

Al-Mustaqbal University College
Department of Pharmacy
General Toxicology
4th stage
Lecture: 4



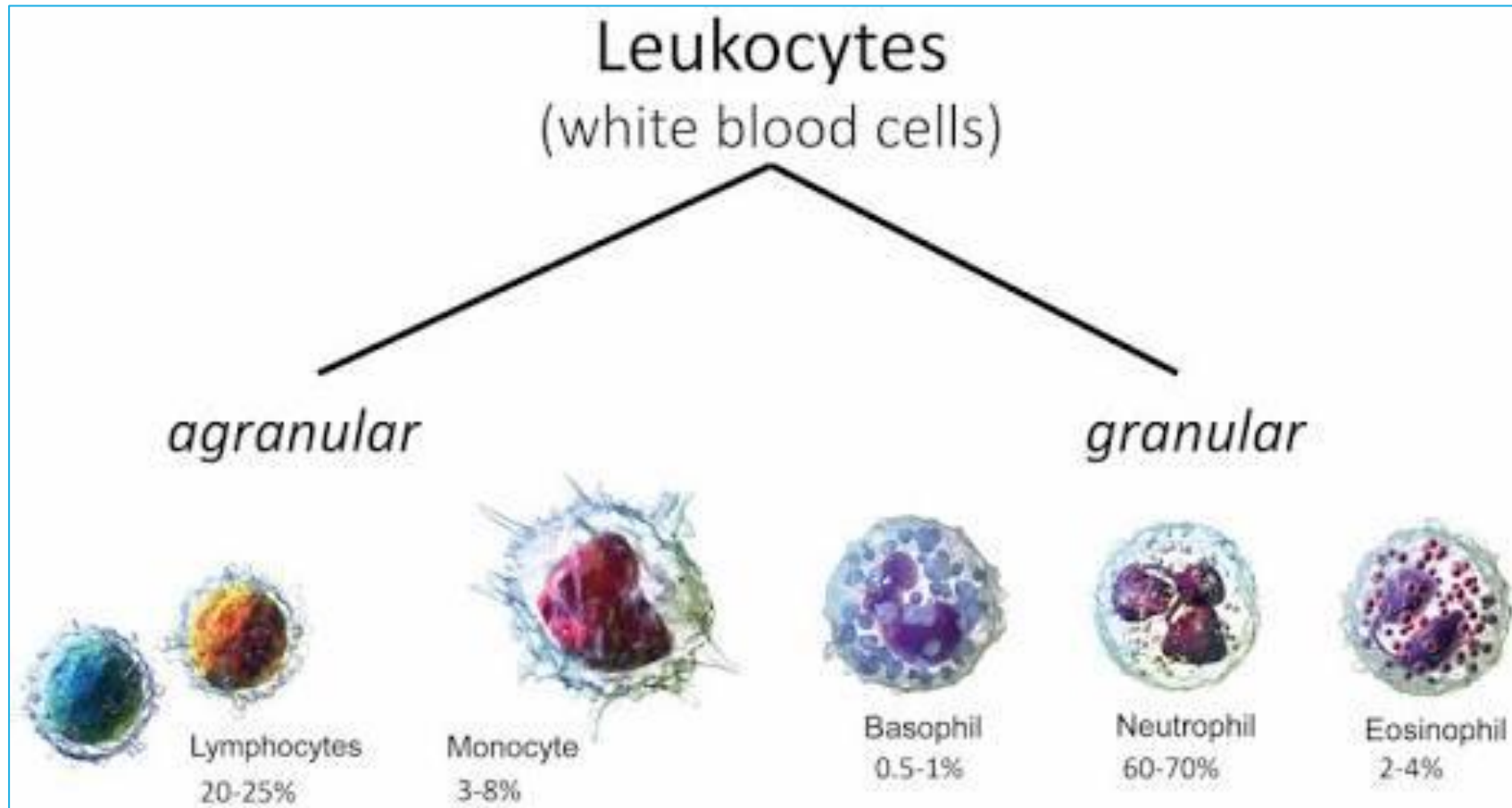
TOXICOLOGY OF THE LEUKON & PLATELET

QASSIM A ZIGAM

Components of Leukon

- ✓ **The leukon** consists of **leukocytes** or white blood cells.
- ✓ They include:
 1. **Granulocyte**: which include neutrophils, eosinophils, and basophils.
 2. **Agranulocytes**: which include monocytes; and lymphocytes.

