ZSMU Pharmacology Department

Lecture № 4

Drugs Affecting Blood

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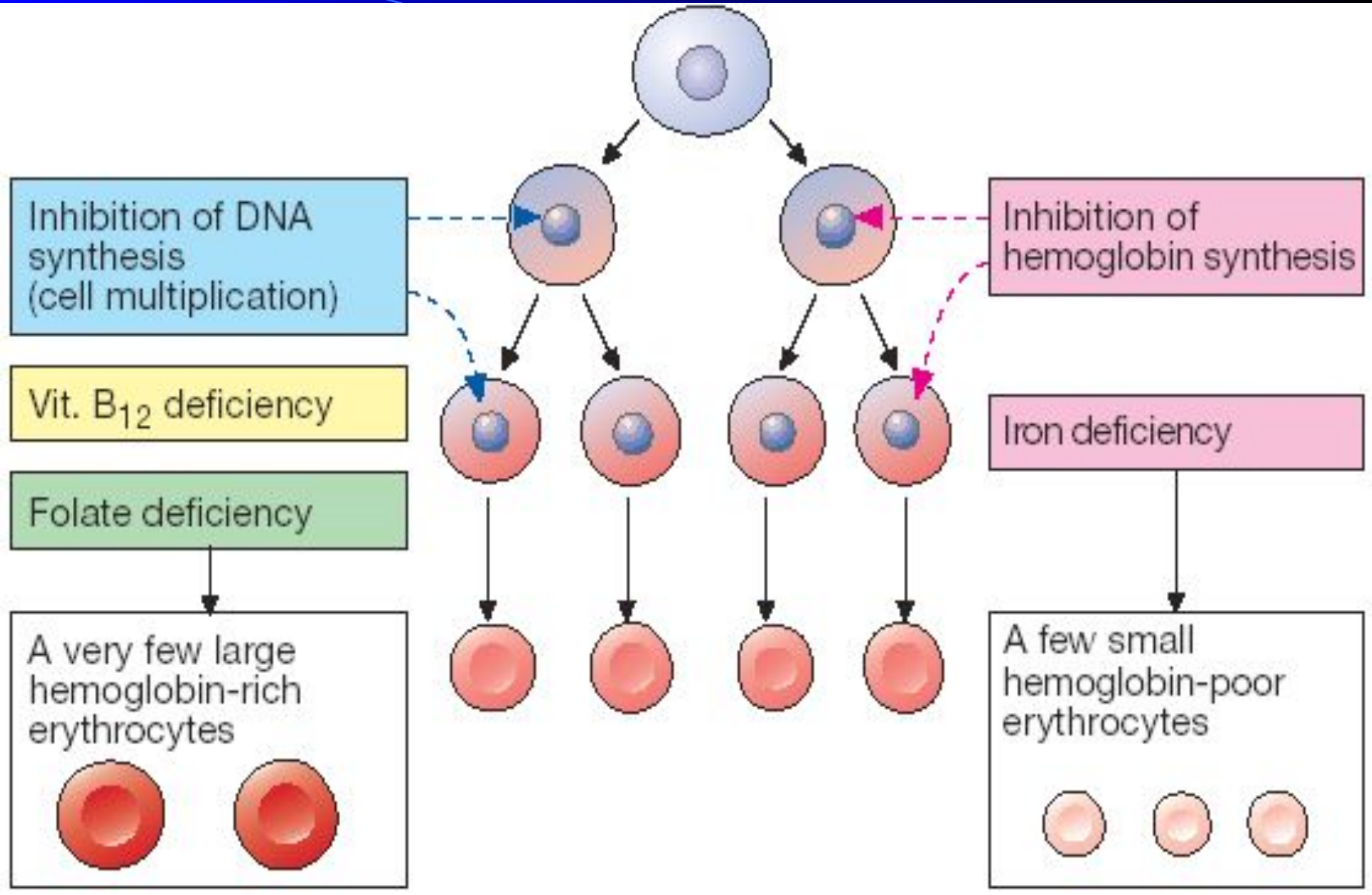
Principal Causes of a Disturbance of Erythropoiesis :

1. Hemoglobin synthesis is impaired -
   in **Fe2+** deficiency –
   Microcytic Hypochromic Anemia.
2. Cell multiplication is inhibited –
   DNA synthesis is insufficient -
   in deficiencies of *Vitamin B_{12}* or *Folic Acid*
   - Macrocytic [*Megalocytic*]
   Hyperchromic Anemia



Erythropoiesis in bone marrow

Agents Affecting Erythropoesis

I. Agents Stimulating Erythropoiesis

1. Used in Hypochromic Anemias

A. IN **iron-deficient** anemias:

a) Iron Agents:

Ferrous sulfate – *caps. 0.25 g*

Ferrous Lactate – *pulv., PO 1 g*

Fercoven – amp. 5 ml

Ferrum Lek - amp 5 ml

b) Cobalt agents:

Coamid – amp. 1%-1 ml

Fercoven

B. Hematopoietic Growth Factor:

Erythropoietin - *vial 2000, 4000, 10,000 IU/mL*

2. In **HYPERCHROMIC** Anemias:

Vitamin B12 **(*Cyanocobalamin*)**

amp. 0.01%, 0.05%-1 ml

Folic Acid [Vit **Bc, B9**] – Tab. 1 mg

II. AGENTS INHIBITING ERYTHROPOIESIS:

Sodium Phosphate liquor labelled Phosphor-32

Iron Agents:

Ferrous Sulfate, Ferrous Lactate, Fercoven, Ferrum Lek -
contain the divalent **Fe^{2+}** that is markedly better absorbed than trivalent Fe^{3+} .

