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I. NORMAL HEMOSTASIS - BRIEF PHYSIOLOGICAL REVIEW

Hemostasis, the cessation of bleeding, is a process which requires the combined activity of 3 categories of factors: vascular, platelet, and plasma factors. Regulatory mechanisms counterbalance the tendency of clots to form.

1. Primary hemostasis leads to the generation of the hemostatic plug and requires the activity of vascular and platelet factors

1.1. Blood vessels contribute to hemostasis via several processes:

- **vasoconstriction**: an immediate and transient response (less than 1 minute duration), which reduces the blood loss from the damaged zone through:
  - **Reflex (neurogenic) mechanisms**
  - **Humoral mechanisms**: endothelin released by endothelial cells and thromboxane A2 (TxA2) released by platelets

- **vascular endothelium**:
  - synthesizes the von Willebrand factor (fW), with an essential role in platelet adhesion (fW is also the carrier for the clotting factor VIII)
  - synthesizes prostacyclines (PGI2) with antiagregant and vasodilator effects
  - releases the tissue factor (TF), a process induced by cytokines (TNF, IL-1); TF activates further the extrinsic pathway of coagulation

- **subendothelial structures** (collagen, fibronectine), which are exposed, due to the damage of the vascular endothelium:
- initiates the adhesion, aggregation, and secretion (release of granule content) ⇒ **platelet plug formation**
- activates **factor XII** (Hageman) which initiates the **intrinsic pathway of coagulation**.

### 1.2 Thrombocytes:
- potentiate the vascular spasm via the release of vasoconstrictor factors (TxA₂, serotonin, histamine)
- contribute to the primary haemostasis via the **platelet plug formation**
- participate in the secondary haemostasis via the release of **platelet membrane phospholipids**, which act as elective sites for calcium ions binding.

### 2. Secondary hemostasis (coagulation)
Involves a series of enzymatic reactions occurring through the activation of 2 pathways: **intrinsic pathway** and **extrinsic pathway**. Coagulation requires the activity of **plasma coagulation factors** which interact to produce thrombin, which converts soluble fibrinogen to the fibrin (Fig. 1).
- In the **intrinsic pathway** (*contact phase*), factor XII (Hageman), in the presence of high molecular weight kininogen (HMW-kininogen) and prekallikrein, will activate factor XI (to XIa) that in turn will trigger the generation of factor IXa from factor IX. Factor IXa then combines with factor VIIIa and procoagulant phospholipid (present on the surface of activated platelets and tissue cells) to form a complex that activates factor X.
- In the **extrinsic pathway** (*tissue factor dependent phase*), factor VIIa and tissue factor directly activate factor X.

![Figure 1. The coagulation cascade.](http://sbi.imim.es/web/files/projects/master/2010/Coagulation_serine_proteases/coagulationProcess.html)
Both intrinsic or extrinsic pathway elicit the activation of the common pathway, resulting in formation of the fibrin clot. Three steps are involved in the common pathway:

1. A prothrombin activator (also called the prothrombinase complex) is produced on the surface of activated platelets and tissue cells. The activator is a complex of factor Xa, factor Va, procoagulant phospholipid and calcium ions).

2. The prothrombin activator cleaves prothrombin to generate thrombin.

3. Thrombin induces the generation of fibrin polymers from fibrinogen. Thrombin also activates factor XIII, an enzyme that catalyzes formation of stronger bonds between adjacent fibrin monomers, i.e. fibrin stabilization and the generation of the fibrin clot.

Ca\(^{2+}\) ions are needed in most thrombin-generating reactions.

Factors II, VII, IX, and X are vitamin K–dependent clotting factors.

3. Control of haemostasis
Several inhibitory mechanisms prevent activated coagulation reactions from amplifying uncontrollably, causing extensive local thrombosis or disseminated intravascular coagulation. These mechanisms include:

- Inactivation of the soluble activated clotting factors
- Fibrinolysis (lysis of the fibrin clot)

3.1 Inactivation of clotting factors
Plasma protease inhibitors inactivate the clotting factors in order to prevent the further generation of the fibrin clot.

