Microscopic Anatomy: Blood

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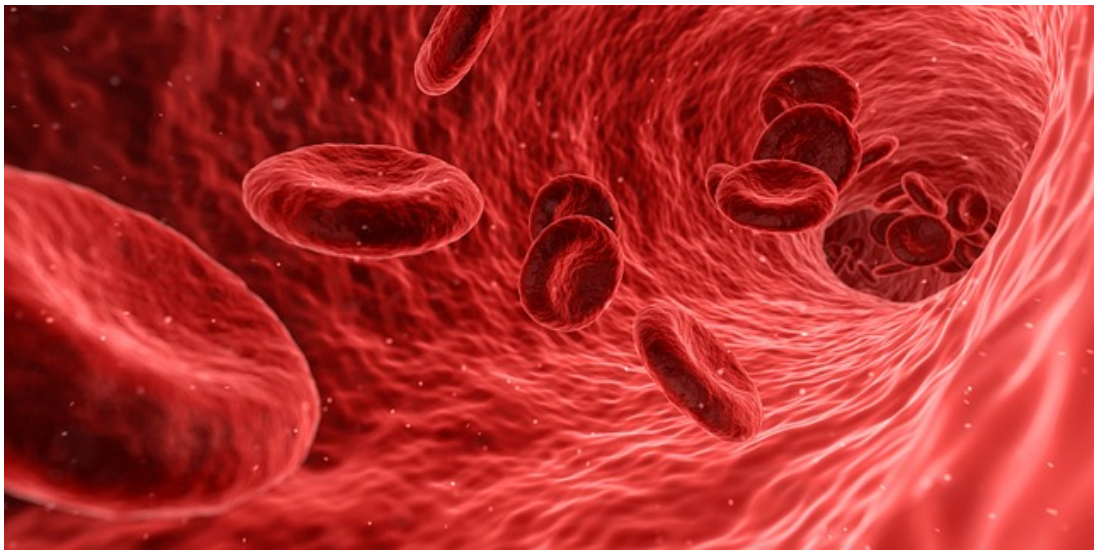
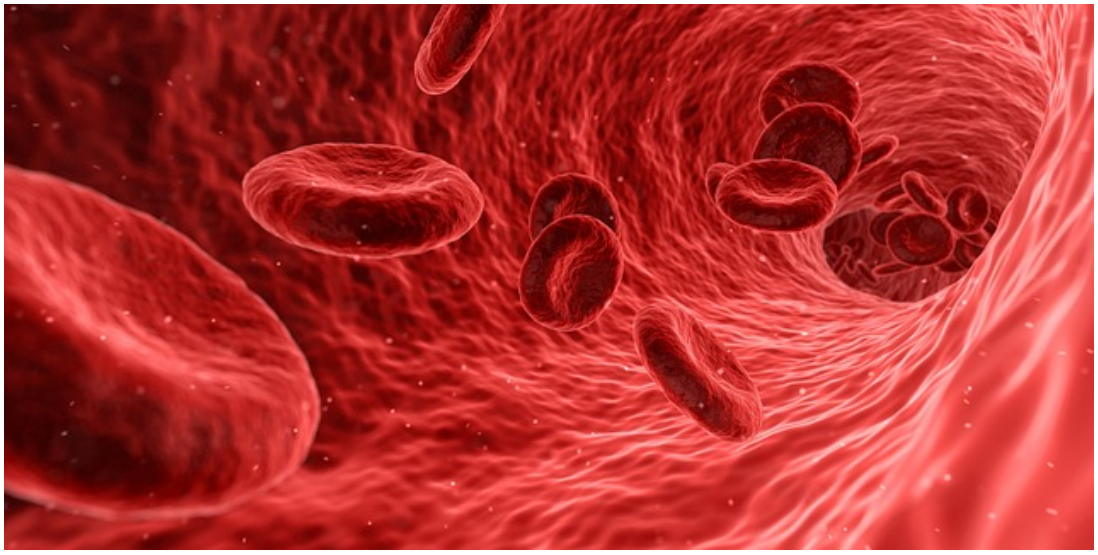
Blood (Latin: *sanguis*, Greek: *haima*) is a suspension of cells in a saline solution containing protein. It makes up 6–8% of the total body weight and has a pH value of 7.4. The blood carries out many essential functions and is the pivotal point of the whole organism. The following article provides, at a glance, the most important facts about this vital body fluid called blood.



