Lecture datafiles from
Pathophysiology
3rd year Medical faculty
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GENERAL MEDICINE
DENTISTRY

# Disseminated intravascular coagulation

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# Definition and characteristics

- **Def.:** is and acquired acute, subacute or chronic thrombohemorrhagic disorder induced by systemic activation of coagulation with general micro to macro deposits of fibrin and **polytopic microvascular thrombosis** in various organs.Complication of DIC is **mutifocal tissue microischemia**, **microinfrarcions** as a startpoint to **multiple organ dysfunction syndrome (MODS).**
- **Epi**: 1% of hospitalized patients; DIC does not occur by itself but only as a **secondary acquired complication of other diseases**, usually **critical illnesses**
- **Etio:**. DIC can be severe in some cases, but milder and insidious in others.
  - **Solid tumors** and blood cancers **( acute promyelocytic leukemia)**
  - **Obstetric complications:** abruptio placentae, pre-eclampsia or eclampsia, amniotic fluid embolism, retained intrauterine fetal demise, septic abortion, post partum haemorrhage, ow platelets (HELLP) syndrome;
  - **Massive tissue injury**: severe polytrauma, burns, hyperthermia, rhabdomyolysis, extensive surgery, Organ destruction (e.g, pancreatitis)
  - **Sepsis or severe infection of any kind** (bacterial (G-/ G+), viral, fungal, protozoan infections
  - **Transfusion reactions** (i.e., ABO)
  - Severe **toxoallergic or toxic reactions** (i.e. snake venom)
  - Giant haemangiomas (Kasabach-Merritt syndrome)
  - **Large aortic aneurysms, Severe hepatic failure, etc.**

# Pathogenesis of DIC

Acute form of DIC = extreme intravascular coagulation with a complete breakdown of homeostasic

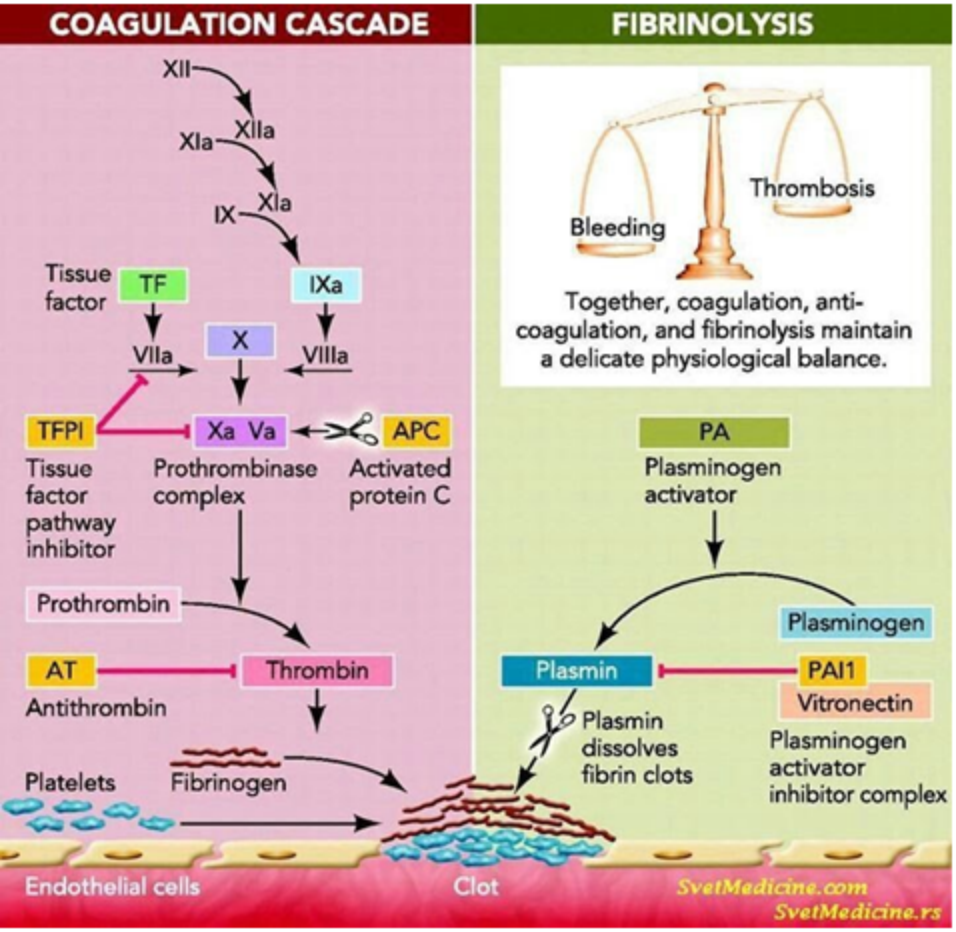
**I. Stage – Thrombosis – ischemia**

- **tissue factor (TF)** transmembrane glycoprotein expressed on the surface of cell (endothelial, macrophages, monocytes) after vascular damage, exposure to cytokines (IL1, TNF, endotoxin) = **critical mediator of DIC**; TF is abundant in **lungs, brain, placenta**.
- TF binds with **activated factor VIIa** (trace amounts in the blood) after exposure to blood and platelete → **extrinsic tenase complex** → activates factor IX and X to IXa and Xa, formation **of thrombin and fibrin**.
- **Thrombin** → **fibrinogen to fibrin**; excess clots trap platelets to become larger clots, which leads to **microvascular and macrovascular thrombosis**.
- Clots in the microcirculation, in the large vessels, and in the organs is what leads to the **ischemia, impaired organ perfusion, and end-organ damage.**