- Antithrombin III (AT III) inhibits thrombin (f. IIa), factor Xa, factor Xlla, factor Xla, and factor IXa. This inhibitory effect is enhanced up to 2000 times by heparin (endogenous, released by mastocytes, and exogenous, drug products).

- Protein C and free protein S (cofactor of protein C), which are vitamin K–dependent proteins, form a complex that inactivates factors VIIIa and Va by proteolysis.

3.2 Fibrinolysis
The fibrinolytic system is responsible for the dissolution of the already existent fibrin clot by means of plasmin that will split fibrin into soluble fibrin degradation products (FDP) that are swept away in the circulation. Plasmin result from the activation of plasminogen under the action of:

- tissue plasminogen activator (tPA), released from endothelial cells,
- kallikrein
- urokinase (released by epithelial cells that line excretory passages, eg, renal tubes)
- drugs: streptokinase, recombinant tPA

Fibrinolysis is regulated by:

- plasminogen activator inhibitors (PAlS), released by endothelial cells (inactivate tPA and urokinase)
- plasmin inhibitors (α2-antiplasmin, thrombin-activatable fibrinolysis inhibitor = TAFI).
II. DEFECTIVE HAEMOSTASIS - BLEEDING DISORDERS

1. VASCULAR disorders (vascular purpuras)

General features
Disorders within this category are relatively common but do not usually cause serious bleeding problems. Most often, small blood vessels are affected (capillaries and arterioles) and they induce small hemorrhages (petechiae and purpura) in the skin or mucous membranes (nose, gingivae – epistaxis, gingivorragia). Occasionally, more significant hemorrhages can take the form of menorrhagia, gastrointestinal bleeding, or hematuria. The platelet count and the coagulation tests (PT, aPTT) are usually normal, while bleeding time (BT) is prolonged.

1.1 Hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber syndrome)

- **Definition:** hereditary disorder of vascular malformation transmitted as autosomal dominant disorder, with an equal incidence in both men and women.
- **Clinical features:**
  - dilated, tortuous small blood vessels with thin walls that are very fragile ⇒ bleeding from capillaries and arterioles.
  - bleeding can occur anywhere in the body but is most common at the mucous membranes of the nose (epistaxis – the most frequent sign), tongue, mouth, eyes, and the gastrointestinal tract (which eventually lead to iron deficiency anemia).
- **Pathogenesis:** mutations of genes which codes for endothelial proteins involved in signal transduction of hormones of the transforming growth factor β superfamily (TGFβ), which are decreased. The exact mechanism is not known, probably is due to an imbalance between pro- and antiangiogenic signals in blood vessels.
- **Diagnosis** is based on the finding of characteristic arterio-venous malformations on the face, mouth, nose, and digits.

1.2 Acquired vascular purpuras

1.2.1 Purpura from vitamin C deficiency (scurvy)

- **Definition:** microvascular bleeding resulting from impaired formation of collagens (defect in synthesis of hydroxyproline & hydroxylisine required for collagen synthesis) → fragile vessel walls.
- **Manifestations:**
  - gingival tumefaction with bleeding gums
  - perifollicular hemorrhages
  - disseminated petechiae

1.2.2 Senile purpura

- **Definition:** easy bruising in elderly people due to dermal tissues atrophy → fragile vessel walls.
- **Manifestations:** persistent dark purple ecchymosis without known trauma, characteristically located on the surfaces of the hands and forearms.
1.2.3 Purpura from Cushing syndrome or due to chronic therapy with steroids is characterized by a predisposition to skin hemorrhages, due to:
- **protein-wasting effects** of excessive corticosteroid production causing loss of perivascular supporting tissue,
- **impaired collagen synthesis**.

1.2.4 Purpura due to infections occurs in severe infectious diseases associated with septicemia/viremia (typhoid fever, infective endocarditis, meningitis) responsible for the toxic damage to the vascular walls:
- **directly**: bacterial toxins damage the microvasculature ⇒ vasculitis
- **indirectly**: by triggering disseminated intravascular coagulation (DIC)

1.2.5 Allergic vascular purpuras
- **Definition**: group of syndromes characterized by cutaneous petechiae and purpura induced by deposition of immune complexes (IC) in the vessel walls, leading to hypersensitivity vasculitis (type III HS).
- **Causes**: viruses, drugs (phenacetin, penicillin, quinidine), serum sickness, collagen disorders.