Components of Leukon



Components of Leukon

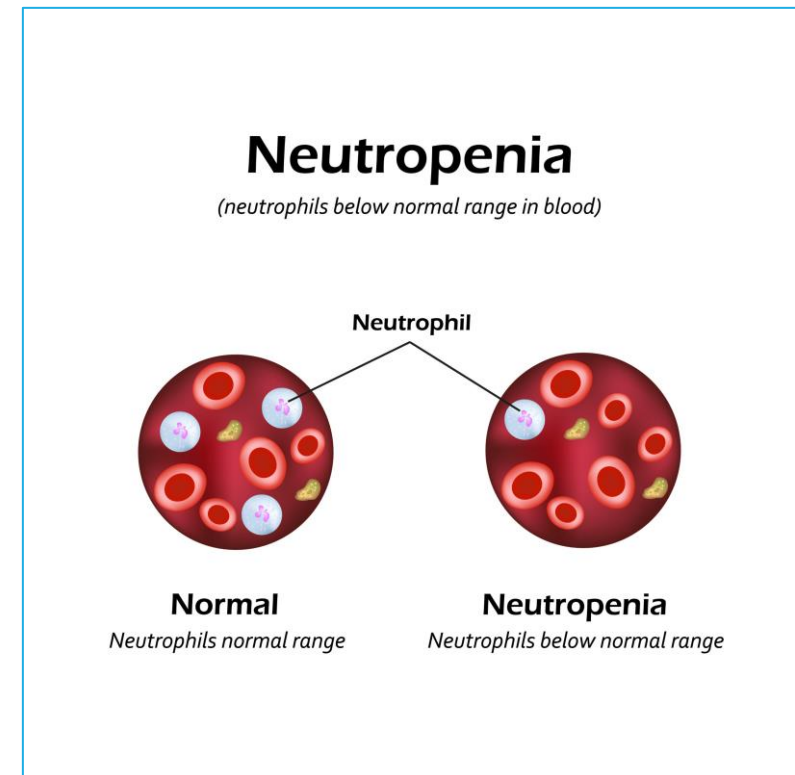
- ✓ The **neutrophil** is the focus of concern when evaluating **granulocytes** as possible targets for **drug** and **non-therapeutic** chemical effects.
- ✓ **Eosinophils** and **basophils** are far more **difficult** to study, with **changes** in these populations most frequently associated with reactions to **other** target organs or systemic toxicity.

Evaluation of Granulocytes

- ✓ The most **informative** test to assess the neutrophil compartment is the **blood neutrophil count**.
- ✓ **Accurate** interpretation requires an **understanding** of neutrophil **kinetics** and the **response** of this tissue to physiologic and pathologic changes.
- ✓ A blood neutrophil count assesses only the **circulating pool**, which remains between **1800/ μ L and 7500/ μ L** in a healthy adult human.

Evaluation of Granulocytes

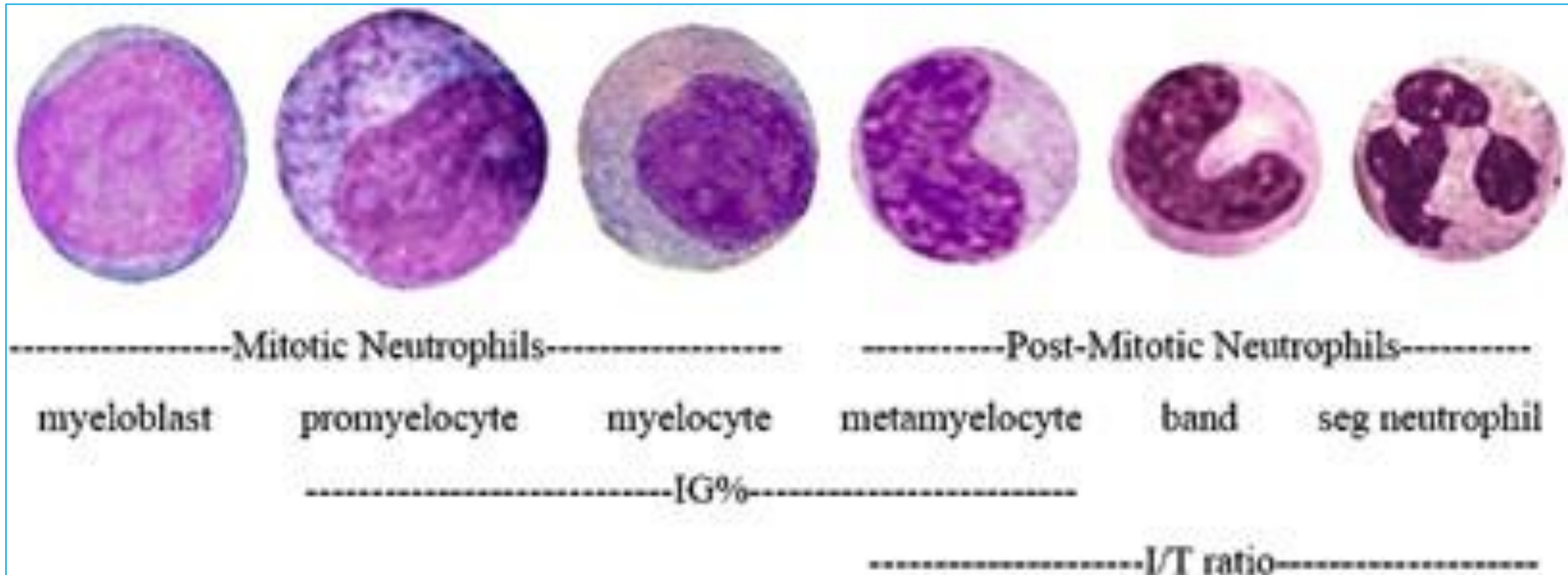
- ✓ In humans, **clinically significant neutropenia** occurs when the blood neutrophil count is **< 1000/ μ L**.
- ✓ But **serious** recurrent infections do not usually occur until counts fall below **500/ μ L**.



