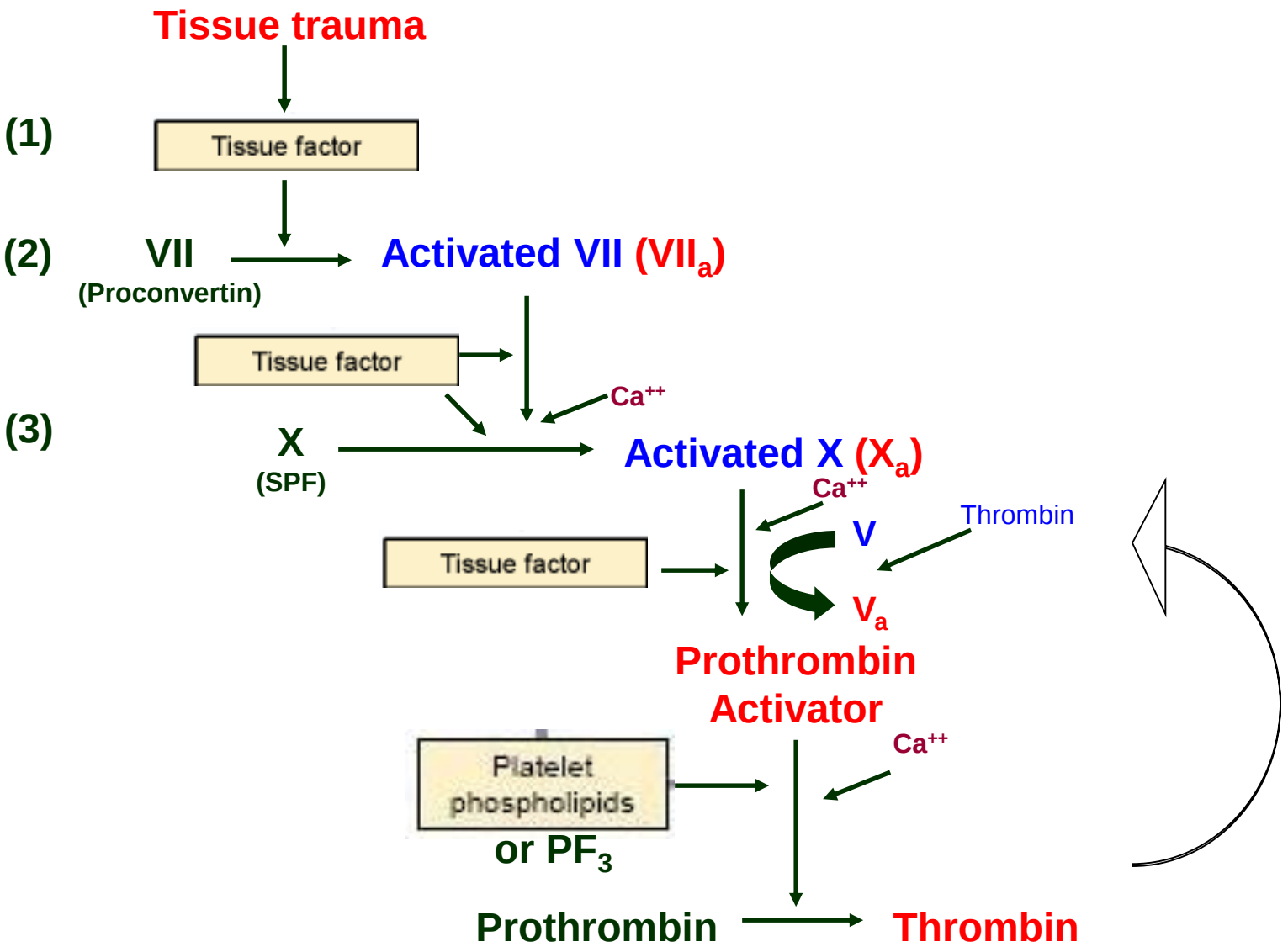
  By contrast, when blood is exposed to an additional factor in tissues underneath the damaged endothelium called tissue factor (TF), factor III, or **tissue thromboplastin**, the "shortcut" extrinsic mechanism, which bypasses several steps of the intrinsic pathway, is triggered.

