Introduction

• CVS = blood, heart, blood vessels

• Source of fluids needed by all body cells to obtain nutrients, O$_2$, and eliminate CO$_2$ and other wastes
Functions of Blood – 3

- Transportation
  - Of $O_2$ from lungs to cells
  - Of $CO_2$ from cells to lungs
  - Of waste from cells to GI/kidneys
  - Of nutrients from GI to cells
  - Of hormones from glands to targets
Functions of Blood – 3

- Protection
  By contributing to the inflammatory response
  By clotting – Prevents excessive fluid transport and loss
Functions of Blood –3

• By immune system cells (antibodies & WBC)

By special proteins (interferons, complement) that protects against diseases
Functions of Blood – 3

- Regulation
  Of pH with buffers

Of temperature by absorbing and releasing heat

Of H₂O content of cells by changing concentration of ions and proteins
Components & General Properties

- Plasma, buffy coat [WBC, platelets], erythrocytes
- Formed Elements (rbc’s, wbc’s, platelets)
Components & Genera I Properties

Withdraw blood and place in tube

1. Withdraw blood and place in tube
2. Centrifuge

Plasma (55% of whole blood)

Buffy coat: leukocytes and platelets (<1% of whole blood)

Erythrocytes (45% of whole blood)
Components & General Properties

• RBC’s – Hematocrit = % of total blood volume that is rbc’s
  ✓ Female – normal = 37-48 (average = 42)
  ✓ Male = 42-52 (average = 47)
Components & General Properties

• WBC’s < 1% of blood volume
  Neutrophils, lymphocytes, eosinophils, basophils, monocytes

• Platelets = fragments of thrombocytes
Physical Characteristics of Blood

• Temperature around 38 °C.

• pH around 7.35-7.45 (alkaline)

• About 8% of body weight 4-5L for females, 5-6L for males.
Blood Plasma 55% (acellular part)

- 90% H₂O; 10% solutes (8% proteins)

- Plasma proteins - Help maintain osmotic pressure; Synthesized by liver
  - Albumins – 60% [transport, osmolarity & buffer]
  - Fibrinogen – 4% [clotting]
  - Globulins – 36% [transport, clotting & immunity]
Blood Plasma 55% (acellular part)

- Other solutes
  - Electrolytes (ions) [90% sodium]
  - Nutrients
  - Enzymes, hormones, gases – regulatory substances
  - Waste – urea, uric acid, creatine, ammonia, bilirubin
Blood Viscosity & Osmolarity

• Viscosity - 4.5-5.5 times as viscous as water

• Osmolarity – total molarity of all dissolved particles that cannot pass through the vessel wall.
  – Mainly due to Na+, protein & RBC’s
  – Directs filtration and resorption [high to low, etc.]
How Blood is Produced

• Most have short lifetimes and are continuously being replaced [~600 billion+formed elements/day]
How Blood is Produced

• Hemopoiesis = process by which formed elements of blood are produced
  – Fetal – in yolk sac, liver, spleen, thymus, lymph nodes, & red marrow
  – Adult – only in red marrow
How Blood is Produced
(Hemopoiesis continued)

– Pluripotent stem cells in red marrow can make more of themselves or make blood stem cells (2 types – myeloid and lymphoid)

– Plasma much comes from absorption from the GI, other components [proteins] come from the liver and plasma cells.
Erythrocytes [Red Blood Cells]

• Anatomy
  – 7-8 microns, biconcave, no organelles, large SA/V ratio for gas exchange
  – Female – 4.2-5.4 million/µliter
  – Male – 4.6-5.4 million/µliter
  – 97% of cell is hemoglobin
Erythrocytes [Red Blood Cells]
Erythrocytes [Red Blood Cells]

• Physiology
  – Anaerobic respiration
  – Hemoglobin
    • 4 protein subunits – 2 alphas and 2 betas
Erythrocytes [Red Blood Cells]

• Concentration – 18g/dL in men; 12-16g/dL in women.

• Infants – 14-20 g/100mL, Males 13-18g/100mL, Females 12-16g/100mL; varies from adult by having two gamma chains in place of beta chains.