Evaluation of Granulocytes

- ✓ **Morphologic** assessment of peripheral blood granulocytes can be helpful in **characterizing neutropenia**.
- ✓ In humans **mature** (segmented) and a few **immature** (band) neutrophils can be identified on blood films stained with **Wright** or **Giemsa** stain.
- ✓ During **inflammation**, a “shift to the left” may **occur**, which refers to an increased number of **immature** (nonsegmented) granulocytes in the peripheral blood, which may include **bands**, **metamyelocytes**, and occasionally **myelocytes**.

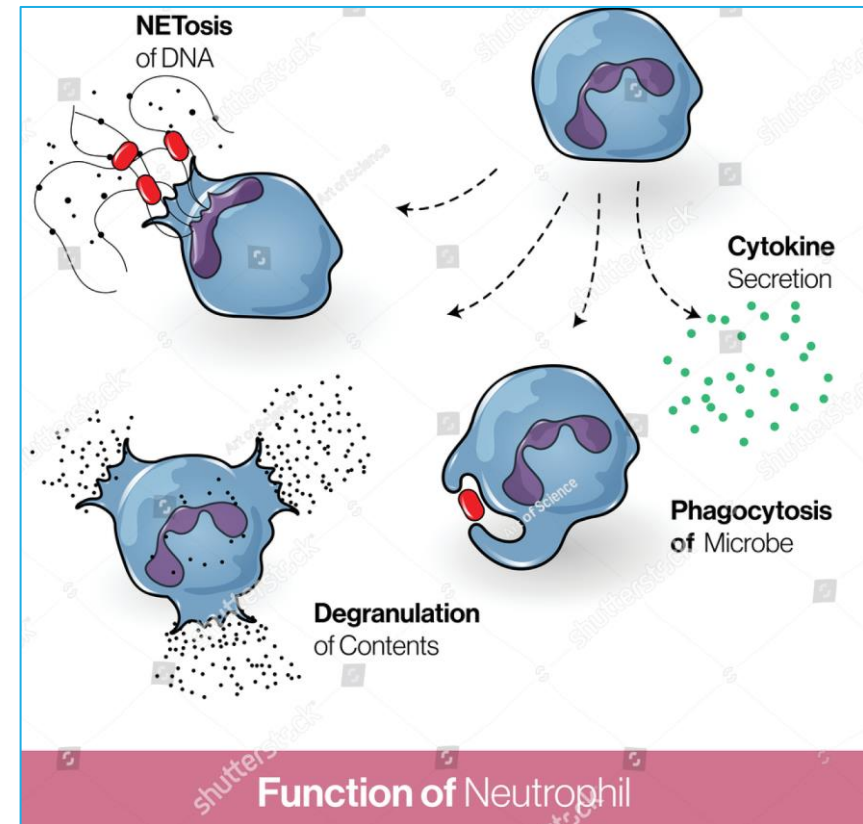
Evaluation of Granulocytes



Toxic Effects on Granulocytes

✓ The toxicologist is concerned with the effect of **xenobiotics** on granulocytes as relates to:

1. **Proliferation** (granulopoiesis) and Kinetics
2. The vital **functions** these cells perform



Toxic Effects on Proliferation and Kinetics

- ✓ The **high rate** of proliferation of neutrophils **makes** their progenitor and precursor granulocyte pool particularly **susceptible** to inhibitors of mitosis.
- ✓ Such effects by **cytotoxic** drugs are generally **nonspecific**.
- ✓ The toxicity associated with **cytotoxic drugs**, include **febrile neutropenia** associated with **life-threatening infections**.
- ✓ Such cytotoxic drugs may include Azathioprin, Bendamustine, and Bleomycin.

