5: Blood (Disorders of the Hematological System)

Learning Outcomes

- Describe the cellular and fluid components of blood and functions of blood cells (review).
- Define *anemia* and describe the various methods of classifying the anemias.
- Describe the manifestations of *anemia* and the pathophysiology underlying the clinical manifestations.
- Compare and contrast the pathophysiology underlying *iron deficiency, pernicious* and *folate deficiency anemias.*
- Describe the *normocytic-normochromic anemias*.
- Define *polycythemia vera* and describe its causes and multiple system manifestations related to the increased viscosity and volume of blood.
- Describe the different types of alterations in leukocyte function.
- Define *agranulocytosis* and describe its clinical manifestations.
- Describe the manifestations of *infectious mononucleosis* and *its* complications beyond the immune system.
- Classify *leukemias* as it relates to the maturity of the cells and appearance of the total leukocyte count and differential.
- Differentiate the *leukemias* by manifestations, treatment options and prognosis.
- Describe *Hodgkin* and *non-Hodgkin lymphomas*, focusing on differential diagnosis, manifestations, treatment and prognosis.
- Describe the pathophysiology, clinical manifestations, and treatment of *multiple myeloma*.
- Describe the causes of *splenomegaly*.
- Describe the causes of *thrombocytopenia*.
- Describe the various causes of *impaired hemostasis*.
- Describe the pathophysiology of *disseminated intravascular coagulation*.
- Describe the conditions that predispose an individual to the development of *thrombosis*.

Definitions: Blood (Disorders of the Hematological System)

Term	Definition
Anemia	- -Reduction in number and/or function of erythrocytes, hemoglobin, hematocrit, or any combination of these
Ecchymosis	- Subcutaneous spot of bleeding with diameter larger than 1 centimetre (more than 5mm)
Sideroblastic Anemia	- Anemia related to inefficient iron uptake and subsequent abnormal hemoglobin synthesis - Characterized by ringed sideroblasts in bone marrow
Sideroblasts	- RBCs containing iron granules that have not been synthesized into hemoglobin and form a ring around the nucleus
Leukemia	- Abnormal increase of WBC count
Pallor sign in blood smear	- Pale central regions of the red cells seen on blood smear, indicating low Hb.
Petechiae	- Red/purple discolored skin spots - Do not blanch on applying pressure - Caused by subcutaneous bleeding - Secondary to platelet, vascular or, coagulation disorders - Measure less than 3 mm
Plasma Oncotic Pressure	- Pressure exerted by proteins in plasma that helps contain the fluid within the blood vessel
Polycythemia	- Increased red cell count above normal
Polycythemia Vera	- Myeloproliferative disorder of BM leading to excess production of red cells
Purpura	- Same as petechiae but measure less 3–10 mm

Heme	- A complex formed of an iron atom surrounded by protoporphyrin ring. This complex structure is located in the centre of each of the 4 globin chains making the Hb

Review: Anatomy and Physiology of the Hematological System

Composition of Blood

- **Critical facts at a glance**:
- Albumin is the most abundant plasma protein
- *Plasma oncotic pressure*
  - Solutes within blood that holds the fluid within the vessel
  - Loss of albumin (or other plasma proteins) causes fluid to leak into the interstitial space
- Manifested as edema
- *Leukemia* = immature cells in blood circulation
- Bone marrow contains multiple stages of cellular development and maturation but only mature cells are released into the blood
- There are 5-6 million RBC, 9-11 thousand of WBCs and 150-450 thousand of platelets per cubic millimeter
- Vacutainers have different colored caps, indicating the type of anticoagulant added to the container to prevent clotting of the blood sample
- If no anticoagulant were added, the sample would begin to clot once collected
- Hemoglobin is a quaternary protein composed of heme + globin (peptide chains).
- Four globin chains; 2 alpha and 2 beta, each chain has *heme* (iron surrounded by porphyrin ring) in its centre
- RBC has a 120-day life span

