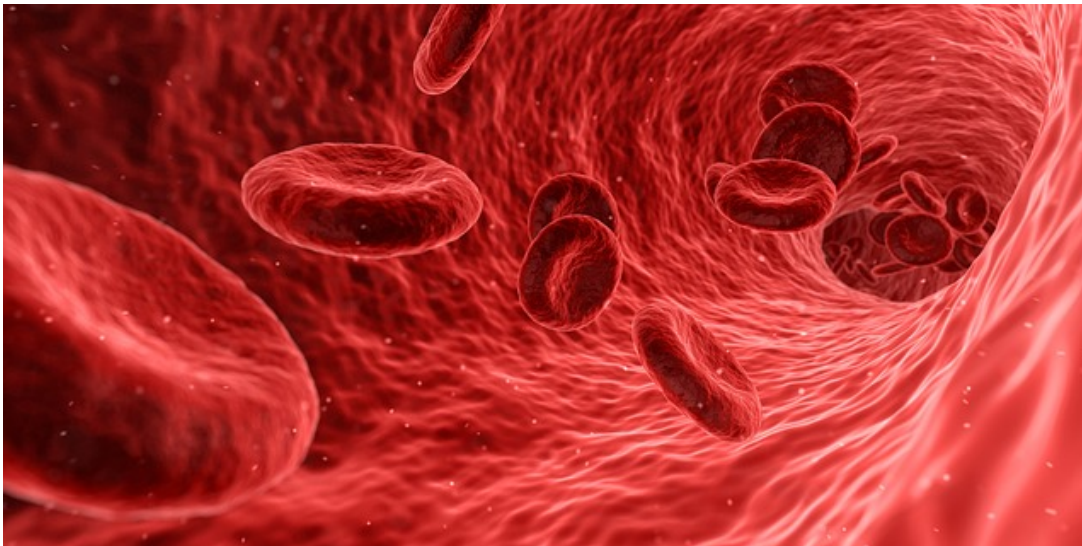


Hemostaseology: Differential Diagnosis of Blood Disorders

[See online here](#)

Regardless if it's playing sport, around the home or at work, cuts can happen everywhere in day to day life! There is a short spray of blood then a few minutes later the wound has closed itself with only a plaster reminding us of the little faux pas. But what happens if the apparently minor moment of carelessness suddenly becomes a life-threatening event? What is 'hemophilia' as it's commonly known? This article explains the range of blood disorders, which of them are hereditary and how an almost incident-free life can still be led despite having one.



Definition of Hemostaseology

Within the wider context of the physiology of the blood, the science of hemostaseology focuses specifically on the **processes of blood clotting, the inhibition of the coagulation pathway and the dissolution of existing blood clots**. Research topics in this area include the following three aspects:

1. The complete process of clotting with all participating coagulating factors which mutually regulate each other to trigger a coagulation cascade
2. Synthesis of coagulation factors in the vascular endothelium
3. The role of platelets (thrombocytes) in hemostasis (clotting)

In summary: hemostaseology is about the complex interactions between blood vessels, coagulation factors, and blood cells. The co-founder of this discipline, Rudolf Marx, described this scientific field in 1953 as the 'slowing down and stopping' of the blood.

The process of coagulation is divided into the following three phases: Constriction of the vessels, **primary hemostasis**, and **secondary hemostasis**. A detailed description of the mechanism of the coagulation cascade can be found in the article: [The biochemistry of blood](#).