• 1 heme molecule per subunit – ring structure – Fe ions in center.
Erythrocytes [Red Blood Cells]

- [1 rbc has ~280 million hemoglobin molecules – each carries up to 4 O$_2$’s – 1 cell can carry ~1 billion O$_2$’s]

- 20% of CO$_2$ in tissues diffuses into rbc $\rightarrow$ combines with protein part of hemoglobin [carbaminohemoglobin] to lungs $\rightarrow$ reaction reversed and CO$_2$ released
Erythrocytes [Red Blood Cells]
Erythrocytes [Red Blood Cells]

- Erythropoiesis: production of rbc’s [3-5 days]— from myeloid stem cells
Erythrocytes [Red Blood Cells]

- Erythrocyte production
  - Pluripotent stem cell → erythrocyte colony-forming unit → under influence of erythropoietin → erythroblast → produces cells that synthesize hemoglobin
Erythrocytes [Red Blood Cells]

– Erythrocyte production
  • These, ultimately, after several divisions, eject their nuclei, which makes them biconcave → now called reticulocytes (still have other organelles)
  • Reticulocytes enter blood stream and in 1-2 days lose rest of organelles to become true erythrocytes
Erythrocytes [Red Blood Cells]
Erythrocytes [Red Blood Cells]

Iron Metabolism

- Women lose more than men in waste – must replenish more

- Only Fe$^{2+}$ can be absorbed from GI

- Gastroferritin transports it to small intestine $\rightarrow$ absorbed $\rightarrow$ transferring $\rightarrow$ bone marrow, etc. [iron has more than one use]

- Surplus iron is stored in the liver
Erythrocytes [Red Blood Cells]

- Erythrocyte Homeostasis - the number remains constant and reflects a balance between RBC production and destruction.
  - Too few red blood cells leads to tissue hypoxia
  - Too many red blood cells causes undesirable blood viscosity
Erythrocytes [Red Blood Cells]

– Erythrocyte Homeostasis
  • Control – Erythropoiesis is hormonally controlled (erythropoietin and testosterone) and depends on adequate supplies of iron, amino acids, and B vitamins.
Erythrocytes [Red Blood Cells]

– Erythrocyte Homeostasis
  • Control
    – Erythropoietin (EPO) release by the kidneys is triggered by:
      » Hypoxia due to decreased RBCs
      » Decreased oxygen availability
      » Increased tissue demand for oxygen
      » Stimulated by testosterone
Erythrocytes [Red Blood Cells]

– Erythrocyte Homeostasis
  • Control
    – Enhanced erythropoiesis increases the:
      » RBC count in circulating blood
      » Oxygen carrying ability of the blood
Erythrocytes [Red Blood Cells]

Enhanced erythropoiesis increases RBC count

Erythropoietin stimulates red bone marrow

Exposes O₂-carrying ability of blood

Reduces O₂ levels in blood

Start

Stimulus: Hypoxia due to decreased RBC count, decreased availability of O₂ to blood, or increased tissue demands for O₂

Normal blood oxygen levels

Kidney (and liver to a smaller extent) releases erythropoietin
Erythrocytes [Red Blood Cells]

– Erythrocyte Homeostasis

• A decrease stimulates erythropoietin production in the kidneys, which increases erythrocyte production, and visa versa.
Erythrocytes [Red Blood Cells]

– Erythrocyte Homeostasis

  • Testosterone stimulates erythropoietin in kidneys which stimulates rbc’s production and depends on adequate supplies of iron, amino acids, and B vitamins

  • Diet – Fe, B12 and Folic acid [last two needed for DNA synthesis]
Erythrocytes [Red Blood Cells]

• Erythropoiesis
  • Life Cycle of RBC’s – live about 120 days
    – Worn out rbc’s are picked up and phagocytosed by fixed macrophages in the spleen, liver or red bone marrow.

    – Hemoglobin is split into heme and globin portions
      » Globin is split into aa’s which can be recycled into new proteins
      » Heme iron is removed and the Fe ion associates with the transport protein transferrin
Erythrocytes [Red Blood Cells]

• Erythropoiesis
  • Life Cycle of RBC’s
    – Transferrin is carried to muscle fiber, liver cells and liver and spleen macrophages, where Fe detaches and is stored in ferritin and hemosiderin proteins.