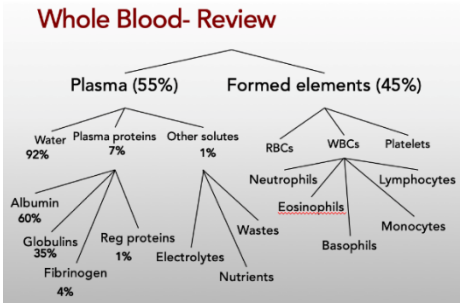

Figure 1: Whole Blood Composition (Review)

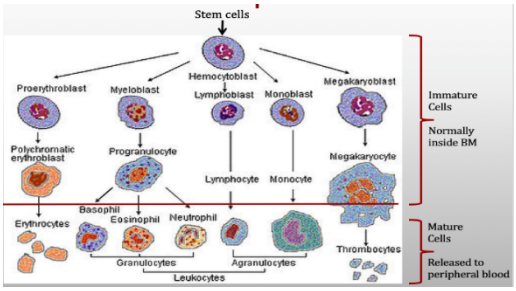

Figure 2: Maturation of white blood cells

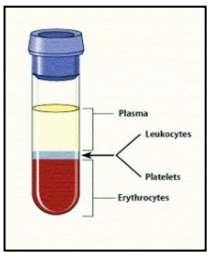

Figure 3: Separated blood components

- Platelets have 10 day life span
- Some WBCs live for years

- Life Cycle of a Red Blood Cell
- Hemoglobin is broken into heme and globin
- Globin is recycled to amino acids
- Heme is broken into iron and biliverdin
- Iron is reused as it goes back the bone marrow through blood circulation via transferrin
- Biliverdin (green) turns into bilirubin (yellow) that goes to the liver
- Bilirubin has three possible outcomes:

1. Some goes with bile to the intestine to help fat digestion; part of which then gets reabsorbed into circulation
2. Some turns into urobilin and is excreted in stool.
3. Some goes straight to the kidney from the liver (via circulation) to be excreted in urine.

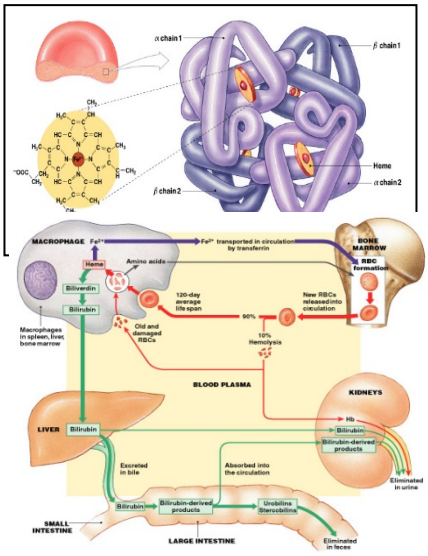

Figure 5: Life Cycle of a Red Blood Cell

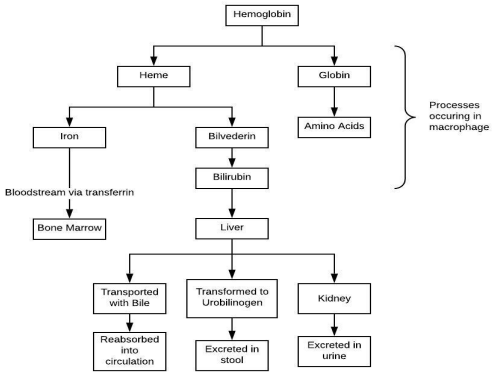

Figure 6: Life Cycle of an RBC

Disorders of the Hematological System

Anemia

- Reduced number and/or function of erythrocytes (red blood cells), hemoglobin, hematocrit, or any combination of these
- Anemia is a very common pathophysiology worldwide

Etiology

- Impaired erythrocyte production
- Increased erythrocyte destruction
- Or a combination of both impaired production and increased destruction
- Blood loss (acute or chronic)
- Leads to overall decrease in erythrocytes
- Anemia may also result with:
- Increased erythrocyte destruction in the spleen