*Anaphylactoid purpura (Schonlein-Henoch syndrome)* = immune vasculitis induced 2-3 weeks after an infection with *streptococcus β-hemolytic* in children/young adults.
- **Pathogenesis**: deposition of circulating IC within vessels throughout the body and within the glomerular mesangial regions.
- **Manifestations**
  - extrarenal manifestations – triade:
    - cutaneous rash
    - colicky abdominal pain (due to focal hemorrhages in GI tract)
    - polyarthralgia (transient arthralgia of large joints)
  - renal
    - acute glomerulonephritis → renal failure

2. Platelet disorders (thrombocytic purpuras) are classified in 2 major categories:
- **Thrombocytopenia**: decreased platelet number.
- **Thrombocytopathia**: decreased platelet function.

2.1 Thrombocytopenia
- **General features**:
  - Reduction in platelet number < 100.000/mm³
  - However, spontaneous bleeding does not become evident until the count falls below 20.000/mm³
  - Spontaneous bleeding associated with thrombocytopenia most often involves small vessels.
  - **The common sites**: skin and the mucous membranes of the gastrointestinal and genitourinary tracts. Intracranial bleeding is a threat to any patient with a markedly depressed platelet count.
- **Mechanisms of thrombocytopenia**:
The main causes of thrombocytopenia are presented in Table 1
Table 1. Causes of Thrombocytopenia.

1. Decreased production of platelets
   - Bone marrow deficit
     - Aplastic anemia: congenital and acquired
     - Marrow infiltration: leukemia, disseminated cancer, multiple myeloma
   - Toxic effect: selective impairment of platelet production
     - Drug-induced: thiazides, cytotoxic drugs, radiotherapy, etc.
     - Infections: human immunodeficiency virus (HIV) which suppresses the production of megakaryocytes
     - Toxins in chronic use (alcohol, cocaine)
   - Ineffective megakaryopoiesis
     - Megaloblastic anemia (Vitamin B12/Folic acid deficiency anemia)

2. Increased peripheral destruction and utilization
   - Immuneologic destruction: antibodies targeted against platelets
     - Primary: idiopathic thrombocytopenic purpura,
     - Secondary: systemic lupus erythematosus; post-transfusion; Infections: infectious mononucleosis, HIV, cytomegalovirus; Drug-associated: quinidine, heparin, etc.
   - Non-immune destruction: excessive platelet consumption in thrombi
     - Thrombotic thrombocytopenic purpura
     - Hemolytic uremic syndrome
     - Disseminated intravascular coagulation

3. Redistribution
   - Splenomegaly/Hypersplenism

2.1.1. Idiopathic/Immune Thrombocytopenic Purpura (ITP, Werlhof disease)

- **Definition:** the most common cause of thrombocytopenia due to increased immune destruction of platelets.
- **Pathogenesis:**
  ITP is caused by the formation of autoantibodies (IgG type, in 80% of the cases) against platelet membrane glycoproteins (IIb-IIIa or Ib). The mechanism of platelet destruction is similar to that seen in autoimmune hemolytic anemias: opsonized platelets are rendered susceptible to phagocytosis by the cells of the mononuclear phagocyte system. About 75% to 80% of patients are remarkably improved after splenectomy, indicating that the spleen is the major site of removal of sensitized platelets. Since it is also an important site of autoantibody synthesis, the beneficial effects of splenectomy may in part derive from removal of the source of autoantibodies. Although destruction of sensitized platelets is the major mechanism responsible for thrombocytopenia, there is some evidence that megakaryocytes may be damaged by autoantibodies, leading to impairment of platelet production. In most cases, however, megakaryocyte injury is not significant enough to deplete their numbers.
Clinical forms:

1. The acute form
   - Common in children
   - The onset of thrombocytopenia is abrupt, following a viral infection (1-2 weeks)
   - Clinical features: petechiae, purpura, mucous hemorrhages
   - Is a self limited disorder usually resolving spontaneously within 6 months