    – Waste – non-iron part of heme $\rightarrow$ converted to biliverdin(green) $\rightarrow$ converted to bilirubin(yellow-orange)

    – Bilirubin $\rightarrow$ into blood $\rightarrow$ to liver
Erythrocytes [Red Blood Cells]

• Erythropoiesis
  • Life Cycle of RBC’s
    – Secreted into bile → secreted into small intestine → then into large intestine
    – In large intestine, bilirubin is converted into urobilinogen
    – Some urobilinogen is resorbed and secreted in urine (yellow color); some is excreted in feces as stercobilin (brown pigment)
Erythrocytes [Red Blood Cells]

1. Low O₂ levels in blood stimulate kidneys to produce erythropoietin
2. Erythropoietin levels rise in blood
3. Erythropoietin and necessary raw materials in blood promote erythropoiesis in red bone marrow
4. New erythrocytes enter bloodstream; function about 120 days
5. Aged and damaged red blood cells are engulfed by macrophages of liver, spleen, and bone marrow; the hemoglobin is broken down

- Hemoglobin
  - Bilirubin
  - Heme
  - Globin
  - Iron stored as ferritin, hemosiderin
  - Amino acids

- Iron is bound to transferrin and released to blood from liver as needed for erythropoiesis

- Bilirubin is picked up from blood by liver, secreted into intestine in bile, metabolized to stercobilin by bacteria and excreted in feces

- Food nutrients, including amino acids, Fe, B₁₂, and folic acid are absorbed from intestine and enter blood

- Raw materials are made available in blood for erythrocyte synthesis
RBC Disorders

• **Polycythemia** – excess rbc’s that increase blood viscosity
  – Polycythemia vera [cancer of erythropoeitic line]
  – Secondary polycythemia – Altitude, smoking, dehydration, etc.
RBC Disorders

- **Polycythemia** – excess rbc’s that increase blood viscosity
  - Cause ↑ in Bp, Blood volume & viscosity → stroke or heart failure
  - Blood doping
RBC Disorders

• **Anemias** – deficiency in oxygen transport
  – Inadequate number of red blood cells
    • Hemorrhagic anemia – result of acute or chronic loss of blood
    • Hemolytic anemia – prematurely ruptured erythrocytes
    • Aplastic anemia – destruction or inhibition of red bone marrow
    • Kidney failure results in too little EPO \( \rightarrow \) need transfusions
    • Hemoglobin deficit
RBC Disorders

• **Anemias**
  • Hemoglobin deficit
    – Iron-deficiency anemia results from:
      » A secondary result of hemorrhagic anemia
      » Inadequate intake of iron-containing foods
      » Impaired iron absorption
RBC Disorders

• **Anemias**
  
  • Hemoglobin deficit
    
    – Pernicious anemia results from:
      
      » Deficiency of vitamin B12
      
      » Lack of intrinsic factor needed for absorption of B12
      
      » Can be inherited
    
  • Treatment:
    
    – IM injection of B12
    
    – application of Nascobal
RBC Disorders

• **Anemias**
  • Consequences of anemia
    – Tissue hypoxia → shortness of breath, lethargy, pallor, brain, kidney & heart necrosis
    – Blood osmolarity is reduced → edema
    – Blood viscosity is reduced → increased heart rate, Bp drops
RBC Disorders

• **Sickle-cell anemia** — results from a defective gene coding for an abnormal hemoglobin called hemoglobin S (HbS) exhibits pleiotrophy [multiple effects from a single gene].

• HbS has a single amino acid substitution in the beta chain
RBC Disorders

• **Sickle-cell anemia**
  – This defect causes RBCs to become sickle-shaped in low oxygen situations → agglutinate → block vessels
  – Evolutionarily – protects against malarial infestation
RBC Disorders
Immunohematology

- **Blood groups** – there are many blood group antigens (100+ groups, 500+ antigens – MN, Duffy, Kell, Kidd, Lewis, etc.)

- RBC membranes have glycoprotein antigens on their external surfaces.
RBC Antigens

Surface proteins (antigens) on foreign blood cells
Blood group antigens

- Presence/absence of these antigens is used to classify blood groups.

- Recognized as foreign if transfused into another individual

- Individuals produce antibodies to antigens they DON’T have
Blood Group Antigens

- Glycolipid antigens A and B
- Only A = type A
- Only B = type B
- A&B = type AB [least common]
- Neither = type O [most common]
Blood Group Antigens

– ABO system unique. Has preformed antibodies that form at about 6 months and circulate in plasma.