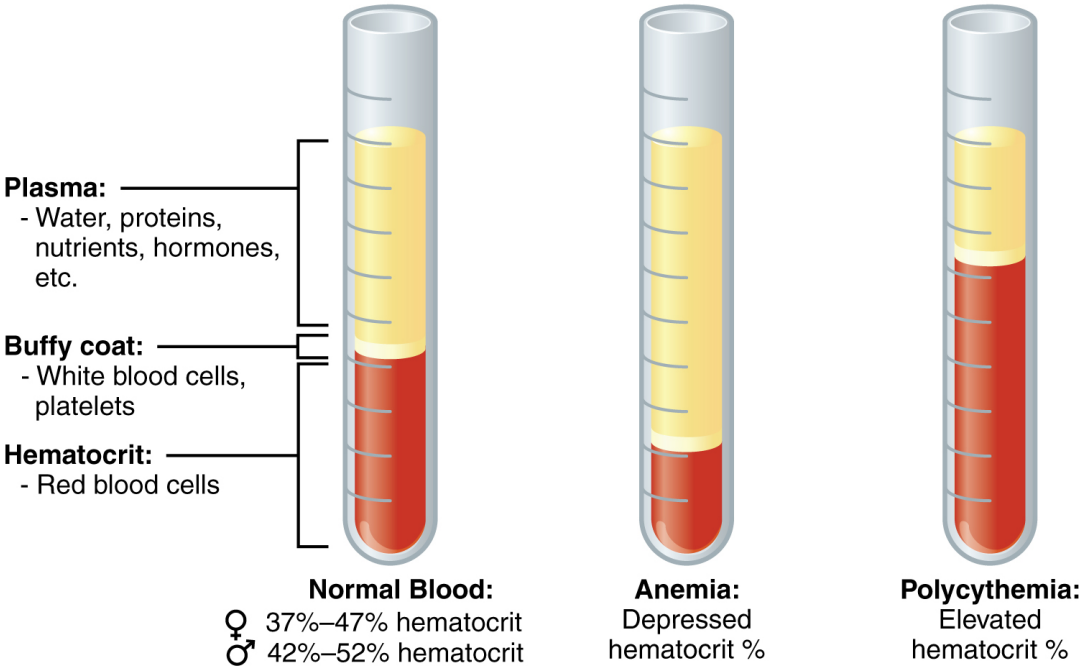


Blood Components

The average 70 kg human being has approx. 4.2 L of blood. If a blood sample is centrifuged, a more or less turbid liquid (depending on the fat content of the blood) becomes visible with red sediment set off against it. The liquid component represents the blood plasma; the sediment is the so-called blood clot made out of blood cells. The ratio of plasma to blood cells is indicated by the hematocrit. This is physiologically at 42% for women and 45% for men.

Blood plasma

The plasma represents approx. 55% of the blood. It contains water, proteins, ions, hormones, and physically dissolved gases. The serum that is free of coagulation factors can be obtained from the blood plasma.



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Normal values of plasma electrolytes:

- Na^+ 140 mmol/L
- K^+ 4.5 mmol/L
- Ca^{2+} 2.4 mmol/L
- Cl^- 105 mmol/L
- HCO_3^- 24 mmol/L

This yields an osmotic pressure of 5,600 mm Hg and an osmolarity of 290 mOsm/L for the plasma. The largest part of the plasma with 75 g/L is the plasma proteins. They hardly contribute to osmolarity but do play an important role in the colloid osmotic (or oncotic) pressure, i.e. the osmotic pressure between the plasma and the interstitium. It comes to 25 mm Hg and is thus significantly higher than that of the interstitium (5 mm Hg), which prevents too much plasma fluid from diffusing from the blood vessels into the tissue.

The most common protein is albumin (54–60%). It is, therefore, essential for the oncotic pressure. Albumin is produced in the liver and is 1 of the smallest plasma

proteins. It is used as a transporter of cations, bilirubin, fatty acids, and cholate.

Other important plasma proteins are the globulins. These are divided into alpha, beta, and gamma. **Alpha and beta globulins, like albumin, act as a vehicle.** E.g., the fat transporting LDL (low-density lipoproteins) and HDL (high-density lipoproteins) are important representatives of the globulins.