- Impaired bone marrow production (either in producing too few, or poor quality)
- Nutrient deficiencies (i.e. Iron, B12, Folic Acid)
- There is a relationship between RBC structure and anemia
- RBCs are 7um biconcave discs, this is the size/shape is required to enable them to stack and move through capillaries
- Low hemoglobin is visible microscopically in a blood smear as a, "*pallor sign*", the RBC looks empty, no redness in the middle

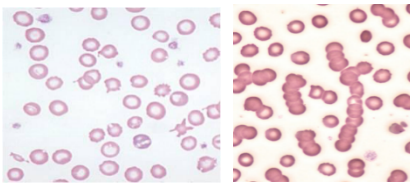

Figure 7: The "pallor sign" of anemia

Table: Abbreviations Related to Diagnostic Studies in Anemia	
Abbreviation	**Full Term**
CBC	Complete blood count (gives full picture of blood)
Hb (g/dL)	Hemoglobin
RBC count	Number of RBCs
RDW	Red cell distribution width (represents variation in size among red cell population)
Hct (%)	Hemotocrit (also known as PCV) Normal value 40-50% depending on gender (males have higher Hct)
PCV	Packed cell volume Another term for hematocrit referring to the length of sedimented RBCs column following centrifugation in capillary tubes
Three Blood Indices	
MCV	Mean corpuscular volume. A measure of the average volume of a red blood cell (fL)
MCH	Mean corpuscular hemoglobin. Amount of Hb in an average red cell (pg)
MCHC	The concentration of haemoglobin in a given volume of packed blood (%)
Other Cellular Components of Blood	
WBC count	White blood cell count. Includes both the total WBCs and differential which gives percentages of each type of WBC

Platelet count	Platelet count. Normal = 150,000-450,000 / mm^3
MPV	Mean platelet volume. Represents platelet size

Table: Normal Values for Complete Blood Count (CBC)	
Component	**Normal values**
Total erythrocytes	4.2-6.1 x 10^{12}/L
Erythrocyte size (RDW)	11.5-14.5%
Hb (total Hb in the blood)	13-17 g/dL
Hematocrit (PCV)	40-45%
MCV (mean corpuscle volume)	84-96 femtolitres
MCH (mean corpuscle HB)	28-34 picograms
MCHC (mean corpuscle hemoglobin concentration)	32-36%
Total leukocytes	5-10 x 10^9/L
Lymphocyte	20-40% of leukocyte differential
Monocyte/Macrophage	5-10% of leukocyte differential
Eosinophil	1-4% of leukocyte differential
Neutrophil	55-70% of leukocyte differential
Basophil	0.5-1% of leukocyte differential
Platelet count	150-400 x 10^9/L
MPV (mean platelet volume)	7.4-10.4 femtolitres

Classification of Anemia

- Anemia is classified according to:
-
  - Red cell volume (MCV)
  - Hb content (MHC, MCHC)
  - Microcytic hypochromic anemia
- Low indices
- RBC are small and low Hb

- Normocytic normochromic anemia
- Normal indices
- Normal cell and normal Hb but reduced number/ impaired function
- Macrocytic anemia
- High MCV
- MCHC is never high (RBCs can't be overpacked)

Pathophysiology & clinical manifestations of anemia

- Pathophysiology
- Reduced blood oxygen-carrying capacity
- Hypoxemia leading to hypoxia which impair functions of al body cells (all organs can be affected)
- Manifestations vary according to severity and the ability of the body to compensate
- Classic symptoms
- Fatigue
- Weakness
- Dyspnea
- **Pallor**
  - Key sign of anemia
  - *Always check the conjunctiva

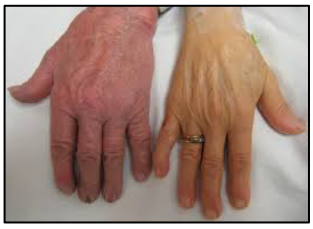

Figure 8: Pallor in the hand (right) compared to normal coloration

Microcytic-Hypochromic Anemias

- Red cells are small and contain less hemoglobin (MCV <80 fL)

General causes:

- Iron deficiency
- Impaired iron uptake, metabolism, absorption, transport
- Impaired porphyrin formation (ring around heme)
- Impaired globin synthesis (the structure of the protein that makes hemoglobin; hemoglobinopathies)
- Will details 3 examples of microcytic-hypochromic anemias:
- Iron deficiency anemia
- Sideroblastic anemia
- Thalassemia (form of Hemoglobinopathies)

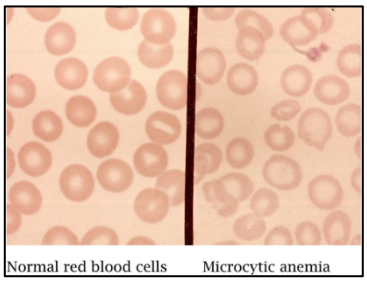

Figure 9: Microscopic comparison of normal RBCs (left) to Microcytic-hypochromic RBCs (right)

Iron deficiency anemia

- The most common type of anemia worldwide

Etiology:

- *Chronic blood loss*. Potential causes include:
- Women with heavy menses or chronic spotting related to menses
- Bleeding gastric or duodenal ulcer
- Medications:
  - E.g. Excessive use of Ibuprofen inducing gastritis or ulcer
- *Defective iron utilization*
- The body is unable to absorb, uptake and use the iron effectively
  - E.g. Surgical procedures such as gastric bypass that decrease stomach acidity, intestinal transit time, and/or absorption
  - Chronic disease eg renal failure
- *Nutritional*
- Low dietary iron

Pathophysiology

- Impaired function of mitochondrial enzymes (dependent on iron as cofactor) leads to impaired metabolism and ATP generation. This explains fatigue
- Decreased iron stores (ferritin) combined with increase need for hemoglobin synthesis to compensate for blood loss
- Eventually low serum iron

Clinical Manifestations

- *Early*:
- Fatigue, weakness, shortness of breath, pallor
- *Advanced*:
- Brittle, thin, coarsely rigid, and spoon shaped nails (koilonychia)
- Angular stomatitis
  - Inflamed and dry mouth, lips, tongue
  - Atrophied tongue papillae leading to soreness, redness and burning
  - Typically resolves within 1-2 weeks of iron replacement
- Other manifestations related to additional physiological processes requiring iron:
- Gastritis
- Neuromuscular changes
- Irritability, headache

- Numbness, tingling, vasomotor disturbances
- Pica: cravings for non-nutritional substances such as clay, dirt and chalk

Main lab data:

- Low serum iron
- Low ferritin (iron storage protein)

Sideroblastic anemia

- A group of disorders characterized by anemia of varying severity related to inefficient iron uptake leading to abnormal hemoglobin synthesis, as well as the presence of ringed sideroblasts in the bone marrow
- *Sideroblasts* = erythrocytes containing iron granules that have not been incorporated into hemoglobin

Causes:

- May be hereditary or acquired
- **Hereditary**
- Rare and almost exclusively in males
- Present in infancy or childhood but may not manifest until midlife when other conditions occurring from iron overload (e.g. diabetes, cardiac failure) begin to manifest
- **Acquired**:
- Myelodysplastic syndromes (MDS)
  - Usually all stem cell lineage are abnormal; however, in some cases only the erythrocytic line of stem cells is affected
  - If all stem cell lineages, impaired platelets = bleeding, and impaired granulocytes = infection will be observed
- Patients are treated with blood transfusions with the risk of iron overload
- Of those who survive, 40% develop Acute myeloblastic leukemia (AML)
- **Reversible**:
- Acquired SA associated with secondary conditions that can be corrected once treatment is initiated to treat underlying cause. Includes:
  - Excessive alcohol use resulting in folate deficiencies
- Drug reactions
  - E.g. Anti-tuberculous agents which can interfere with B12 metabolism or directly injure mitochondria
- Copper deficiency
- Hypothermia
- Pyridoxine deficiency (vitamin B6)

- Lead poisoning

Pathophysiology

- Ineffective iron uptake dysfunctional hemoglobin synthesis
- Cell injury due to inflammatory reaction and altered mitochondrial activity