– Source of antibody - produced in response to pollens & intestinal bacteria cross-react with blood cell antigens.
Transfusion reactions

• Occur when mismatched blood is infused.

• Donor’s cells are attacked by the recipient’s plasma agglutinins causing:
  • Diminished oxygen-carrying capacity, clumped cells that impede blood flow, ruptured RBCs that release free hemoglobin into bloodstream. Circulating hemoglobin precipitates in kidneys and causes renal failure.
Blood Typing

• Commercial Anti-A and Anti-B used to type blood, detects antigens

• Positive reactions indicated by agglutination (clumping).
Blood Typing

B+  O -
Transfusions

- Transfusions- donated blood fractions:
  - Packed red blood cells (cells with plasma removed) used for anemia.
  - Fresh frozen plasma is used to treat fluid loss and some clotting problems.
Transfusions

– Platelet transfusions are used to treat thrombocytopenia.

– Cryoprecipitate, Vit K and lyophilized clotting factors are used to treat clotting disorders.
Transfusions

• Compatibilities for RBCs - the patient’s circulating antibodies MUST be compatible with the donor’s red blood cells (since only RBCs are infused, you do not have to worry about the donor’s antibodies).
Transfusions

• A can get A and O
• B can get B and O
• AB can get anything
• O can only get O
Transfusions

• Transfusion of fluids: When low blood volume shock is imminent, volume must be replaced.

• Plasma or plasma expanders can be administered – preferred is normal saline or Ringer’s solution.
Transfusions

• Different blood group system inherited separately from ABO

• There are over 50 different Rh antigens; most common are C, c, D, E, and e.
Transfusions

• Rh type is determined by presence or absence of D antigen.
  – Rh+ you have the antigen, Rh- you don’t.
  – Antibodies form in usual way – after exposure to the alien form.
Blood Typing

B+  O -
Transfusions

• Rh type is determined by presence or absence of D antigen.
  – Antigen-antibody reaction causes hemolysis – all the rbc’s are destroyed.
Transfusions

• Rh type is determined by presence or absence of D antigen.
  – HDN = Hemolytic Disease of the Newborn
  – Rh- mother forms antibodies to blood of Rh+ fetus
  – These destroy the baby’s blood
Transfusions

- Rh type is determined by presence or absence of D antigen.
  - Need transfusion before or immediately at birth
  - Treat by giving mother RhoGAM = anti-Rh antibodies.
Leukocytes

• **Physiology**
  – General function – to combat invading microbes and their toxins.
  – Emigration [most do this] = leaving the bloodstream
Leukocytes

• **Emigration**
  - initiated by signals/substances in vicinity of invasion
  - adhesion molecules on endothelia slow down wbc
  - adhesion molecules on wbc tether wbc to vessel wall
Leukocytes

- **Emigration**
  - wbc squeezes between endothelial cells into external interstitial fluid [= diapedesis]
  - examples of adhesion Molecules – for neutrophil = selectins and integrins, respectively
Leukocytes

- Emigration
Leukocytes

• **Types** – 2 subgroups
  – Granular and agranular

  – Granular leukocytes – contain chemical filled cytoplasmic vesicles that can be seen with different stains.
Leukocytes

- **Neutrophil** – granules pale purple due to attraction to both acidic & basic dyes. Nucleus - 3-5 lobes clearly visible (# of lobes increases with cell age → “polymorphonuclear cells”)
Leukocytes

– Phagocytic

– Kill – defensins poke holes in microbe membranes.

– Most abundant WBC – 60-70%

– Neutrophils increase with bacterial and some fungal infections; burns; stress; inflammation.
Leukocytes

- **Eosinophil** - Acidic stain (Eosin) stains granules in red/orange. Granules are large and uniform. Nuclei usually have 2-3 lobes visible.
  - 2-4%

  - Release enzymes that combat histamine and other mediators of allergic reactions. Increase with parasitic worm infections, allergies and autoimmune diseases, disease of spleen and CNS.
Leukocytes
Leukocytes

– Basophil - Basic stain (methylene blue) stains variable-sized granules blue/purple. The nucleus usually has 3 lobes that are obscured by granules.
  • <0.5-1%
  • Similar to mast cells. Increase in inflammatory response, allergic reactions, and chicken pox, diabetes mellitus, myxedema & polycythemia.
  • Release histamine.
Leukocytes

• Basophils
Leukocytes

• Agranular leukocytes
  – **Lymphocytes** – nucleus round, stains purple.
    • Cytosol stains blue to light purple – often just a small rim visible.