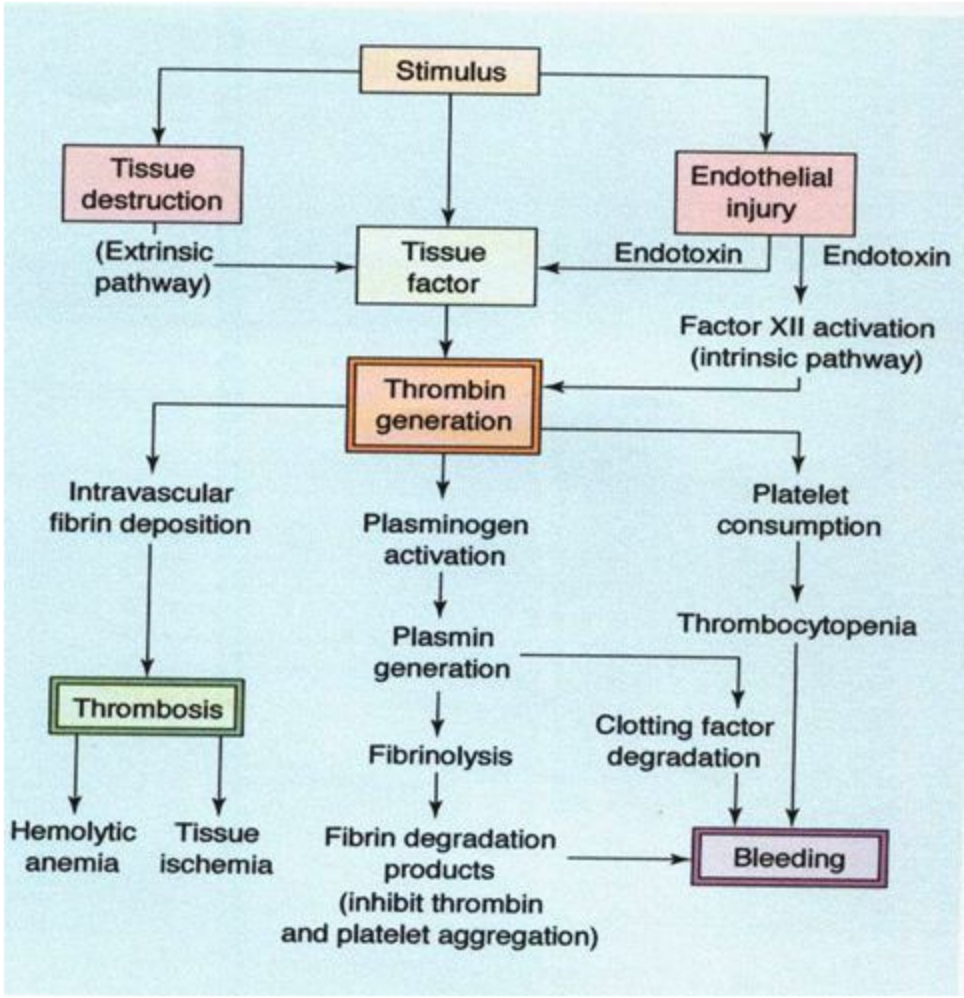
**II. Stage - Haemorrhage**

- Coagulation inhibitors - **antithromboin, plasmin** are consumed → more clotting
- Thrombocytopenia ← **entrapment and consumption of platelets.**
- Clotting factors are consumed in multiple clots → **bleeding**
- excess circulating **thrombin** → conversion of plasminogen to plasmin, resulting in fibrinolysis. The **breakdown of clots results in an excess of FDPs** → anticoagulants contributing to hemorrhage