Uptake is efficient in the form of heme (present in ***hemo***- and ***myoglobin***).

Iron is stored in intestinal mucosal cells as **ferritin** (an iron/protein complex) until needed by the body and passed on to the transport protein - **transferrin**, a **β_1-glycoprotein**.

The transferrin–iron complex undergoes endocytotic uptake mainly into erythroblasts to be utilized for Hb synthesis.

Fercoven (*amp. 5 ml*) contains 20 mg of Saccharate Iron and 0.09 mg of Gluconate Cobalt in 1 ml.

It is introduced IM slowly (for 8–10 min) once a day during 10–15 days; first 2 injections – 2 ml, then – 5 ml.

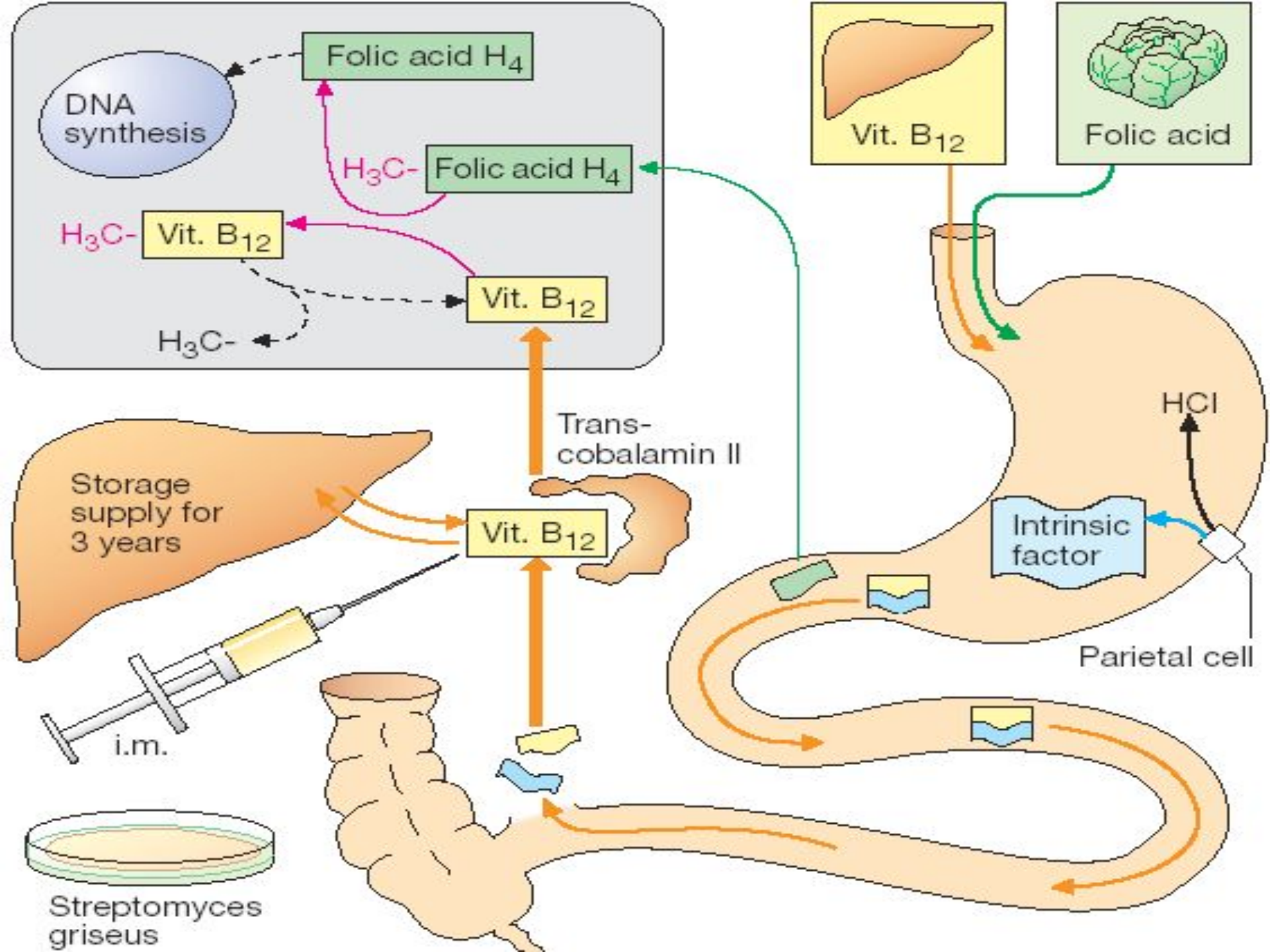
Ferrum Lek (*5 ml* containing 100 mg of Saccharate Iron) is administered IM or IV.

Interactions: Antacids inhibit iron absorption.

Adverse effects: GI disturbances (epigastric pain, diarrhea, constipation) caused by local irritation necessitates the intake of iron preparations with or after meals.

Adverse effects **with IM injection** are persistent pain at the injection site and skin discoloration;

with IV injection: flushing, hypotension, anaphylactic shock.