Gamma globulins, by contrast, have an immunological function and contain immunoglobulin (Ig). They can be subdivided into 5 Ig classes according to their different chemical structures. In the plasma, there are primarily immunoglobulins IgG, IgA, and IgM present.

Blood components in %	**Sub-components of the blood in %**	**Type in % (if applicable)**	**Production site**	**Main tasks**
Plasma 43–63%	Water 92%	Liquid	Absorbed through the intestinal tract or produced during metabolism	Transport medium
	Plasma proteins 7%	Albumin 54–60%	Liver	Maintains the osmotic concentration, transports lipid molecules
		Globulins 35–38%	Alpha globulins: liver	Transport, maintain the osmotic concentration
			Beta globulins: liver	Transport, maintain the osmotic concentration
			Gamma globulins (immunoglobulins): plasma cells	Immune response
		Fibrinogen 4–7%	Liver	Blood clotting during hemostasis
	Regulatory proteins < 1%	Hormones and enzymes	Various locations	Regulate various body functions
	Other dissolved substances 1%	Nutrients, gases, and waste	Absorbed through the intestinal tract, replacement of cells in the respiratory tract or produced in the cells	Many different functions

Formed Elements 37–54%	Erythrocytes 99%	Erythrocytes	Red marrow	Transports gases, primarily oxygen and some carbon dioxide
	Leukocytes < 1%, platelets < 1%	Granular leukocytes: neutrophils, eosinophils, and basophils	Red marrow	Non-specific immune response
		Agranular leukocytes: lymphocytes, monocytes	Lymphocytes: bone marrow and lymphoid tissue	Lymphocytes: specific immune response
			Monocytes: red marrow	Monocytes: non-specific immune response
	Platelets < 1%		Megakaryocytes: red marrow	Hemostasis

Blood cells

Erythrocytes/red blood cells (RBCs)

The RBCs are easily recognized by their biconcave shape. They have a diameter of 7.5 µm, and, with a count of 4.5 x 10^6/ µL in women and 5.2 x 10^6/µL in men, they are the most common cells in the blood. RBCs contain hemoglobin. They have no cell nucleus or cell organelles and, therefore, have only a life span of approx. 120 days, before they are decomposed in the spleen.

The formation of erythrocytes takes place in the red bone marrow and is stimulated by the erythropoietin released in the kidney. If the marrow does not produce enough RBCs then extra-medullary hematopoiesis takes place in the peripheral organs.

RBCs have a larger diameter than some capillaries. For this, the deformability of the RBCs is extremely important. It is ensured through its distinctive **membrane skeleton made out of ankyrin, spectrin, and actin**.

Thrombocytes/platelets

Platelets in their free form have a biconvex shape, and, with a diameter of only 2.5 µm, they are **far smaller than erythrocytes**. Healthy human blood contains 150,000–400,000 platelets/µL of blood. Platelets are **nucleus-lacking cell fragments formed by shedding off of the megakaryocytes** of the bone marrow and circulate in the blood around 10 days if they do not become activated for blood coagulation.

Leukocytes/white blood cells (WBCs)

WBCs are the immune cells of the blood. Their number varies between 4,000 and 10,000/µL in the blood. WBCs are divided into monocytes, granulocytes, and lymphocytes.

1. **Monocytes** stand out in the blood smear due to their size (15–20 µm). Monocytes typically have a kidney-shaped nucleus, and the cytoplasm appears pale grey under a light microscope. Monocytes are very rare (6% of the leukocytes) and

circulate only 1–3 days in the blood. During this time, **they mature to macrophages, which then migrate into the tissue**. Accordingly, monocytes are sparse in peripheral blood smears.

2. **Granulocytes** are 10–12 µm in size; like all blood cells, granulocytes develop in the red bone marrow and are divided into 3 groups:
    - **Neutrophils:** constitute the largest proportion of WBCs and usually have a segmented nucleus**.** These are called segmented neutrophils. Eight % of the neutrophil granulocytes are banded neutrophils (or stab neutrophils) whose nucleus is not segmented but rather curved. In the Pappenheim stain, the granules of the neutrophils appear as a faint pink.
    - **Eosinophil granulocytes:** make up only 3% of the WBCs and have a nucleus that consists of 2 lobes. Their granules stand out in a blood smear by their brick-red coloration.
    - **Basophil granulocytes** are the least frequent in the blood smear. The granules usually cover the cell nucleus and are colored dark blue.
3. **Lymphocytes** have a round, purple-colored cell nucleus that is surrounded by a thin, pale gray cytoplasmic border. They are classified as natural killer cells, B cells (**b**one marrow) and T cells (**t**hymus). Under the light microscope, however, the 3 types cannot be distinguished.