# Coagulopathy in DIC

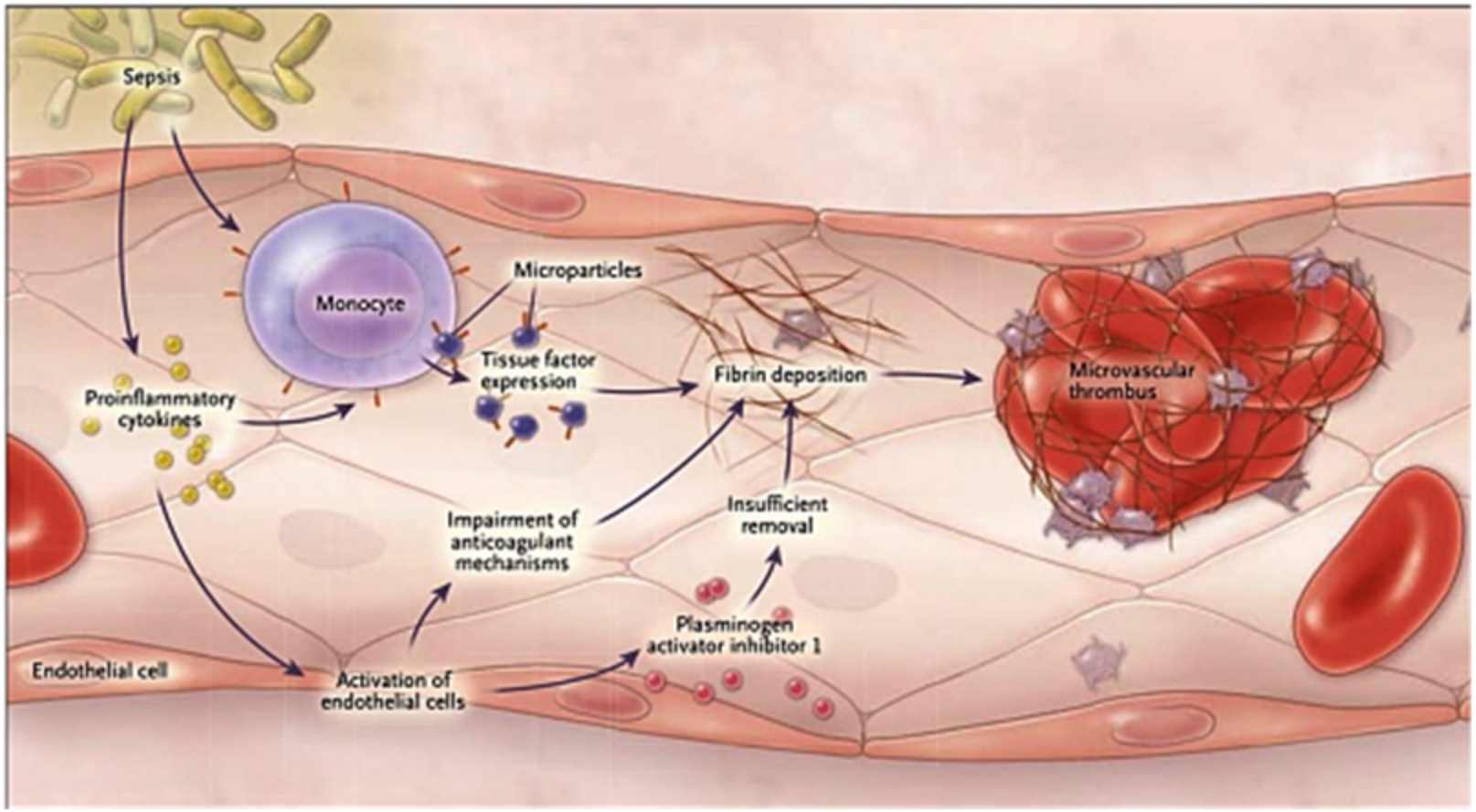



Coagulation and fibrinolytic systems work in the balance under physiological conditions



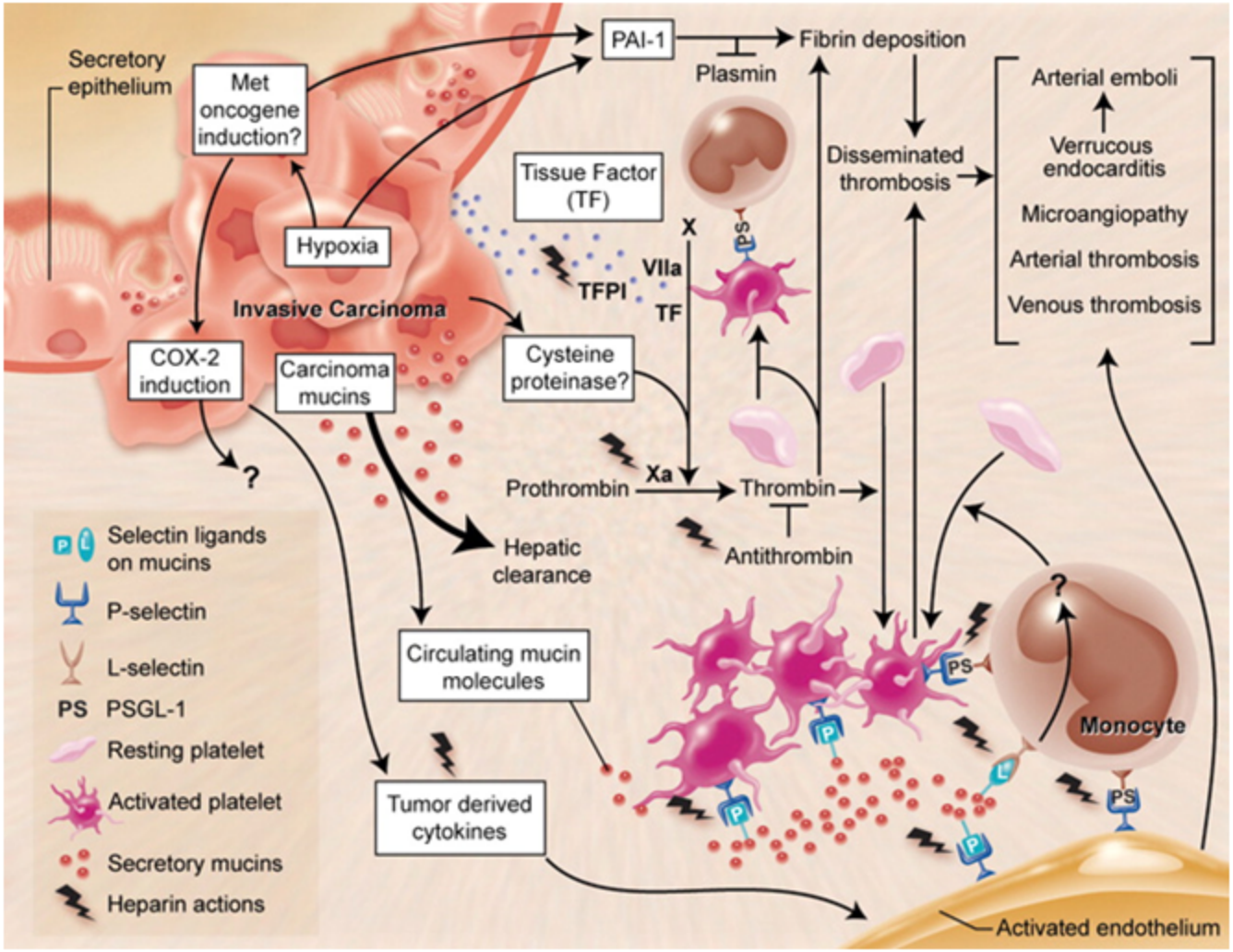

Initial events followed by diffuse coagulation response and thrombosis is accompanied by consumption of factors leading to bleeding

# Induction of DIC in sepsis - example




- Through generation of of proinflammatory cytokines and activation of monocytes, bacterias induce tissue factor overproduction, activation coagulation, endothelial activation, inpaires anticoagulant system and fibrinolysis by the formation of an increased **amounts of plasminogen activator inhibitor.**