Toxic Effects on Proliferation and Kinetics

- ✓ While **cytoreductive** drugs such as **alkylating agents**, **cisplatin**, and **nitrosoureas** can be **toxic to both** resting and actively dividing cells.
- ✓ **Nonproliferating** cells such as metamyelocytes, bands, and mature neutrophils are relatively **resistant**

Toxic Effects on Function

- ✓ Other xenobiotics such as **ethanol** and **glucocorticoids** may **impair phagocytosis** and **microbe ingestion**.
- ✓ **Iohexol** and **ioxaglate**, components of radiographic contrast media, have also been reported to **inhibit phagocytosis**.
- ✓ In addition to glucocorticoids, several **drugs** and **nontherapeutic chemicals** have been shown to **inhibit neutrophil chemotaxis**.
- ✓ Examples include **macrolide** antibiotics, which **suppress** the expression of the adhesion molecule ICAM

Idiosyncratic Toxic Neutropenia

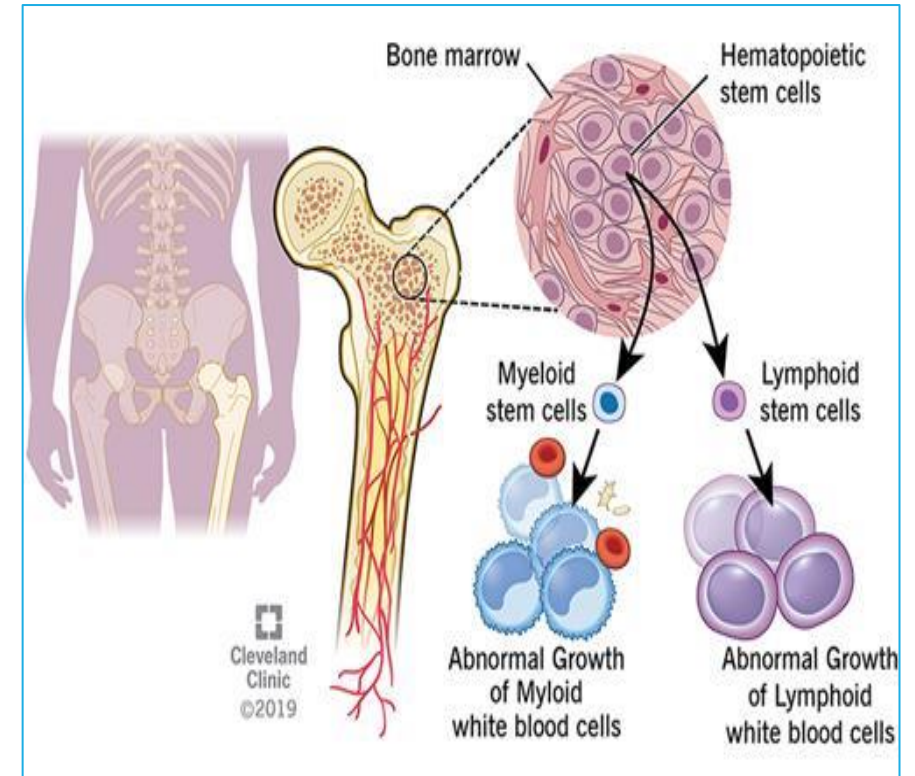
- ✓ Such toxicity occurs in **specifically** conditioned individuals and is therefore termed “**idiosyncratic.**”
- ✓ While it is **rare**, the **seriousness** of this disorder makes it among the **most important** hematotoxicities.
- ✓ **Chemicals** that unexpectedly damage neutrophils and granulocyte precursors.
- ✓ It is **characterized** by a profound depletion in blood neutrophils to **< 500/ μ L.**

Idiosyncratic Toxic Neutropenia

- ✓ In **immune-mediated** neutropenia, antigen-antibody reactions lead to the **destruction** of peripheral neutrophils, granulocyte precursors, or both.
- ✓ An **immunogenic** xenobiotic can act as a **hapten**, where the chemical must be **physically** present to **cause** cell damage or may **induce** immunogenic cells to produce **antineutrophil antibodies** that do not require the drug to be present.
- ✓ Examples of drugs that have been implicated include **fludarabine**, **propylthiouracil**, and **rituximab**.

Leukemia

- ✓ **Leukemia** is the **sixth** leading cause of **cancer deaths** among males and females in the **US**.
- ✓ Leukemias can arise when **hematopoietic stem** or **progenitor** cells in the bone marrow undergo **uncontrolled** proliferation or **clonal** expansion and **cannot differentiate** normally into mature blood cells.



