HAEMODYNAMIC DISORDERS

This pdf was developed by
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for ReviewPathology.com

Note on References

See box to the right for reference notations.

PubMed references usually link to abstracts, which provide useful information. But most abstracts link to a free, full-text article for in-depth reading.

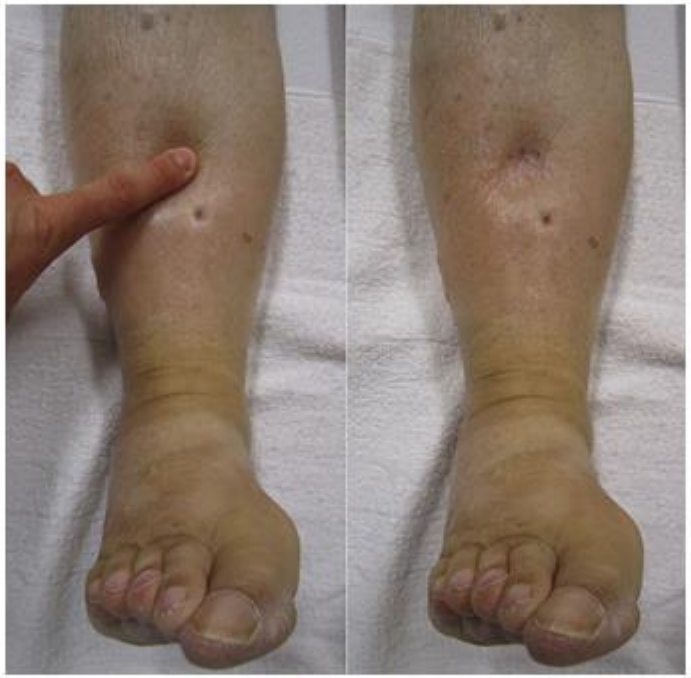
Image references usually link to a whole page of images. The images themselves may be useful, but care must be taken to ensure that they relate to the topic of the text. Images are most valuable as a gateway to publications related to the topic. Clicking on the image will take you to the publication. However, to get the full publication it sometimes may be necessary to copy the url and transfer it to your browser.

- **Reference notations: when references are listed, the following suffixes indicate:**
- **pm = PubMed**
- **w = Wikipedia**
- **i = Images (usually Google images)**
- **rg = ResearchGate**
- **yt = YouTube**
- **sd = Science direct**
- **ow = Other website**
- **Selected text = PubMed, Wikipedia, or images**

What are the main consequences of haemodynamic disorders?

- Edema
- Haemorrhage
- Thrombosis

Edema



Pitting edema of the lower limbs.
(courtesy James Heilman, MD)

What is edema?

- **Edema is the swelling caused by vascular fluid extravasating into extracellular spaces or failing to drain normally through the lymphatic system.**
- **It may be localized (as seen with lymphatic obstruction) or generalized (as seen in nephrotic syndrome).**
- **Manifestations range from uncomfortable swelling (lower limb edema) to life-threatening (pulmonary edema).**

What are the most common causes of edema?

- **Increased hydrostatic pressure – produces protein-poor (specific gravity <1.012) transudate from the arteriolar ends of capillaries. Caused by impaired venous return (congestive heart failure, ascites, venous obstruction/compression, constrictive pericarditis) or arteriolar dilation (heat, neurohumoural dysregulation – e.g., the activation of the renin-angiotensin-aldosterone system (1w, 2i) and subsequent retention of sodium and water, increasing volume without increasing plasma protein).**
- **Decreased plasma osmotic pressure – plasma protein loss; reduced osmotic pressure leads to diminished reabsorption of interstitial fluid at the arteriolar end of the capillary. Caused by nephrotic syndrome (1w,), malnutrition (1w), protein-losing gastroenteropathy.**

What are other causes of edema?

- **Lymphatic obstruction – inflammatory, neoplastic, post-surgical, post-irradiation, parasitic. The removal of axillary lymph nodes to treat metastatic breast cancer may cause lymphedema of the arm. Filariasis is a parasitic infection in which the filaria worm invades the lymphatics, usually of the lower extremities, and causes extreme swelling and skin thickening (elephantiasis [1w, 2i).**
- **Sodium retention**
- **Inflammation**

What are the clinical manifestations of edema?

- **Subcutaneous edema – swelling of lower limbs when upright, over sacrum when recumbent (dependent) or in areas of loose connective tissue when more generalized (suggested by periorbital edema). Pitting may be observed with pressure. Characteristic of congestive heart failure and nephrotic syndrome.**
- **Pulmonary edema (1w) Causes: O2 transfer impaired by fluid in alveoli; associated with left ventricular failure, adult respiratory distress syndrome, renal failure, hypersensitivity reactions.**
- **Brain edema – either localized to site of lesion or generalized with swelling, flattening against the skull, and increased intracranial pressure. Foramen magnum herniation and vascular compression are potentially deadly.**

What are hyperemia and congestion?

- **Hyperemia (flushing) is the localized increase of blood volume due to arteriolar dilation (exercise, inflammation, irritation). The tissue is reddened.**
- **Congestion is the localized increase of blood volume due to impaired venous return. The tissue is bluish-red due to the buildup of deoxygenated hemoglobin (cyanosis).**
- **Capillary bed congestion is usually associated with edema. When congestion is ongoing, it leads to chronic hypoxia, ischaemic tissue destruction, and ultimately fibrosis.**

Bleeding and Coagulation

What are the disorders of bleeding and coagulation?

- Haemorrhage
- Coagulation factor deficiencies
- Disseminated intravascular coagulation
- Thrombocytosis and thrombocytopenia
- Thrombosis

What is haemorrhage?

- Haemorrhage is the loss of blood from vessels to extravascular space (external, bodily cavities, or into skin and tissue). It is classified as follows:
- Class I haemorrhage: loss of <15% blood volume. Little to no physiological effect.
- Class II: loss of 15-30% blood volume. Tachycardia; constriction of capillaries in skin (pale, cold); systolic/diastolic pressure gap reduced.
- Class III: loss of 30-40% blood volume. Increased tachycardia; decreased BP; peripheral hypoperfusion, mental changes.
- Class IV: loss of >40% blood volume. Death follows if aggressive resuscitation is not performed.

What are the types of haemorrhage?

- Petechiae (1w, 2i) – small haemorrhages into skin, mucosa, serosa. 1-2 mm diameter. Usually the result of platelet or clotting factor deficiencies or raised vascular pressure; also a symptom of certain diseases (fulminant meningococciemia) (1w, 2i).
- Purpurae (1w, 2i) – 3-5 mm; same causes as petechiae, plus trauma, vasculitis, vessel wall fragility.
- Ecchymoses (1w, 2i) – 1-2 cm, subcutaneous haematomas.
- Large volumes of blood in body cavities: haemopericardium (1w, 2i), , haemothorax ((1w, 2i), haemoperitoneum (1w, 2i), haemarthrosis (1w, 2i).

Normal Haemostasis

What are the steps in normal haemostasis?

- Vascular constriction (vasospasm)
- Formation of platelet plug (primary haemostasis)
- Fibrin consolidation of platelet plug (secondary haemostasis)
- Thrombus stabilization and resorption

What factors contribute to vascular spasm with trauma to vasculature?

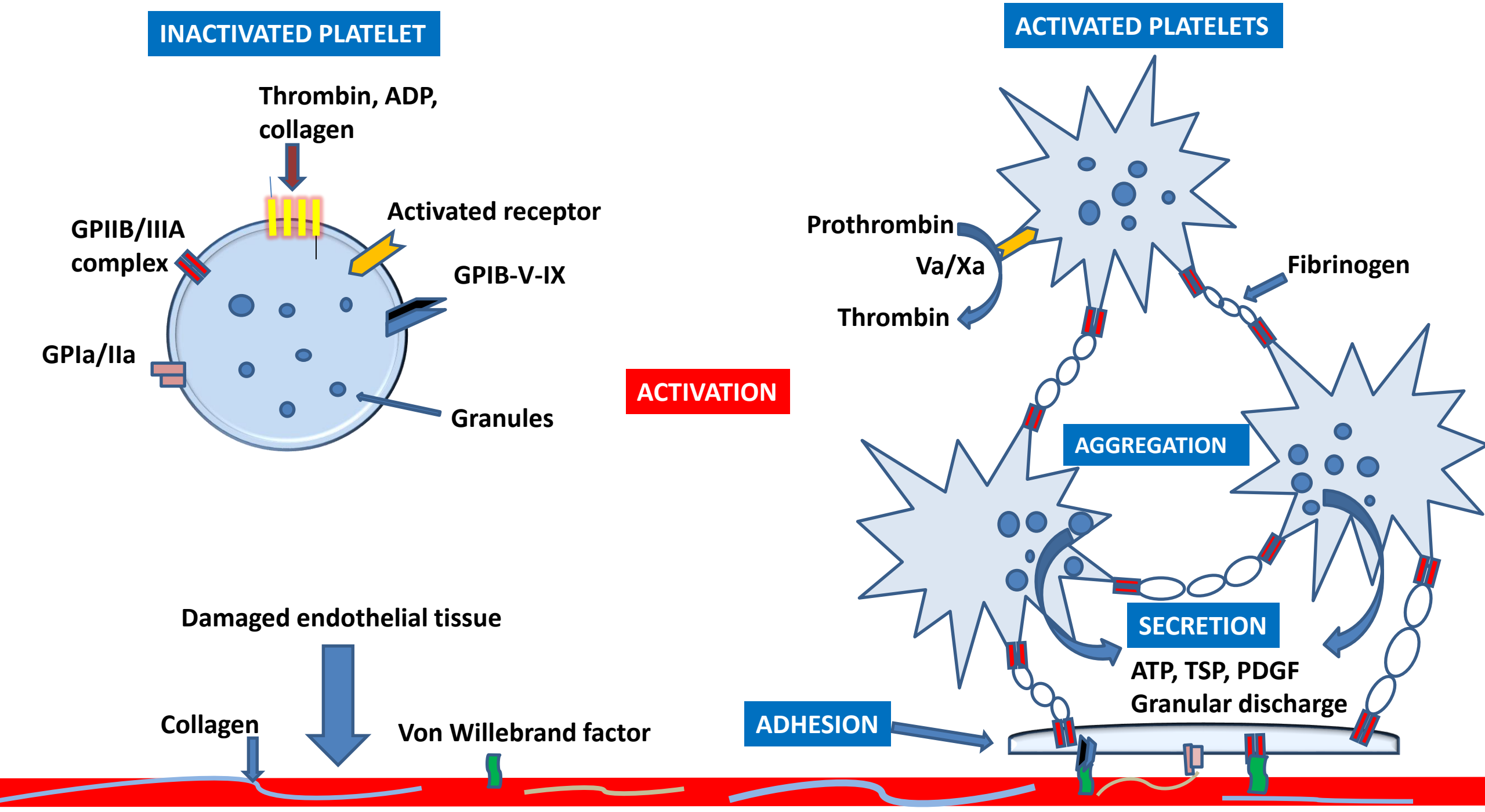
- Activation of nervous system reflexes that constrict vascular smooth muscle cells.
- Release of endothelial and platelet vasoconstrictors.

What are platelets?

- Platelets (1w, 2i) are small unnucleated fragments of cytoplasm produced from bone marrow megakaryocytes (1w, 2i).
- When vessel endothelium is damaged, platelets become activated and form a plug.
- They do this by *adhesion* (1w, 2i), *activation* (1w, 2i) (shape changes from lenslike discoid to an dendritic form; receptors are activated and chemical messengers secreted), and *aggregation* (receptor bridging together) (1w, 2i).

What are the steps in primary haemostasis (formation of platelet plug)?

- Platelet adhesion at the site of vascular trauma
- Platelet activation
- Platelet aggregation to form a platelet plug


INACTIVATED PLATELET
Thrombin, ADP, collagen
Activated receptor
GPIIB/IIIA complex
GPIB-V-IX
GPIa/IIa
Granules
ACTIVATION
ACTIVATED PLATELETS
Prothrombin
Va/Xa
Thrombin
Fibrinogen
AGGREGATION
SECRETION
ATP, TSP, PDGF
Granular discharge
ADHESION
Damaged endothelial tissue
Collagen
Von Willebrand factor

What conditions can impair platelet activation?

- Von Willebrand's disease – a cluster of diseases in which either the quantity or the function of von Willebrand's factor (vWF) is compromised.
  - Von Willebrand factor carries (inactive) factor VIII in the bloodstream; thrombin releases factor VIII for activation.
  - vWF is required for platelet adhesion to wound sites, and links platelets to collagen fibrils.
- Thrombotic thrombocytopenic purpura (TPP) and haemolytic uremic syndrome (HUS) are both caused by a defect in metalloprotease ADAMTS13, which normally breaks down vWF large monomers. Fibrin and platelets are deposited in small vessels, leading to ischaemic necrosis. TTP chiefly affects the brain; HUS affects the kidneys.

What medications inhibit platelet activation and aggregation?

- COX inhibitors (1w, 2i)– such as aspirin
- ADP receptor inhibitors – clopidogrel, ticragrelor, prasugrel, ticlodipine. Prevent activation of IIb/IIIa complex.
- Glycoprotein IIb/IIIa receptor inhibitors (IV only) – abciximab, tirofiban, eptifibatide. Block fibrinogen and vWF receptors on platelets.
- Adenosine reuptake inhibitor – dipyramidole.
- Thromboxane inhibitors—aspirin, ifetroban, naproxen

What is thrombocytopenia?

- Thrombocytopenia (1w, 2i)
  - Platelet count = <150,000 platelets/microliter of blood)

-- Emergency treatment levels are <50,000 platelets/microliter.

What are causes of thrombocytopenia?

Mechanisms and causes of thrombocytopenia are:

- **Reduced production –** Vitamin B9 (folate) and/or B12 deficiency, bone marrow cancer, sepsis, chronic liver disease (CLD) (decreased thrombopoetin production), hereditary causes.
- **Increased destruction (in spleen)–** auto-immune, viral (and other infections) or CLD.
- **Iatrogenic –** a number of medications can cause thrombocytopenia. These include methotrexate, sodium valproate, carboplatin, interferon, isotretinoin, and proton-pump or H2 inhibitors. Heparin (both unfractionated and low molecular weight) notoriously can produce heparin-induced thrombocytopenia (HIT).
- **Miscellaneous –** snakebite, lab error, niacin toxicity.

What are the consequences of deficient platelets (thrombocytopenia)?

- Often asymptomatic or presenting only as malaise.
- Petechiae (1w), purpurae(1w), and ecchymoses (1w) may appear spontaneously.
- Prolonged bleeding may be observed.
- Besides bleeding into the skin, other examples of bleeding include prolonged bleeding from cuts, gums, nose, as well as hematuria, melena, and menorrhagia

What is thrombocytosis?

- **Thrombocytosis is a platelet count of >450,000 platelets/microliter of blood).**

What are the causes and consequences of thrombocytosis?

- Often thrombocytosis is asymptomatic and requires no treatment.
- The most common type (85-97% in adults, 100% in children) is ***reactive thrombocytosis***, in reaction to infections, trauma, and malignancy.
- ***Clonal thrombocytosis*** is the result of myeloproliferative disease: chronic myelogenous leukaemia, polycythaemia vera, essential thrombocythaemia, primary myelofibrosis.

What are the steps in secondary haemostasis (fibrin consolidation of platelet plug)?