Folic acid H_4
DNA synthesis
H_3C- Folic acid H_4
H_3C- Vit. B_{12}
Vit. B_{12}
H_3C-
Vit. B_{12}
Folic acid
Trans-cobalamin II
HCl
Storage supply for 3 years
Vit. B_{12}
Intrinsic factor
Parietal cell
i.m.
Streptomyces griseus

OVERDOSE with Fe^{2+} COMPOUNDS

Manifestation: lethargy, nausea and vomiting green then tarry stools, weak and rapid pulse, hypotension, dehydration, acidosis, and coma.

Treatment: support of airway, respiration, and circulation. Gastric lavage, using a 1% *Sodium Bicarbonate solution,* to convert iron to less irritating, poorly absorbed form.

Deferoxamine (powder for injection: 0.5 g)
-chelates IRON by binding *ferric ions* to the 3 hydroxamic groups of the molecule

[1 g IM].

HEMATOPOIETIC GROWTH FACTORS:

- ERYTHROPOETIN
- Granulocyte Colony-Stimulating Factor - G-CSF, Filgrastim
- Granulocyte-Macrophage Colony-Stimulating Factor - GM-CSF, Molgramostim

Erythropoietin (*Epoetin alfa) –*
vial 2000, 4000, and 10,000 IU/ml IV, SC

Human erythropoietin, produced by
recombinant DNA technology

- Stimulates Erythroid Proliferation and Differentiation by interacting with **Specific Erythropoietin Receptors** on red cell progenitors.
- Induces release of Reticulocytes from the bone marrow.

Clinical uses: anaemia caused by end-stage renal disease, HIV-infection, and anaemia in some cancer patients.

Filgrastim (G-CSF) is lineage-specific growth factor –

- supports Proliferation, Differentiation and

  Functional Activity of neutrophils causing a rapid rise in leucocytes within 2–3 days in patients with normal bone marrow function or 7–14 days in patients with bone marrow suppression.

Clinical uses: to decrease incidence of infection

- after cancer chemotherapy for non-myeloid malignancies,
- chronic severe neutropenia,
- after bone marrow transplantation in cancer patients;
- agranulocytosis, pancytopenia, acute leukaemia, myelodysplastic syndrome,
- hematologic toxicity with drug therapy.

Molgramostim (GM-CSF) has broader actions than G-CSF.

- stimulates Proliferation and Differentiation of Granulocytic Progenitor Cells as well as **Erythroid** and **Megakaryocyte** progenitors.
- increases functional activity of mature neutrophils, enhancing phagocytosis.

GM-CSF acts together with IL-2 to stimulate T cell proliferation and appears to be a locally active factor at the site of inflammation.

- mobilizes peripheral blood stem cells, but it is significantly less efficacious than G-CSF in this regard.
- enlarges the extent of expression of "*respiratory explosion*" (ensuring formation of 90% active forms of O_2 and which is one of the most important mechanisms of phagocytosis).

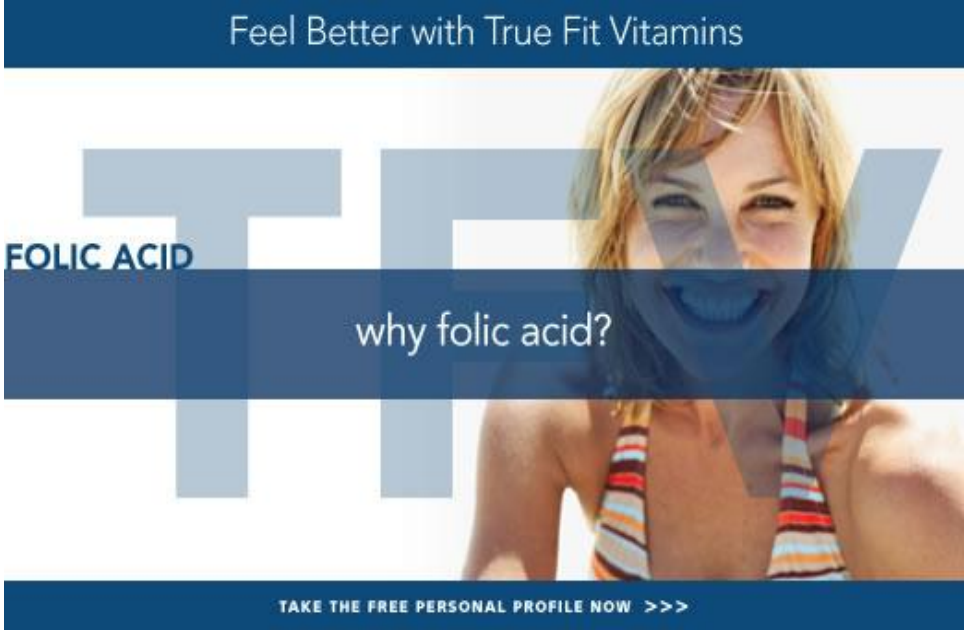
Folate Deficiency:

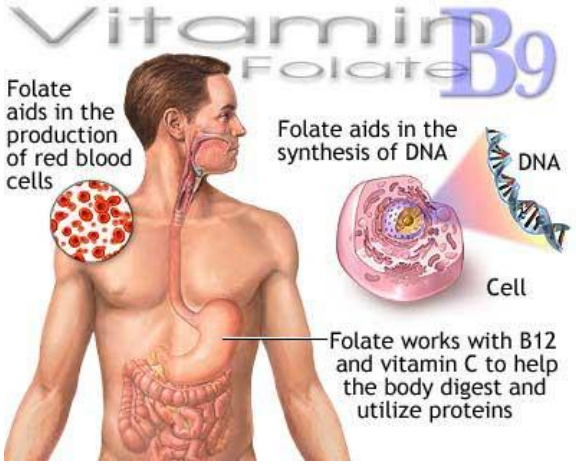
1) Increased Demand (pregnancy and lactation)
2) Poor Absorption

caused by pathology of the small intestine

3) Alcoholism
4) Treatment with drugs **that are** Dihydrofolate Reductase Inhibitors –
   - Methotrexate
   - Trimethoprim
   - Biseptol

A primary result of *folic acid* deficiency is Megaloblastic Anemia





Vitamin B12

Food sources of vitamin B12:

Eggs, meat, poultry, shellfish, milk and milk products

The minimal requirement: ≈ 1 μg/day.