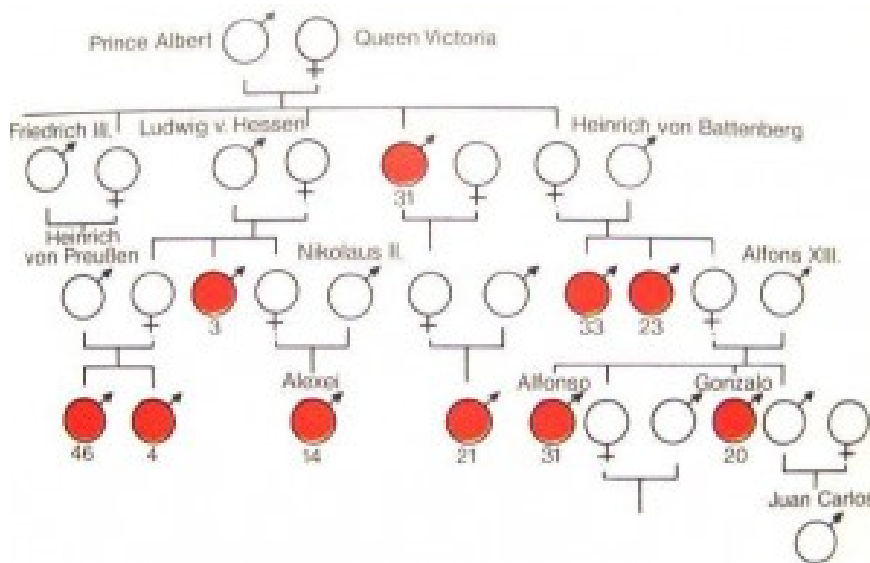


Image: "Inheritance of hemophilia" by Caro1409. License: [CC BY-SA 3.0](#)

Definition of Bleeding Disorders

Bleeding and blood coagulation disorders are more commonly known as 'hemophilia'. They result in a **pathologically changed bleeding time**, i.e. an extended period of time until coagulation occurs, which depending on the severity of the case can either be managed by therapy or might require medication for treatment. Blood coagulation disorders can be hereditary or can stem from other causes.

Hemophilia Types A and B

Hemophilia stems from a **genetic defect** and is inherited **recessively** on the **X chromosome**. This explains the fact that there are **more male** than female patients affected, as the defect in females can be canceled out by the presence of a second X chromosome in female genes.

The condition can be distinguished by the lack of a protein, a coagulation factor, which, in certain physiological conditions, promotes the coagulation of the blood and therefore instigates wound healing following an injury.

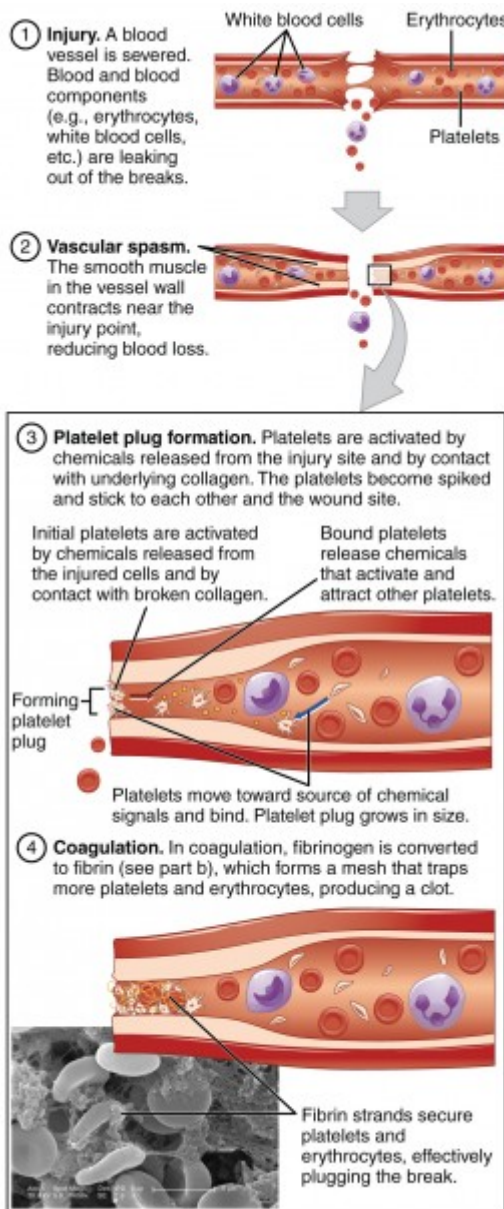
Epidemiology of Hemophilia Types A and B

There are two distinct forms of hemophilia, type A and type B. According to the World Federation of Hemophilia, 1 in 10,000 patients are affected by type A, whereas only 1 in 50,000 patients suffer from type B. It is estimated that 400,000 people have hemophilia worldwide, which indicates that this disease is one of the rarer hereditary diseases.