Leukemia

✓ Depending on the **lineage** of origin leukemias are broadly characterized as:

1. Myeloid

2. Lymphoid

✓ Based on the **stage** of differentiation and **rate** of clonal expansion, they are also characterized as:

1. Acute (rapid onset, immature blast cells)

2. Chronic (more gradual onset over months or years, more mature cells).

Leukemia

Using this basic classification, four major types of leukemia are commonly referred to :

1. Acute lymphoblastic leukemia (ALL)

2. Acute myeloid leukemia (AML) also known as acute nonlymphocytic leukemia (ANLL)

3. Chronic lymphoblastic leukemia (CLL)

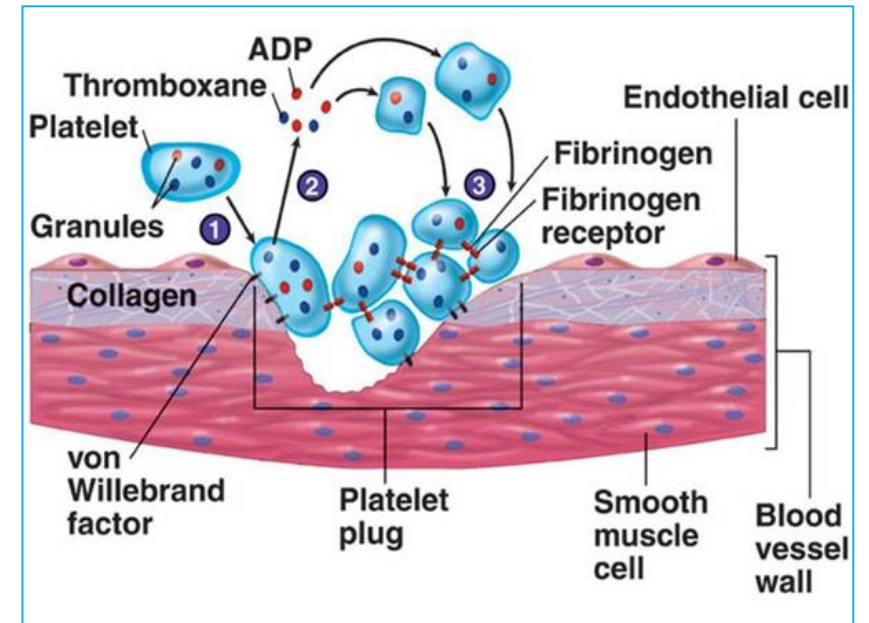
4. Chronic myeloid leukemia (CML)

Leukemia

- ✓ Many **toxicants** can cause leukemia such as **industrial chemicals**, some forms of **radiation**, **immunosuppressive drugs**, and **infectious agents**.
- ✓ The **established nongenetic causes** of AML are ionizing radiation, cytotoxic chemotherapeutic drugs, tobacco smoking, and occupational exposure to benzene or high levels of formaldehyde.

Toxic Effects on Platelets

- ✓ Platelets are **essential** for the formation of a stable **hemostatic plug** in response to vascular **injury**.
- ✓ They **initially** adhere to the damaged wall through binding of **von Willebrand factor (vWF)** with the platelet **glycoprotein** receptor complex.



Toxic Effects on Platelets

- ✓ Xenobiotics may interfere with:
 1. Platelet **number** by causing thrombocytopenia
 2. Platelet **function**
 3. **Both** platelet number and function.

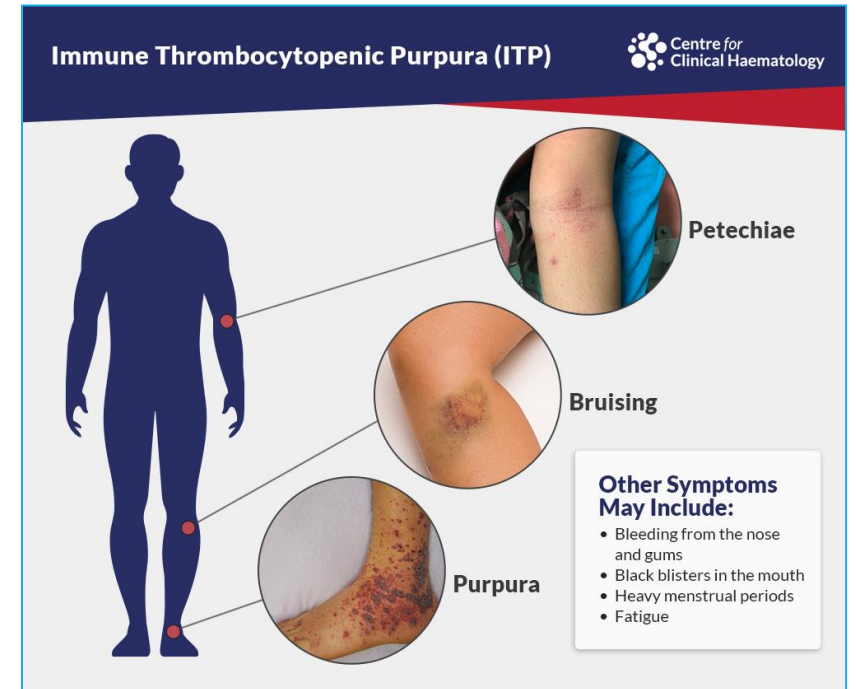
Thrombocytopenia

- ✓ A state of **low platelet count**, it can range from **mild** to **severe**, depending on its underlying cause.
- ✓ **Thrombocytopenia** may be due to **decreased production** or **increased destruction**.
- ✓ It is a common **side effect** of intensive **chemotherapy**, due to the predictable effect of antiproliferative agents on hematopoietic precursors, including those of the **megakaryocytic** lineage.