2. The chronic form
   - Common in adults (most commonly in adult women 20-40 years of age).
   - Progressive onset: cutaneous purpura, epistaxis, bleeding gums; the disease may manifest first with melena, hematuria, or excessive menstrual flow. Subarachnoid hemorrhage and intracerebral hemorrhage are serious consequences of thrombocytopenic purpura but, fortunately, are rare in treated patients.
   - The bleeding time is prolonged, but PT and APTT are normal.
   - The clinical signs and symptoms associated with ITP are not specific for this condition but rather reflective of thrombocytopenia.
   - Bad prognosis, due to a chronic evolution with remissions and recurrences.
   - Treatment: corticotherapy, splenectomy, immunosuppressive drugs.

2.1.2 Heparin-Induced Thrombocytopenia (HIT)

- **Definition**: HIT represents a particular importance because heparin is used widely and failure to make a correct diagnosis can have severe consequences.

- **Pathogenesis**: HIT is caused by an immune reaction directed against a complex of heparin and platelet factor 4 (PF4), a normal component of platelet granules that binds tightly to heparin. It appears that heparin binding modifies the conformation of PF4, making it susceptible to immune recognition. Binding of antibody to PF4 produces immune complexes that activate platelets, promoting thrombosis even in the setting of marked thrombocytopenia. The mechanism of platelet activation is not understood.

- **Types**:
  - **Type I HIT** – rapid onset (1-4 days) & good prognosis (typically resolves upon heparin interruption)
  - **Type II HIT** – onset at 5-14 days from tm initiation & severe prognosis due to autoAb (IgG) against heparin – PF4 with 2 consequences:
    - **Heparin induced thrombocytopenia – HIT**: heparin-dependent antiplatelet antibodies → platelet aggregation within the circulation → multiple arterial thrombi in brain, heart, lungs → “white clot syndrome”
    - **Heparin induced thrombocytopenia and thrombosis – HITT**: heparin-dependent antiplatelet antibodies → cross-reaction with endothelial heparan-sulphate molecules → injury & thrombosis of the vessel wall.

2.1.3 Thrombotic Thrombocytopenic Purpura (TTP)

- **Definition**: severe disorder, with fulminant evolution → lethal, characterized by the generalized occlusion of arterioles/capillaries by thrombi.

- **Pathogenesis**
  - Familial form: deficit of a plasmatic metalloprotease, ADAMTS 13, which is responsible for cleaving the multimer von Willebrand factor in monomers (ADAMTS = A Dintegrin And Metalloproteinase with Thrombospondin Motifs). In the absence of this enzyme, very high
molecular weight of vWF accumulate in plasma → platelet microaggregates form throughout the microcirculation.

- **Non-familial form: Ab IgG against the enzyme ADAMTS 13**
  - Manifestations:
    - occurs in adults (especially in women of middle age)
    - severe thrombocytopenia (< 20 000/mm$^3$)
    - fever
    - transient neurologic disturbances
    - microangiopathic hemolytic anemia due to erythrocytes fragmentation through the partly occluded vessels
    - high risk for acute renal failure
  - Treatment: Plasma exchange ± infusion of fresh frozen plasma can be life saving by providing the missing enzyme (curative in 80% of the cases)

### 2.1.4 Hemolytic-Uremic Syndrome (HUS)
- **Definition:** severe disorder, similar to PTT, characterized by the occlusion of small blood vessels localized ONLY at the renal level.
- **Pathogenesis:** widespread formation of hyaline thrombi, comprised primarily of platelet aggregates, in the afferent arterioles and glomerular capillaries. It usually occurs due to infectious gastroenteritis with E.Coli → endotoxin release → damage of endothelial cells → initiation of PLT activation & aggregation (*ADAMTS13 is normal!*).
- **Manifestations:**
  - HUS is also associated with thrombocytopenia, fever, and microangiopathic hemolytic anemia, but is distinguished from TTP by the absence of neurologic symptoms, the prominence of acute renal failure, and frequent incidence in children.
- **Treatment:** dialysis.