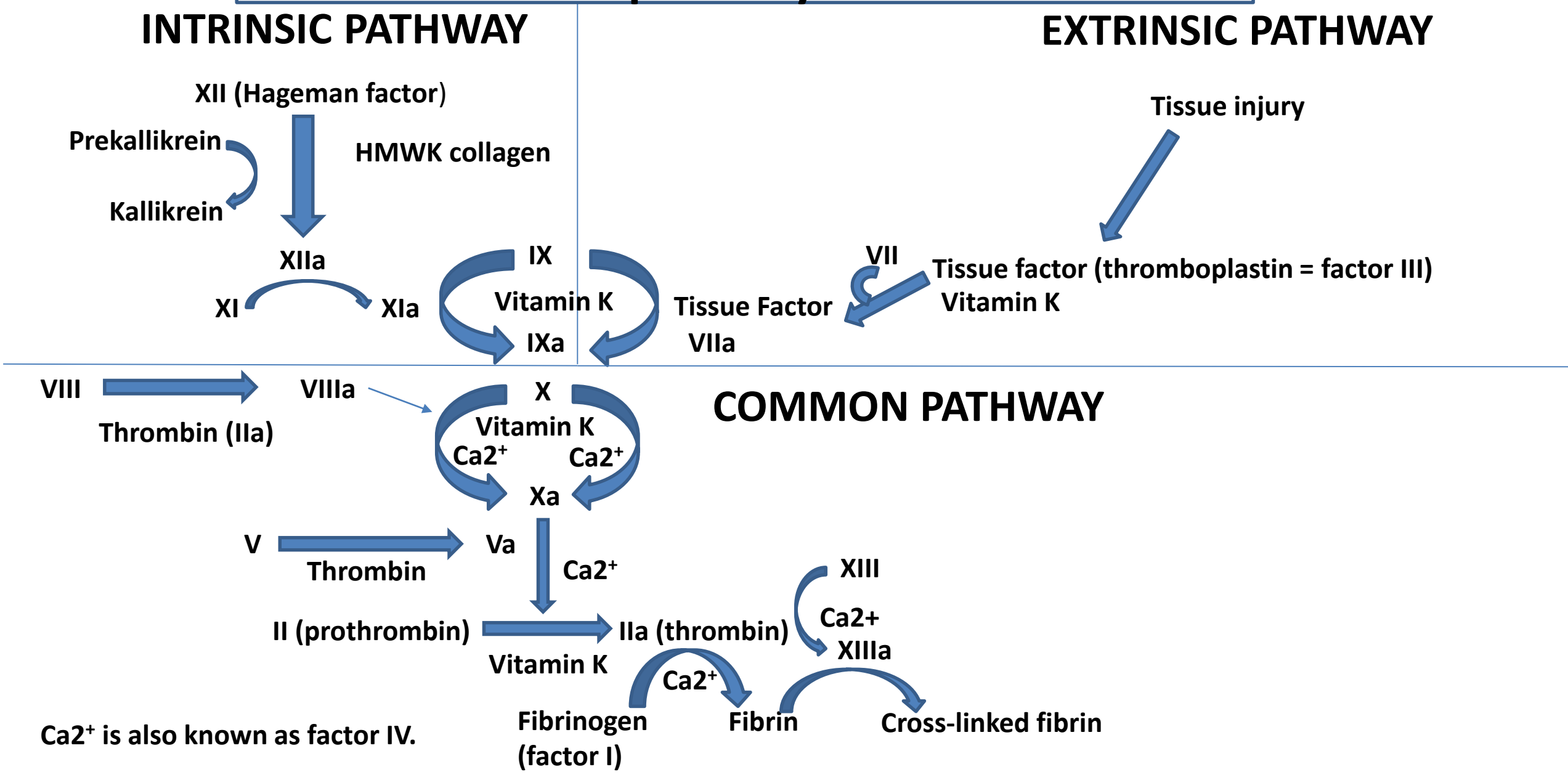
- Generation of fibrin by proteolytic coagulation cascade
- Deposition of insoluble fibrin on platelet plug
- Formation of fibrin mesh to strengthen and stabilize the blood clot

Coagulation Cascade to Form Fibrin

What is the coagulation cascade?

- The coagulation cascade (1w, 2i, 3yt) is a series of enzyme reactions which lead to the production of thrombin.
- Thrombin converts fibrinogen to fibrin, which forms the secondary haemostatic plug by forming a mat of cross-linked fibres, binding the primary plug (formed from activated platelets/collagen fibres) firmly into place.
- Anticoagulant drugs all target elements of the coagulation cascade.

What are the steps of the coagulation pathways?



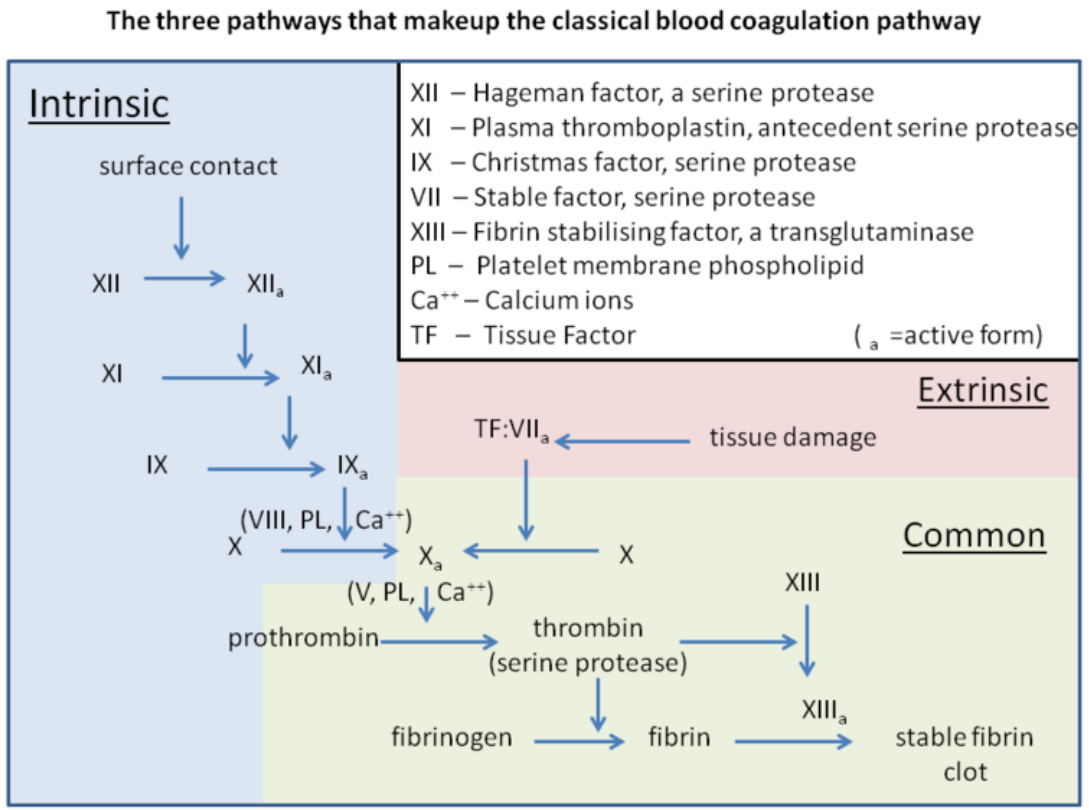
Ca^{2+} is also known as factor IV.

What are the three pathways of the coagulation cascade?

- Tissue factor pathway (extrinsic pathway)
- Contact activation pathway (intrinsic pathway)
- Final common pathway

What is the extrinsic pathway?

- Activated by tissue injury.
- Release of tissue factor (TF) (thromboplastin)
- Complex formation between TF and Factor VII
- Complex converts Factor X to Factor Xa, which initiates the common pathway.



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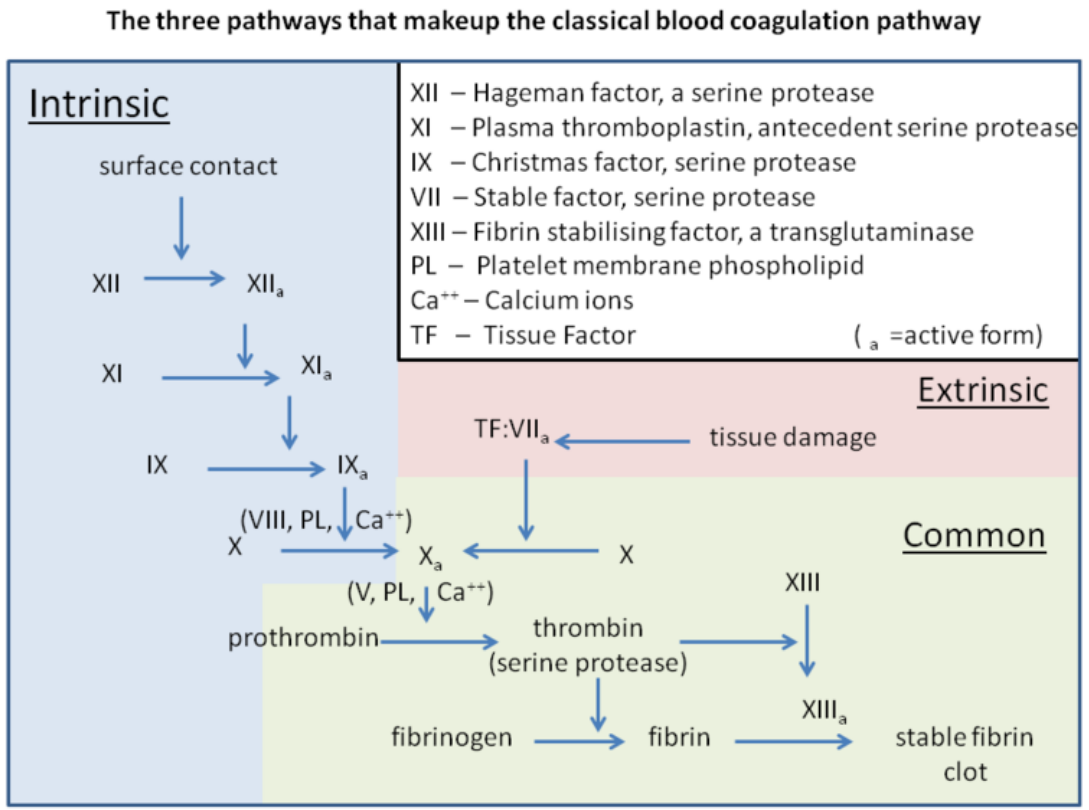
What is the intrinsic pathway?

- **Plasma proteins interact with glass surface or other poly anionic surface**
- **Activation in sequence Factors XII, XI, IX & VIII, and X.**
- **Initiates common pathway**



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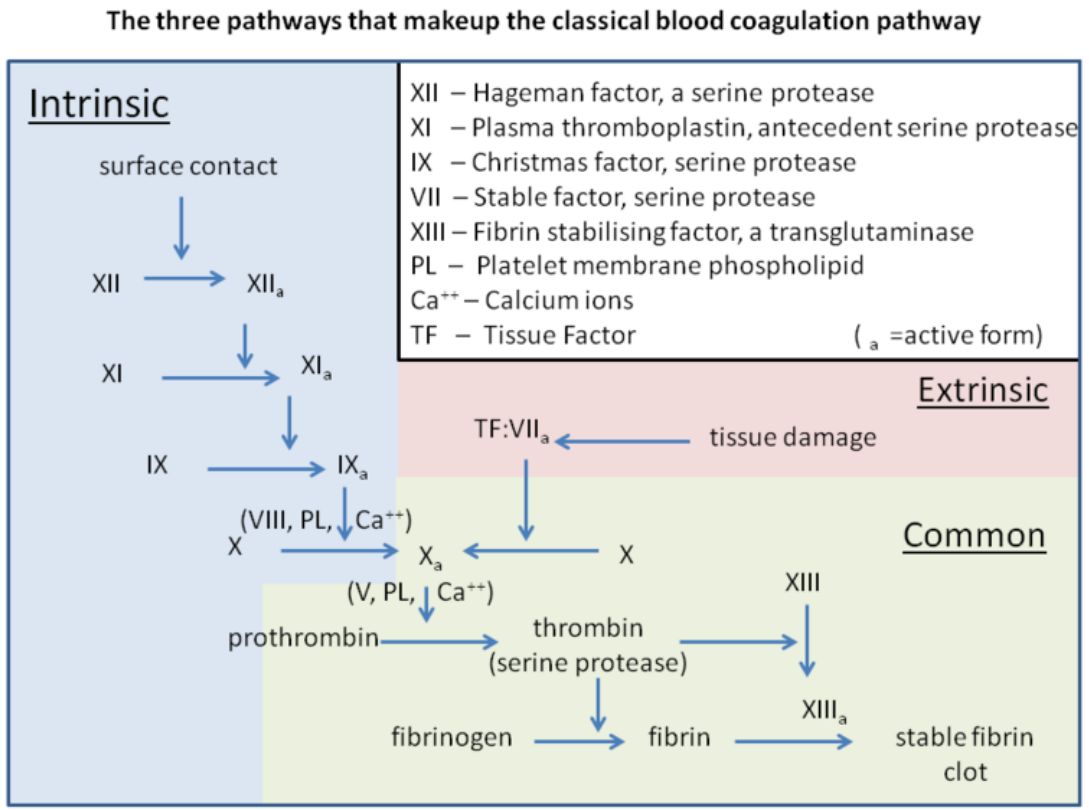
What is the common pathway?

- **Activated factor X plus activated Factor V convert prothrombin to thrombin.**
- **Thrombin converts fibrinogen to fibrin, which forms a cross-linked fibrin mesh**



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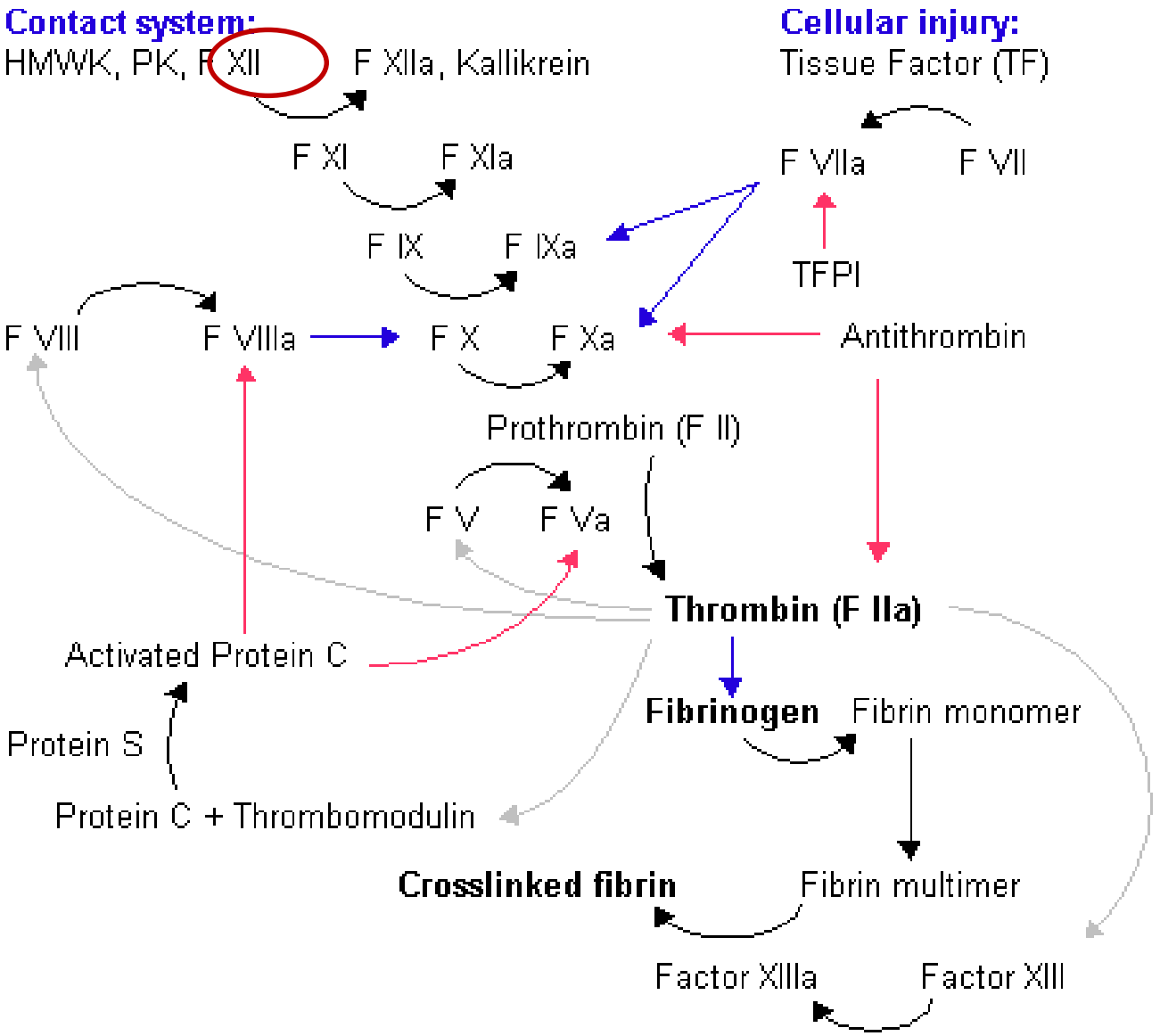
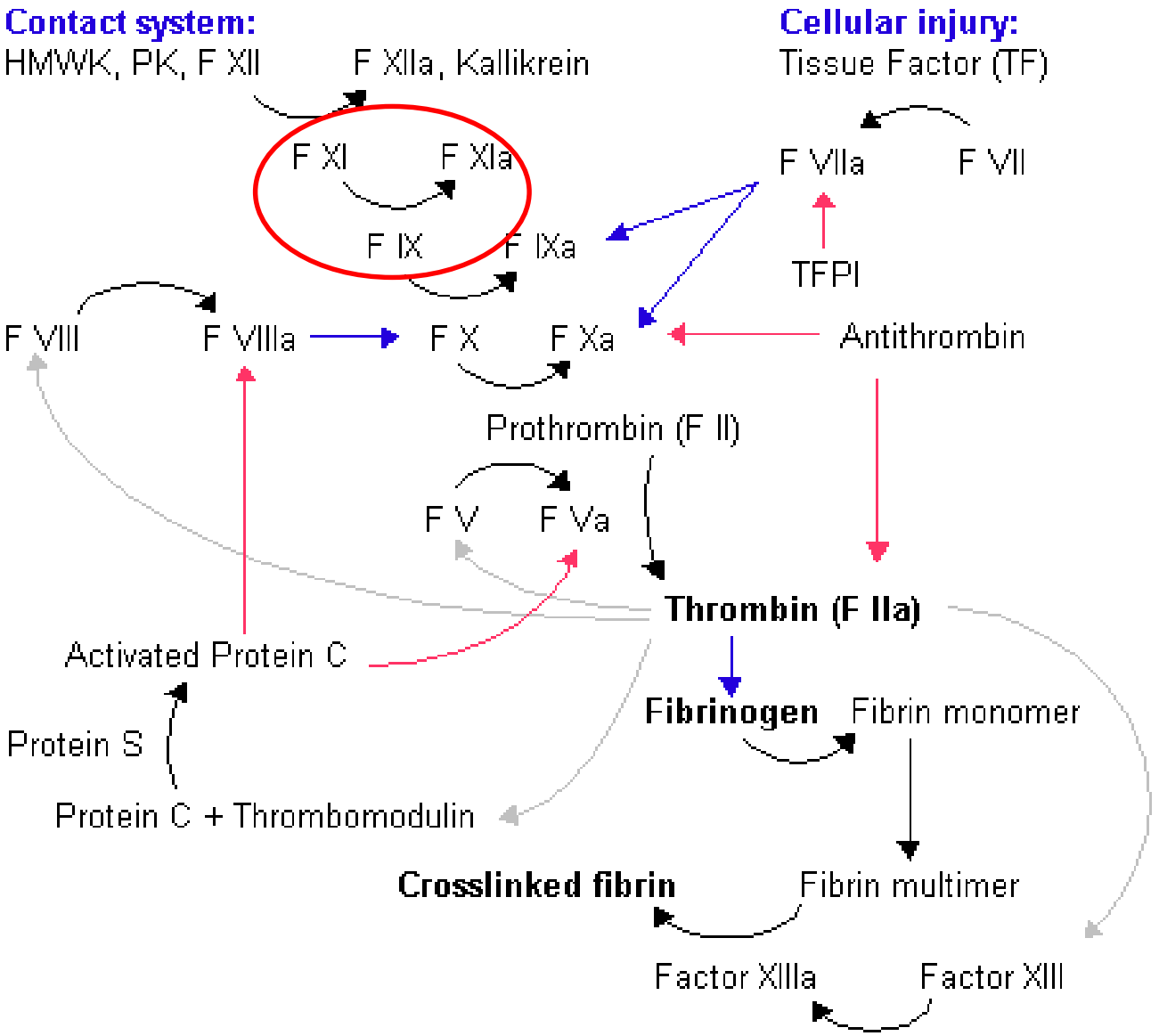
What is Factor XII?