Immune Thrombocytopenia

✓ It was thought to be an **antibody-mediated** disease with:

1. Either the **xenobiotic** acting as a **hapten** after binding to the platelet surface.
2. Or by the **xenobiotic** causing a **neoepitope** to be formed on a platelet membrane.



Immune Thrombocytopenia

- ✓ More than **100 drugs** have been associated with immune thrombocytopenia.
- ✓ The most **frequently** implicated are carbamazepine, ibuprofen, rifampicin, sulfamethoxazole, trimethoprim, quinine, quinidine, and vancomycin.

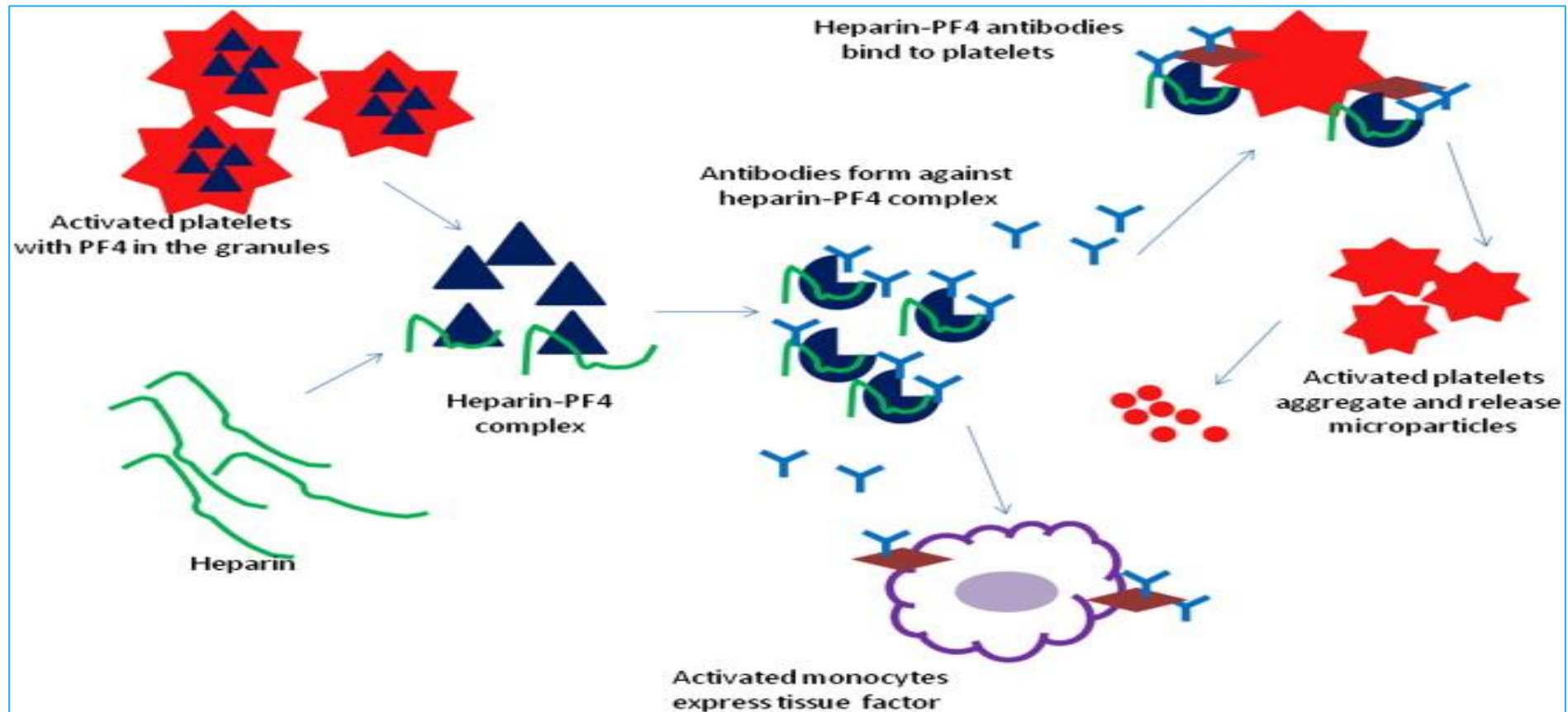
Heparin-induced thrombocytopenia (HIT)

- ✓ HIT represents another mechanism of **immune-mediated** platelet destruction.
- ✓ This disorder is due to the development of **antibodies** that react with a **multimolecular complex** formed by the **interaction** between **heparin** and a **protein**, usually platelet factor 4 (PF4).