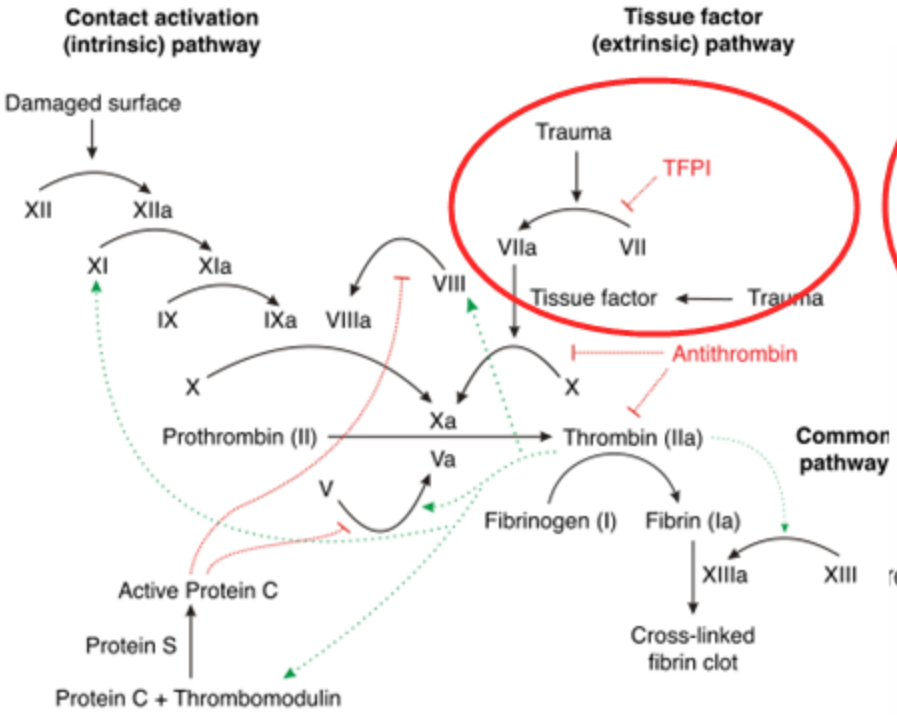
# Induction of DIC in tumors - example



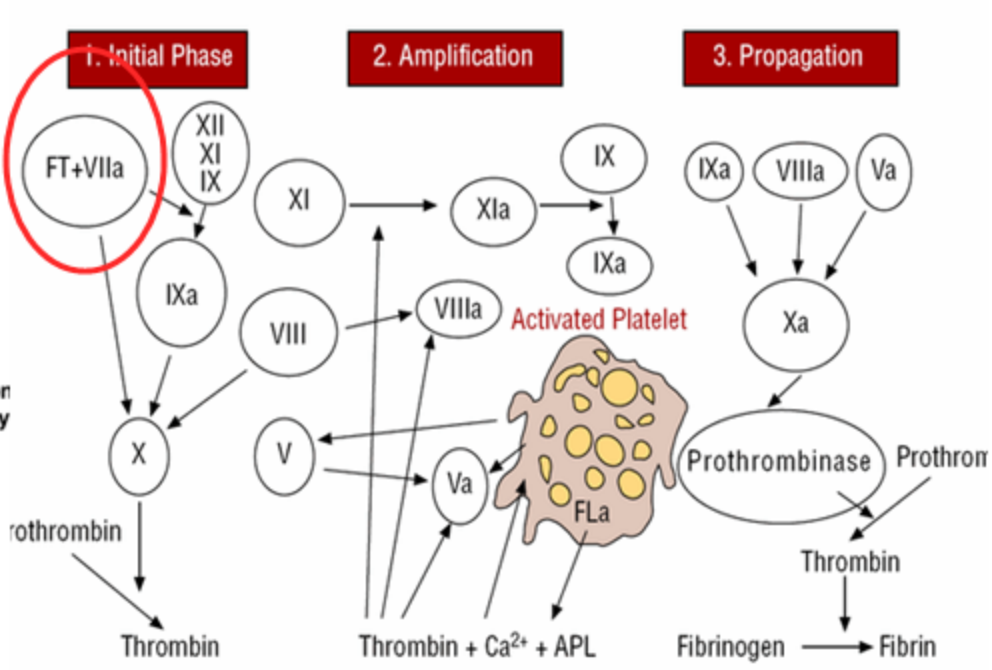

Epithelial cells of many invasive carcinomas produce tissue factors, mucin molecules, enzymes and cytokines which collaborately promote local thrombosis, chronic inflammation, and endothelial activation. Thrombi can be released as emboli into circulation.

