Flattened disk-like cell fragments that are about 1 µm by 4 µm.
Act as a participant in the vascular clotting system called HEMOSTASIS
Continuously being replaced. Each platelet circulates for 9-12 days before being removed by splenic phagocytes.

On average there are ~250,000 platelets/µL of blood.
Produced in the bone marrow. Large cells called megakaryocytes release fragments (platelets) into the circulation.
Platelets formation

Hemocytoblast

- IL-7
- TPO

Lymphoid Stem Cell

- IL-11

Myeloid Stem Cell

- EPO

Megakaryocyte

- Platelet

Erythrocyte

Thrombopoiesis

Platelets Function

- Transport of chemicals important to the clotting process. By releasing enzymes and other factors, platelets help initiate the clotting process.

- Formation of a temporary patch (platelet plug) in the walls of damaged blood vessels.

- What do you suppose thrombocytopenia is? What process would it impact?
HEMOSTASIS

- Is the arrest of bleeding
- Prevents blood loss through the walls of damaged blood vessels
- Also establishes a framework for further tissue repairs
- 3 main phases:
  - Vascular Phase
  - Platelet Phase
  - Coagulation Phase

VASCULAR PHASE

Blood Vessel Damage

Smooth muscle in BV wall contracts – Vascular Spasm

BV diameter ↓

Blood loss slows
PLATELET PHASE

- Occurs within 15 sec of the injury
- Damaged blood vessel have a breached endothelial layer through which collagen fibers are exposed

von Willenbrand Factor (large blood protein)

Attaches to collagen fibers

Makes collagen fibers sticky

Platelets start sticking to collagen fibers
As platelets “stick,” they become “activated.”

Activated platelets release:
- ADP
  - increases the sticky character of platelets
  - *do you see positive feedback here?*
- Serotonin
  - causes local vasoconstriction
- Thromboxane A₂
  - a prostaglandin that causes platelet aggregation and local vasoconstriction
The aggregation of platelets eventually results in a **platelet plug**, a temporary mass of platelets that stops blood loss and forms a framework for the clot.
What prevents the platelet plug from spreading out of control?

- Undamaged endothelial cells don’t have collagen fibers around them.
- ADP, released from platelets, release factors from surrounding undamaged endothelial cells that inhibit platelet aggregation.
- prostacyclin (prostaglandin I₂)
- nitric oxide

PLATELET PHASE

![Diagram of platelet phase with labels for blood vessel, collagen, platelet plug, PG₁₂, NO, TXA₂, and other factors involved in the process.]
• Begins 30 sec or more after vessel damage occurs (unlike the first 2 phases which begin almost immediately)

• Involves a sequence of steps leading to the conversion of fibrinogen (a circulating plasma protein) to the insoluble protein fibrin.

• A network of fibrin grows and covers the surface of the platelet plug. RBCs and additional platelets are trapped in this tangle, forming a blood clot that effectively seals the damaged vessel wall.

GOAGULATION PHASE

• Requires clotting factors such as:
  – Calcium ions. Where are they stored?
  – 11 different proteins, most synthesized by the liver
    • Many are proenzymes (inactive enzymes) that, when converted to active enzymes direct essential reactions in the clotting process.
    • The synthesis of some of them requires Vit. K
During the coagulation phase, enzymes and proenzymes interact. The activation of one proenzyme commonly creates an enzyme that activates a second proenzyme and so on in a chain **reaction or cascade**.

There are actually 3 cascades: intrinsic pathway, extrinsic pathway, and the common pathway.

- The **extrinsic pathway** begins outside the bloodstream;
- The **intrinsic pathway** begins inside the bloodstream.
- The extrinsic and intrinsic pathways converge at a common pathway.

**INRINSIC PATHWAY**

- Begins with the activation of clotting factor XII (Hageman factor) exposed to collagen fibers at the injury site (glass surface acts same way like collagen exposure).
- Activated XII activates in turn factor XI, which in turn activates IX (Christmas factor).
- Finally, IX activates factor X (Stuart factor).
- This last step requires Calcium (factor IV), factor VIII and a Platelet Factor (PF₃).

Hemophilia most often due to a lack of factor VIII.
• Begins with the release of tissue factor (factor III) by damaged endothelial cells or peripheral tissues.

• The greater the damage, the more tissue factor will be released, and the faster clotting will occur.

• Tissue factor combines with calcium and another procoagulant (Factor VII) to activate factor X.

EXTRINSIC PATHWAY

- Begins when Factor V, Calcium, Platelet Factors and activated Factor X form the enzyme prothrombin activator.