Functions of the Blood

Erythrocytes: transport of gas

The oxygen (O_2) content in the arterial blood of a healthy person is about 200 mL O_2/L. Hemoglobin (Hb) binds 85% of the oxygen; the rest is physically dissolved in the plasma.

Hemoglobin is located in the erythrocytes. In an adult, Hb consists of 2 α- and 2 β-subunits. Each subunit has a Fe^{2+} ion, which binds O_2. Thus, 1 Hb can transport 4 oxygen molecules. **The Hb concentration in men is 16 g/dL and in women—14 g/dL.**

In the periphery, Hb releases the oxygen into the tissue and also takes up a portion of the carbon dioxide (CO_2). The majority of the CO_2, however, is carried in the erythrocyte in the form of bicarbonate and is exhaled in the lungs.

Platelets (thrombocytes) and clotting

Blood clotting is also called hemostasis and is divided into primary and secondary hemostasis.

Primary hemostasis occurs when the vascular endothelium is damaged and platelets come into contact with collagen located outside the vessel. **The Von Willebrand factor in t**he collagen binds the **glycoprotein Ib** of the platelets to its receptor**,** and the **platelets** anchor on the damaged endothelium.

At the same time, Ca^{2+} activates the platelets. This means that the tubule ring within the platelet contracts and pseudopods emerge. Together with **adenosine diphosphate (ADP),** released from the injured cells, **thrombocytes** stick together and a so-called **platelet plug** is formed**.** The **activated platelets** also secrete serotonin, fibrinogen, and thromboxane A2. The latter causes, among other things, vasoconstriction, which supports the closure of the vessel.

For the platelet plug not to block the whole vessel, **the endothelium** releases **prostacyclin which inhibits platelet aggregation.** This way, a targeted plug formation at the damaged endothelium is guaranteed.

Secondary hemostasis is divided into **extrinsic** and **intrinsic** systems or pathways.

The extrinsic system comes into action when tissue is destroyed. With a prothrombin time of about 14 seconds (Quick test), it acts very fast. The tissue factor from the vascular smooth muscles forms a complex with phospholipids. This is called tissue thromboplastin and binds the **coagulation factor VII,** which then activates **factor X** with Ca^{2+} present.

In the **intrinsic system, factor XII** comes into contact with negatively charged surfaces, such as collagen (or glass), and becomes activated. Subsequently, **factor XI** and then **IX** is activated. Factor IX along with phospholipids and Ca^{2+} ions form an enzymatic complex, which activates **factor X (thrombokinase)** by limited proteolysis. This process can be greatly accelerated with the **thrombin activated factor VIII**. The partial thromboplastin time comes to 40–50 seconds.

With the activation of factor X, **the intrinsic and extrinsic systems converge**. Factor X, in combination with factor V, phospholipids, and Ca^{2+} ions, forms the prothrombin activator, which splits factor II (prothrombin) to thrombin. **Thrombin**, in turn, divides factor I (fibrinogen) to soluble **fibrin,** which, through factor XIII and Ca^{2+} ions becomes solid, so that a red thrombus is formed.

The process of breaking down coagulation is called **fibrinolysis**. This activates plasminogen to **plasmin** by blood factors. The latter then splits fibrin into individual peptides. Also, it splits the coagulation factors I, II, V, VIII, IX, XI, and XII, thus lowering the clotting ability of the blood.