# Mechanisms of coagulation

## The intrinsic and extrinsic pathway model



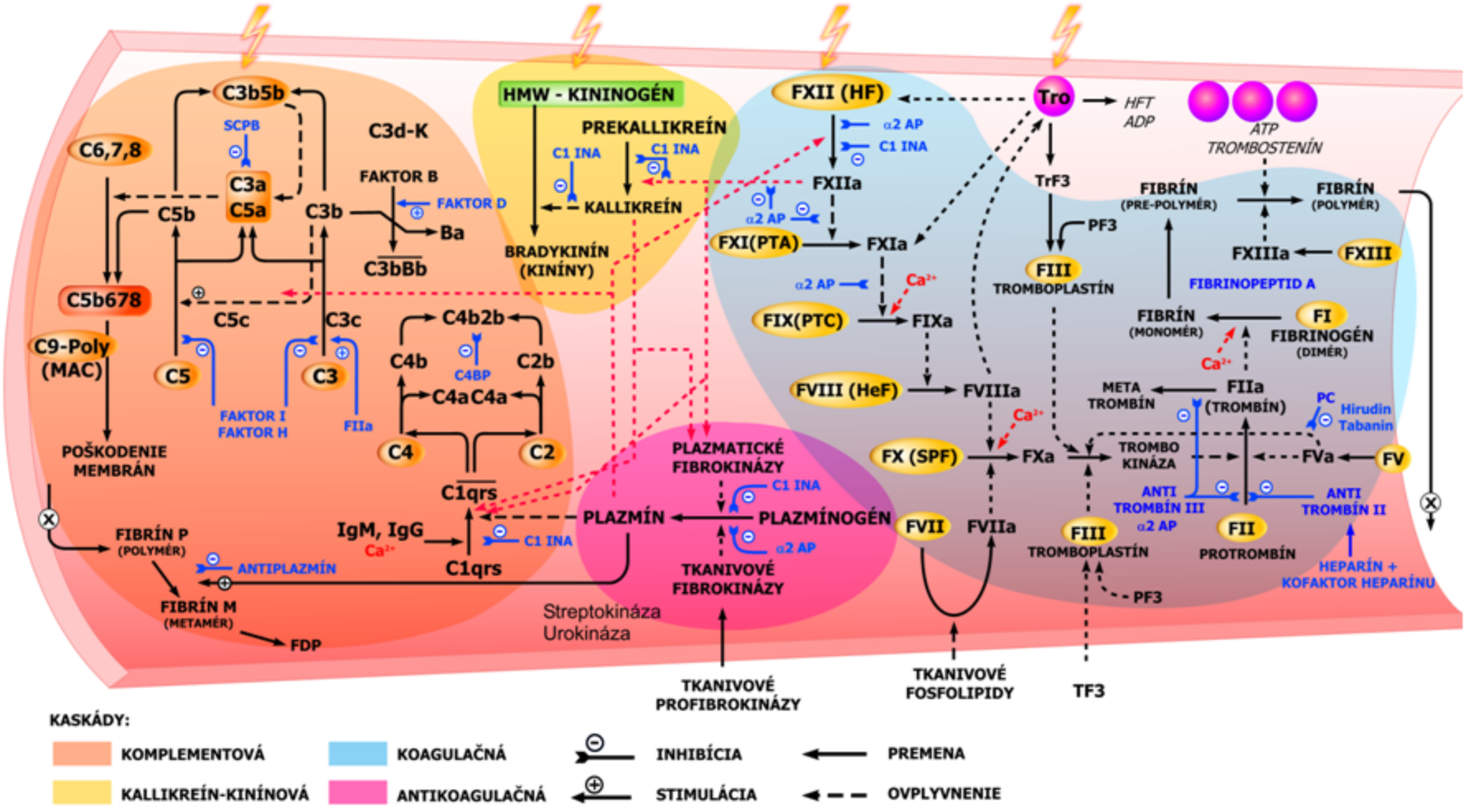

## The cell-based model




- Tissue factor plays important role in early stages of activation of coagulation. **Initiation** occurs after vascular injury, when TF-bearing cells bind to and activate Factor VII. This leads to the production of a small amount of thrombin.
- In **amplification** small amount of thrombin activates platelets .Prothrombinase complex (comprising Factor Xa and co-factors bound to activated platelets) causes a burst of thrombin production.
- **Fibrin formation.** A series of protease reactions causes the conversion of the soluble protein fibrinogen to insoluble fibrin strands by thrombin, leading to thrombus formation .Thrombin also activates Factor XIII, which stabilizes the thrombus by cross-linking fibrin. The resulting fibrin mesh traps and holds cellular components of the thrombus.

# Plasma proteases in inflammation

Activation of coagulation cascade and anticoagulation pathway occurs in coordination with kallikrein - kinnin system and complement system (dashed red lines) *(picture author slov. quoat.)*



# Pathogenesis

### III. Stage – Inflammatory perpetuation

- excess plasmin activates **complement and kinin systems** → **shock, hypotension**, and increased vascular permeability.

- DIC in animal models highly expressed receptor surface of hepatocytes, termed the **Ashwell-Morell receptor,** is responsible for thrombocytopenia in bacteremia and sepsis due to Streptococcus pneumoniae (SPN) and possibly other pathogens.

- **Gram-negative sepsis** - release of **endotoxin** is the mechanism
- In **acute promyelocytic leukemia**, destruction of leukemic granulocyte precursors, resulting in the release of large amounts of proteolytic enzymes from their storage granules, causing microvascular damage.
- **Malignancies** may enhance the expression of various oncogenes that result in the release of TF and plasminogen activator inhibitor-1 (PAI-1), which prevents fibrinolysis.

# Manifestations of DIC

(1) **massive microcoagulation** capillaries is always the first event it procedes **unvisibly.**
the chest pains and shallow breath when blood clots in the patient's heart or lung blood vessels present; redness, hypotension, swelling in the lower leg; paralysis, headaches trouble with speech
(2) second advanced state is typical by: consumptional trombocytopenia and severe depletion of clotting factors with manifestatnt **severe bleeding, ecchymoses, hematomas.**

- **Acute DIC - endotoxic shock** or **amniotic fluid embolismis** usually eminent severe, when a sudden exposure of blood to procoagulant **e.g. tissue factors (TF), thromboplastin** etc., body's compensatory hemostatic mechanism are drastically overwhelmed, leading to **hemorrhage**. bleeding outer but also inner organ bleeding
- **prolongation of PT, APPT, TT** - consumption and inhibition of clotting factors; **Trombocytopenia**,
- **Increased FDPs, increased D-dimer; schizocytes** in peripheral blood smear

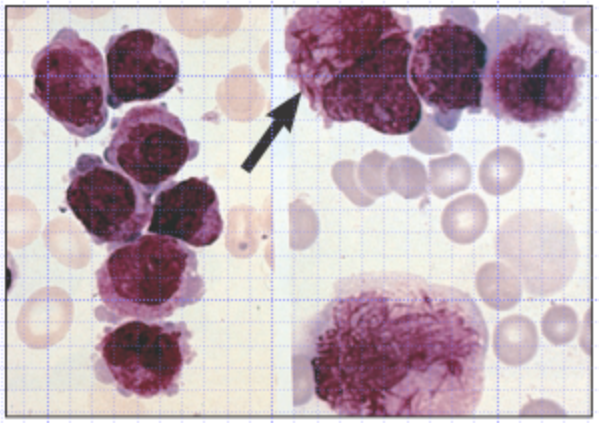
- **Chronic DIC - compact tumors, aortic aneurysms.**
- compensated state that progresses more slowly ( weeks or months), occurs when blood is continuously exposed to small amount of Tissue factors.
- compensatory mechanisms (in the liver and bone marrow) are not overwhelmed
- **prolongation of PT, Increased FDPs, D-dimer, normalized APPT**