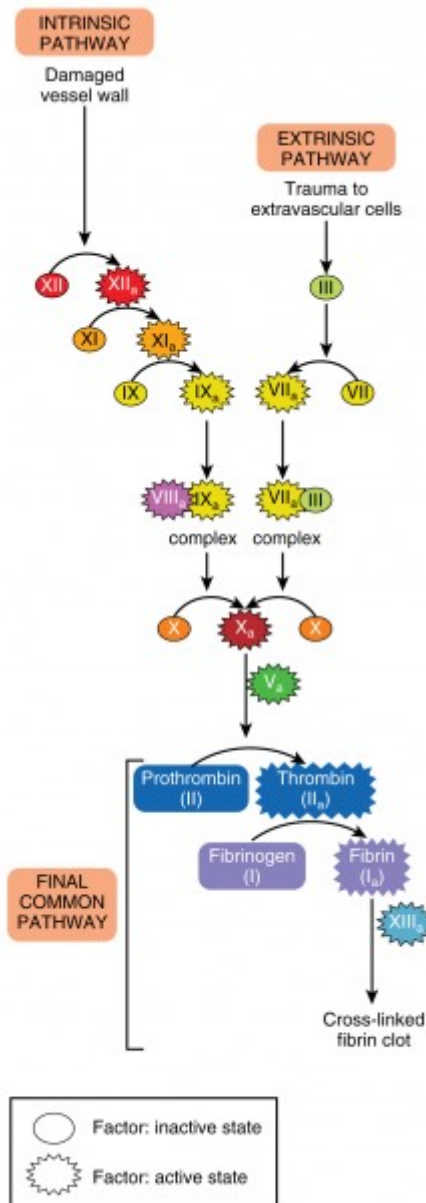
Hemophilia A, where coagulation factor VIII is missing, accounts for 80% of cases, and, in the remaining 20% of hemophilia B cases, coagulation factor IX is the missing factor. The

signal cascade of **intrinsic coagulation** is therefore not fully functional, meaning the formation of a fibrin framework and the subsequent clotting is not possible. This significantly increases the bleed times and wound healing is impaired.

Symptomatically, hemophilia is indicated by spontaneous bleeding in the joints and muscles without prior injury, which can lead to serious complications and damage such as **arthropathy** for example.



(a) The general steps of clotting



(b) Fibrin synthesis cascade

Image: "Hemostasis" by philschatz. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Therapy of Hemophilia A and B

Substitution Therapy for Hemophilia A and B

As a prophylactic treatment, patients are injected intravenously with a **high-tech recombinant coagulation factor VIII**.

The manufacture of the protein, which is created from 2,200 amino acids, is a challenge

for clinical chemists as the protein in the serum does not have a long shelf life. At present, the coagulation factor is synthesized as a powder and is only combined with the serum and injected when it is required.

Substitution therapy does not run completely without complication, however. First of all, 30% of all treated patients develop an antagonist antibody against the synthetic factor VIII protein. Secondly, the protein has a short half-life within the body and is therefore metabolized relatively quickly.

Research is being carried out in order to improve the therapy and reduce the necessary amount of injections required by patients with particularly severe cases of hemophilia. The latest results of this research show that an extended half-life can be achieved through **PEGylation** of the factor VIII protein. In this process, the molecule Polyethylene glycol (PEG) is covalently attached to the factor VIII protein. This increases the overall size of the molecule and therefore needs longer to be filtered and removed by the [kidneys](#) (**Renal Clearance**).

Gene Therapy for Hemophilia A and B

Furthermore, there is the possibility of gene therapy in which factor VIII producing gene is introduced via a virus to the [liver](#) where the factor is then synthesized. The virus is a non-pathogenic viral vector which is used as a gene transporter.

Inhibition of Fibrinolysis in Hemophilia A and B

Further therapy is targeted at the inhibition of fibrinolysis, in other words, the mechanism which dissolves the blood clots and is designed to physiologically counteract thrombosis in the body. In this case, **antifibrinolytics** are prescribed in order to inhibit the fibrinolysis activating plasminogen and also plasmin. Thanks to these new research findings, it's possible as a patient with hemophilia to enjoy an active, untroubled and almost unimpaired life.

Von Willebrand Disease

[Von Willebrand Disease](#) is named after the Finnish doctor, Erik von Willebrand. He examined a family who lived on the Aaland Islands in the Baltic Sea who suffered from severe bleeding. He jokingly referred to the island as 'nosebleed' island.

The result of his examination led him to document a new clinical picture which could be clearly differentiated from hemophilia. Initially called 'pseudohemophilia', the clinical picture became more commonly known as 'von Willebrand Disease'.