Leukocytes: defense against foreign bodies

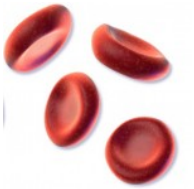
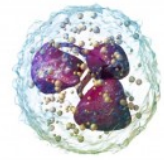
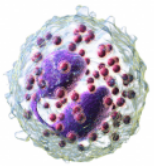
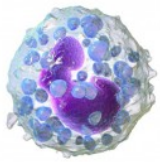
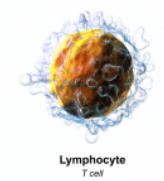
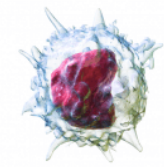
Neutrophil granulocytes act as rapid action force for **inflammation** and thus belong to the non-specific immune system. During an infection, the number of neutrophils increases quickly by using the reserves from the marginal pool (on the endothelium of large veins) or the bone marrow. They fight bacteria and can remove debris of endogenous cells. The suspension of dead neutrophils and tissue debris in the tissue fluid is called pus.

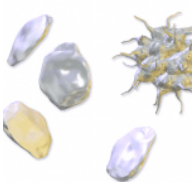
Eosinophil granulocytes serve to defend against worm parasites.

Lymphocytes, except for natural killer cells, are part of the **specific immune system**. In the thymus, T lymphocytes are trained to distinguish the body’s antigens from foreign antigens and to respond accordingly. Hereby, T helper cells and cytotoxic lymphocytes develop. T helper cells support the mechanisms of the specific and non-specific defense; the cytotoxic lymphocytes recognize virus-infected or degenerated cells based on their antigens and kill them.

B lymphocytes can be activated to **plasma cells**, which produce **free antibodies** that bind foreign antigens and neutralize them. This means that B lymphocytes belong to the **humoral component** of the **specific immune** response. When activated, part of the B lymphocytes differentiates to become memory cells that remain in the body for many years. When contact occurs with a known antigen, they already know which antibodies are required.

Natural killer cells are part of the non-specific immune system, and, through their cytolytic granules, they can trigger apoptosis in degenerated cells.

Formed element	Main subtypes	Number/µL and importance (scale)	Appearance in the standard blood smear	Summary of the functions	Comment
Erythrocytes (RBCs) 		5.2 million (4.4–6.0 million)	Flattened biconcave disc; no nucleus; bright red color	Transport oxygen and some carbon dioxide between tissues and lungs	Life: approx. 120 days
Leukocytes (WBCs)		7,000 (5,000 –10,000)	Dark-colored nucleus	All of the functions of the immune system	Leave the capillaries and move into the tissue, life: usually a couple of hours or days
Leukocytes	**Granulocytes**	4,360 (1,800–9,950)	Abundant granules in the cytoplasm; usually capped nucleus	Non-specific disease resistance	Classified according to membrane-bound granules in the cytoplasm
	Neutrophils 	4,150 (1,800–7,300)	Number of nucleus lobes increases with age	Phagocyte; particularly effective against bacteria; releases cytotoxic chemicals of granules	Most common leukocyte, life: minutes and up to days
	Eosinophils 	165 (0–700)	Nucleus usually 2-lobed; bright, red-orange granules	Phagocytic cells; particularly effective with antigen-antibody-complex; release antihistamines; promote action against allergies and parasitic infections	Life: minutes to up to days
	Basophils 	44 (0–150)	Nucleus usually 2-lobed, but difficult to detect due to heavy, dense, and dark purple granules	Promote inflammation	Least frequent leukocyte, life span: unknown
	Agranulocytes	2,640 (1,700–4,950)	Lack of granules in the cytoplasm; has a simply shaped nucleus, which can be indented	Immune response	Group consists of 2 main cell types from several different origins
	Lymphocytes 	2,185 (1,500–4,000)	Sphere-shaped cell with a single, often large nucleus, which accounts for a large part of the cell volume; dark spots; appears as a large (natural killer cells) and small (B and T cells) variant	Primary specific (adaptive) immune response; T cells directly attack other cells (boost cellular immunity); B cells release antibodies (humoral immunity); natural killer cells are similar to the T cells, but are non-specific	Initial cells derived from the bone marrow, secondary production occurs in the lymphoid tissue; several different subtypes; memory cells are formed after contact with a pathogen and provide a faster reaction; lifetime: many years
	Monocytes 	455 (200–950)	Largest leukocyte with an indented or horseshoe-shaped nucleus.	Particularly effective phagocytes, swallow up pathogens or worn cells; also serve as antigen-presenting cells for the other components of the immune system	Produced in the red bone marrow; after leaving the circuit, called macrophages

Blood platelets 	350,000 (150,000 –500,000)	Cell fragments surrounded by the plasma membrane, contain granules; purple spot	Hemostasis and release of growth factors to repair and heal tissue	Formed from megakaryocytes that remain in the red bone marrow and release platelets into the bloodstream

Diseases of the Blood

Levels of Inflammation in the blood

Inflammation values play an important role in diagnostics, typically obtained by the analysis of a blood sample. This usually includes the **erythrocyte sedimentation rate (ESR)**, **C-reactive protein** and **WBC** count. Also, there is a differential leukocyte count.