AGENTS AFFECTING LEUCOPOIESIS

1. Agents Stimulating Leucopoiesis:

- Sodium nucleinate
- Pentoxyl
- Methyluracil
- Molgramostim
- Filgrastim

2. Agents Inhibiting leucopoiesis:

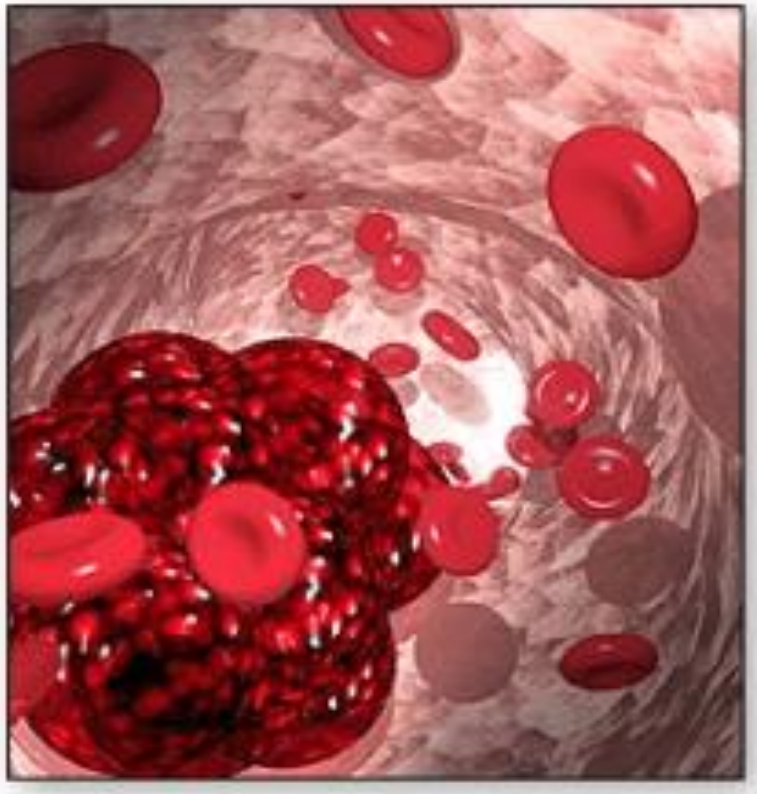
- Cyclophosphamide
- Dopan
- Chlorambucil
- Myelosan
- Mercaptopurine
- Methotrexate