- Hageman factor
- Starts intrinsic pathway
- F XII activated to F XIIa by negatively charged surfaces (ie., glass)
- F XII = zymogen of serine endopeptidase (F XIIa)
- F XIIa activates F XI and prekallikrein (PK) in vitro.
- Factor XII deficiency is a rare autosomal recessive condition (rarely causes bleeding)
- Excess F XII can predispose to venous thrombosis



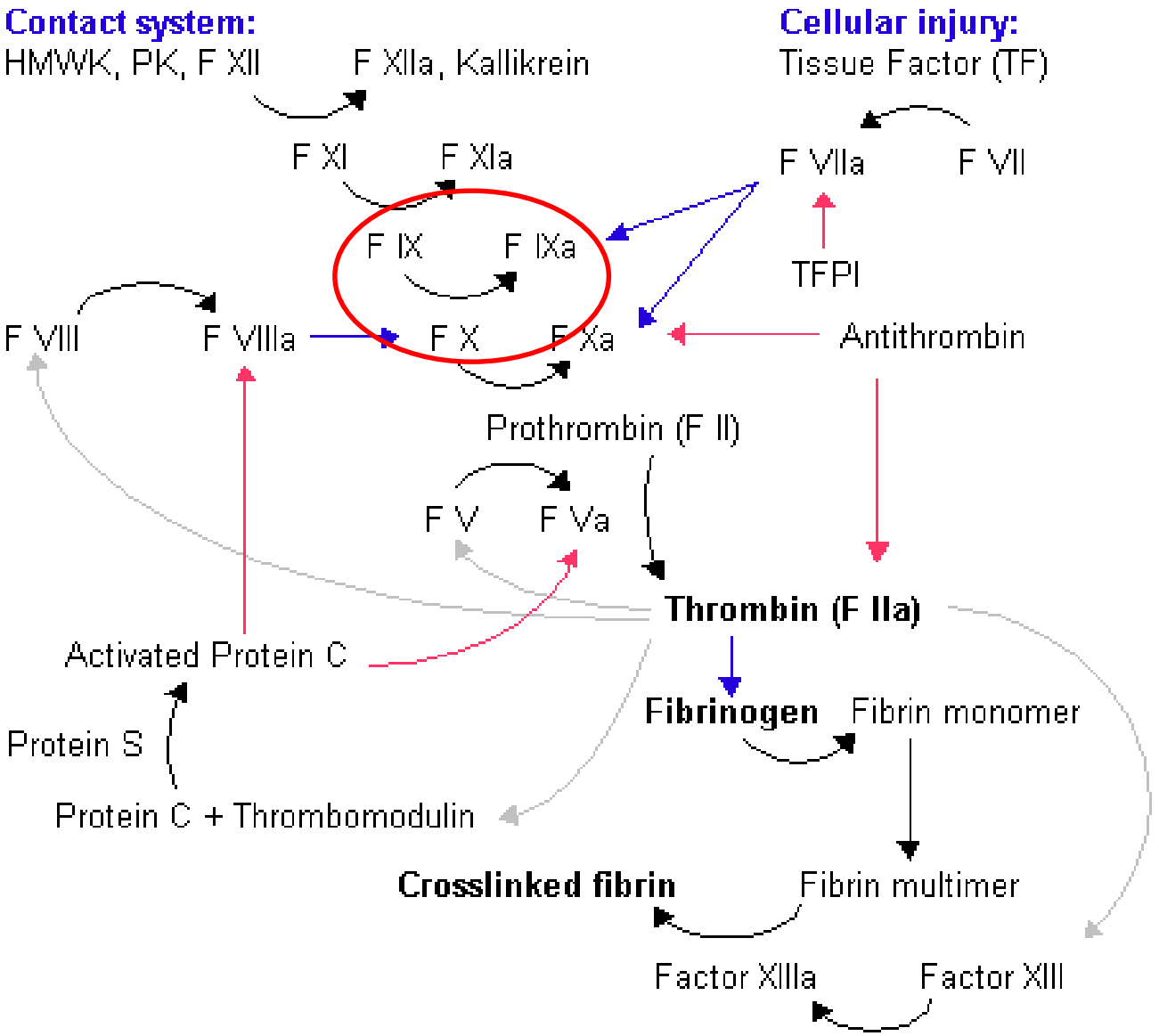
What is Factor XI?

- F XIa activates F IX
- Deficiency of Factor XI causes hemophilia C.
- An excess of F XI predisposes to thrombosis.



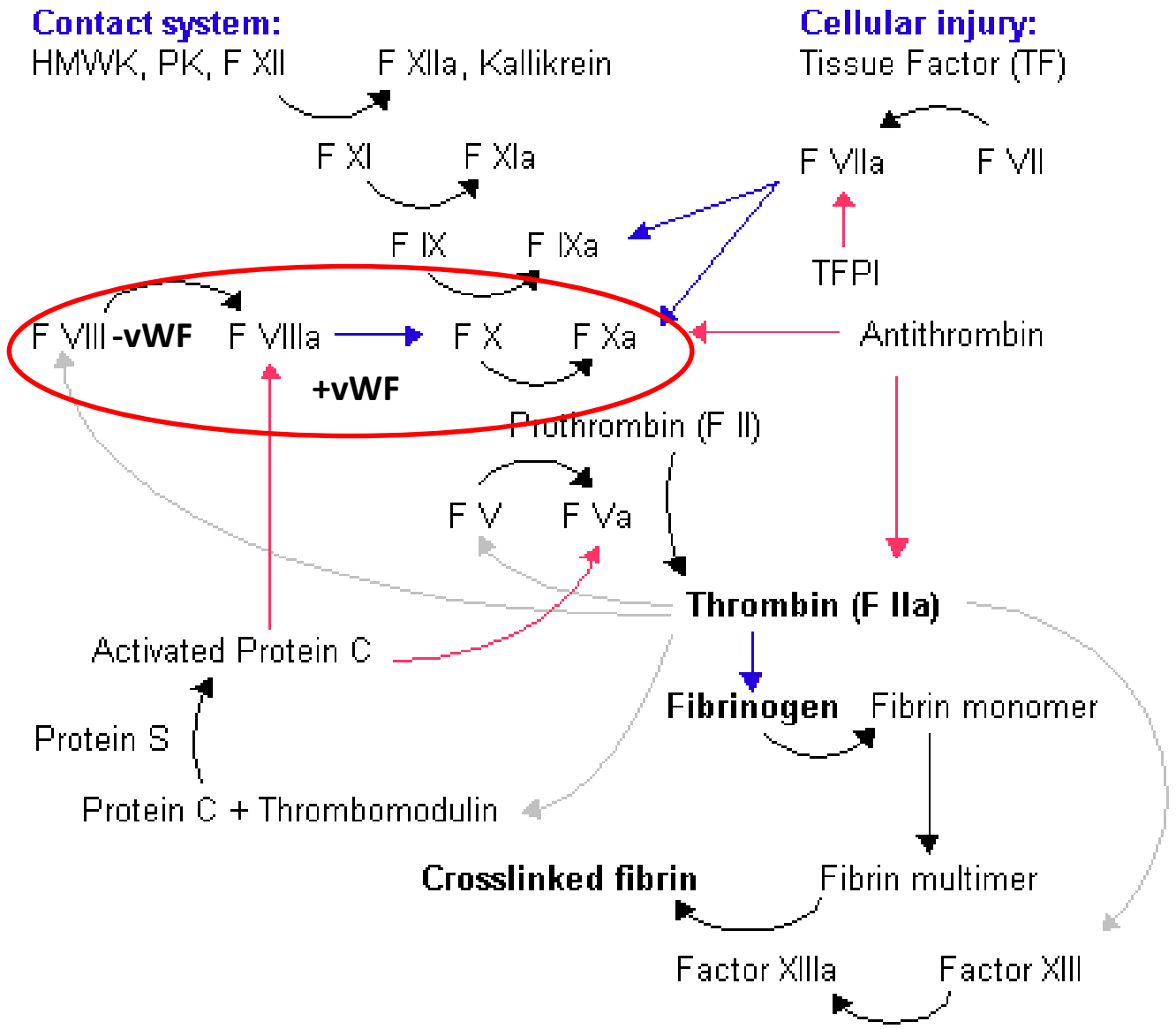
What is Factor IX?

- Christmas Factor
- In the presence of Ca^{2+}, membrane phospholipids, and F VIIIa, F IXa converts F X to F Xa
- Deficiency of F XI causes hemophilia B.
- F IXa is inhibited by anti-thrombin.
- Deficiency results in X-linked recessive disorder, which is more common in males than females.
- Rare mutations predispose to thrombosis.



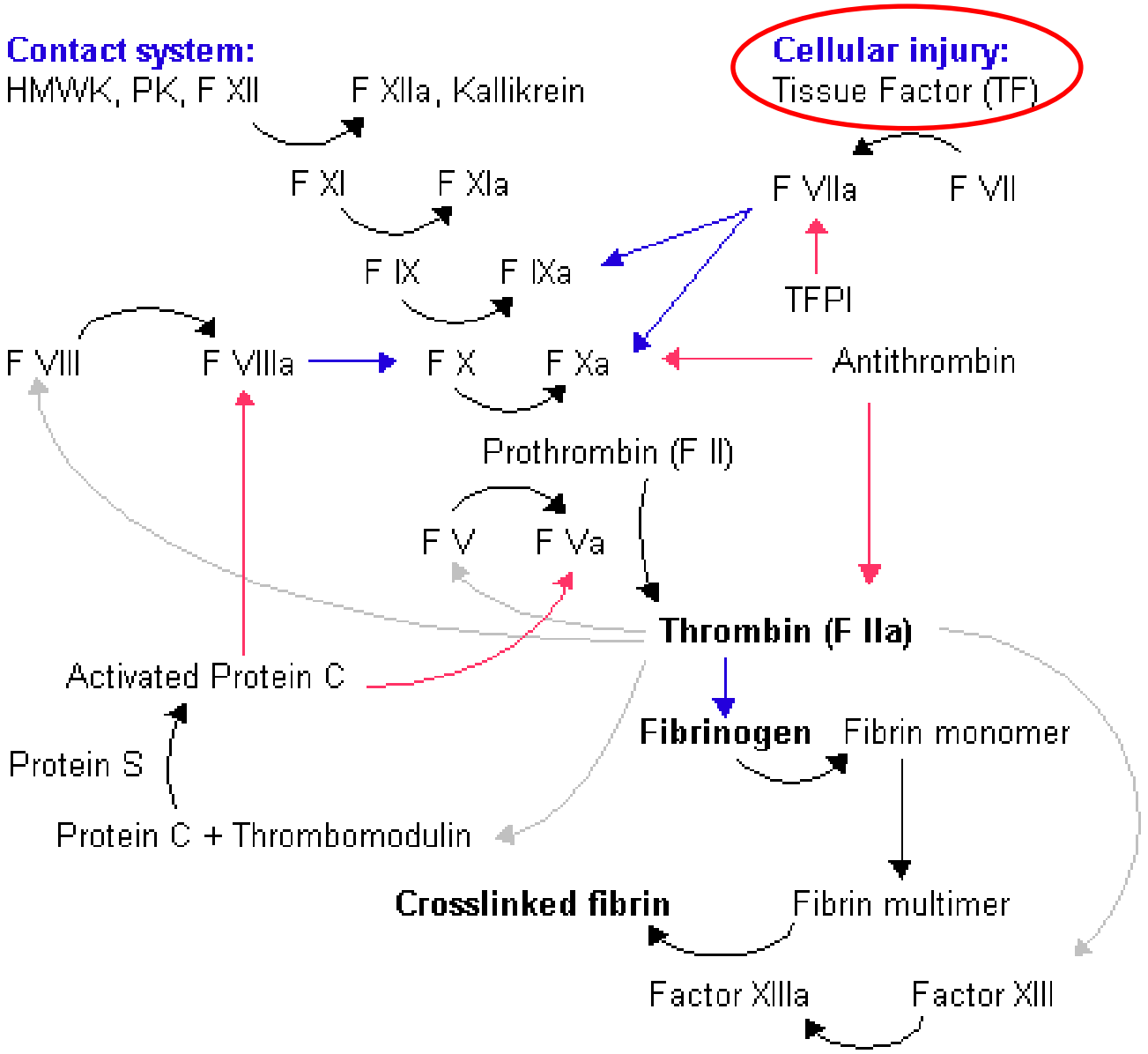
What is Factor VIII?

- Anti-hemophilic factor (AHF)
- Circulates bound to von Willebrand factor (vWF)
- Vessel injury activates F VIII and dissociates F VIIIa from von Willebrand factor.
- F VIIIa acts as a co-factor with F IXa to convert F X to F Xa.
- Deficiency of F VIII causes hemophilia A (X-linked recessive disorder)



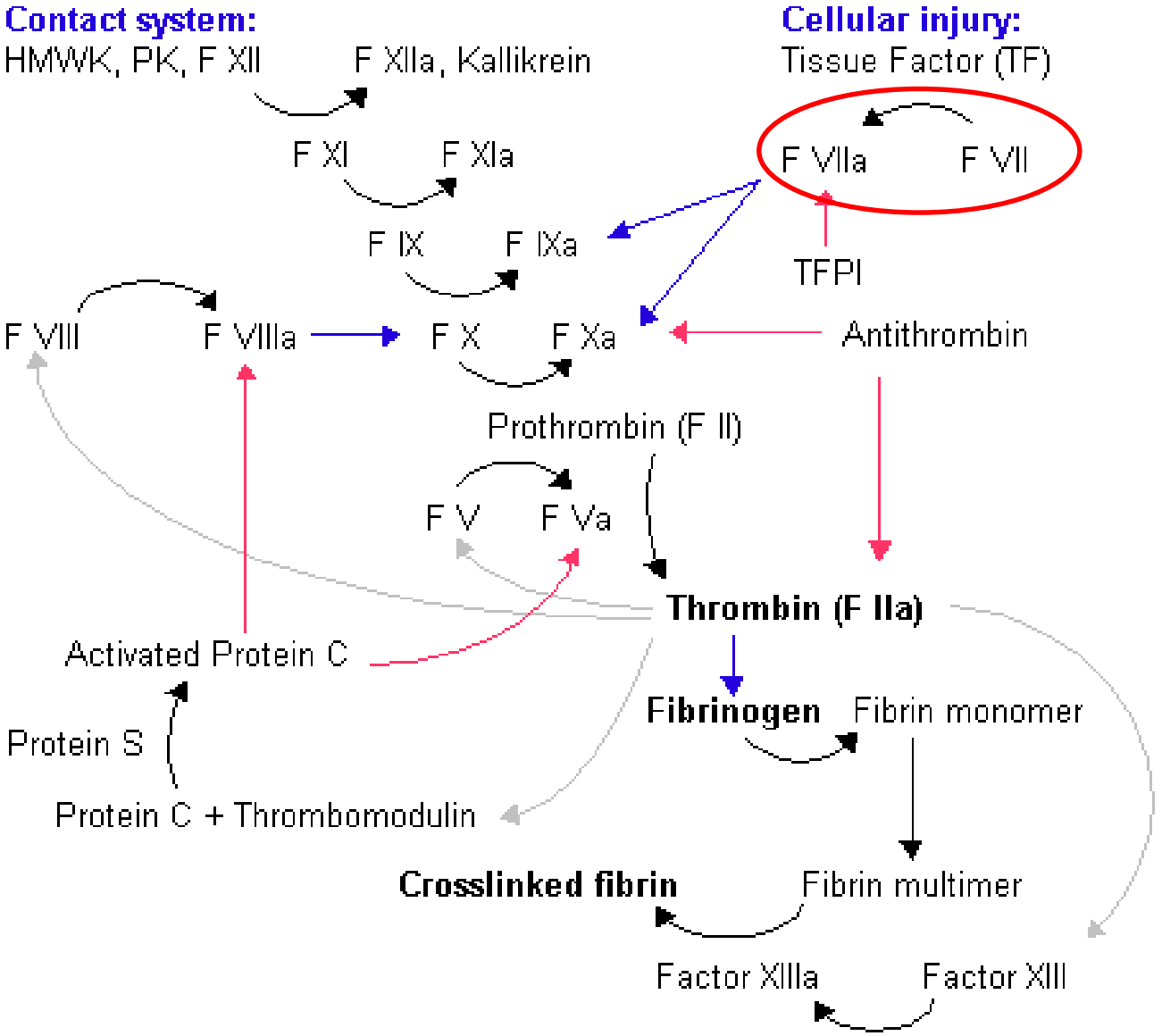
What is tissue factor?