- **Role of calcium**
  - Each pathway requires ionic calcium and involves the activation of a series of procoagulants, each functioning as an enzyme to activate the next procoagulant in the sequence.
  - The intermediate steps of each pathway cascade toward a common intermediate, factor X.
  - Activated factor X complexes with calcium ions, PF3, and factor V to form prothrombin activator.
  - Slowest step of the blood clotting process, but once formed, the clot forms in 10 to 15 seconds.

Intrinsic Pathway

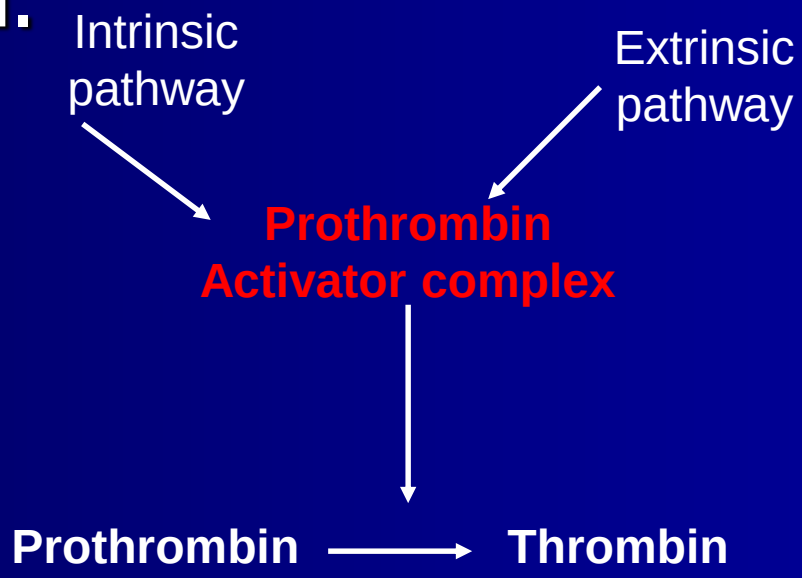


Extrinsic Pathway



Phase 2: Common Pathway to Thrombin

- Prothrombin activator catalyzes the transformation of the plasma protein prothrombin to the active enzyme **thrombin**.



Phase 3: Common Pathway to the Fibrin Mesh

1. Thrombin catalyzes the polymerization of **fibrinogen** (another plasma protein made by the liver).

2. Thrombin is a protein *enzyme* with weak proteolytic capabilities. It acts on fibrinogen to remove four low-molecular weight peptides from each molecule of fibrinogen, forming one molecule of *fibrin monomer.*

3. Fibrin monomers has the automatic capability to polymerize with other fibrin monomer molecules to form fibrin fibers.

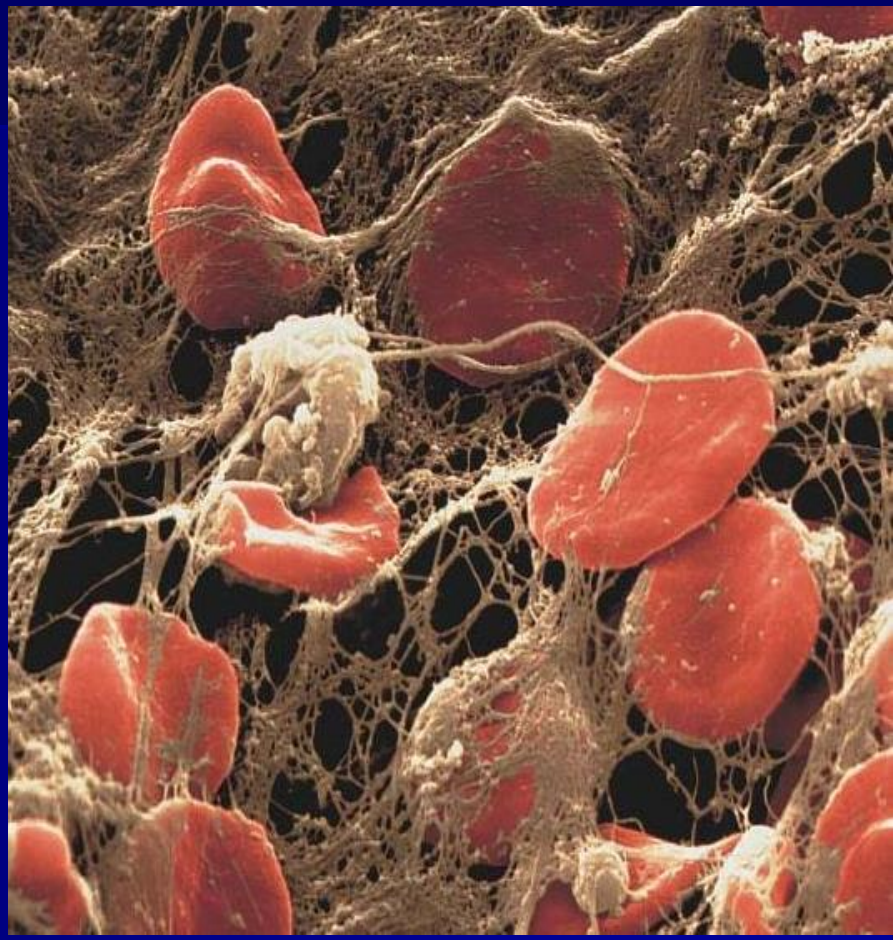
4. Many fibrin monomer molecules polymerize within seconds into *long fibrin fibers.*