AGENTS USED FOR PROPHYLAXIS AND TREATMENT OF THROMBOSIS

1. PLATELET AGGREGATION INHIBITORS

2. ANTICOAGULANTS

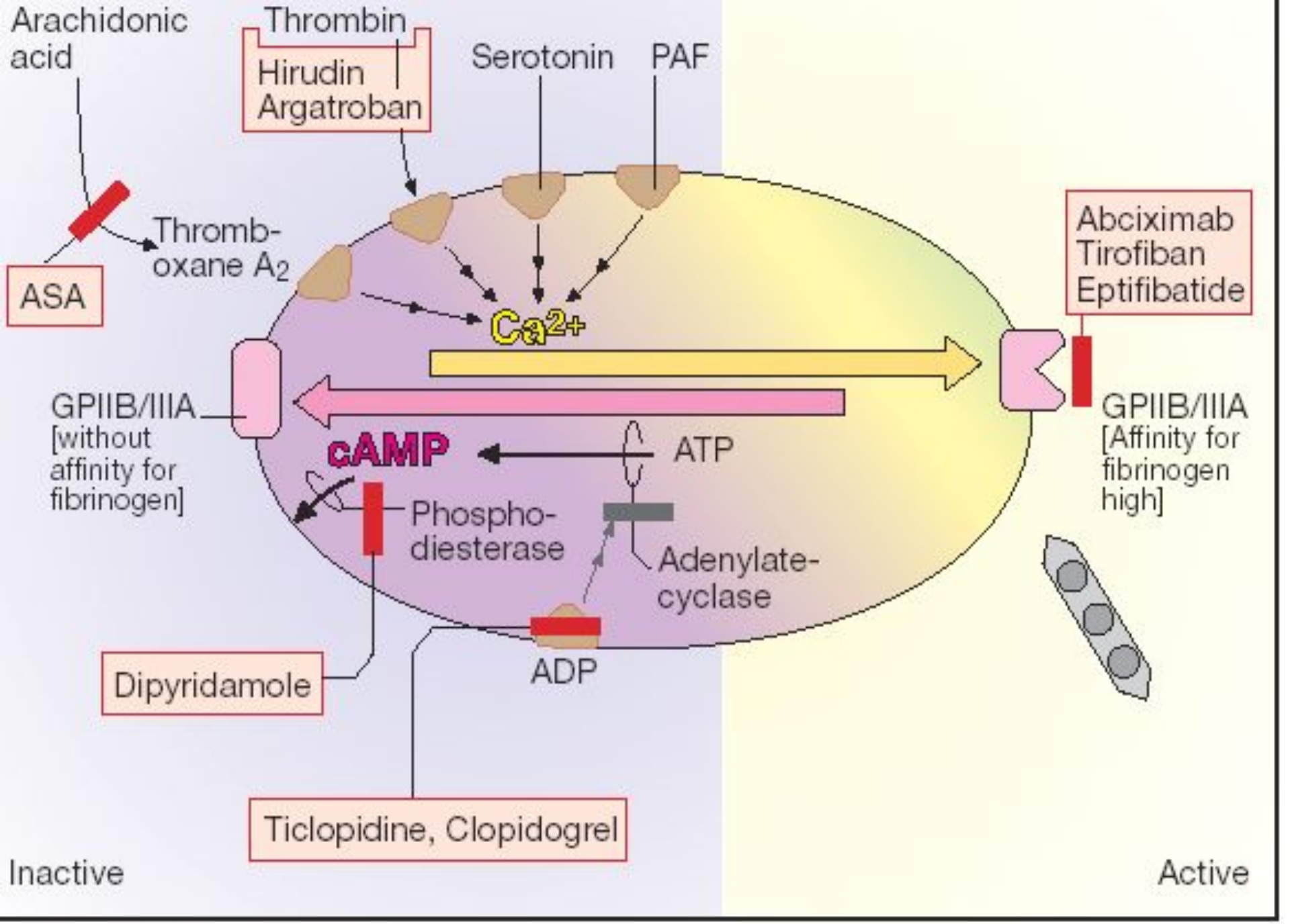
3. THROMBOLYTIC AGENTS



PLATELET AGGREGATION INHIBITORS (ANTIPLATELET AGENTS):

Aspirin, Ticlopidine, Dipyridamole, Pentoxifylline, Abciximab

<u>Clinical Uses:</u> AMI, Prior MI, Unstable or Stable Angina, Stroke, Transient Ischemic Attack, Arterial Bypass Surgery, Angioplasty, Peripheral Vascular Disease.



.. Inhibitors of platelet aggregation

ASPIRIN blocks Thromboxane A_2 *synthesis* from *arachidonic acid* in platelets by irreversible Acetylation and Inhibition of COX –

a key enzyme in PG and TxA_2 synthesis.

ASPIRIN 75 - 325 mg/day

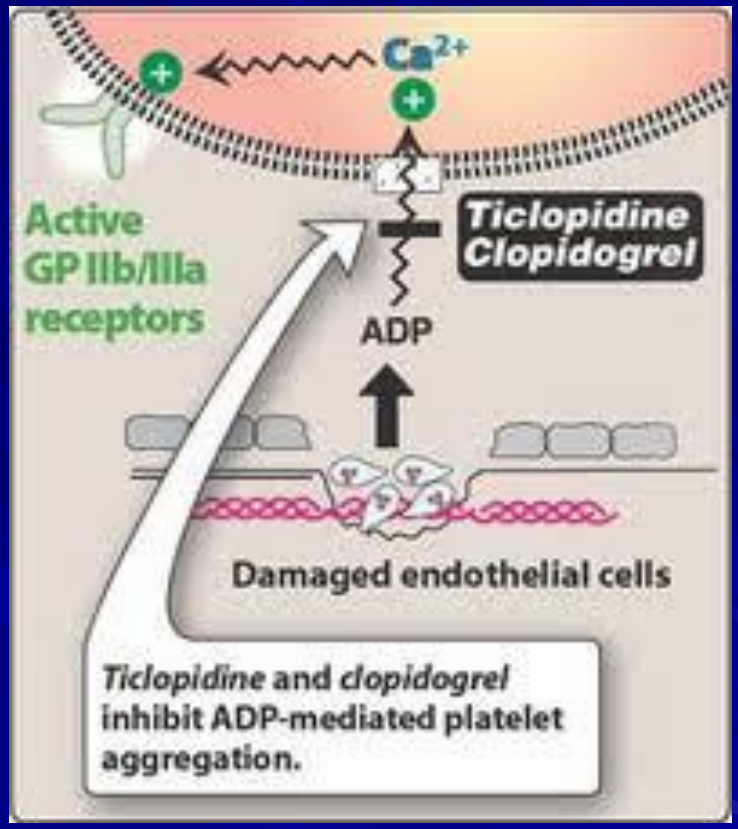
is the Most Widely Tested Regimen.

Ticlopidine **and** Clopidogrel inhibit the ADP pathway involved in the binding of platelets to fibrinogen and to each other.