- Also called: platelet tissue factor, factor III, CD 142.
- Located in subendothelial tissues and leukocytes.
- Initiates extrinsic pathway of coagulation.
- Converts F VII to F VVIa



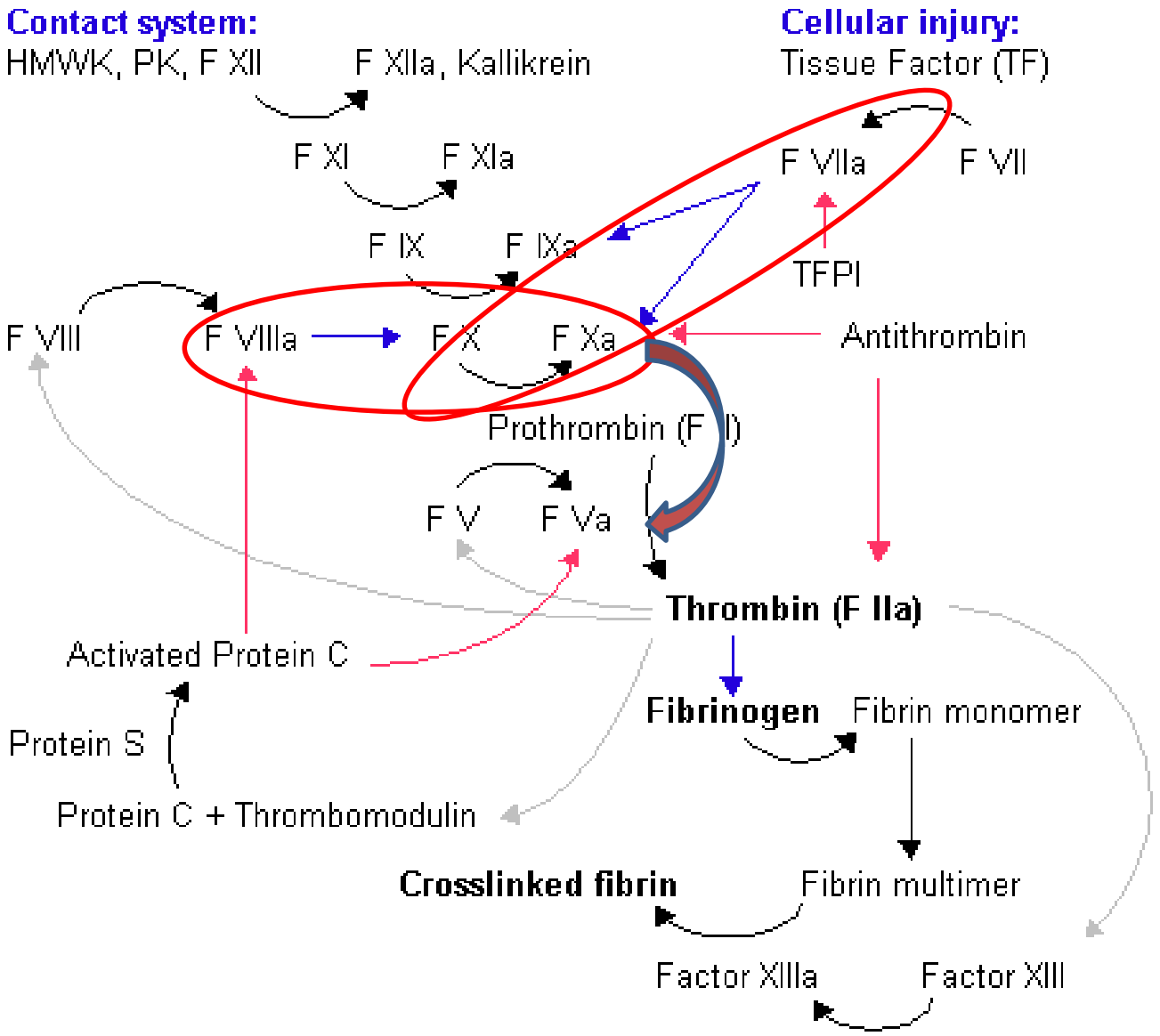
What is Factor VII?

- **Located outside blood vessels.**
- **Binds to tissue factor (TF) upon blood vessel injury.**
- **Activated to F VIIa by different coagulation factor proteases.**
- **F VIIa-TF complex converts F IX and F X to activated forms.**



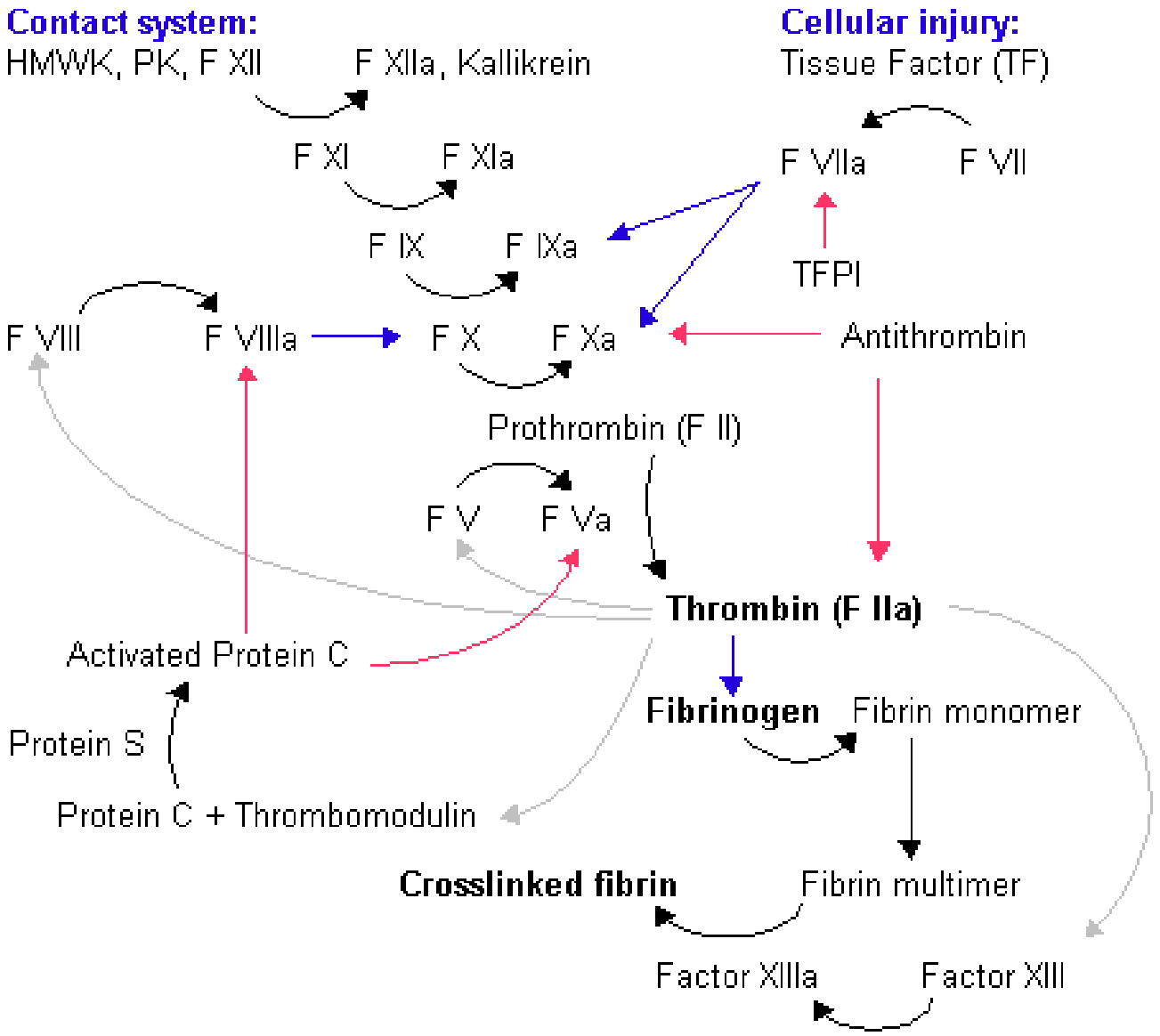
What is Factor X?

- Stuart–Prower factor
- Made in liver
- Requires Vitamin K for synthesis
- Activated by F XI-F VIII complex
- Also, F X is activated by F VII-TF complex
- F Xa converts prothrombin to thrombin
- F X deficiency causes bleeding but is extremely rare.
- F X inhibitors are widely used anticoagulants



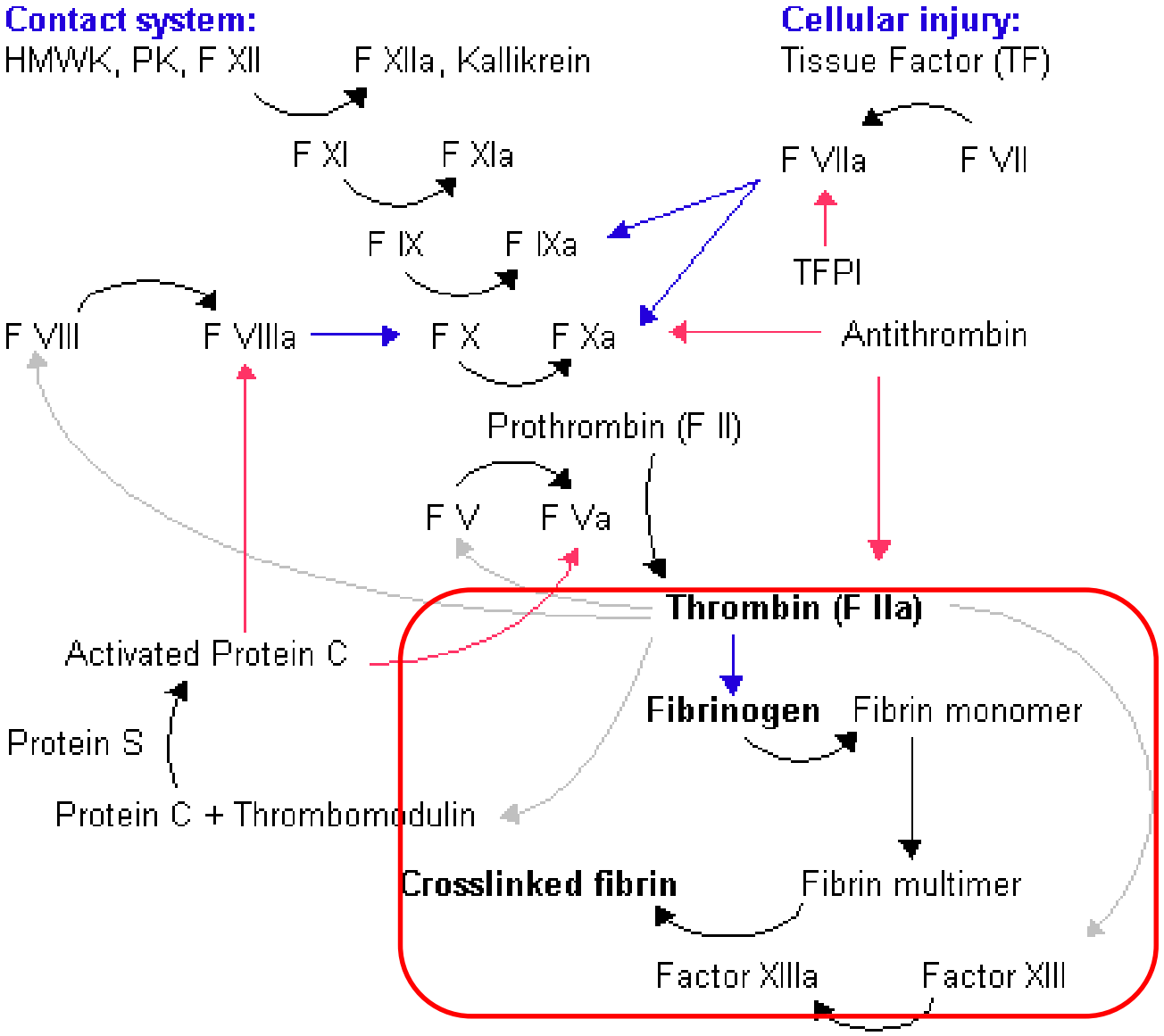
What is thrombin?

- Serine protease
- Formed by cleavage of prothrombin
- Prothrombin activated by F Xa--F Va complex.
- Prothrombin made in liver by vitamin K -dependent reaction
- Thrombin converts fibrinogen into fibrin



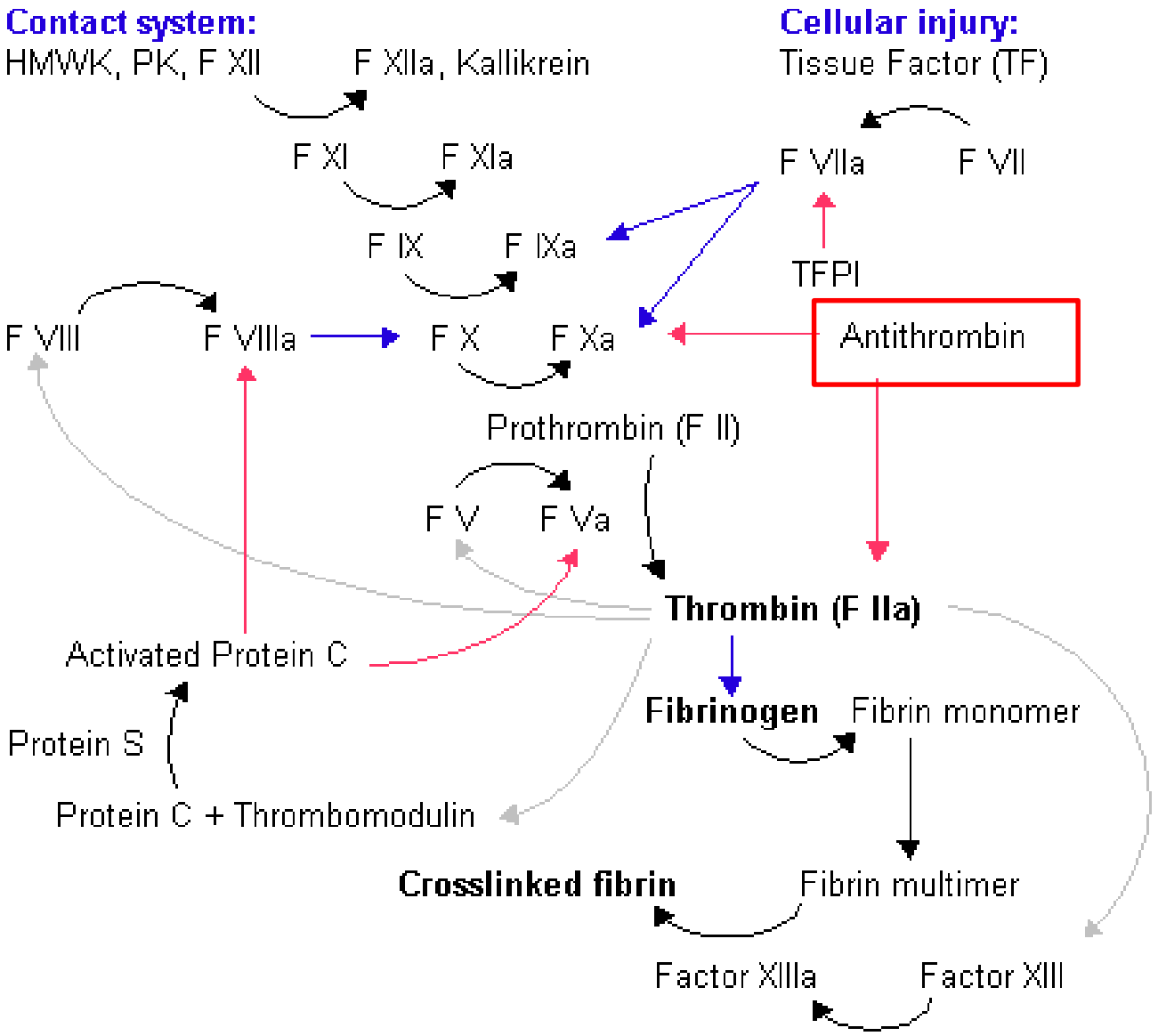
What is fibrin?