5. During early polymerization, fibrin fibers are held together by weak non covalent hydrogen bonding, No cross-linkage with one another.

6. *fibrin-stabilizing factor causes the cross linkage of fibrin fibers* (Released from platelets entrapped in the clot).

7. Activated by thrombin

8. This activated substance operates as an enzyme to form *covalent bonds* between fibrin monomer molecules, as well as multiple cross linkages between adjacent fibrin fibers.



4-Clot Retraction and Repair

1. Within 30 to 60 minutes, the clot is stabilized further by a platelet-induced process called clot retraction.
2. Platelets contain contractile proteins (actin and myosin), and they contract in much the same manner as muscle cells.
3. As the platelets contract, they pull on the surrounding fibrin strands, squeezing serum (plasma minus the clotting proteins) from the mass, compacting the clot and drawing the ruptured edges of the blood vessel more closely together.
4. Even as clot retraction is occurring, vessel healing is taking place.
5. Platelet-derived growth factor (PDGF) released by platelet degranulation stimulates smooth muscle cells and fibroblasts to divide and rebuild the wall.
6. As fibroblasts form a connective tissue patch in the injured area, endothelial cells, stimulated by vascular endothelial growth factor (VEGF), multiply and restore the endothelial lining.

Fibrinolysis

- A process called **fibrinolysis** removes unneeded clots when healing has occurred.
- Because small clots are formed continually in vessels, this cleanup is important. Without fibrinolysis, blood vessels would gradually become completely blocked.
- The critical natural "clot buster" is a fibrin-digesting enzyme called **plasmin**, which is produced when the plasma protein plasminogen is activated.

- Large amounts of plasminogen are incorporated into a forming clot, where it remains inactive until appropriate signals reach it.

  The presence of a clot in and around the blood vessel causes the endothelial cells to secrete
  - tissue plasminogen activator (tPA).

  Along with that
  - Activated factor XII and
  - thrombin

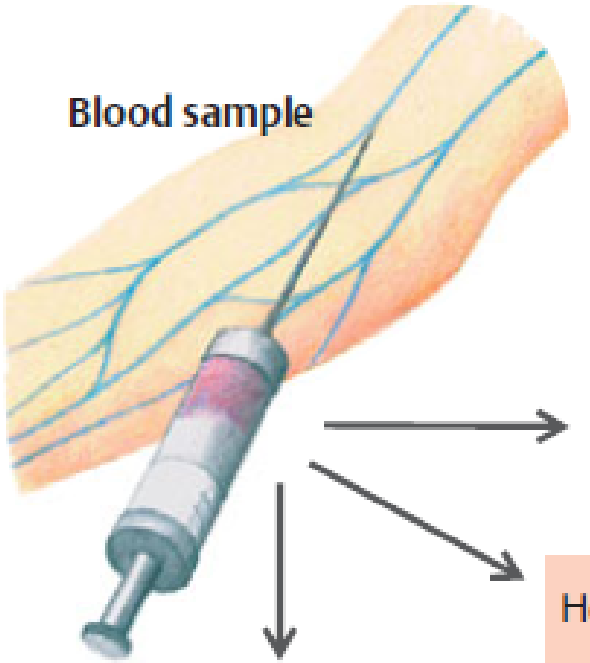
  released during clotting also serve as plasminogen activators. As a result, most plasmin activity is confined to the clot, and any plasmin that strays into the plasma is quickly destroyed by circulating enzymes.
- Fibrinolysis begins within two days and continues slowly over several days until the clot is finally dissolved.