For the determination of the ESR, blood is stored in a narrow tube for 2 hours in an upright position. After 1 hour, the distance the RBCs have traveled downwards to settle at the bottom of the tube is measured. Normal values after an hour are less than 15 mm in men and under 20 mm in women. A change in these values can indicate anemia, inflammation, and even cancer.

The C-reactive protein is part of the immune system and is considered a marker for acute inflammation. In a healthy person, the concentration of C-reactive protein in the blood is under 10 mg/L.

The number of WBCs is determined automatically. Very high number of WBCs is called leukocytosis. If the value is very low, in turn, this is called leukopenia.

For a differential blood count, the leukocytes in the blood smear are identified by subtypes. One hundred leukocytes are usually comprised of 4 monocytes, 58 neutrophil granulocytes (of which only 3 are segmented), 1 eosin granulocyte, up to 1 basophil granulocyte, and 35 lymphocytes. If the number of **band neutrophils** is significantly elevated, this is called a **left shift.** It is an indication of bacterial infection. If too many granulocytes are overly segmented, this is called a right shift. This can be due to a deficiency of vitamin B12.

Anemia

Anemia is defined as a low hemoglobin level for a person’s age, sex, and prevailing conditions. Anemia is classified based on the cause of low hemoglobin:

- Iron deficiency anemia: erythrocytes are microcytic and hypochromic; cause: chronic blood loss, insufficient iron intake.
- Megaloblastic anemia: erythrocytes are macrocytic and normochromic; cause: vitamin B12 deficiency, folic acid deficiency, and alcoholism.
- Anemia of chronic disease such as renal anemia due to insufficient erythropoietin production; cause: renal insufficiency.
- Aplastic anemia: RBC deficiency; cause: damage to bone marrow.
- Hemolytic anemia: abnormal destruction of RBCs; cause: defective cytoskeleton (hereditary spherocytosis, sickle-cell disease, and thalassemia), sepsis, malaria, and poisoning.

Leukemia

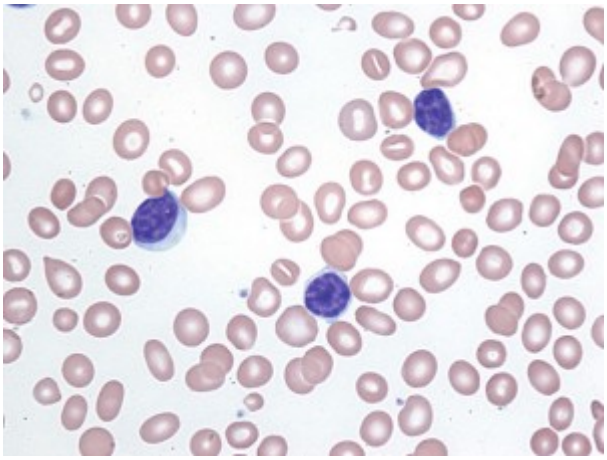


Image: “Peripheral blood with chronic lymphocytic leukemia” by Gabriel Caponetti, License: CC BY-SA 3.0

Leukemia is characterized by a greatly increased number of WBCs **(leukocytes),** in particular, their **precursor cells** (also called **blast cells**). Blast cells have no immune function and spread into the bone marrow, the blood, and the lymphoid organs, thereby reducing their function, which also interferes with the formation of the other blood cells. Consequences include **aplastic anemia, reduced blood clotting,** and a dramatically weakened **immune defense.**

Coagulation disorders

Coagulation disorders are either **inherited** or **acquired**. Increased bleeding is mostly due to a disturbed functioning or the lack of 1 of the coagulation factors:

- **Hemophilia A: factor VIII** deficiency
- **Hemophilia B: factor IX** deficiency
- Von Willebrand’s disease syndrome: Von-Willebrand factor deficiency
- **Vitamin K deficiency:** reduced synthesis of factors II, VII, IX, and X

Notes