- Fibrin = F Ia
- Fibrin = fibrous, non-globular protein
- Fibrin produced by actions of thrombin on fibrinogen
- Forms of fibrin: monomer → multimer → cross-lined fibrin
- Polymerized (cross-linked) fibrin bound to platelets to form hemostatic plug
- Factor XIII cross-links fibrin to complete the clot.
- Liver makes fibrinogen



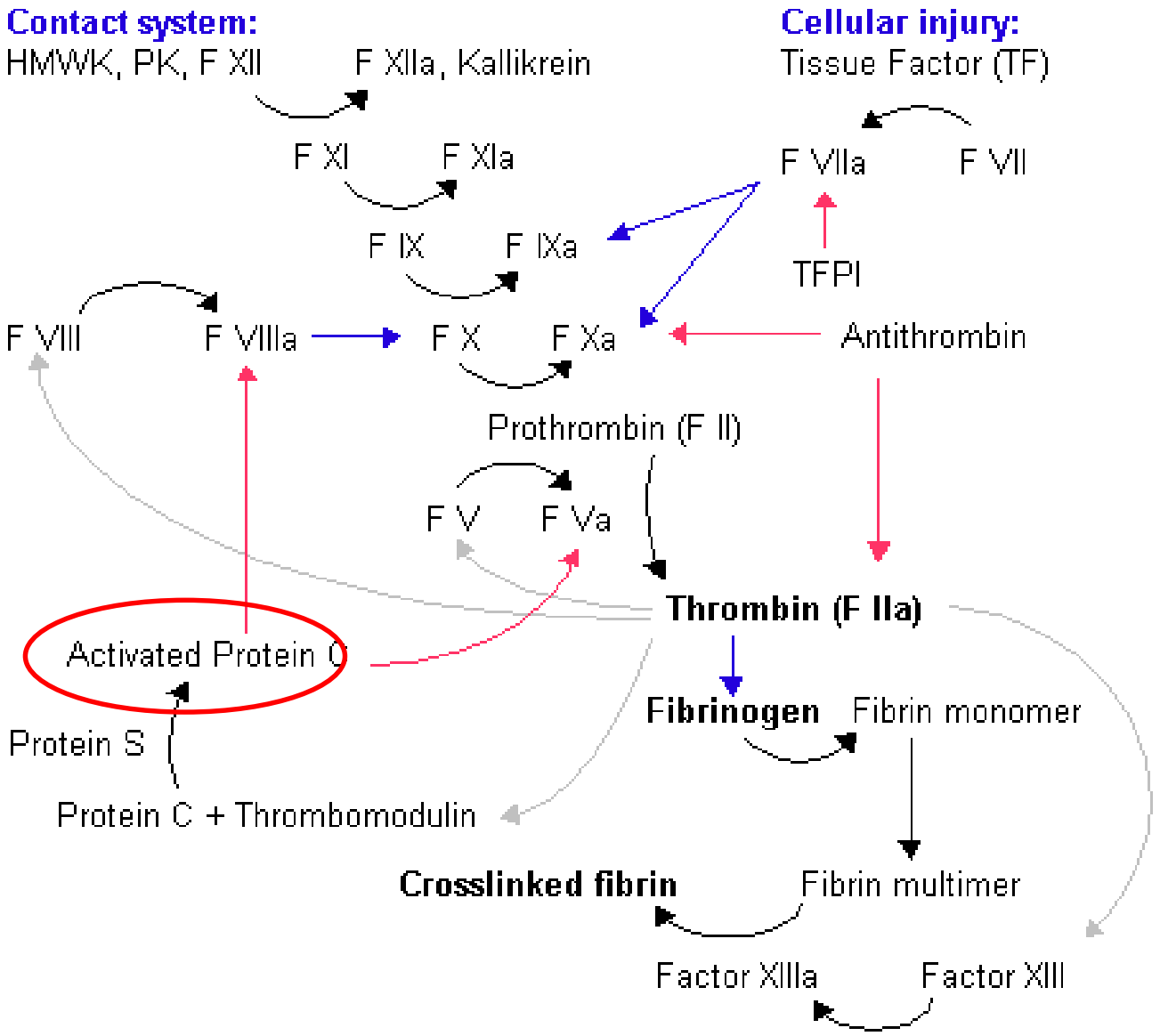
What is antithrombin?

- Also called Antithrombin III (AT III).
- Small protein that inactivates several coagulation enzymes.
- Inhibits F IIa (thrombin) and F Xa.
- Antithrombin action enhanced by heparin.
- Antithrombin is a serpin (serine protease inhibitor).



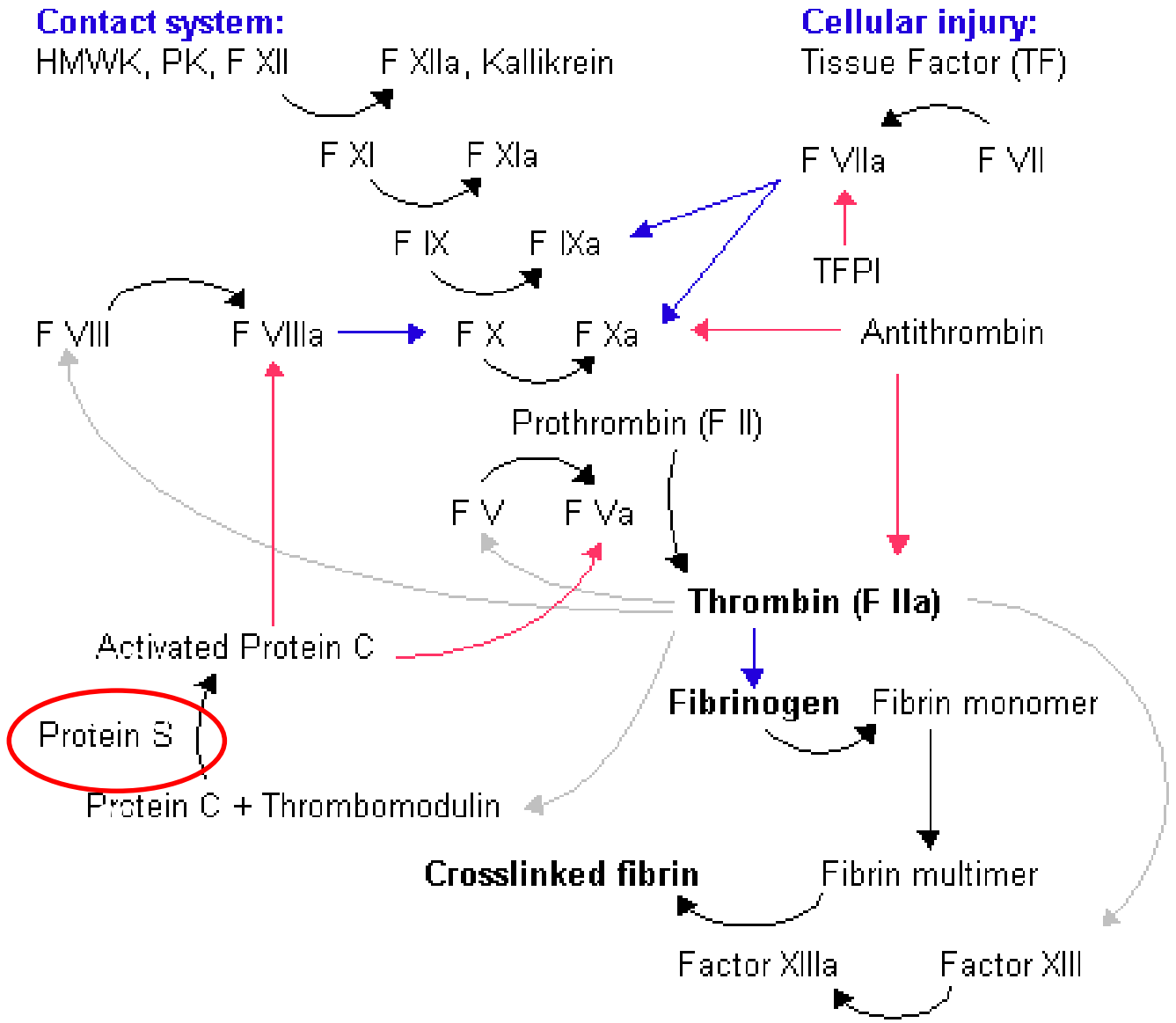
What is Protein C?

- **Also known as autoprothrombin IIA and blood coagulation factor XIV.**
- **Activated protein C inactivates F Va and F VIIIa.**
- **Protein C acts as an anticoagulant, and deficiency promotes venous thrombosis.**



What is Protein S?

- **Acts as a cofactor to Protein C in inactivation of F Va and F VIIIa.**
- **Protein S deficiency promotes venous thrombosis.**



What is thrombomodulin?

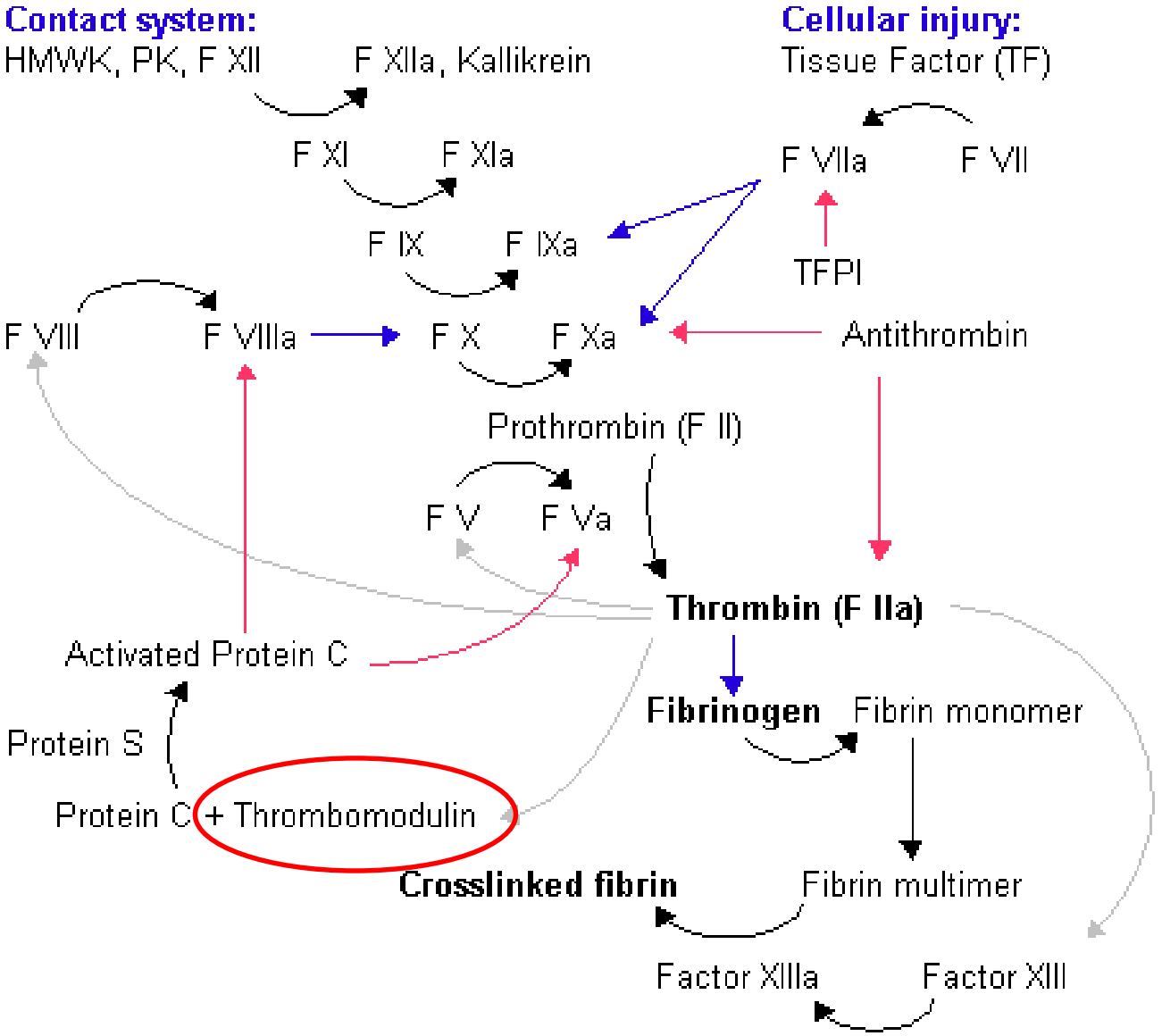
Thrombomodulin –

Present in endothelial cell linings.

Activated by the presence of thrombin.

Binds thrombin to increase Protein C activation x1000

Activates thrombin-activated fibrinolysis inhibitor by cleavage.



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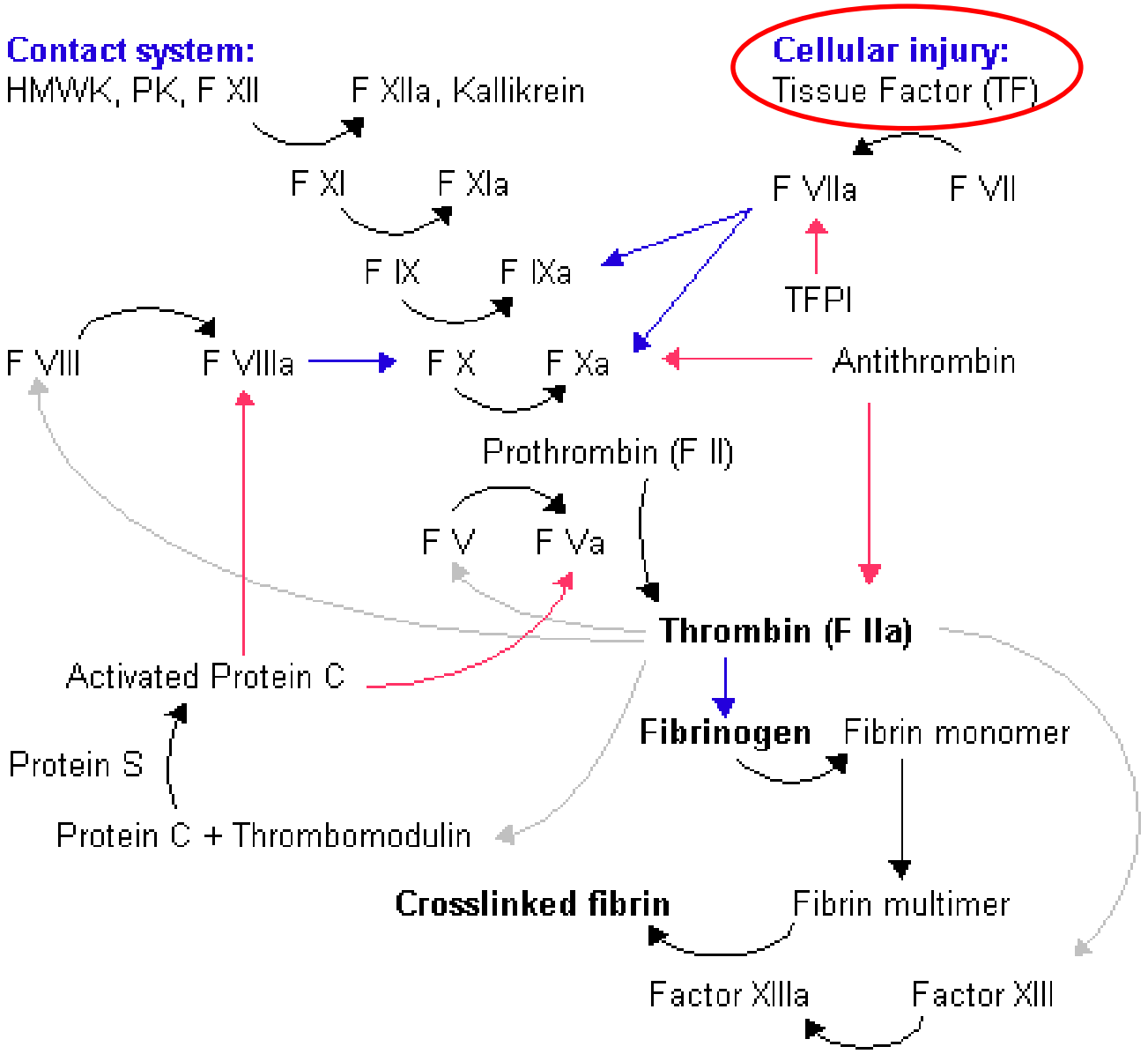