# Manifestations of DIC in various organs

| Organ | Ischemic | Hemorrhagic | Evaluation |
|---|---|---|---|
| Skin, subcutaneous tissue | Purpura fulminans<br>Gangrena, Acral cyanosis | Petechiae, Ecchymoses,<br>Oozing | Visual, |
| Wounds | Swelling | Bleeding from surgery wounds, iv lines, tracheo-stomies, serous cavities | Visual |
| CNS | Delirium/Coma, Infarction | Intracranial hemorrhage | CT, NMR, |
| Renal | Oligurua/Azotemia, ARF,<br>Cortical necrosis | Hematuria | Urineanalysis |
| Cardiovascular | Myocardial weakness, ischemia, compens. tachycardia,<br>Redness, hypotension | --- | ECG, Doppler, NMR |
| Pulmonary | Dyspnoea, Hypoxia tachypnoea, Pulmonary infarction, chest pain | Intrapulmonary hemorrhage, alveolar edema, hemoptysis, cough | Perfusion scan, Ventilation scan, CT, auscultation |
| GIT | Ulcers, infarcts, infarsation, stop of passage | Intraluminal GI bleeding, petechias, necrosis, | Abdominal CT |
| Adrenal | Infarctions | Hemorrhage (scarse) | USG, CT, NMR |
| Liver | Hepat.failure, Jaudice, | Intraparenchymal hemorrhages | USG, NMR |

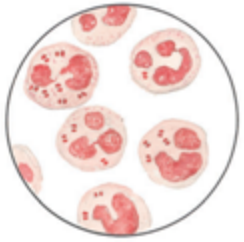
# DIC – examples

*Endotoxin activates the Hageman factor (clotting factor XII), which causes disseminated intravascular coagulation (DIC).*

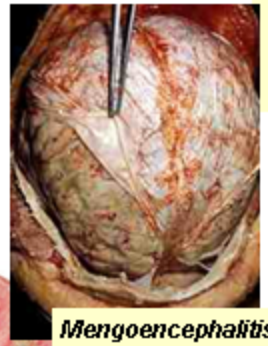


*Blood smear of acute promyelocytic leukemia. Myeloblasts and promyelocytes with Auer rods and bundles (arrow).*

*Acute adrenal cortical in-sufficiency (adrenal cri-sis, Waterhouse- Fride-richsen sy.) acute necro-sis and hemorr-hage of the adrenal cortex secon-dary to bacterial septice-mia.*



*Meningococci from blood, spinal fluid and throat.*



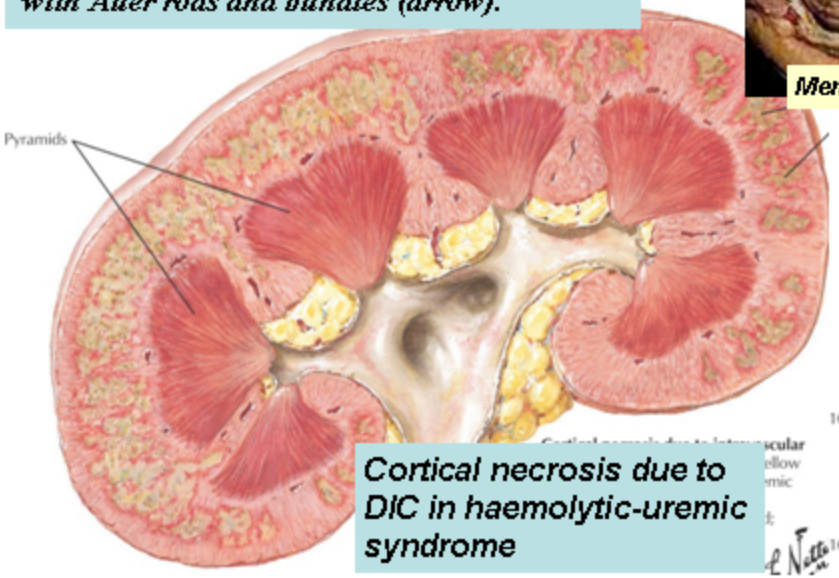
*Mengoencephalitis*

*Circulatory shock*



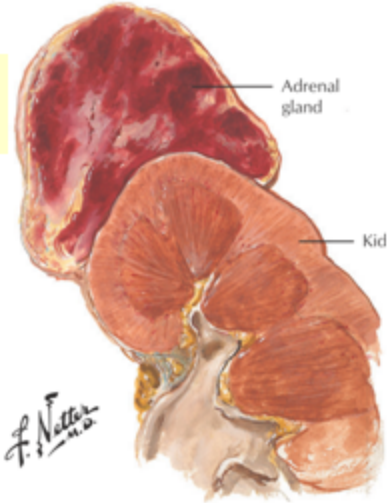
*Extensive purpura Cyanosis*

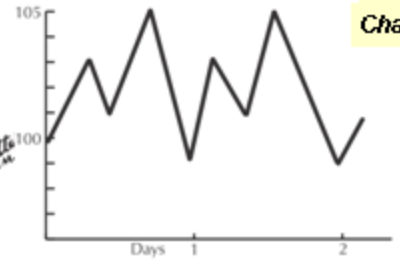
*Meningococcal septicemia, Pseudomonas, Pneumococci, Haemophilus influenzae*