• Increase with viral infection and or leukemia. 25-33%. Smallest WBC.
Leukocytes

• Immune system cells – most found in lymphoid tissues.
  – B – produce antibodies & act against bacteria.
  – T – act against viruses, fungi, transplants & certain cancers.
  – Killer cells – fight infection and some tumor cells.
Leukocytes

- Lymphocyte
Leukocytes

– **Monocytes** – large – become macrophages. Nucleus is kidney or horseshoe shaped, can be oval or round. Foamy cytosol (with vacuoles)
  - 3-8%
  - Become wandering macrophages. Increase with viral or fungal infection, TB and chronic diseases and leukemia
Leukocytes

- **Monocyte**
Leukocytes

- **Complete Blood Count [CBC]** – Quantifies all measures – rbc numbers, hemoglobin, etc., percentages of each WBC, etc.

- Review causes for deviations in accompanying tables in the chapter.
Leukocytes

• Leukopoiesis- Production of WBCs
• Hormonally stimulated by 2 groups of cytokines (hematopoietic factors) – interleukins and colony-stimulating factors (CSFs).
  • Interleukins are numbered (IL-1, IL-2), whereas CSFs are named for the WBCs they stimulate (granulocyte-CSF stimulates granulocytes).
Leukocytes

• Macrophages and T cells are the most important sources of cytokines.

• Many hematopoietic hormones are used clinically to stimulate bone marrow.
Leukocytes

• Pathway – pluripotent stem cell → myeloid or lymphoid stem cell → colony-forming units → one of the following: myeloblasts [neutrophils, eosinophils, basophils], monoblasts [monocytes], lymphoblasts [all forms of lymphocytes]

• Bone marrow stores granulocytes & monocytes until needed. Lymphocytes migrate to thymus or other lymphoid tissues.
Leukocytes

• Leukocyte Disorders
  – Leukocytosis – high numbers [infection, allergy]
  – Leukopenia – reduced numbers [poisoning, radiation sickness, many viral infections]
Leukocytes

– Leukemias – Leukemia refers to cancerous conditions involving white blood cells → usually large numbers are produced

• Named according to the abnormal white blood cells

• Myeloid leukemia – involves granulocytes cells

• Lymphoid leukemia – involves lymphocytes
Leukocytes

• Acute leukemia involves blast-type cells and primarily affects children – rapid onset & progression → death within a few months

• Chronic leukemia is more prevalent in older people. Slower onset & progression – death in ~3yrs.

• Mononucleosis – caused by Epstein Barr virus. Increased agranulocytes.
Leukemia (acute myelocytic)
Platelets & Hemostasis

• Platelets
  – Platelets are disk-shaped, very small fragments of megakaryocytes with a blue-staining outer region and a purple granular center
Platelets & Hemostasis

• Platelets
  – Contain lysosomes, mitochondria, granules with secretions & open cinalicular system opening to the surface.
  – Secrete vasoconstrictors, procoagulants, chemical that attract neutrophils & monocytes, growth factors and more.
Platelets & Hemostasis

• Platelets
  – Platelets function in the clotting mechanism by forming a temporary plug that helps seal breaks in blood vessels, contain chemicals that promote clotting
Platelets & Hemostasis

• Platelets
Platelets & Hemostasis

• Platelets
  – Thrombopoietin stimulates myeloid stem cells $\rightarrow$ megakaryoblasts $\rightarrow$ megakaryocytes
  
  – Megakaryocytes fragment into 2-3000 pieces per cell = platelets; as much as 40% are stored in the spleen [live 10 days].
Platelets & Hemostasis

• Hemostasis – sequence of events that stops bleeding – 3 mechanisms
  – Vascular spasm – smooth muscle in vessel walls contracts.
  – Platelet plug formation
    • Platelets stick to damaged vessels (e.g., collagen fibers)
      =platelet adhesion
Platelets & Hemostasis

- Hemostasis
  - Platelet plug formation
    - Adhesion activates platelets to release contents of granules and to form projections to touch each other.
Platelets & Hemostasis

• Hemostasis
  – Platelet plug formation
    • Granules release ADP [attracts more platelets], ATP, Ca^{2+}, serotonin [enhances spasms]. Thromboxane A2 (prostaglandin).