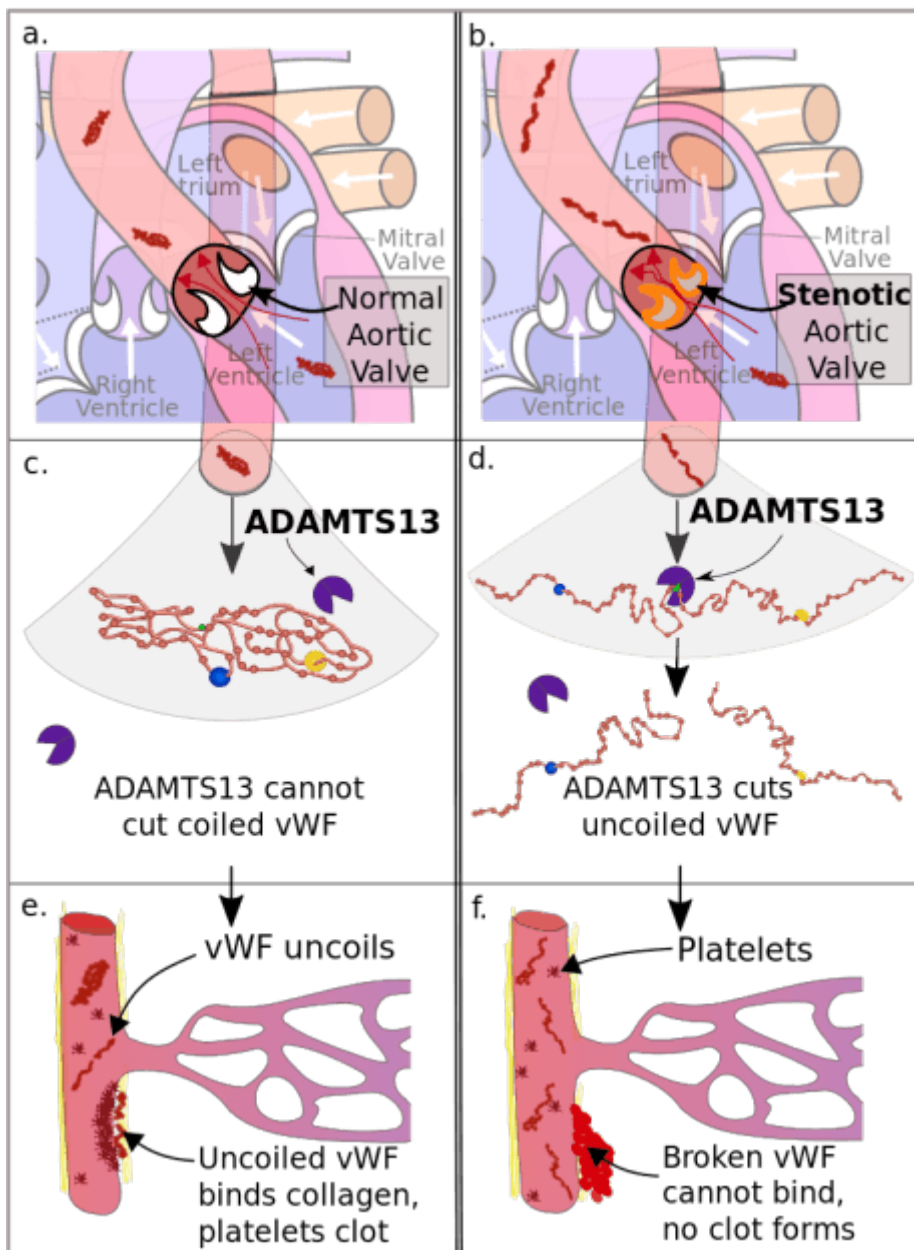


Image: "The pathophysiology of acquired von Willebrand's Disease type 2A (vWD-2A) from an aortic stenosis (Heyde's Syndrome)." by Michael D. Dacre. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

- Von Willebrand factor (VWF) fits through a normal aortic valve and remains in a folded, high molecular weight form.
- VWF passes through a stenotic aortic valve and unravels due to the high load on it.
- The coiled up VWF is uninfluenced by the catabolic enzyme ADAMTS-13 and passes into the circulatory system through the aorta.
- The unraveled active VWF is split into two parts by ADAMTS-13 and rendered inactive.
- In small, damaged arterioles under a lot of strain, the VWF unravels and becomes active. It binds to the collagen on the other side of the damaged wall of the arteriole. Platelets bind to the VWF and release a cytokine signal which activates other clotting factors, leading to the binding of more thrombocytes and the creation of a clot; the bleeding stops.
- The split, inactive VWF cannot bind to the collagen and, due to the high blood flow, the platelets also cannot bind (we require VWF for this to occur).

Etiology of von Willebrand Disease

Causes for the Emergence of von Willebrand Disease

The underlying cause of the disease lies in an insufficiency of a factor that is involved in **primary hemostasis** and which is called 'von Willebrand Factor' (VWF) after the doctor. This factor is responsible for the interlinking of the thrombocytes with the sub-endothelial tissue of the ruptured, damaged blood vessel. Furthermore, VWF, paired with factor-VIII, works as a complex of the intrinsic clotting system and protects it from proteolytic degradation.