Heparin-induced thrombocytopenia (HIT)

- ✓ When the **relative concentration** of heparin to PF 4 is **appropriate**, formation of this **complex** is associated with exposure of a **neoepitope** on PF 4 (or another target protein) and development of an **IgG** response to the neoepitope.

Heparin-induced thrombocytopenia (HIT)

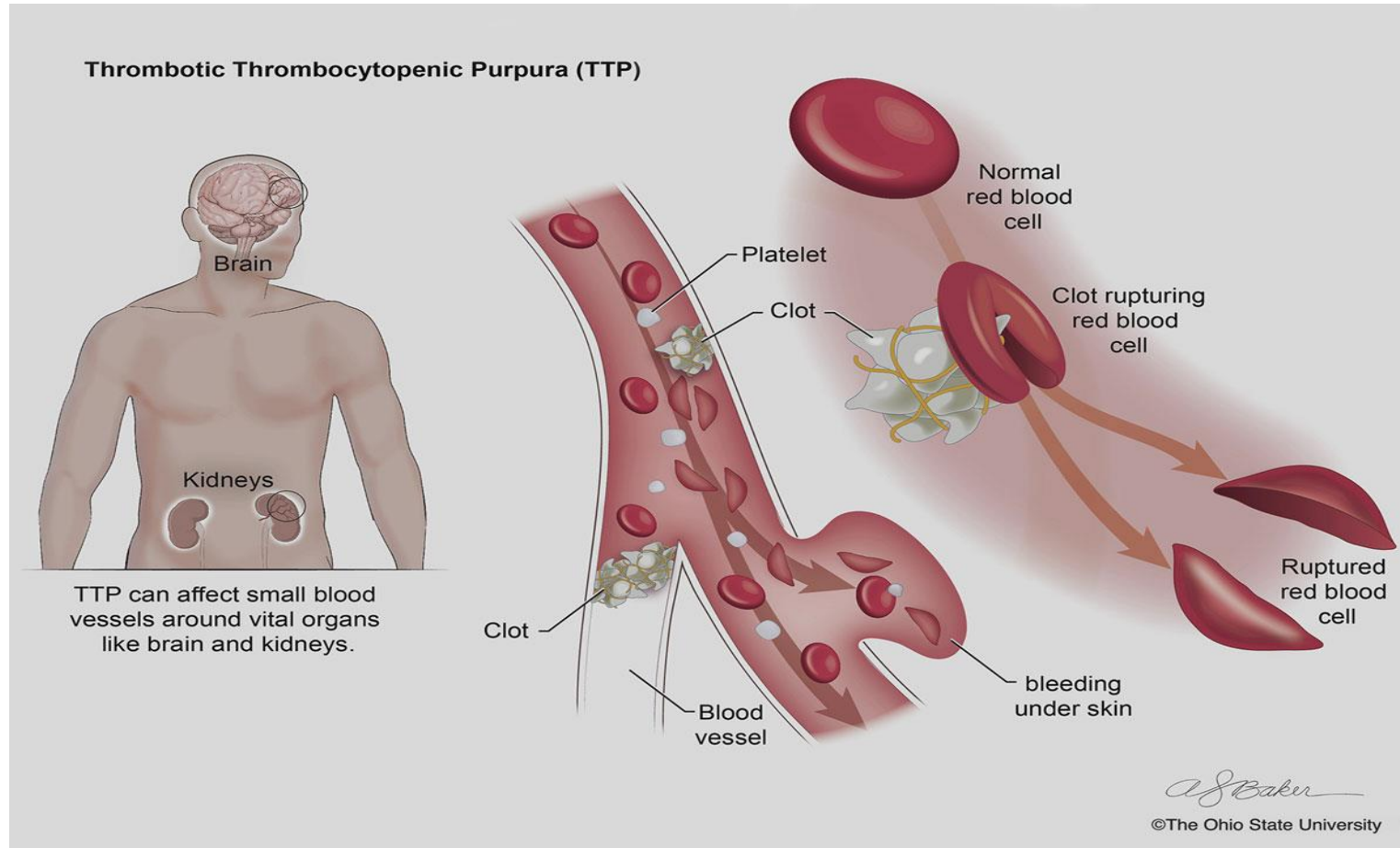


Thrombotic Thrombocytopenic Purpura (TTP)