Adverse Effects:

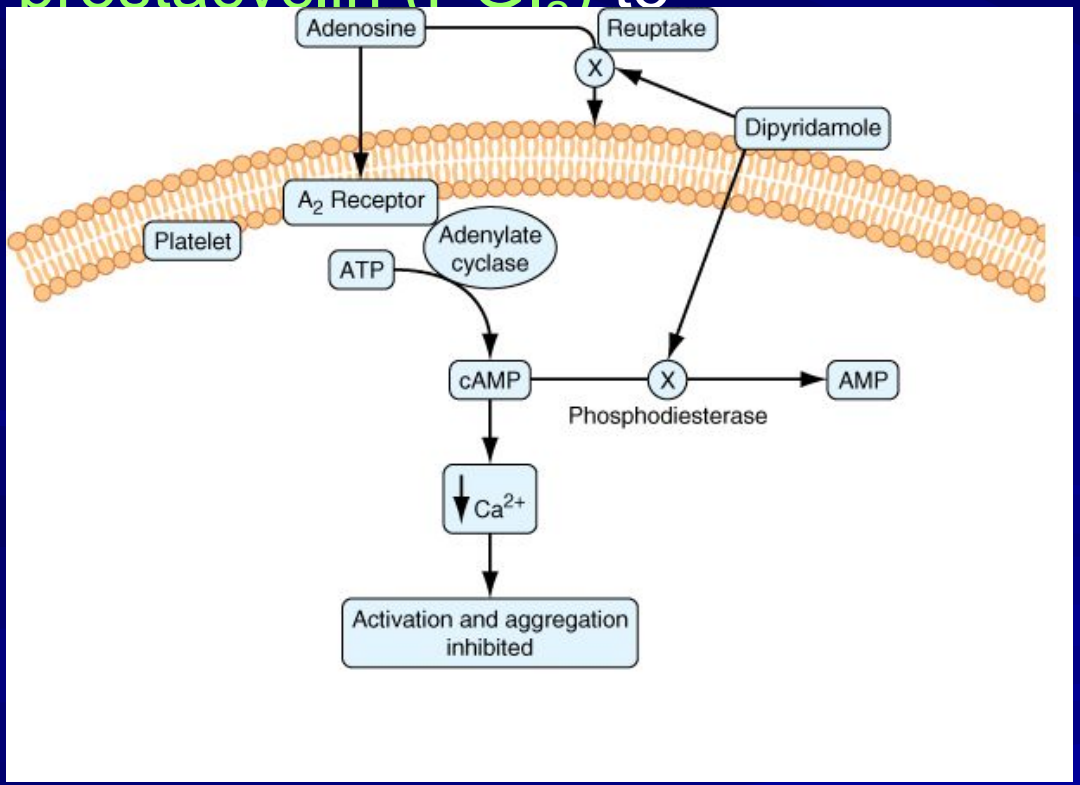
- Prolonged Bleeding
- Neutropenia

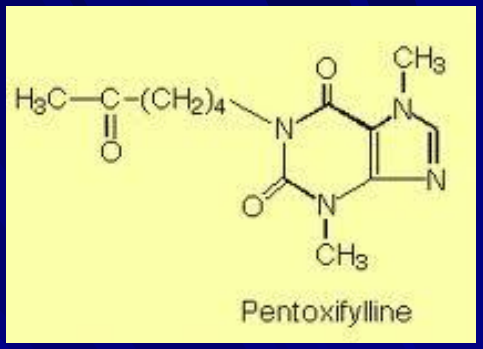
They **are reserved** for patients who cannot tolerate **ASPIRIN.**



Dipyridamole (*Curantil, Persantine*) is a coronary vasodilator which was introduced for Angina Pectoris.

Mechanism of action: it inhibits PDE and blocks reuptake of Adenosine to increase platelet cAMP which inhibits TxA_2 synthesis and potentiates the effect of prostacyclin (PGI_2) to





Pentoxifylline (*Trental*)

inhibits PDE, ↓Platelet and Erythrocytes Aggregation, has desaggregational properties, enhances fibrinolysis, lowers viscosity, IMPROVES MICROCIRCULATION.

ABCIXIMAB

ReoPro 2 mg/ml

IV injection

a Humanized Monoclonal Antibody directed against the platelet **Glycoprotein** IIb/IIIa Receptor Complex and inhibits platelet aggregation.

II. ANTICOAGULANTS:

1. DIRECT ACTION

   HEPARIN - amp 5 ml – 5000 U/ml and 10000 U/ml

   FRAXAPARIN - syringe 0.3 ml, 0.5 ml, 1 ml (1 ml-9,500 IU)