VWF is synthesized in the endothelial cells of the blood vessels. The disease is hereditary in the same way as hemophilia A and B are. The genes can be inherited both in an **autosomal dominant** and **autosomal recessive manner**.

Diagnosis of von Willebrand Disease

In order to diagnose von Willebrand Disease, tests are conducted on the **activated Partial Thromboplastin Time (aPTT)**, as well as for the normal **bleeding time** taken until the first signs of coagulation and clotting.

Symptoms of von Willebrand Disease

If a patient has the disease, bleeding times until the start of coagulation are significantly longer than normal, as there is not only inadequate vasoconstriction but also insufficiency in factor VIII, which is involved with secondary hemostasis. The following symptoms indicate the disease in descending order of prevalence:

- Tendency towards bruising
- Frequent secondary bleeding in dental treatments or during operations and heavy menstrual bleeding
- Bleeding times of around 10-15 minutes

Therapy for von Willebrand Disease

The Three Types of Therapy for von Willebrand Disease

Von Willebrand Disease can be subdivided into three types, each of which has its own form of treatment.

1. Type 1 therapy: DDAVP, Factor VIII / VWF concentrate, estrogen treatment in women
2. Type 2 therapy: factor VIII concentrate
3. Type 3 therapy: factor VIII / VWF concentrate

DDAVP is a synthetically manufactured protein and is structurally related to the body's own peptide hormone vasopressin (also known as Antidiuretic Hormone or ADH). It binds to the V2 receptors and triggers the release of von Willebrand Factor. It is therefore prescribed as an **anti-hemorrhagic** drug.

As well as being prescribed in tablet form, a nasal spray is also offered. Due to its low molecular mass, the hormone can easily pass through the nasal mucosa into the bloodstream. The tablet form remains the most reliable method of administration.

Treatment with **estrogen** in women serves to reduce the severity of menstrual bleeding.

The contraceptive pill that can be prescribed by a doctor is usually sufficient for this purpose.

Naturally, patients with von Willebrand Disease can also suffer from fevers or headaches.

Note: when taking medication for headaches, fever or similar symptoms, the highest caution is recommended! Mono-preparation drugs such as aspirin, acetylsalicylic acid (ASA), Alka-Seltzer and other solely ASA based drugs, as well as combined preparations such as ASA combined with Paracetamol or tablets containing ASA and caffeine. These medications have a 'blood-thinning' effect and lengthen the bleeding time in the case of injury.

Vascular Diseases

Vascular diseases can, in part, be hereditary, but can also have other causes. The next section covers three clinical pictures: **allergic purpura**, **Ehlers-Danlos Syndrome (EDS)** and **hemorrhagic telangiectasia**.

Allergic Purpura

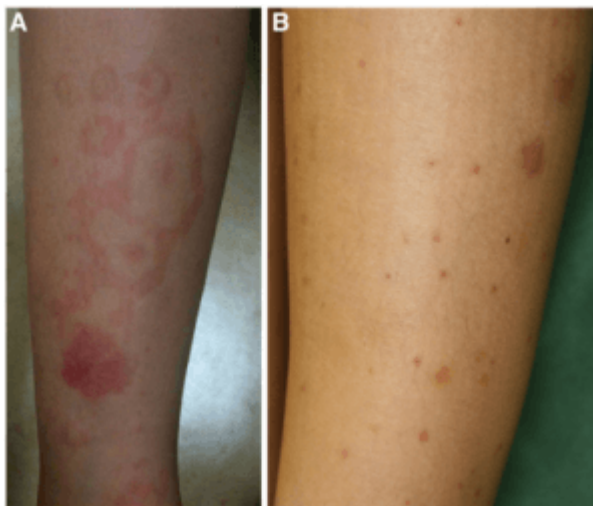


Image: "Purpura allergic (A) Erythema multiforme. Multiple papular, macular and target lesions of the right lower leg 6 days before admission. (B) Henoch-Schönlein purpura. Purpuric rash over the right lower leg was observed on admission." by Openi.
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Definition of Allergic Purpura

Purpura is an **autoimmune disease** that is defined by minor capillary bleeding in the skin, subcutaneous tissue or the mucous membranes. The extent of the bleeding can be small (**ecchymosis**), large (**bruises**) or small spots (**petechiae**).