- ✓ It is a **rare** and **life-threatening** thrombotic microangiopathy characterized by:
 1. Microangiopathic hemolytic **anemia**
 2. Severe **thrombocytopenia**
 3. Organ **ischemia** linked to **disseminated** microvascular platelet rich-thrombi.
- ✓ Some **drugs** that accounted for TTP are **quinine, cyclosporine, and tacrolimus.**



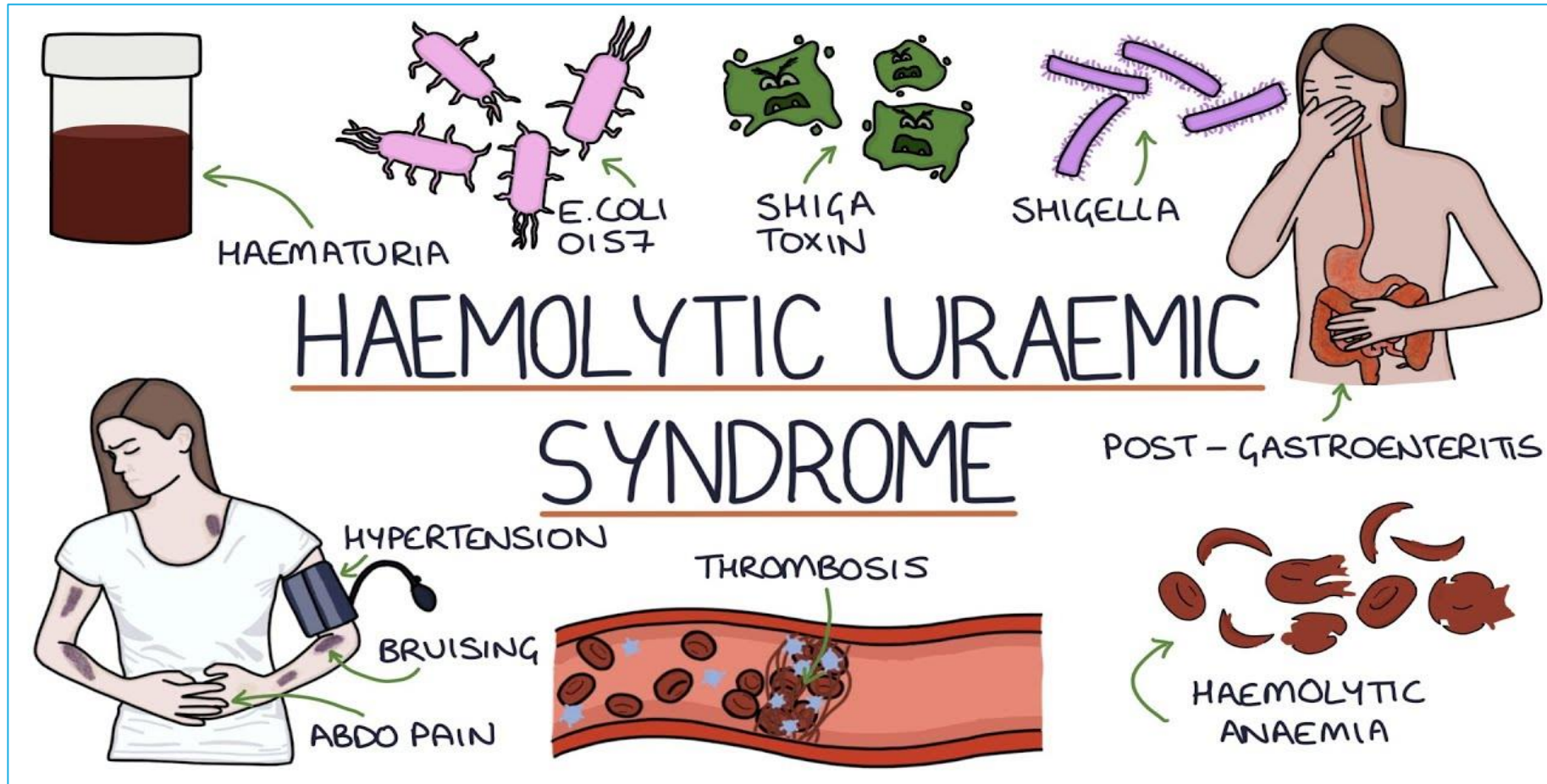
Thrombotic Thrombocytopenic Purpura (TTP)



Hemolytic uremic syndrome (HUS)

- ✓ HUS has **clinical features** similar to those of **TTP**, with **microangiopathic hemolytic anemia, thrombocytopenia, and renal failure.**
- ✓ HUS is usually categorized as:
 1. **Typical**, caused by **Shiga toxin-producing *E. coli* (STEC)** infection.
 2. **Atypical**, usually caused by **uncontrolled complement activation**, or as **secondary** HUS with a coexisting disease.

Hemolytic uremic syndrome (HUS)



**THANK YOU
FOR YOUR ATTENTION**