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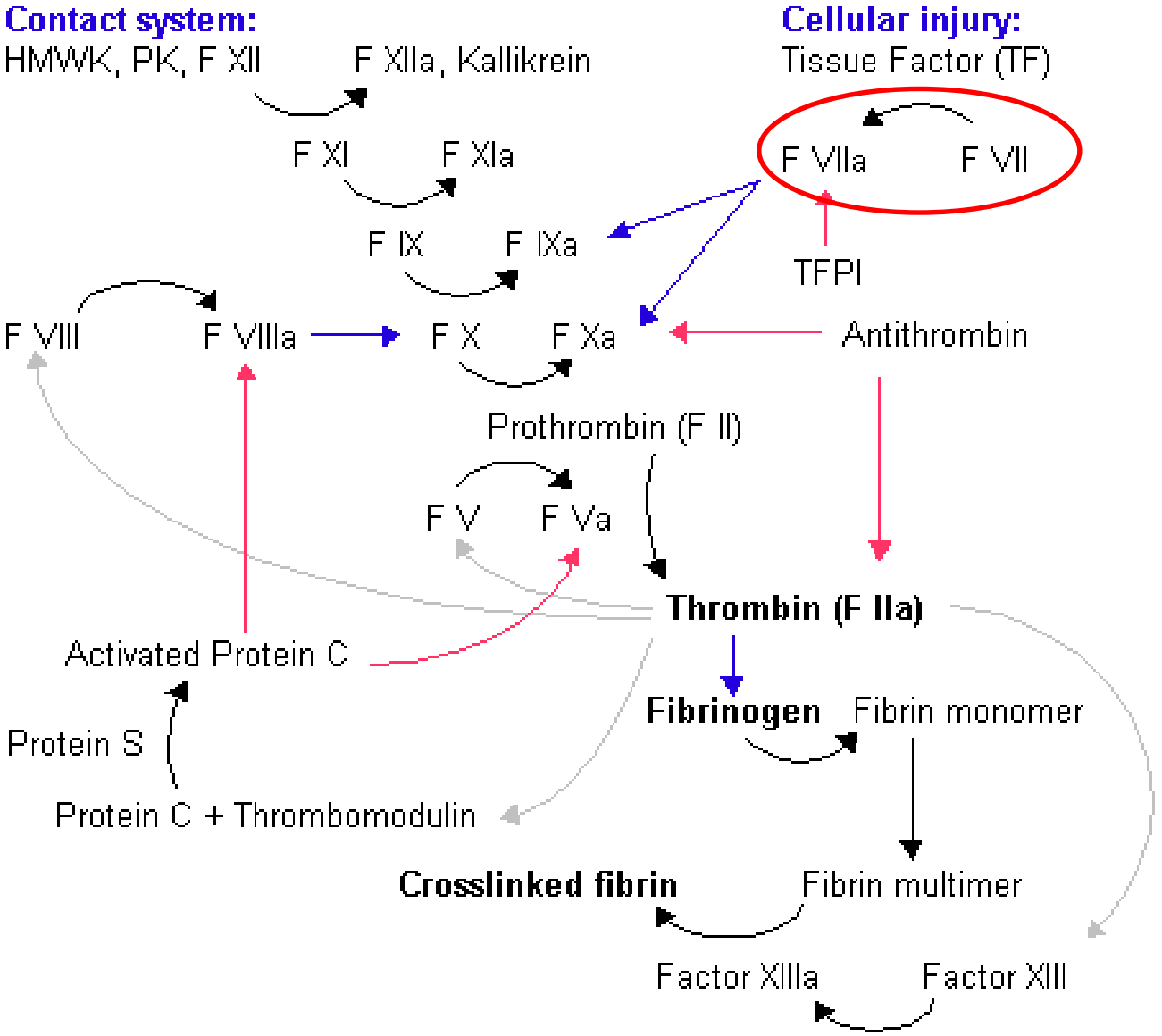


BLEEDING DISORDERS

What are diseases of the clotting process?

- Factor deficiencies: XII (von Hageman), XI (haemophilia C), X, IX (haemophilia A), VIII (hemophilia B), V (para-haemophilia).
- Von Willebrand disease (deficient quantity or function of vWF).
- Autoimmune diseases: antibodies to coagulation factors, usually factor VIII.
- Acquired: infectious haemorrhagic diseases, anti-coagulant treatment, vitamin K deficiency, liver failure, haemorrhagic snake venom.
- Genetic: Bernard-Soulier syndrome (defect in GPIb, part of the vWF receptor); Glanzmann's thrombasthenia (defective/reduced GPIIb/IIIa); Wiskott-Aldrich syndrome (thrombocytopenia, eczema, immunodeficiency, bloody diarrhoea.

What is haemophilia C?

- Factor XI deficiency
- Also called thromboplastin antecedent (PTA) deficiency
- Aslo called Rosenthal syndrome
- Mild form of haemophilia
- Affects both sexes
- More common in Ashkenazi Jews
- Risk factors for bleeding
    - Oral surgery
    - Nosebleeds
    - Kidney stones
    - Postpartum
- Does not bleed into joints
- Treatment: rarely necessary

What is haemophilia B?

Haemophilia B (1pm, 2w, 3i)

- Deficiency of Factor IX
- Also called Christmas disease (Stephen Christmas, first patient)
- Symptoms : easy bruising, haematuria, epistaxis, haemarthrosis.
- X-linked recessive trait (M> >> F)
- Treatment: pure Factor IX (cloned)

What is Haemophilia A?

Haemophilia A (1w, 2i-a, 2i-b)

- Deficiency of Factor VIII (haemophilia in history)
- Usually X-linked recessive (M >> F)
- Rarely spontaneous mutations.
- Bleeding episodes vary--mild to severe. and mild forms.
- Typical bleeding sites: Joints, muscle, GI tract, brain
- Antibodies often develop against replacement F VIII --> bleeding
- Treatment: recombinant F VIII; gene therapy under study
- Incidence: 1 in 5,000 males

What is para-haemophilia?

Para-haemophilia (Factor V deficiency) (1nih, 2ow, 3em)

- Autosomal recessive disorder with abnormal factor V levels.
- Several mutations in F V gene a been reported.
- Clinical manifestations of F V deficiency include:
  - Bleeding into the skin
  - Excessive bruising with minor injuries
  - Nosebleeds
  - Bleeding gums
  - Excessive menstrual bleeding
  - Excessive loss of blood with surgery or trauma
  - GI bleeding
  - Urinary tract bleeding
  - Bleeding in the joints
  - Intracerebral hemorrhages
  - Pulmonary hemorrhage

What is von Willebrand disease?

von Willebrand disease (1w, 2i-a, 2i-b)

- **Bleeding disorder due to a deficiency of von Willebrand factor.**
- **Deficiency due to defect that in VWF gene.**
- **VWF deficiency results in a bleeding tendency (VWF promotes platelet adhesion and clot formation).**
- **There are four different variants of VFW with variable symptomatology.**
- **There are five different products approved by the FDA for treatment of VFW deficiency.**

What are the viral haemorrhagic diseases?

Viral haemorrhagic diseases

- Alkhurma hemorrhagic fever
- Argentine hemorrhagic fever
- Bolivian hemorrhagic fever
- Chapare hemorrhagic fever
- Crimean-Congo hemorrhagic fever
- Ebola (Ebola Virus Disease)
- Hantavirus Pulmonary Syndrome (HPS)
- Hemorrhagic fever with renal syndrome (HFRS)
- Lassa fever
- Lujo hemorrhagic fever
- Lymphocytic choriomeningitis (LCM)
- Marburg hemorrhagic fever
- Omsk hemorrhagic fever
- Rift Valley fever
- Sabia-associated hemorrhagic fever
- Tick-borne Encephalitis (TBE)
- Venezuelan hemorrhagic fever

What is the relation between bacterial infections and haemorrhage?

Common examples of hemorrhagic conditions that can be associated with various bacterial infections include:

- **Disseminated intravascular coagulation**
- **Bacterial haemorrhagic enterocolitis**
- **Adrenal gland haemorrhage**
- **Intra-cerebral haemorrhage**
- **Pulmonary haemorrhage**
- **Haemorrhagic cystitis**
- **Bacterial meningitis and subarachnoid haemorrhage**
- **Haemorrhagic gastroenteritis**
- **Haemolytic uremia syndrome**
- **Vasculitis**

What is haemorrhagic disease of the newborn (HDN)?

- Haemorrhage due to vitamin K deficiency. Causes of HDN are:
- Early HDN can be caused by failure to provide vitamin K supplementation with breast feeding.
- Late HDN can be caused by chronic diarrhea, cystic fibrosis, biliary atresia, α_1-antitripsin deficiency, hepatitis, abetalipoproteinemia and chronic warfarin exposure.

What are causes of vitamin K deficiency in adults?

- Warfarin anticoagulant therapy
- Exposure to rat poison (rare but should be kept in mind)
- Malabsorption disorders, such as short bowel syndrome, biliary tract obstruction, cystic fibrosis, celiac disease, and chronic pancreatitis.

What are biological functions of vitamin K?

Biological functions of vitamin K

1. Blood coagulation: synthesis of prothrombin and factors VII, IX, and X, and proteins C and S, and protein Z
2. Bone metabolism: synthesis of osteocalcin, matrix Gla protein (1w), periostin, and Gla-rich protein
3. Vascular biology: synthesis of growth arrest-specific protein 6 (GAS6)

What are causes of hemorrhage in cirrhosis and/or liver failure?

Causes of hemorrhage in cirrhosis and/or liver failure

1. Portal hypertension and esophageal varices
2. Deficient synthesis of of vitamin K dependent coagulation factors
3. Reduced platelet count
4. Non-variceal gastrointestinal hemorrhage, e.g., gastroapathy
5. Hemorrhoidal bleeding (due to portal hypertension?)

How do snake bites (viperid venoms) cause haemorrhage?

- Haemorrhagic toxins in viperid venoms are zinc-dependent metalloproteinases.
- They hydrolyze basement membrane proteins of capillaries.
- Apparently, their main action is to degrade microvascular type IV collagen and thus destroy capillary networks.

What is Bernard-Soulier syndrome?

Bernard-Soulier syndrome (1w, 2i)

- Bleeding diathesis due to platelet dysfunction.
- Autosomal recessive condition.
- Due to mutations in one of three genes: GP1BA, GP1BB and GP9
- Mutations block GPIb-IX-V complex from binding to von Willebrand factor, which prevents normal platelet aggregation.
- Symptoms include surgery related bleeding, bleeding gums, easy bruising, nosebleeds, prolonged menstrual bleeding

What is Glanzmann's thrombasthenia?

Glanzmann's thrombasthenia (1w, 2i)

Autosomal recessive disorder (or autoimmune disorder)

Abnormal platelet function

Reduced glycoprotein IIb/IIIa (GpIIb/IIIa) (receptor for fibrinogen)

Reduced platelet aggregation.

Prolonged bleeding time

Typical bleeding diathesis (non-severe)

Basis for GpIIb/IIIa inhibitors (antiplatelet agents)

What is Wiskott-Aldrich syndrome?

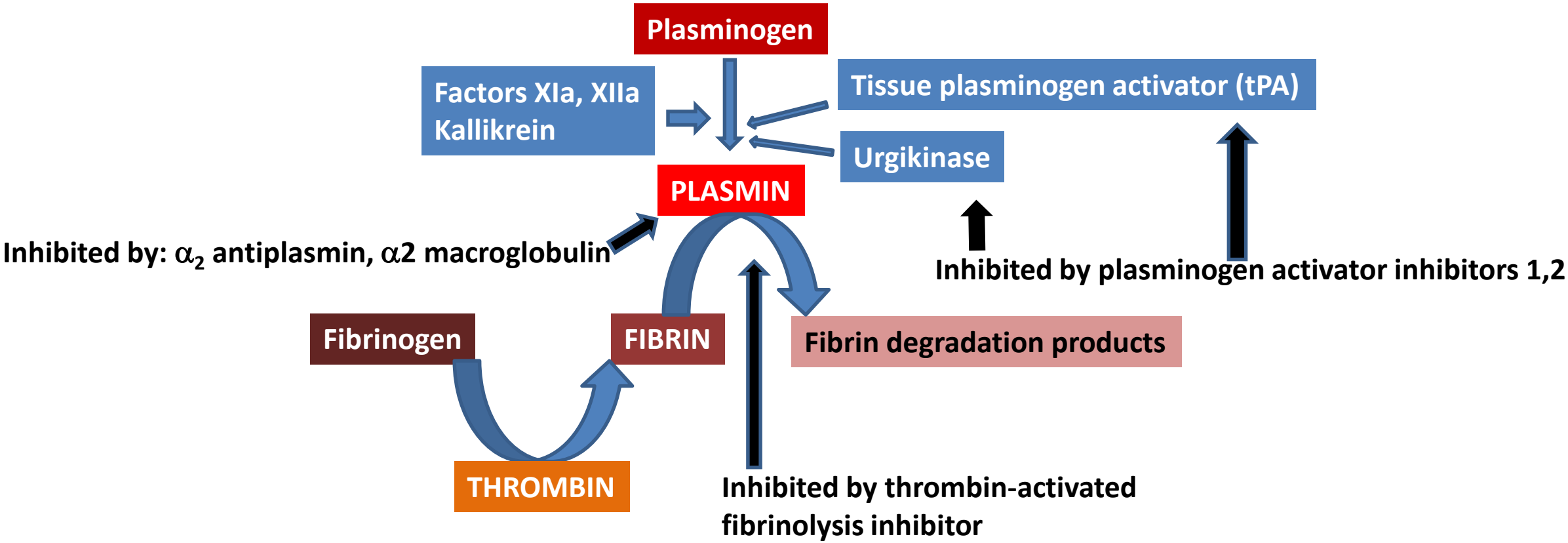
- Wiskott-Aldrich syndrome (1pm (has pdf), 2pm, 3w, 4i) is:
- Rare X-linked recessive (1 to 10 males per million)
- Symptoms: eczema, petechiae/brusing, thrombocytopenia, immune deficiency, and bloody diarrhoea
- Deficiency or elevations of immunoglobulins
- Genetics: deficiency of multifunctional WAS protein
- Increased risk for lymphatic malignancies

FIBRINOLYSIS

What is fibrinolysis?

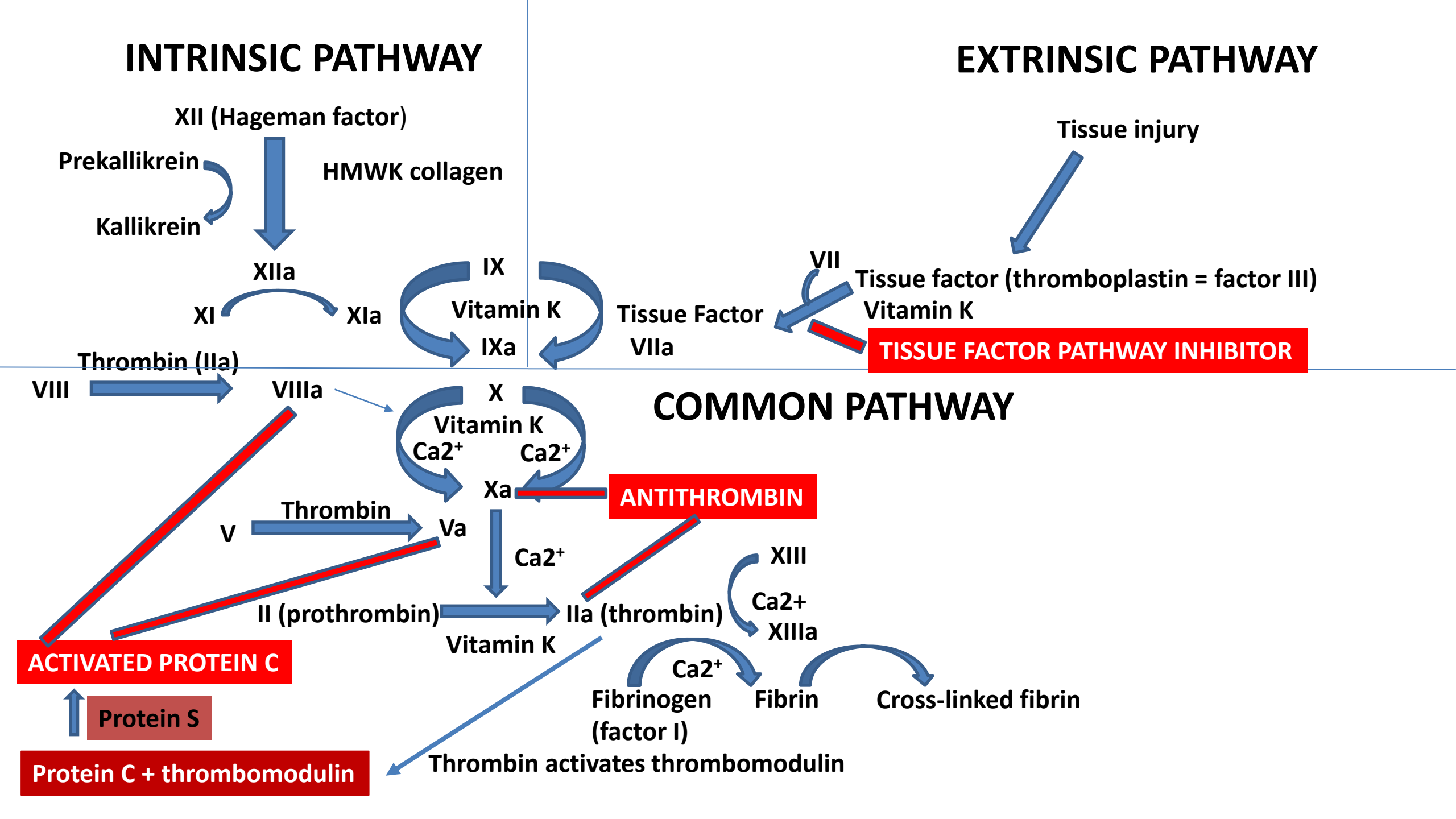
- Fibrinolysis (1i) is the process that halts the growth of blood clots before they can cause thrombosis, and breaks down clot material when it is no longer needed.
- Primary fibrinolysis is the body's natural response to clot formation.
- Secondary fibrinolysis is when pharmaceutical means are used to break down a thrombus, e.g., a thromboembolism in coronary arteries, ischaemic stroke, or large pulmonary embolism.