*Cortical necrosis due to DIC in haemolytic-uremic syndrome*

*Hemoragic destruction of adrenal gland*



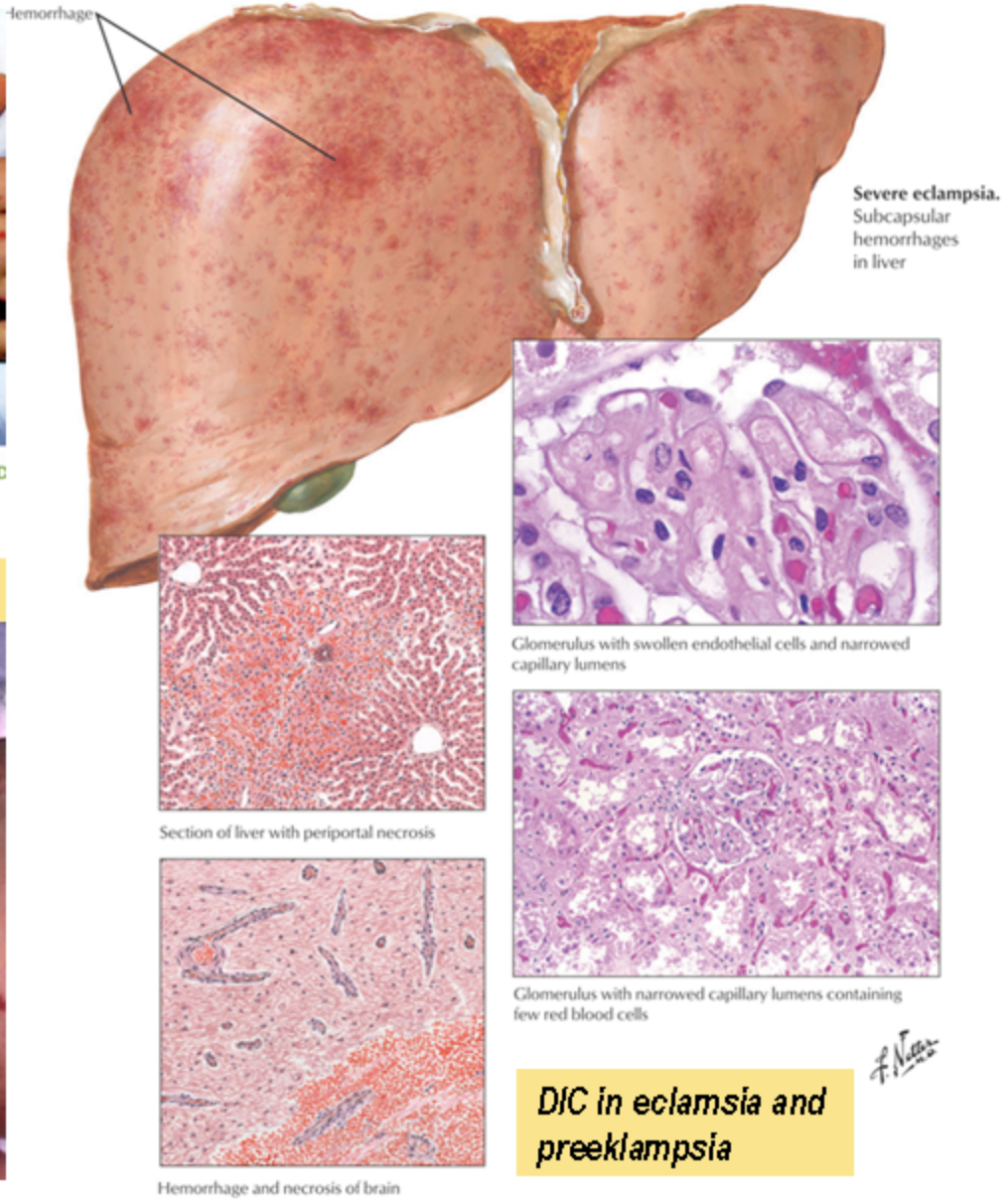




*Characteristic fever*

# Manifestations of DIC


Purpura fulminans u DIC

DIC u meningokokovej sepsy




DIC in eclamsia and preeklampsia

# Laboratory tests

| *Laboratory test* | *Normal values* | *DIC* |
|---|---|---|
| *Thrombocytes* | *150-350. $10^9$ /l* | *< 50 .$10^9$ /l* |
| *Fibrinogen degradation products (FDPs)* | *< 10 mg/ml* | *> 40 mg/ml* |
| *D- dimer* | *< 1 mg/ml* | *> 4 mg/ml* |
| *Fibrinogen* | *150-400 mg/dl* | *< 100 mg/dl* |
| *Prothrombin time PT* | *10-15 sec* | *> 20 sec* |
| *Partial prothrombine time PPT* | *60-70 sec* | *> 100 sec* |
| *Activated partial prothrombine time aPPT* | *20-36 sec* | *> 70 sec* |
| *Thrombin test (TT)* | *9-13 sec* | *15-23 sec* |
| *Antitrombin III* | *> 50% of control* | *decreased* |

# Laboratory evaluation

**International normalized ration (INR) = 0.9-1.1**

- INR = (Patient's PT/mean PT of reference range) x ISI
- International sensitivity index (ISI) is an experimentally derived provided by the thromboplastin manufacturer More sensitive thromboplastins have low ISI (1.0-1.2),
  - **Standard intensity warfarin therapeutic range: 2.0-3.0**
  - **High intensity warfarin therapeutic range: 2.5-3.5**

**Thrombin test (TT) = 15-23 seconds**

- Eval: presence of heparin or heparin-like anticoagulants (enhance antithrombin's inhibition of thrombin) warfarin)
- Dg: prolongation in use of heparin-like anticoagulants, hypofibrinogenemia, dysfibrinogenemia, fibrin degradation products, and antibody inhibitors of thrombin.

**D-Dimer** < or =500 ng/mL Fibrinogen Equivalent Units (FEU)

- D-dimer values < or =500 ng/mL FEU may be used in conjunction with clinical pretest probability to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).
- **Dg:** Elevated D-dimer levels are found in association with disseminated intravascular coagulation (DIC), pulmonary embolism (PE), deep vein thrombosis (DVT), trauma, and bleeding. D-dimer may also be increased in association with pregnancy, liver disease, malignancy, inflammation, or a chronic hypercoagulable state.