   ENOXAPARIN

   SODIUM HYDROCITRATE

2. INDIRECT ACTION

   Neodicumarin - Tab 0.05 and 0.1 g

   Warfarin - Tab 2 and 10 mg

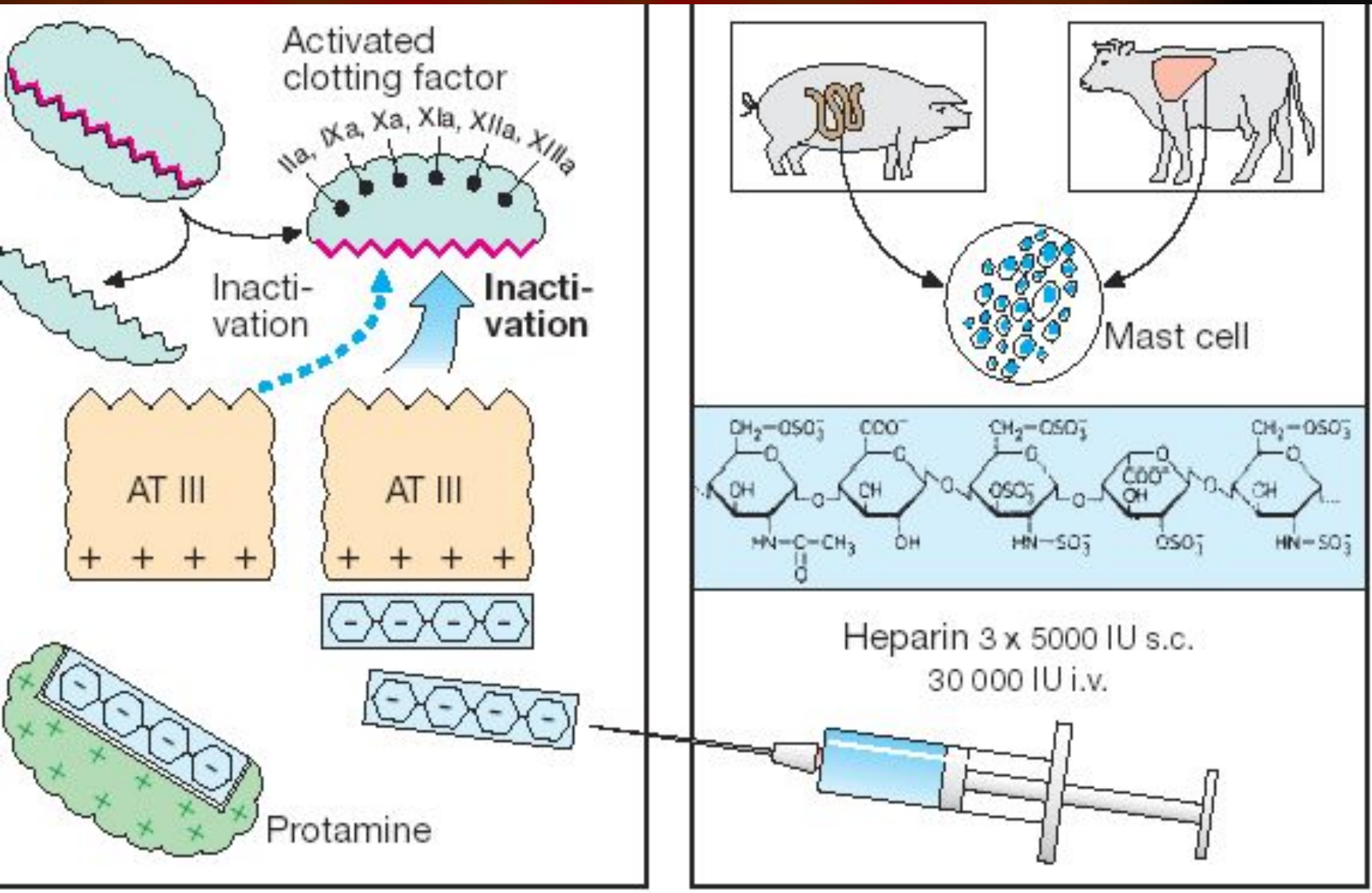
   Phenylin - Tab 0.03 g

   Syncumar - Tab 2 and 4 mg

Heparin

Mechanism of action:

acts indirectly by binding to Antithrombin III. The Heparin-AT III complex binds to clotting factors of intrinsic pathways – IIa, Xa, IXa, XIa, XIIa and XIIIa and inactivates them.



Heparin: origin, structure, and mechanism of action

CONTRAINDICATIONS to *Heparin*:

- Bleeding Disorders, Thrombocytopenia
- Hypertension, Threatened Abortion, Piles, Ulcers
- Subacute Bacterial Endocarditis
- Large Malignancies, Tuberculosis (Hemoptysis)
- Ocular and Neurosurgery, lumbar puncture

ADVERSE EFFECTS of HEPARIN:

1. Bleeding complications.

Excessive bleeding may be managed by suspending the drug or treating with PROTAMINE SULFATE.

2. Hypersensitivity reactions: chills, fever, urticaria, Anaphylactic Shock.
3. Thrombocytopenia.

Clinical uses of *Heparin*:

- Pulmonary Embolism and Deep Vein Thrombosis
- Myocardial Infarction and Unstable Angina
- Prevention of Thromboembolism
- Intravascular Catheters
- Disseminated Intravascular Coagulation Syndrome

Vitamin K is regenerated from the *epoxide* by vitamin K Epoxide Reductase.

It is the enzyme that is inhibited by Neodicumarin, Syncumar and Warfarin.

Neodicumarin (Tab 0.05 and 0.1 g)

is a coumarin derivative.

- It inhibits the hepatic synthesis and activation of

vitamin K-dependent clotting factors II, VII, IX and X, decreasing the blood's coagulation potential.

Clinical Uses of *Neodicumarin*:

- Thrombophlebitis
- Deep Vein Thrombosis
- Myocardial Infarction
- Artificial Heart Valves
- Atrial Arrhythmias