• ADP and thromboxane A2 attract and activate more platelets = platelet aggregation → platelet plug
Platelets & Hemostasis

• Hemostasis
  – Coagulation
    • Clotting factors – Ca\(^{2+}\), enzymes from liver, molecules released by platelets and damaged tissues – Roman numerals are in order of discovery NOT of participation].
Platelets & Hemostasis

• Hemostasis
  – **Clotting cascade** – 3 stages
    • Stage 1 – formation of prothrombin activator – 2 pathways.
      • Extrinsic pathway – very fast
        – 2. III combines with factor VII to form a complex which, in presence of Ca^{2+}, activates X
Platelets & Hemostasis

• Intrinsic pathway – slow
  – 1. When platelets degranulate, they release factor XII.
  – 2. Factor XII leads to activated XI, IX, & VIII, in that order, and finally to X. This requires Ca$^{2+}$ & PF3
Platelets & Hemostasis

• Stages 2 and 3 = “common pathway”
  – Once factor X is activated, the remaining cascades are identical in both pathways - X combines with III and V in the presence of Ca\(^{2+}\) to produce prothrombin activator
Platelets & Hemostasis

– Stage 2 – prothrombin activator and Ca$^{2+}$ catalyze the formation of thrombin from prothrombin

– Stage 3 – Thrombin and Ca$^{2+}$ convert fibrinogen to fibrin and activate XIII (Fibrin stabilizing factor).
Platelets & Hemostasis

Coagulation:

- Injury to lining of vessel exposes collagen fibers; platelets adhere
- Platelet plug forms
- Fibrin clot with trapped red blood cells

- Collagen fibers
- Platelets
- Fibrin

- Platelets release chemicals that make nearby platelets sticky
  - PF3 from platelets and tissue factor + from damaged tissue cells
  - Calcium and other clotting factors in blood plasma

Coagulation:

1. Formation of prothrombin activator
2. Prothrombin leads to Thrombin
3. Fibrinogen (soluble) leads to Fibrin (insoluble)
Platelets & Hemostasis

– Positive feedback – thrombin increase increases V which increases prothrombin activator, etc. Thrombin increase also increases platelet activation

– Clotting is a positive feedback system.
Platelets & Hemostasis

- Fibrinolysis - Two homeostatic mechanisms prevent clots from becoming large.
  - Swift removal of clotting factors
  - Plasminogen in plasma is activated $\rightarrow$ plasmin $\rightarrow$ dissolves clot by digesting fibrin and inactivating clotting factors (fibrinolysis)
  - Inhibition of activated clotting factors
Platelets & Hemostasis

• Prostacyclin – from endothelial cells and wbc’s – inhibits platelet adhesion

• Anticoagulants – antithrombin III, protein C, heparin [endothelial cells, basophils and mast cells].
Platelets & Hemostasis

• Clotting disorders:
  – Intravascular clotting = thrombosis
  – May produce an embolus $\rightarrow$ embolism $\rightarrow$ infarction
Platelets & Hemostasis

• Bleeding disorders
  – Disseminated Intravascular Coagulation (DIC): widespread clotting in intact blood vessels using up clotting factors
  – Residual blood cannot clot
  – Blockage of blood flow and severe bleeding follows
Platelets & Hemostasis

– Most common as a complication of pregnancy or result of septicemia or incompatible blood transfusions.
Platelets & Hemostasis

– Thrombocytopenia – condition where the number of circulating platelets is deficient.
  • Patients show petechiae (small purple blotches) due to spontaneous, widespread hemorrhage
  • Caused by suppression/ destruction of bone marrow (e.g., malignancy, radiation)
  • Platelet count less than 100,000/mL is diagnostic for this condition
Platelets & Hemostasis

• Bleeding Disorders
  – Treated with platelet transfusions.

Petechiae
Platelets & Hemostasis

• Bleeding Disorders
  – Hemophilias – hereditary (autosomal recessive) bleeding disorders.
    • Hemophilia A – most common type (83% of all cases) due to a deficiency of Factor VIII.
    • Hemophilia B – results from a deficiency of factor IX.
    • Hemophilia C – mild type, caused by a deficiency of factor XI.