What is the pathway of fibrinolysis?



What other innate substances modify the clotting process?

- Thrombomodulin – present in endothelial cell linings; activated by the presence of thrombin; binds thrombin to increase Protein C activation x1000 and activates thrombin-activatable fibrinolysis inhibitor by cleavage.
- Protein C – produced in the liver as inactive form (zymogen); activated protein C (APC) inhibits factors VIIIa and Va.
- Protein S – produced in the liver; acts as a cofactor to protein C.


INTRINSIC PATHWAY
EXTRINSIC PATHWAY
XII (Hageman factor)
Prekallikrein
Kallikrein
HMWK collagen
Tissue injury
XIIa
XI
XIa
IX
Vitamin K
IXa
Tissue Factor
VIIa
VII
Tissue factor (thromboplastin = factor III)
Vitamin K
TISSUE FACTOR PATHWAY INHIBITOR
Thrombin (IIa)
VIII
VIIIa
X
Vitamin K
Ca2+
Ca2+
Xa
ANTITHROMBIN
COMMON PATHWAY
Thrombin
V
Va
Ca2+
XIII
Ca2+
XIIIa
II (prothrombin)
IIa (thrombin)
Vitamin K
ACTIVATED PROTEIN C
Protein S
Protein C + thrombomodulin
Ca2+
Fibrinogen
(factor I)
Fibrin
Cross-linked fibrin
Thrombin activates thrombomodulin

What inherited conditions lead to thrombosis?

- Protein C deficiency or defect – diminishing degradation of factors Va and VIIIa; increased risk of venous thrombosis. Most commonly heterozygous; homozygous patients are at risk of purpura fulminans and disseminated intravascular coagulation.
- Protein S deficiency – reduces activated Protein C, diminishing degradation of factors Va and VIIIa; increased risk of venous thrombosis.
- Antithrombin III deficiency – thrombin and Xa are not inhibited appropriately.
- Factor V Leiden – mutation in factor V which reduces the binding of activated protein C, producing a hypercoagulable state. Ca. 2-15% of the Caucasian population.

What acquired causes lead to hypercoagulability?

- “Lupus anticoagulant” antibody; binds to platelet phospholipids, increasing adhesion and aggregation to create an inappropriate prothrombotic state.
- Heparin-induced thrombocytopenia – leads to platelet activation and endothelial cell injury to produce a prothrombotic state.
- Some cancers: pancreatic, leukaemia, multiple myeloma, monoclonal gammopathies.
- Hormonal birth control: oestrogen (increased risk of venous thromboembolism) and progesterone/oestrogen (increased risk of arterial and venous thromboembolism).

What lab tests are used to evaluate coagulation dysfunctions?

- **PT – Prothrombin time. Blood sample is put into a tube with sodium citrate (calcium-binding anticoagulant); centrifuged for plasma extraction; calcium is added to plasma sample to reverse anticoagulation; tissue factor is added. PT is the time it takes blood to coagulate from the addition of tissue factor. Normal time: 11-15 seconds. Tests for prothrombin, fibrinogen, and factors V, VII, and X.**
- **PTT or aPTT – partial or activated thromboplastin time. Considered more sensitive than PT. Instead of tissue factor, kaolin (factor XII activator) and cephalin (platelet phospholipid mimic) are added to start the clotting process. Normal time: ca. 35 seconds. Tests for factors VIII, IX, XI, XII and the common coagulation pathway.**

What is the Internationalized Normal Ratio (INR)?

- The Internationalized Normal Ratio (INR) is the main test used to monitor oral anticoagulation medications, in particular warfarin.
- It consists of the ratio of the measured PT to a standard value, raised to the power of the manufacturer's International Sensitivity Index for that specific batch of tissue factor compared to a international reference for tissue factor:

  $INR = (patient's\ PT/normal\ PT)^{ISI}$
- A normal INR = 1 +/- 0.2. The target range for warfarin patients is usually 2.0-3.0, though may be higher with exceptional risk factors.

Disseminated Intravascular Coagulation (DIC)

What is disseminated intravascular coagulation (DIC)?

- Disseminated intravascular coagulation (DIC) is a condition in which excessive thrombin and fibrin are generated into the bloodstream. Release of tissue factor [1pm, 2pm appears to be the major causative factor.
- This causes small clots throughout the body, leading to thrombosis, potential thromboembolism, ischaemia, and the overall depletion of platelets and coagulation factors.
- Hence, a patient with DIC may demonstrate unexplained or uncontrollable bleeding as well as inappropriate clotting.
- Chronic DIC is chiefly characterized by thrombi and thromboembolisms.
- Acute DIC is most often characterized by bleeding and bruising.

What are the defining markers of DIC?

- Defining markers for types of disseminated intravascular coagulation are the following:
  - Acute – thrombocytopaenia; increased D-dimers, PTT, and PT; dropping plasma fibrinogen.
  - Chronic – mild thrombocytopaenia; increased D-dimers; mildly reduced/gradually dropping plasma fibrinogen; normal or mildly reduced PTT and PT.

What are the usual causes of DIC?

- **Infections – bacterial, particularly Gram- (Gram- bacteria produce an endotoxin which stimulates or exposes tissue factor [1pm, 2pm]); viral – notably haemorrhagic fevers: Ebola, Marburg, Rift Valley, dengue.**
- **Cancers in which tumour cells release tissue factor, particularly seen in acute promyelocytic leukaemia and adenocarcinomas of the pancreas or prostate.**
- **Obstetrical complications (*abruptio placentae*, retention of dead fetus, amniotic fluid embolism – all release placental material with tissue factor activity into maternal circulation).**
- **Traumatic shock with ischaemic injury.**

What are some other situations in which to watch for DIC?

- Severe tissue damage (including burns, frostbite, gunshot wounds)
- Post-prostatic surgery (TURP) (prostate material with tissue factor released into circulation)
- Aortic aneurysm or cavernous haemangioma.
- Profound intravascular haemolysis.

Why was "snakebite" missing from the previous slide?

- There is considerable debate as to whether any snake venom actually causes DIC.
- VICC (venom-induced consumption coagulopathy), associated with the bites of many vipers and elapid (cobra-family) species, is similar to DIC in terms of lab test results, but lacks the microthrombosis and end-organ damage of DIC.
- In some of these species, a further stimulation of thrombotic microangiopathy occurs, increasing the likeness to DIC; however, this appears to be a "distinct but related process".

How do pharmaceutical anticoagulants act?

- **Pharmaceutical anticoagulants specifically target and inhibit one or more crucial steps in the coagulation cascade.**
- **Warfarin – vitamin K antagonist. Given orally; requires regular monitoring; cannot be given in pregnancy (teratogenic).**
- **Heparins – IV or subcutaneous administration (cannot be absorbed from GI tract); short half-life. Safe in pregnancy.**

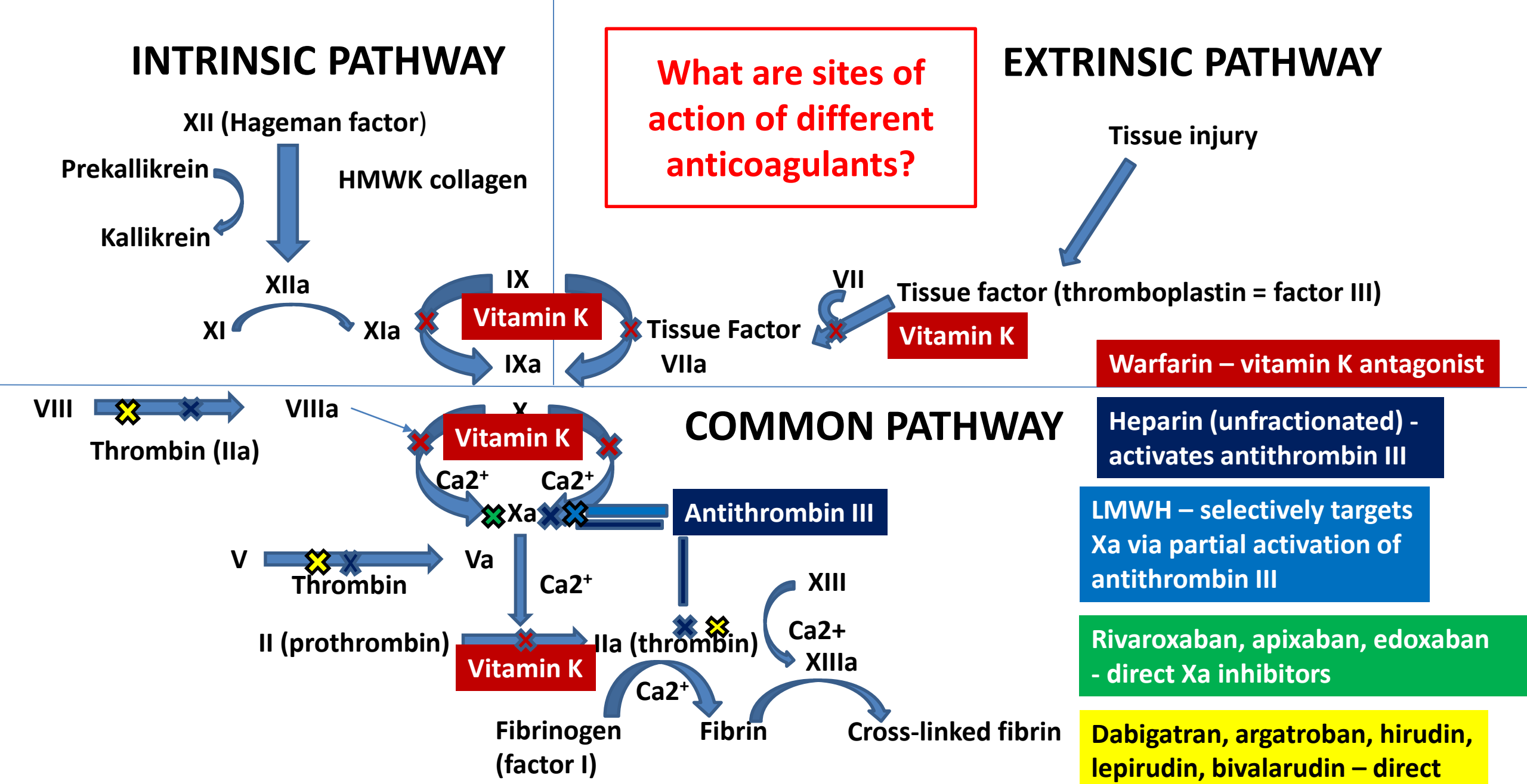
- Unfractionated heparin – activates antithrombin III, which exponentially inactivates thrombin and factor Xa.

- Fractionated heparin (low molecular weight heparin), fondaparinux – inactivate factor Xa only through activation of antithrombin III; reduced risk of heparin-induced thrombocytopaenia.

What are NOACs?

- NOACs (novel oral/non-vitamin K anti-coagulants) are recently developed anticoagulants which target specific aspects of the clotting cascade. Also known as DOACs (directly acting oral anticoagulants).
- Direct thrombin inhibitors (1w, 2i): Dabigatran, argatroban, hirudin, lepirudin, bivalarudin
- Direct Xa inhibitors (1w, 2i): Rivaroxaban, apixaban, edoxaban (1w)
- Can be given orally and do not require monitoring; the only currently available reversal agent is idarucizumab (reverses dabigatran); expensive in comparison to warfarin or heparin.

What are sites of action of different anticoagulants?



How do the various anticoagulants compare?

Type of drug	Method of administration	Safety in pregnancy	Monitoring requirements	Efficacy	Expense
Warfarin	Oral	Highly unsafe	Once monthly after initial stabilization	Good	Low
Unfractionated heparin	Injection (SC or IV)	Safe	No	Good	Low
LMWH	Injection (SC or IV)	Safe	No	Good	Low
Direct factor Xa inhibitors	Oral	Safe	No	Good	High
Direct thrombin inhibitors	Oral	Safe	No	Good	High

Thrombosis

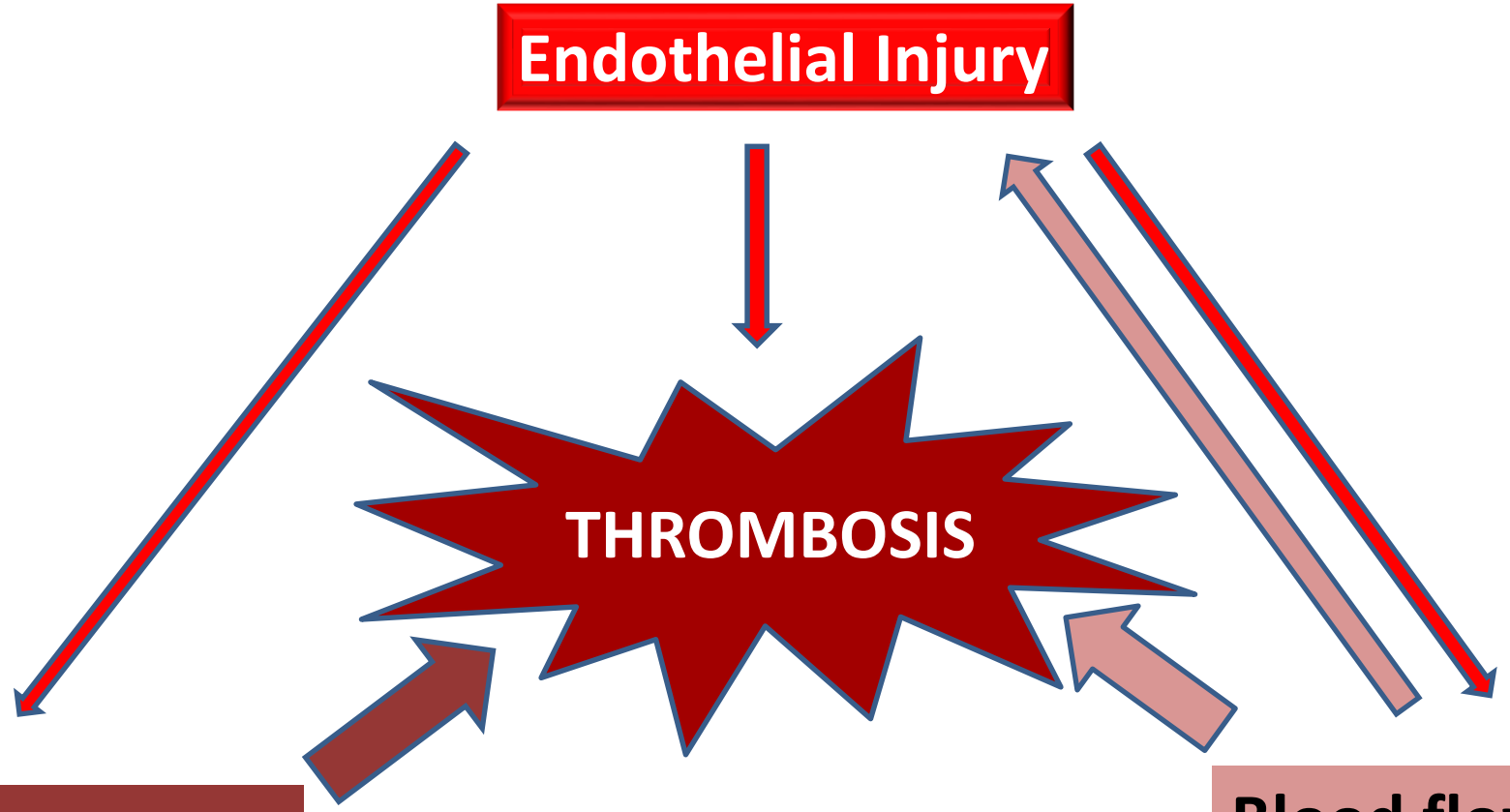
What is thrombosis?

- Thrombosis is an abnormal state leading to the formation of inappropriate thrombus.
- A thrombus is a combination of an aggregation of activated platelets and red blood cells with a stabilizing network of fibrin.
- The production of a thrombus is a normal part of the healing response to bleeding wounds.
- However, in thrombosis, thrombi form inappropriately and may either block vessels locally with ischaemic and/or vascular damage resulting, or break off to form a thromboembolus, which may block vessels elsewhere in the body.

What are the three primary elements of thrombus formation?

- Known as Virchow's Triad, these three elements are:
- Vessel wall condition – endothelial injury.
- Blood flow stasis or turbulence – static blood flow is usually seen in venous thrombosis; turbulence in, for example, atrial fibrillation.
- Hypercoagulability – many conditions can cause this: for instance, Leiden V, lupus antiphospholipid, increased viscosity (seen in, among others, polycythaemia, multiple myeloma, sickle-cell anaemia, sepsis).