Etiology of Allergic Purpura

This disease stems from the inflammation of blood vessels which often occurs as a result of, or in conjunction with, a cold or 'flu. **IgA antibodies** can be detected in the blood which attaches themselves to vessel walls and triggers an autoimmune response. The inflammation partly destroys the vessels in some places, leading to leakage of the vessels. Blood no longer flows completely through the capillaries, but escapes the vessel and distributes itself in the surrounding connective tissue.

Diagnosis of Allergic Purpura



Image: "Image of the first necrotic purpura eruption on the feet (A), elbows (B) and knees (C)." by Openi. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Doctors can diagnose this disease by analyzing the immune complexes for the IgA antibodies in the blood or through a **biopsy**. In a biopsy, a tissue sample of the skin is taken and the characteristic changes caused by purpura are determined under a microscope. In advanced stages of this disease, increased plasma protein values can be detected in the urine (**proteinuria**), which leads to the conclusion that the kidney function is worsening and that the inflammation has spread to the kidneys.

Treatment for Allergic Purpura

This disease is treated with either corticosteroids or immunoglobulin, which should reduce the inflammation. In most cases, no therapy is necessary and the inflammation subsides on its own.

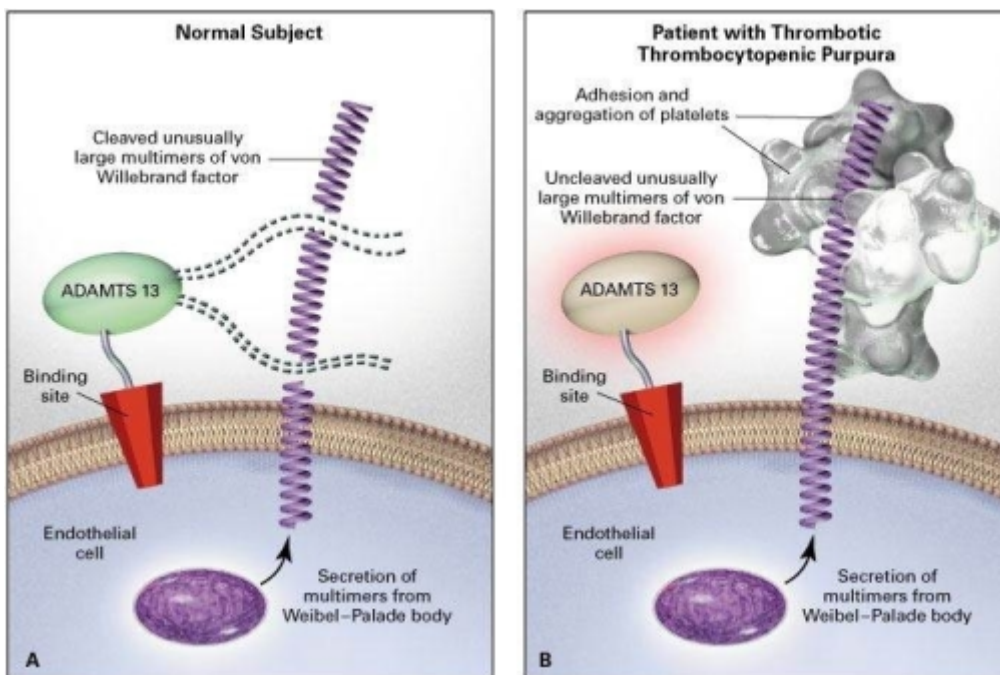


Image: "Thrombotic Purpura" by Openi. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Ehlers-Danlos Syndrome

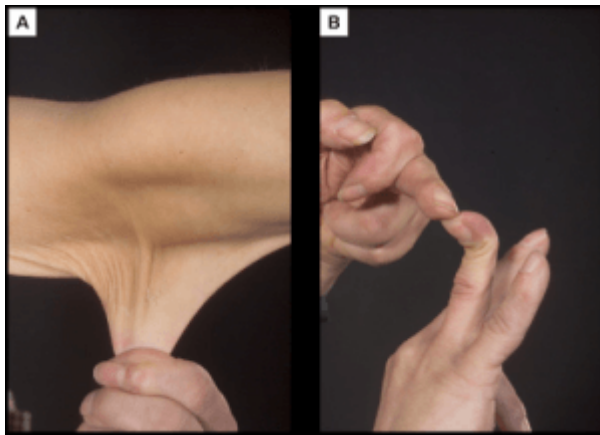


Image: "(A) Prominent hyperextensible skin (B) hypermobile joints." by Openi. License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Definition of Ehlers-Danlos Syndrome

A characteristic feature of this hereditary disease is a weakness of the connective tissue.