### 2.2 Thrombocytopathia
Are characterized by altered platelet function, with normal number of thrombocytes due to:
1. Inherited disorders of:
   a. Adhesion (von Willebrand disease and Bernard-Soulier syndrome)
   b. Aggregation (Glanzmann thrombasthenia)
2. Acquired functional defects caused by:
   a. Drugs (aspirin and NSAIDs)
   b. Toxins (uremia)

**Observation!**

Adhesion requires:
- von Willebrand factor synthesized by the endothelium that functions as a bridge between platelets and subendothelial collagen
- Gplb receptor on the platelets
  
  Aggregation involves: the Gplb-IIIa receptors that link platelets via fibrinogen bridges.

#### 2.2.1 Disorders of adhesion

**Bernard–Soulier syndrome** is a rare autosomal recessive disorder. It impairs platelet adhesion via a defect in the glycoprotein Ib (the platelet receptor which interacts with von Willebrand factor for the adhesion of thrombocytes to the subendothelial collagen). Bleeding may be severe. On
peripheral blood smear, unusually large platelets can be identified. Bleeding time is prolonged. Platelet transfusion is necessary to control serious bleeding.

2.2.2 Disorders of aggregation

Glanzmann thrombasthenia is a rare autosomal recessive disorder causing a defect in the platelet glycoprotein IIb/IIIa complex (role of receptor for fibrinogen): platelets cannot aggregate. Patients may have severe mucosal bleeding (eg, nosebleeds that stop only after nasal packing and transfusions of platelet concentrates). Platelet transfusion is necessary to control serious bleeding.

2.2.3 Disorders of activation

Disorders of amplification of platelet activation are the most common hereditary intrinsic platelet disorders and produce mild bleeding. They may result from decreased ADP in the platelet granules (storage pool deficiency), from an inability to generate TxA$_2$ from arachidonic acid, or from an inability of platelets to aggregate in response to TxA$_2$. Platelet aggregation tests reveal impaired aggregation after exposure to collagen, epinephrine, and low levels of ADP and normal aggregation after exposure to high levels of ADP. The same pattern can result from use of NSAIDs or aspirin:

- Aspirin = irreversible inhibition of COX-1 → risk of hemorrhages that continue 3-7 days after stopping the administration
- NSAID = reversible inhibition of COX-1 (during the treatment period).

2.3. Coagulation disorders

Disorders of coagulation can be acquired or hereditary.

A. INHERITED coagulation disorders = hereditary defects of clotting factors:
1. Von Willebrand disease
2. Hemophilia A – factor VIII deficiency
3. Hemophilia B – factor IX deficiency

B. ACQUIRED coagulation disorders
1. Decreased synthesis of clotting factors:
   a) Liver diseases
   b) Vitamin K deficiency
2. Increased consumption of clotting factors:
   a) Disseminated intravascular coagulation (DIC)

2.3.1 Inherited coagulation disorders

2.3.1.1 von Willebrand disease (vWD)
- **Definition:** vWD is a hereditary deficiency of von Willebrand factor (vWF), which causes platelet dysfunction. vWF is synthesized and secreted by vascular endothelium to promote the platelet adhesion of platelets to the vessel wall. vWF is also required to maintain normal plasma factor VIII activity. Thus, deficiency in vWF will be responsible for:
  - Reduced platelet adhesion = abnormal primary hemostasis.
  - Reduced levels of factor VIIIa = abnormal secondary hemostasis.
- **Deficit:**
  - quantitative = slight or severe decrease in vWF
  - qualitative = synthesis of monomer vWF
- **Manifestations:** mixed hemorrhagic syndrome (mild to moderate):
  - bruising, purpura, petechiae (rapid, superficial hemorrhages)
– excessive menstrual flow, GI bleeding (late, profound hemorrhages)
– Screening coagulation tests reveal a normal platelet count, normal INR, prolonged BT and aPTT.

2.3.1.2 Hemophilias

- **Definition:** hereditary bleeding disorders caused by deficiencies of either clotting factor VIII or IX (factor VIII deficiency is 10x more common than factor IX deficiency). Both types of hemophilias are **X-linked recessive disorders**, which primarily affects males, all daughters of affected men being **obligate carriers**. However, one-third of new cases represent spontaneous mutations (no family history).