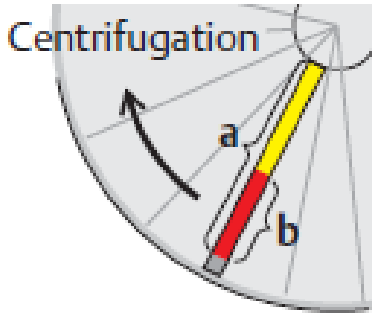
Factors Limiting Normal Clot Growth

- Normally, two homeostatic mechanisms prevent clots from becoming unnecessarily large:
  - swift removal of clotting factors, and
  - inhibition of activated clotting factors.
- Limiting the Activity of Thrombin
  - As a clot forms, almost all of the thrombin produced is bound onto the fibrin threads.
  - This is an important safeguard because thrombin also exerts positive feedback effects on the coagulation process prior to the common pathway.
    - It speed up the production of prothrombin activator by acting through factor V,
    - It also accelerates the earliest steps of the intrinsic pathway by activating platelets.
  - Thus, fibrin effectively acts as an anticoagulant to prevent enlargement of the clot and prevents thrombin from acting elsewhere.
  - Thrombin not bound to fibrin is quickly inactivated by **antithrombin III**, a protein present in plasma. It inactivates the protease activity of thrombin and factors IXa, Xa, XIa and XIIa by forming complexes with them.
  - **Heparin**, the natural anticoagulant contained in basophil and mast cell granules, inhibits thrombin by enhancing the activity of antithrombin III.

Blood Testing

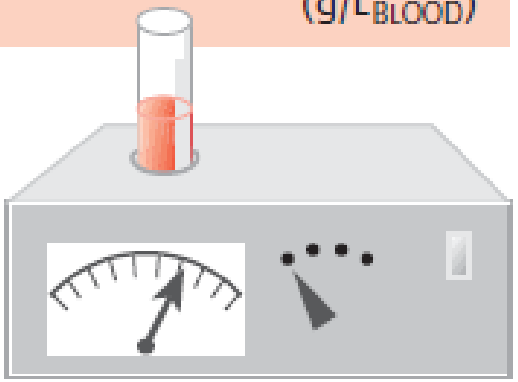
C. Erythrocyte parameters MCH, MCV and MCHC



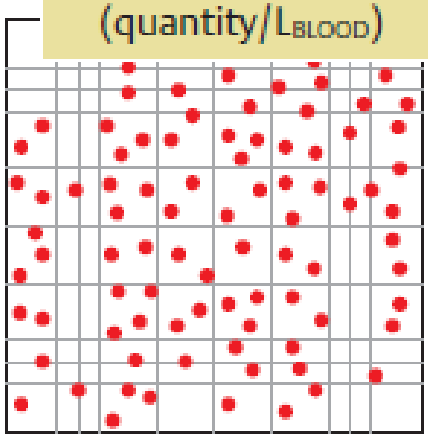


Hematocrit (Hct) = **b/a**
(L_{RBC}/L_{Blood})

Hemoglobin concentration
(g/L_{BLOOD})



Red cell count (RCC)
(quantity/L_{BLOOD})



MCH (mean Hb mass/RBC)

$$= \frac{\text{Hb conc.}}{\text{red cell count}} \text{ (g/RBC)}$$

Normal: 27 – 32 pg

MCV (mean volume of one RBC)

$$= \frac{\text{Hct}}{\text{red cell count}} \text{ (L/RBC)}$$

Normal: 80 – 100 fl

MCHC (mean Hb conc. in RBCs)

$$= \frac{\text{Hb conc.}}{\text{Hct}} \text{ (g/L}_{RBC}\text{)}$$

Normal: 320 – 360 g/L