# Disorders of hemostasis

**Tests for primary hemostasis**

- Bleeding Time (Duke test)
- Platelet Count (Pltc, trombo)
- Rumpel-Leede capillary-fragility test (tourniquet test, Hess test)

**Tests for secondary hemostasis**

- Partial Thromboplastin Time (PTT);
- Activated partial thromboplastin time (aPTT).
- Prothrombin Time (PT) (Quick)
- International normalized ration (INR)
- Thrombin Time (TT)

**Tests for degradation of fibrin**

- FDP (fibrin degradation products)
- D-dimers

**Primary hemostasis disorders**

- Bleeding Time (Duke test)
- Platelet Count (Pltc, trombo)
- Rumpel-Leede capillary-fragility test (tourniquet test, Hess test)

**Secondary hemostasis disorders**

- Epistaxes
- Difficult menstruation
- Easy bruising
- Bleeding into mucosa (GIT, urinary sy. - hematuria)
- Delayed bleeding

# Laboratory evaluation

**Partial thromboplastin time (PTT), Activated Partial Thromboplastin time (aPTT) = 25-35 sec**

- **Eval:** evaluate function of the **intrinsic clotting system**, monitor overall speed at which blood clots by means of "intrinsic" ( contact activation pathway) and common coagulation pathways
- **Not eval.**: extrinsic procoagulant pathway ( factor VII and tissue factor, factor XIII; monitors **treatment with heparin**
- **Dg:**
  - < 25 sec: elevation of factor VIII activity; acute or chronic illness or inflammation, or spurious results;
  - > 37 sec: defic. of coagulation fact. (acquired or congenital ), **heparinisation** monoclonal immunoglobulin, fibrinogen deficiency, liver disease, and vitamin K deficiency

**Prothrombin time (PT) Quick = 10-13 sec**

- **Eval:** deficiency of one or more of the clotting factors of the extrinsic coagulation system (I, II, V, VII, or X) due to a hereditary or acquired deficiency, liver disease, vitamin K deficiency, or
- specific coagulation factor inhibitors, Lupus-like anticoagulant inhibitors (eg, antiphospholipid antibodies), nonspecific prothrombin time inhibitors (eg, monoclonal immunoglobulins, elevated fibrin degradation products)
- **Not eval:** deficiencies of coagulation factors factors VIII, IX, XI, XII, XIII).
  - **Dg:** prolonged due to deficiencies of factors X, VII, V, and II of the extrinsic pathway, presence of inhibitors, or oral anticoagulation therapy.

# Laboratory tests

| *Laboratory test* | *Normal values* | *DIC* |
|---|---|---|
| *Thrombocytes* | *150-350. $10^9$ /l* | *< 50 .$10^9$ /l* |
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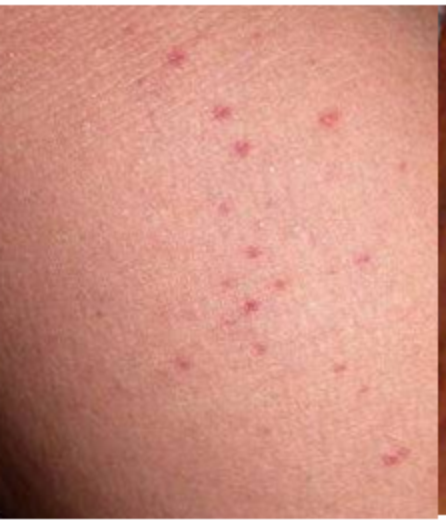
| *Thrombin test (TT)* | *9-13 sec* | *15-23 sec* |
| *Antitrombin III* | *> 50% of control* | *decreased* |

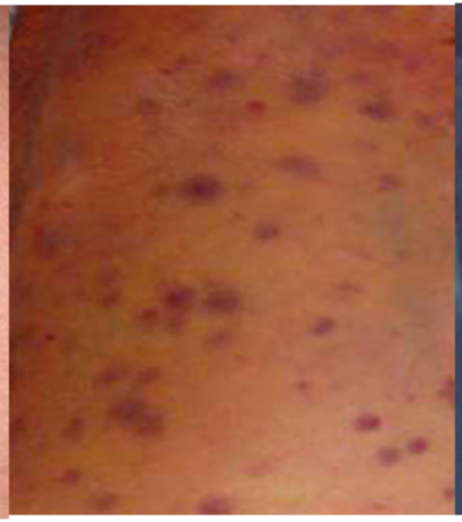
# Disorders of primary hemostasis

- **Petechia** = red or dark red or purple pinpoint spots on the skin (< 2 mm) caused by cutanous capillary bleed; Etio: Physical trauma = facial petechia around the eyes, conjuctiva (hard coughing, holding breath, choking, vomiting or crying, weightlifting, childbirth), asphyxiation, excessive pressure applied to tissue (e.g. tourniquet); Infections = scarlet fever, typhus, babesiosis, hemorrhagic fevers (Ebola, Hantavirus, Marburg virus), viroses (Influenza A, cytomegalovirus, infectious mononucleosis); Non-infectious conditions = Vitamin C + K deficiency, leukemia, thrombocytopenia, Von Willebrand disease, aplastic anaemia, marasmus
- **Purpura** = red - purple sharply marginated spots on the skin (2–10 mm) caused by cutanous or subcutanous bleeding (arterioles, venules); do not dissapear after pressure. Etio: vasculitis (e.g. Henoch–Schönlein purpura), scurvy (deficiency of vitamin C), typhus, meningitis (meningococci septicaemia ; Neisseria meningitidis), thrombocytopenic purpuras, post-transfusion purpura,
- **Ecchymosis** = purple large sharply marginated spots (> 1 cm; same as purpura except larger) due to subcutaneous bleeding (escape of blood into the tissues from ruptured venules); sometimes indistinguishable from hematoma but sharper in margins); similar to bruise which is caused by trauma. Etio: traumas, infections
- **Hematoma (bruise)** = reddish violet contusion with more diffuse margins (in skin), capillaries, venules are damaged by trauma, allowing blood to seep, hemorrhage, or extravasate into the surrounding skin, subcutaneous tissue, muscle, or bone interstitial tissues. Etio: various traumas

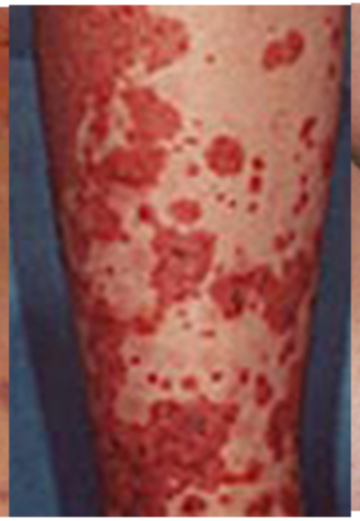
# Disorders of primary hemostasis



*Petechiae*



*Ecchymoses*



*Purpura*