**HEMOPHILIA A** - factor VIII deficiency, represents 80% of cases.

- **Classification:** severity of the disease is given by the percent of normal factor VIII activity in the circulation:
  - **Mild hemophilia:** factor levels 5 to 40% of normal (*bleeding occurs after serious trauma or surgery*)
  - **Moderate hemophilia:** factor levels 1-5% of normal (*bleeding occurs after minimal trauma*)
  - **Severe hemophilia:** factor levels < 1% of normal (*spontaneous bleeding throughout life, usually beginning soon after birth, eg, scalp hematoma after delivery or excessive bleeding after circumcision*).

- **Clinical manifestations:**
  - Bruises and hematoma
  - Bleeding into joints with pain and swelling (**hemarthrosis**): most common manifestation responsible for the **chronic hemophilic arthropathy**:
    ✓ Repeated joint bleeds lead to synovial inflammation and increased vascularity and thickening of the synovium. This progressively increases the risk of a re-bleed.
    ✓ Vicious cycle (the synovium degenerates away and then cartilage and bone are attacked)
    ✓ Most severe hemophiliacs need knee joint replacement by adulthood.
  - Gastrointestinal and urinary tract hemorrhage → blood in stool and urine
  - ! **Never purpura and petechiae** (since primary hemostasis is not affected)

- **Positive diagnosis:**
  - prolonged APTT
  - normal BT, PT, and platelet count
  - Factor VIII assay determine the severity of the hemophilia.

- **Treatment:**
  ✓ recombinant factor VIII (in the last century **purified factor VIII concentrate** derived from multiple donors was used, leading to HIV and hepatitis B infestation of several hemophilic patients)
  ✓ Sometimes antifibrinolytics

**HEMOPHILIA B**, factor IX deficiency (Christmas disease), unfrequent, is clinically indistinguishable from hemophilia A and presents the same screening test abnormalities. Specific factor assays are required to distinguish the two.

- **Treatment:** recombinant factor IX.

2.3.2 Acquired coagulation disorders
2.3.2.1 Vitamin K deficiency
Vitamin K is required for the carboxylation (activation) of the clotting factors II (prothrombin), VII, IX, X.
- **Pathogeny:** in vitamin K deficiency, gamma-carboxyglutamic acid is replaced by glutamic acid, which is incapable to fix the mentioned factors, **impairing the activation of prothrombin to thrombin.**
- **Causes** of vitamin K deficiency:
  - decreased synthesis by intestinal bacteria (only in newborns after broad-spectrum antibiotherapy)
  - impaired intestinal absorption (in liver & gall bladder diseases due to the lack of bile salts)
  - inhibition of activity in vitamin K antagonists over dosage (oral anticoagulant drugs of coumar type)
- **Diagnosis:** Koller ‘test is positive (administration of vitamin K normalizes PT).

2.3.2.2 Liver disease results in coagulation defects due to:
- Hepatocellular damage → decreased coagulation factors synthesis
- Cholestasis is associated with vitamin K malabsorption → decreased activation of clotting factors
- Portal hypertension → splenomegaly and hypersplenism → thrombocytopenia
- Acute liver failure (increased consumption of coagulation factors) can be associated with DIC

2.3.3 Disseminated intravascular coagulation (DIC)
- **Definition:** DIC is not a disease entity but an event that can accompany various disease processes.
  - DIC is a complex alteration in the blood clotting mechanism characterized by the:
    - **Primary activation of coagulation resulting in thrombosis**
    - **Secondary activation of fibrinolysis resulting in thrombolysis**
- As a result of the depletion of clotting factors, **hemorrhage occurs simultaneously,** a paradoxical clinical association of “clotting and hemorrhage”.
- DIC that evolves slowly (over weeks or months) causes primarily venous thrombotic and embolic manifestations; DIC that evolves rapidly (over hours or days) causes primarily bleeding.
- Severe, rapidly evolving DIC is diagnosed by demonstrating thrombocytopenia, an elevated PTT and PT, increased levels of plasma D-dimers (or serum fibrin degradation products), and a low plasma fibrinogen level.