The primary cause of this is a synthesis defect in collagen, which is responsible for cohesion and elasticity. Another term for this disease is '**Cutis hyperelastica**'.

Symptoms of Ehlers-Danlos Syndrome

Patients are affected by this syndrome to different extents. The spectrum of possible symptoms ranges from minor anomalies, such as bruises, to agonizing pains, minor encumbrances to a reduced life expectancy. Blood vessels become extraordinarily flexible, thinner than average, easily damaged, they tend to form hematomas and leak easily and rupture easily.

Epidemiology of Ehlers-Danlos Syndrome

In Germany, around 1 in 10,000 people are affected and figures are similar worldwide. The disease is therefore considered quite rare.

Clinical Diagnosis of Ehlers-Danlos Syndrome

Patients often have a long history of suffering as knowledge of this syndrome amongst doctors is lacking even today. Doctors with no other explanation have, in the past, suspected that the patients were falsifying symptoms. Other particularly serious misdiagnoses included the assumption that hematomas, bruises, and injuries in children with EDS were possibly the result of abuse.

There are six distinct types of EDS:

1. **Classical Type:** hematomas, abnormal wound healing, hyperkinesia of the joints, easily damaged blood vessels
2. **Hypermobility Type:** very pronounced motility of the joints
3. **Vascular Type:** thin skin, pronounced hematoma formation, internal organs, and blood vessels are also affected.
4. **Kyphoscoliosis Type:** eyes are affected, medium to severely abnormal wound healing, hyperkinesia of the joints.
5. **Arthrochalasia Type:** thin skin, hip dislocation, pronounced hyperkinesia of the joints
6. **Dermatosparaxis Type:** very loose skin, internal organs also affected



[Image](#): "Hyper extensibility of the fingers in proband's sister" by Openi. License: [CC BY 2.0](#)

Treatments for Ehlers-Danlos Syndrome

The disease is incurable and often progresses unpredictably. If joints are badly affected, sporting activities that are often enjoyed by children have to be avoided. A program of sport that reflects the load the joints can cope with needs to be created.

Hypermobility of the joints, which is often of interest or amusement for the general public, is the source of chronic and, in many cases, continually worsening pain. Treatment is usually in the form of **pain management therapy**. Next, to the medication used to help manage pain, **psychological therapy** targeted at the issues arising from chronic pain, such as depression, anger and fear are also utilized.

In general, it can be said of EDS therapy that, at present, there is no complete cure for the condition; only the symptoms can be treated. To protect against impact and bruising to particularly prone parts of the body such as the shins, knees or elbows, for example, it can be beneficial to wear specially made neoprene protective bandages, particularly for children. A program of physiotherapy should also be undertaken. Pain management therapies can be utilized to alleviate painful symptoms.

Hemorrhagic Telangiectasia

Definition of Hemorrhagic Telangiectasia

Hemorrhagic telangiectasia also counts as a disease of the blood vessels. This is an **autosomal dominant** hereditary condition, meaning that if a couple where one partner is affected have children, then on average, half of their children would also be affected, regardless of gender.

Etiology of Hemorrhagic Telangiectasia

Symptomatic of the disease is a pathological widening of the blood vessels. These widened vessels are very fragile and can easily be torn or start bleeding.

Symptoms of Hemorrhagic Telangiectasia

This disease can be recognized macroscopically by prominently protruding capillaries on the surface of the face. A particularly commonly affected area is the nose, which is why **nosebleeds are the main symptom**. Telangiectasia in the gastrointestinal tract is particularly significant as it is often the cause of frequently recurring bleeding.

[Blood vessel](#) widening within the [lungs](#), in the brain or the liver are, at first, rarely noticeable, but can become life-threatening if sudden bleeding occurs. Causal research has found that at least three mutated genes are responsible for the clinical picture;

amongst these are **endoglin**, a TGFβ1 receptor on chromosome 9q and the **ALK1 gene** on chromosome 12q.