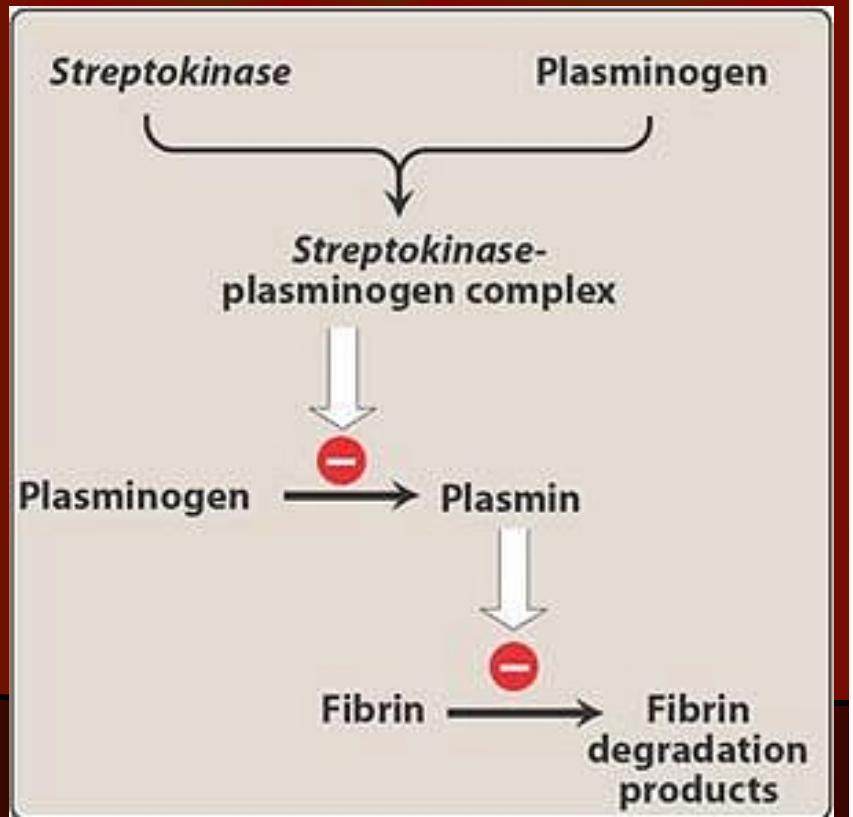
FIBRINOLYTIC (THROMBOLYTIC) DRUGS

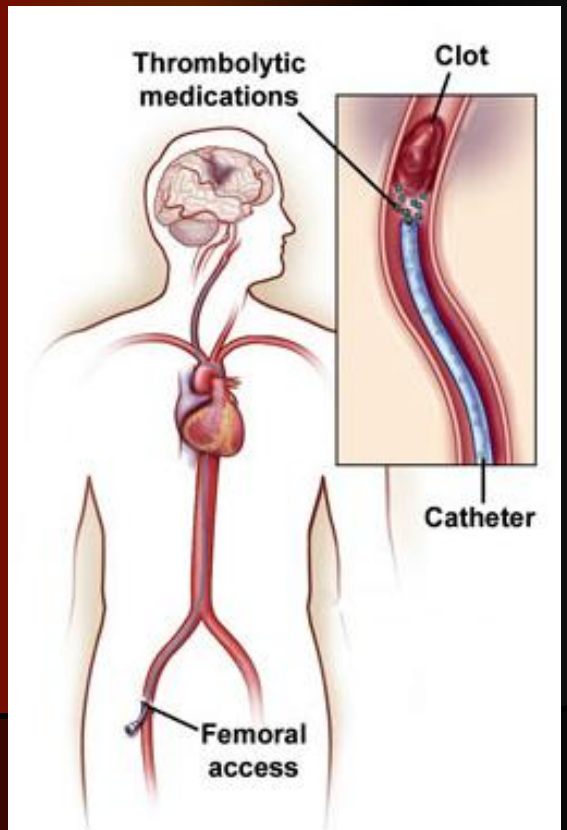
I. Non-selective Activators of Profibrinolysin:
   - Streptokinase
   - Urokinase
   - Streptodekase

II. Selective activators of Profibrinolysin:
   - Alteplase

Streptokinase (amp 250,000 and 500,000 IU) - a non-selective Activator of *Profibrinolysin*, the enzyme extracted from cultures of ***Hemolytic Streptococci.***

It activates Plasminogen (Profibrinolysin) of thrombus and serum to form Plasmin (Fibrinolysin), which degrades fibrin and break up thrombi.





Alteplase and *Duteplase* - recombinant tissue-type Plasminogen Activator (t PA) - act selectively on plasminogen, bound with thrombus and are 'CLOT SELECTIVE'

Agents to Treat Bleeding (Hemostatics**)**

1. Agents enhancing Coagulation of blood:

for Local Application:

Thrombin - amp 125 AU

Sponges hemostatic

System Action:

Gelatin

Fibrinogen

Calcium chloride, Calcium gluconate

Adroxon

Dicynon (*Etamsylat*)

Vitamin K

Protamine sulfate

Adroxon (*amp. 0.025% 1 ml*)

- Hemostatic action
- It is used to stop capillary and parenchymatous bleeding in traumas, during surgery and for prevention of post-operative bleeding and haematomas.

Adroxon is used:

- a) Locally – gauze bandage or tampon moistened with 0.025% solution;
- b) IM or SC 0.025% 1 ml 1–4 times during or after surgery.

Ethamsylate (Dicynon) – amp. 12.5% 2 ml IV or IM, Caps. 0.25 g

- **Antihyaluronidase Action** – improves Capillary Wall stability
- Inhibits PGI_2 production
- Corrects abnormal platelet function

Clinical uses: Prevention and Treatment of Capillary Bleeding in:

- Menorrhagia
- after Abortion, Postpartum Haemorrhage
- Epistaxis (nosebleed)
- Malena (tarry stool)
- Haematuria
- after tooth extraction.

2. ANTIFIBRINOLYTIC AGENTS

Inactivation of the **Fibrinolytic System** can be achieved by **Plasmin Inhibitors** :

- Aminocaproic acid (5% sol.-100 ml)
- Tranexamic acid
- Amben (Pamba) (amp. 1% sol.-5 ml)
- Contrical (Aprotinin, Trasylol)

Thank You for Attention!