Virchow's Triad – venous thrombosis



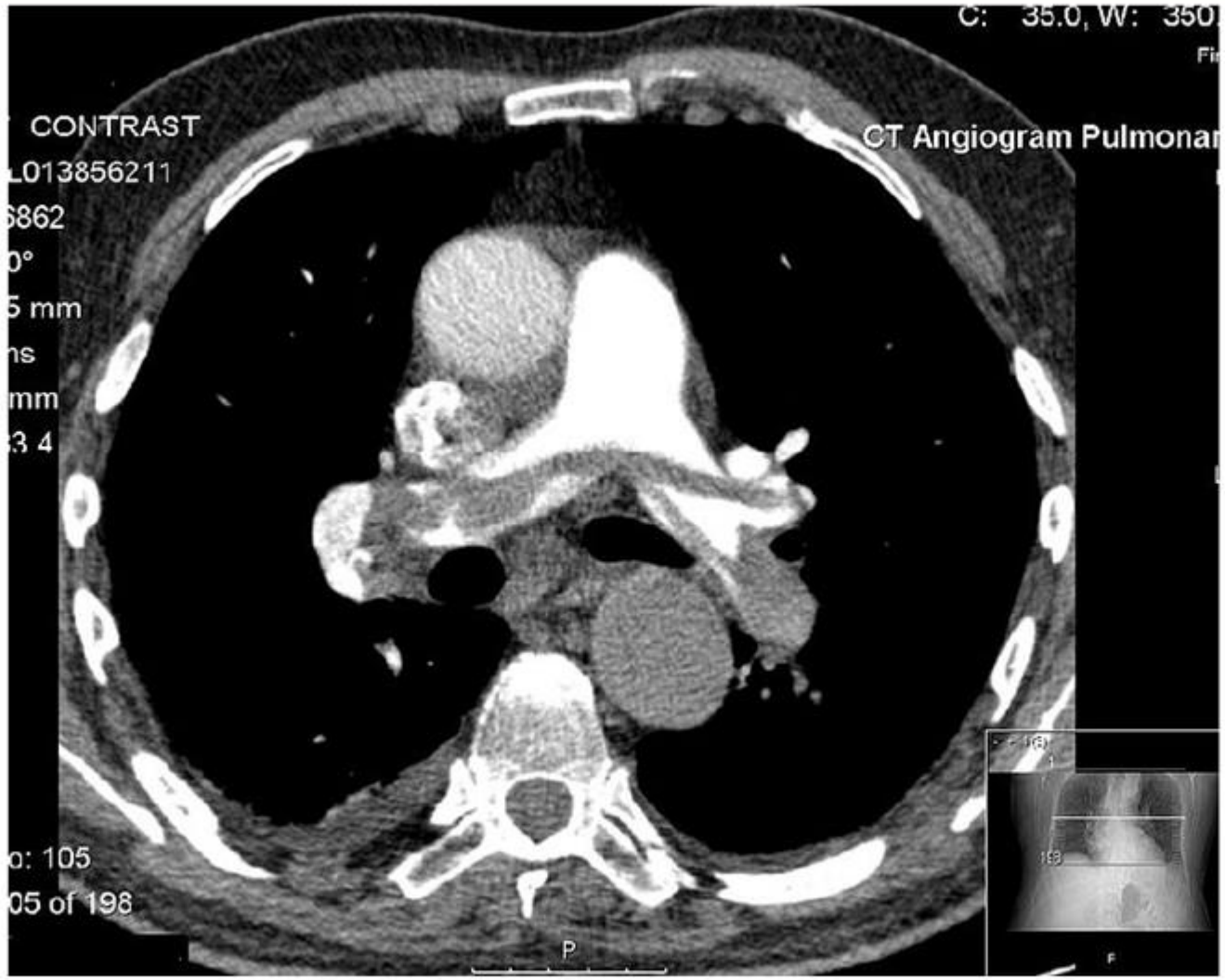
What are the characteristics of venous thrombosis?

- Mostly caused by stasis combined with hypercoagulability; endothelial damage is a lesser factor in venous thrombosis.
- May be in deep or superficial veins. Superficial thrombosis is commonly less concerning, but may pass to the deep veins through perforators, or, if close to the saphenous-femoral junction, may enter the inferior vena cava. Migratory superficial thrombosis may also be an indication of malignancy, particularly gastric or pancreatic (Trousseau's sign of malignancy).
- Often associated with immobilization, oral contraceptives, pregnancy, cancer.
- Red blood cells and fibrin are the primary components ("red thrombus" vs. the "white thrombus" of platelet-rich arterial thrombi).
- Most commonly seen in the lower limbs.
- Characteristic symptoms: redness, swelling, pain, warmth.

What are the main consequences of deep venous thrombosis (DVT)?

- Thromboembolism – a piece of the thrombus breaks off and travels along the vein.
- The thromboembolus passes through the right side of the heart and is trapped somewhere along the pulmonary artery (pulmonary thromboembolism), causing ischaemia in a portion of the lung.
- In a worst-case scenario, the thromboembolus lodges at the bifurcation of the pulmonary artery, blocking blood flow to both lungs (saddle thromboembolism). This is fatal without immediate treatment.

SADDLE THROMBOEMBOLISM ON CT PULMONARY ANGIOGRAM



How are pulmonary embolisms diagnosed?

- **History - Risk factors: hypercoagulability, immobilization, tobacco use, pregnancy, oral contraceptives. Previous or current venous thrombosis (especially DVT and previous PEs).**
- **Symptoms - Shortness of breath, chest pain, hemoptysis.**
- **Signs – elevated respiratory and heart rates, low O_2 saturation, possibly a mild fever or extreme drop in blood pressure.**
- **Imaging - CT pulmonary angiogram**

Note that PEs *do not* show up on X-rays!

How are pulmonary embolisms treated?

- **Prevention – regular walking on long airline flights and mobilization of patients who are able to walk.**

Heparin or another anticoagulant is given prophylactically to patients who are unable to exercise. Some hospitals administer a daily dose of subcutaneous LMWH to post-surgical patients unless contraindicated (bleeding risk).

When an anticoagulant cannot be used and there is sufficient risk to justify invasive surgery, a filter may be placed in the inferior vena cava.

- **Pharmaceutical thrombolysis – tissue plasminogen activator (tPA).**
- **Surgical – thrombectomy.**

What is thrombophlebitis?

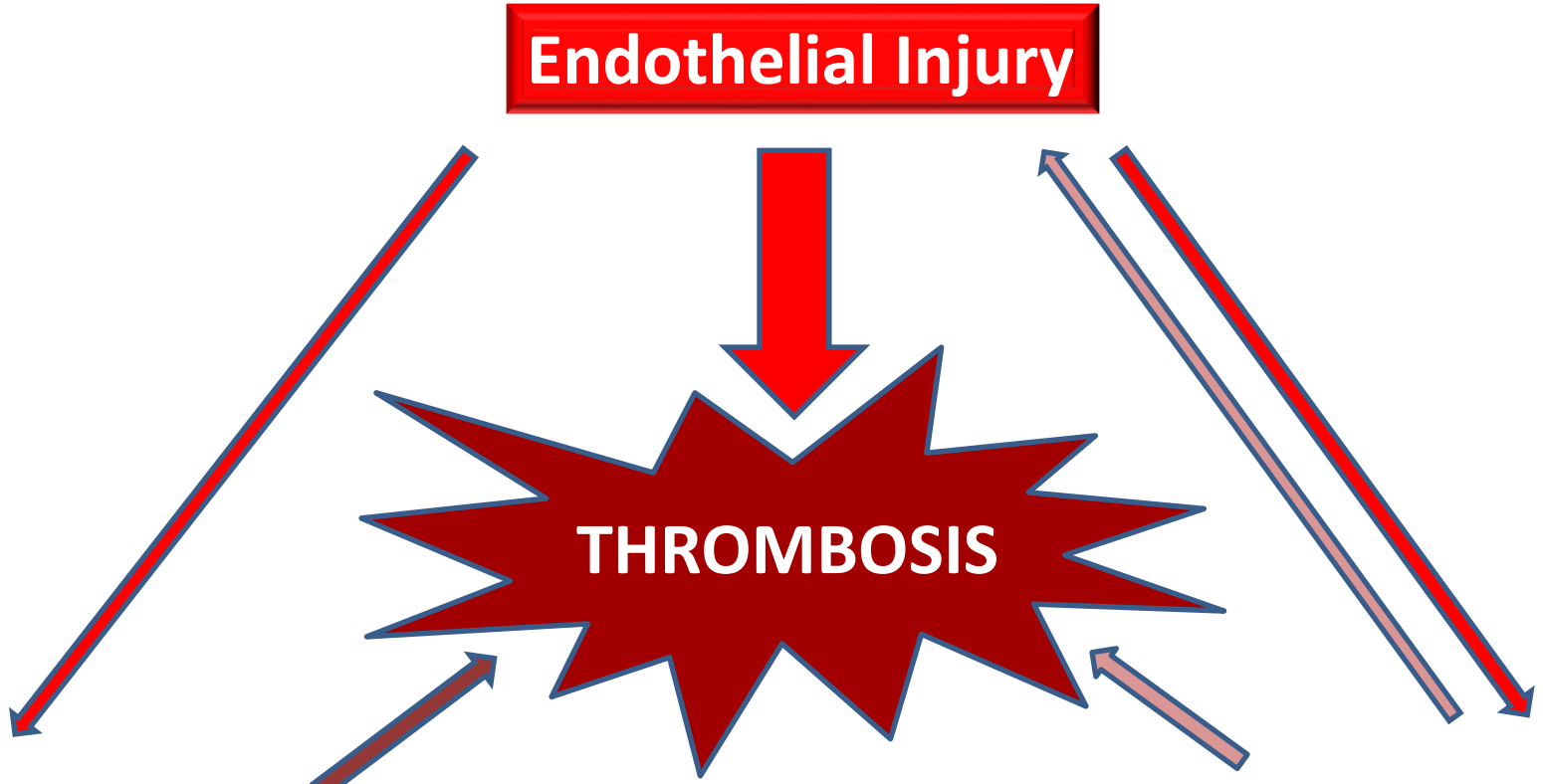
- Thrombophlebitis is venous inflammation often associated with venous thrombosis.
- Symptoms are pain, redness, “cord-like” veins, and (in the lower extremities, most common location) ankle and foot oedema.
- Causes are similar to those of venous thrombosis.
- Thrombophlebitis migrans refers to repeated episodes, recurrent or in varied locations. It may occur in unusual places (arms, chest wall), and may be the first sign of pancreatic, gastric, or lung cancer (Trousseau’s syndrome).

What postmortem artifact can be mistaken for venous thrombi at autopsy?

- Postmortem blood clots superficially resemble venous thrombi.
- They may be distinguished by:

1) Texture – postmortem clots are gelatinous rather than firm.
2) Attachment – postmortem clots are not attached to the vessel wall.
3) Colouring – postmortem clots have a dark red dependent section (RBC pooling with gravity) and a yellowish "chicken-fat" liquid covering the upper surface, causing a glistening effect; thrombi are more even in colour and texture, and show gray fibrin strands when sectioned.

Virchow's Triad – arterial thrombosis



What are the characteristics of arterial thrombosis?

- Arterial thrombus due to ruptured atherosclertic plaque
- May also occur within the heart, most commonly as a result of the turbulence/stasis caused by atrial fibrillation.
- The main component of arterial thrombi is aggregated platelets ("white thrombus") vs. the red cell/fibrin mix of venous thrombi ("red thrombus"). Red cells and fibrin are also found in arterial thrombi; the distinct layers of platelets and red cells/fibrin are called "lines of Zahn".
- May occur in any arteries.
- Arterial or cardiac thrombi and prone to becoming dislodged and float to a distal site (embolus)
- Clinical characteristics: claudication (lower limbs), myocardial infarction, stroke, renal infarction, intestinal infarction.

What are the main consequences of arterial thrombosis?

- Ischaemia in the area served by the artery.
- Thromboemboli from thrombi of the heart, ascending aorta and aortic arch, or carotid artery may lodge in the brain and cause a transient ischaemic attack (self-resolving, but a warning of ongoing risk) or ischaemic stroke. The middle cerebral artery and its branches are most commonly affected.
- Renal and splenic arteries are also particularly vulnerable to embolic obstruction, due to their high blood flow.
- Hepatic artery thrombosis is a severe and life-threatening complication following liver transplant.

What is the most common cause of arterial thrombosis?

- **Ulceration of atherosclerotic plaque.**

How do atherosclerotic plaques form and ulcerate?

Prevailing Theory

1) Low-density lipoprotein (LDL) accumulates in the intima.
2) LDL is oxidized or otherwise chemically modified.
3) Monocytes/macrophages are recruited to the site.
4) Macrophage scavenger receptors uptake LDL; macrophages transform into foam cells.
5) A fibrous cap containing smooth muscle cells forms, stabilizing the plaque.
6) Necrosis occurs in the plaque core, causing rupture of the fibrous cap, which leads to thrombus formation.

What are the sources of arterial thromboembolism?

- Intracardiac mural thrombi
  - Left ventricular thrombus
    - Post-myocardial infarction
    - Dilated left ventricle
  - Dilated left atrium/ atrial fibrillation/atrial flutter
- Arterial thrombosis
  - Ulcerated atherosclerotic plaque
    - Coronary artery
    - Carotid artery
    - Other arteries
- Arterial thromboembolism
  - To brain and other arteries (e.g., kidneys, gut, legs)

What other forms of embolism are there?

- Fat embolism or fat/marrow embolism– caused by fractures of long bones or soft-tissue trauma. Pulmonary insufficiency, anaemia, thrombocytopaenia, neurological symptoms; fatal in ca. 10% of cases. Symptoms (tachypnea, dyspnea, tachycardia, petechial rash) arise 1-3 days after trauma.
- Gas embolism - air embolisms are most commonly caused by chest wall injury or obstetrical procedures. Clinical effects are usually not seen <100 ml. of air, but are similar to other forms of vessel occlusion. “Decompression sickness”, “the bends” - High pressure dissolves nitrogen into the blood; decompressing too rapidly causes it to bubble out in various tissues, including muscles, lungs, brain, and heart.
- Amniotic fluid embolism – placental membrane tearing and uterine vein rupture allow a bolus of amniotic fluid into the maternal circulation. Rapid-onset, severe dyspnea and cyanosis; hypotensive shock; seizures; coma; subsequent pulmonary oedema and DIC. May be fatal in >40% of cases.

Shock

What is shock?

Shock (1pdf, 2w, 3nejm, 4i) is:

- **A state in which the perfusion level of blood has dropped dangerously low.**
- **A medical emergency requiring immediate treatment.**
- **It may lead to generalized hypoxia, cardiac arrest, organ failure, coma, and death.**

What are the major types (and causes) of stroke?

- 1. Low volume (e.g., bleeding, vomiting, or pancreatitis)
- 2. Cardiogenic (e.g., myocardial infarction and cardiac contusion)
- 3. Obstructive (e.g., cardiac tamponade and tension pneumothorax)
- 4. Distributed (e.g., sepsis, spinal cord injury, certain poisons or drug overdoses)

What are leading causes of shock?

- Hypovolemic shock – blood loss, fluid loss, severe anaemia.
- Anaphylactic shock – immune overreaction.
- Septic shock – reaction to bacterial toxins. Characterized by DIC, hypotension, and metabolic abnormalities.
- Cardiogenic shock – failure of heart to supply sufficient blood (myocardial infarction, cardiac trauma, congestive heart failure).
- Neurogenic shock – due to spinal cord injury.

What are the symptoms of shock?

- Low blood pressure
- Tachycardia
- Tachypnea
- Cold, pallid, clammy skin (in septic shock, skin may be flushed and warm)
- Light-headedness
- Weakness
- Also in some cases: agitation, confusion, low urine output, peripheral cyanosis, seizures, sweating, chest pain.

What are the stages of shock?

- **Three stages of shock include:**
  - **Nonprogressive – the initial stage. Physiological methods of compensation are activated.**
  - **Progressive – generalized hypoperfusion of tissues; circulatory and metabolic imbalances manifest and worsen.**
  - **Irreversible – cellular/tissue/organ damage is sufficiently severe that survival is impossible even with aggressive treatment.**

What are the initial physiological compensations in shock?

- Baroreceptor detection of low blood pressure, catecholamine release and general sympathetic stimulation – tachycardia and peripheral vasoconstriction to maintain blood flow to organs (responsible for the characteristic chill and pallor).
- Antidiuretic hormone release and activation of the renin-angiotensin axis – renal conservation of fluids (low urine output may be seen).

What are the physiological changes in the progressive stage of shock?

- Anaerobic glycolysis replaces normal cellular aerobic respiration – lactic acid is produced.
- Lactic acidosis causes blunting of the vasomotor response, which leads to dilation of peripheral arterioles and peripheral blood pooling.
- Global tissue hypoxia leads to the ischaemic failure of vital organs.

What happens in the irreversible stage of shock?

- Irreversible shock is characterized by:
  - Widespread cell injury leads to cell necrosis.
  - Spilt cellular contents, particularly lysosomal enzymes, exacerbate the status of shock.
  - Myocardial contractile function is compromised.
  - Acute renal tubular necrosis occurs and full renal shutdown occurs.
  - Even given heroic measures, a patient who reaches this stage is highly unlikely to survive.

How is shock treated?

1) Determine the underlying cause.

2) Initiate fluid replacement and vital signs monitoring.

3) Give the appropriate medications (IM ephinephrine for anaphylactic shock; antibiotics for septic shock as directly indicated or empirical use of wide-spectrum such as the common ampicillin/gentamicin combination). Ephinephrine, norephinephrine, and dopamine may also be used in general to raise blood pressure and support blood flow to organs.

4) Replace blood if required.

5) Cardiogenic shock may require cardiac catheterization (arterial blockage) or a positive inotropic drug (digioxin, amiodarone, etc.).