Thrombocytopenia

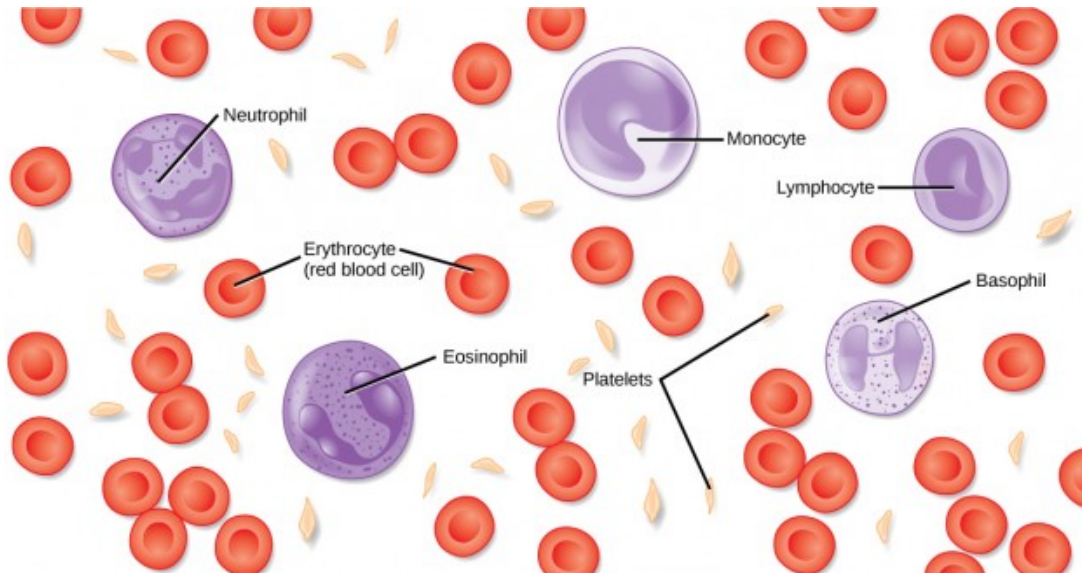


Image: "The cells and cellular components of human blood are shown." by philschatz. License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Diagnosis of Thrombocytopenia

The diagnosis of **thrombocytopenia** is made if there are **less than 150,000 thrombocytes per μl of blood**.

Clinical Diagnosis of Thrombocytopenia

Thrombocytopenia is clinically relevant at blood counts of under 80,000/μl, as it is only below this value that there is an increased tendency towards prolonged bleeding as long as no functional defects are present in the thrombocytes (thrombocytopathy).

Etiology of Thrombocytopenia

Thrombocytes are responsible for primary hemostasis in primary wound closure. If a lot of these 'vessel closers' are missing, bleed times following injury can be significantly prolonged. Hematomas are common, as are nosebleeds and bleeding gums. There is a wide spectrum of causal factors which are simply described here:

Formation Malfunction	Congenital (Wiskott-Aldrich syndrome, TAR syndrome, Fanconi anemia) Acquired (Aplastic anemia, bone marrow disease, Vitamin B12- or folic acid deficiency)
Shortened life expectancy	Antibody response (Transfusion incident, hemolytic disease of the newborn, Idiopathic thrombocytopenic purpura) Coagulation (Heparin-induced thrombocytopenia type II)
Distribution anomalies	Splenomegaly, hypothermic anesthesia
Laboratory phenomenon	Pseudothrombocytopenia

Furthermore, chemotherapy, radiotherapy, AIDS and HIV, as well as leukemia, all have a negative effect on the status of the thrombocytes.

Treatment of Thrombocytopenia

Thrombocytopenia is treated with a transfusion of platelet concentrate. Prior to operative procedures, thrombocyte counts should be elevated to at least 50,000/ μ l to minimize the risk of heavy blood loss. Thrombocyte concentrates are either harvested from whole blood or via apheresis directly from the blood donor.

Review Questions

The correct answers are below the references.

1. Rudolf Marx understood the discipline of hemostaseology to be...

- A. ...the study of the slowing down and stopping of the blood.
- B. ...the study of blood coagulation.
- C. ...the study of the biochemistry of the blood.
- D. ...the study of the blood pigment hemoglobin.
- E. ...the study of the characteristics of blood plasma.

2. Which of these statements about hemophilia A is incorrect?

- A. This hereditary disease is passed on via the X chromosome.
- B. It involves a deficiency in coagulation factor VIII
- C. Investigation into the intrinsic coagulation pathway serves to diagnose the disease.
- D. It leads to a shortened bleeding time.
- E. This type represents 80% of all people who have hemophilia.

3. Allergic purpura...

- A. ...is an autoimmune disease.
- B. ...is expressed through ecchymosis, bruising or petechiae.
- C. ...can be diagnosed by the presence of IgE antibodies in the blood.
- D. ...is accompanied by symptoms such as severe nausea.
- E. ...predominantly affects women.

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Correct answers: 1A, 2D, 3B

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