- **Pathophysiology**
  - DIC is a secondary event from activation of one of the coagulation pathways, either:
    1. **Extrinsic via tissue injury:**
       - Shock or trauma
       - Infections (gram positive and gram negative sepsis)
       - Obstetric complications (eclampsia, placenta abruptio, fetal death syndrome)
       - Malignancies: acute leukemias, cancers of the lung, colon, breast, prostate.
    2. **Intrinsic via blood vessel injury:**
       - Infectious vasculitis (certain viral infections, rickettsial and parasitic infections)
       - Intravascular hemolysis (hemolytic transfusion reactions)
       - Miscellaneous: snakebite, pancreatitis, severe liver disease.

- **Consequences**
Systemic activation of the coagulation system simultaneously leads to a complex disruption of body homeostasis, via:

- **thrombi formation** ⇒ **compromising blood supply to various organs**
- **consumption of platelets and coagulation factors** ⇒ **resulting in hemorrhage.**

**Treatment:** correction of the cause and replacement of platelets, coagulation factors (in fresh frozen plasma), and fibrinogen (in cryoprecipitate) to control severe bleeding. Heparin is used as therapy (or prophylaxis) in patients with slowly evolving DIC who have (or are at risk of) venous thromboembolism.

### III. HYPERCOAGULABILITY STATES

- **Definition:** excessive hemostasis is responsible for **THROMBOSIS** (forming of thrombi in vascular bed).
- **Classification:**

  **A. Primary Hypercoagulability:**
  - Mutations of factor V (factor V Leiden) that make it resistant to its normal inactivation by activated protein C.  
  - **Protein C deficiency:** because activated protein C degrades clotting factors Va and VIIIa, deficiency of protein C predisposes to venous thrombosis.
  - **Protein S deficiency:** because protein S helps activated protein C degrade clotting factors Va and VIIIa, deficiency of protein S predisposes to venous thrombosis.
  - **Antithrombin III deficiency:** because antithrombin inhibits thrombin and factors Xa, IXa, and Xla, deficiency of antithrombin predisposes to venous thrombosis.
  - **Hyperhomocysteinemia** may predispose to arterial and venous thrombosis through unclear mechanisms, possibly because of injury to vascular endothelial cells. By far the most common causes of hyperhomocysteinemia are acquired deficiencies of folate, and vitamin B$_{12}$.

  **B. Secondary Hypercoagulability:**
  - Increased PLATELET function
  - Increased CLOTTING activity
  - Both

#### 1.1 Increased PLATELET function

- **Etiology:**
  - ATS  
  - Smoking  
  - Diabetes mellitus  
  - Hyperlipidemia/Obesity  
  - Increased platelet count (thrombocytosis > 1.000.000/mm$^3$)  
  - Malignancies (myeloproliferative disorders, eg CML)

- **Mechanisms:**
  - Flow disturbances and endothelial damage  
  - Increased sensitivity of platelets to factors that induce adheriveness/aggregation.

- **Type of thrombosis:** ARTERIAL, white thrombi (platelets and little fibrin).

- **Complications:**
  1. **Transient/permanent ischemia** caused by distant sites embolization:
     - in the cerebral circulation ⇒ transient ischemic attack (TIA) or stroke
     - in the retinal circulation ⇒ temporary monocular blindness.
2. **Myocardial infarction** caused by thrombi that form locally after rupturing/fissuring of an ATS plaque.

### 1.2 Increased CLOTTING activity

- **Etiology:**
  - Postsurgical states
  - Prolonged immobility
  - Pregnancy and puerperium (postpartum period)
  - Congestive heart failure
  - Malignant disease
  - Sepsis

- **Mechanisms:**
  - Blood stasis, responsible for:
    - Accumulation of activated clotting factors
    - Prevention of their interaction with the inhibitors
  - Increased release of tissue factor by tumor cells.

- **Type of thrombosis:** VENOUS, red thrombi (few platelets, fibrin, and trapped RBCs).

- **Complications:** Pulmonary embolism caused by embolization to the pulmonary circulation (especially from inferior limb veins)