- Prothrombin activator catalyzes the conversion of prothrombin into thrombin.

- Thrombin catalyzes the conversion of the plasma protein fibrinogen into the insoluble protein fibrin.

Combines with the platelet plug, RBCs, and plasma to form a blood clot.
Damage to blood vessel enacts both the Intrinsic and extrinsic pathways in about 15s.

Extrinsic pathway is short and fast and produces a small amount of thrombin very quickly. The speed of the extrinsic pathway allows for the creation of a small clot quickly.

The positive feedback of Thrombin on Intrinsic pathway allows activation of intrinsic pathway independently from factor XII.

Amplification cascade in blood clotting
The liver plays a critical role in producing and modifying blood-borne proteins, including those used in the clotting pathway.

Moreover, bile salts from the liver facilitate the absorption of lipids in the diet, including vitamin K, which is required for the synthesis of prothrombin.

CLOT RETRACTION

- Once the fibrin meshwork has appeared, RBCs & platelets stick to the fibrin strands.
- The platelets then contract and the clot undergoes clot retraction which:
  - Pulls the torn edges of the vessel closer together, reducing residual bleeding and stabilizing the injury site
  - Reduces the size of the injured area, making it easier for fibroblasts, smooth muscle cells, and endothelial cells to complete repairs.
As repairs proceed, the clot gradually dissolves (fibrinolysis).

This process begins with the activation of the proenzyme plasminogen by 2 enzymes:

- Thrombin: activated by the common pathway
- Tissue plasminogen activator (t-PA): released by the damaged tissue

Plasminogen is converted into plasmin which digests the fibrin strands and erodes the foundation of the clot.

Following tissue repair, fibrin clots are dissolved in a process mediated by plasmin; synthetic plasminogen activators can be used immediately after a stroke or heart attack to help dissolve clots and restore blood flow.
Clotting factors need to reach a certain concentration before the cascade effect takes place. Circulating blood prevents factors from concentrating. However, they start accumulating when blood flows slowly (such as around a forming clot or other obstructions in vasculature).

Most of the thrombin is trapped and absorbed within the fibrin.

Thrombin that ‘escapes’ into the circulating blood can start activating fibrinogen into fibrin and form clots.

Body has a defense mechanism against this un-regulated clotting. These are called anti-coagulant mechanisms.

Anti-coagulant proteins made by the body are called physiological anti-coagulants. Manufactured ones are called therapeutic anti-coagulants.
1. Tissue Factor Inhibitor.
   - Secreted by endothelial cells and binds to Tissue factor/Factor VIIa complex.
   - It thus prevents the extrinsic mechanism from taking off.

2. Thrombomodulin receptor.
   - In an uninjured vessel, thrombin binds to thrombomodulin
   - This activates protein C, which in turn inactivates factors V and VIII.
3. Antithrombin III.

- This is a naturally occurring anticoagulant plasma protein
- It inactivates thrombin and factor X (Stuart factor)
- The effect of Antithrombin III is greatly accelerated when it binds to heparin
- Heparin is produced only in small amounts and is not very active by itself

ANTI CLOTTING BUSTERS/DRUGS

Aspirin
- inhibits the cyclooxygenase (COX) enzyme
- part of the eicosanoid pathway

- It specifically blocks the COX enzyme that produces Thromboxanes
- It does not block production of Prostaglandins

Drugs that block COXs are called nonsteroid-anti-inflammatory drugs (NSAID).
Oral anti-coagulants

• components that interfere with Vitamin K action
• Vit. K is needed for the production of 4 clotting factors
• Examples are Warfarin, Coumadin, Coumarin

Heparin

• works with AntiThrombin III
• also inhibits platelet function

Hirudin

• is an anticoagulant peptide that occurs naturally in the salivary glands of the medical leech *Hirudo medicinalis*.
• Its anticoagulant activity comes from the chemical ability to inhibit thrombin

Interventional Cardiology (April 1999)
Recombinant hirudin found safe for HIT patients
Thrombin inhibitor efficacious for heparin induced thrombocytopenia.
• A thrombus is formed when platelets begin to stick to the wall of an intact blood vessel
  – Platelets are often attracted to plaques – where endothelial and smooth muscle cells contain lots of lipids.
  – *What problems could a growing thrombus pose?*

• If the clot (thrombus) breaks off and begins to drift in the bloodstream, it is called an embolus.
  – *What problems could an embolus cause?*
Clot Busters

- Recombinant t-PA (very expensive ~2000 $/dose)
- Streptokinase (proteolytic drug) ~ 200 $/dose