Clinical and lab manifestations

- Common signs/symptoms of anemia
- Ringed Sideroblasts in bone marrow are diagnostic
- Test with blue stain to see the Sideroblasts
- Manifestation of siderosis (depositing excess iron in body)
- Can be treated with pyroxidine (B6) if that is the issue

Treatment:

- Hereditary SA can be usually treated with pyroxidine (B6) therapy at 50-200 mg/day
- Death related to SA is rare and usually occurs from secondary condition

Hemosiderosis (iron overload)

- Increased plasma iron leading to deposition in various body tissues

Causes:

- *Congenital*:
- Genetic defect increasing iron absorption
- Known as Hemochromatosis
- Iron is absorbed but not utilized, so level rises
- *Acquired* - Severe chronic hemolysis of any cause
- Iron is released from Hb
- Multiple frequent blood transfusions (thalassemias, sickle cell, MDS)
- Excess parenteral iron supplements (iron poisoning)

Clinical manifestations

- Due to deposition of iron in tissues: mainly liver, heart, pancreas, spleen
- *Hemosiderosis* focal iron deposition related to excess iron within an organ that does not result cause no tissue damage

- *Hemochromatosis* is typically a systemic process in which iron deposition can cause tissue damage

Treatment

- Phlebotomy

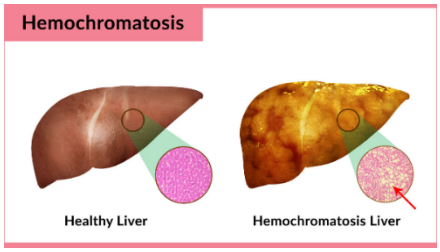

Figure 10: Comparison of healthy liver to hemochromatosis liver

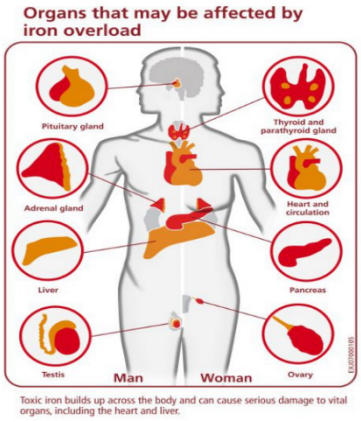

Figure 11: Organs affected in iron overload

Haemoglobinopathies

- Hemoglobinopathies are a set of inherited disorders affecting the protein structure and thus function of the hemoglobin molecule

Pathophysiology

- Increased RBC destruction due to altered structure
- Impaired function of RBCs will affect oxygen carrying capacity and distribution to tissues
- Increased destruction combined with altered function leads to manifestations of anemia

Thalassemias

- The most common hemoglobinopathy
- Hereditary disorder primarily affecting those of African, Middle Eastern, and Mediterranean descent
- Defective hemoglobin synthesis due to defects in the alpha or beta chains of the globin molecule
- Results in low intracellular hemoglobin (hypochromic); and
- Relative excess of the unaffected chain

Pathophysiology and symptoms:

- **Bone marrow hyperplasia**
- BM increase synthesis of RBCs to compensate for low levels of Hb
- This hyperactivity leads to abnormal bone (face and skull) structure
- **Splenomegaly**
- Due to increased destruction of old/damaged cells
- Worsens the anemia
- **Iron overload**
- If multiple transfusions are required

Normocytic-Normochromic Anemia

- Red cells are relatively normal in size and Hb content but low in number

Causes and classifications:

- *Bone marrow failure* (aplastic anemias)

- Disorder affecting hemopoetic stem cell precursors (located in the bone marrow) and therefore affecting all blood cell lines
- Leads to pancytopenia
- Bone marrow biopsy is required to determine whether cause is pure red cell aplasia or hypoplasia

- *Post-hemorrhagic anemia*:

- *Hemolytic anemia*:

- Increased hemolysis of cells stemming from hereditary abnormalities in RBCs or acquired disease conditions
- Trauma to RBCs within blood vessels from shear forces against vessel wall cause RBC fragmentation and intravascular hemolysis
  - This can occur with prosthetic heart valves
  - Conditions with both hemolysis and deposition of fibrin and platelets within the blood vessel that leads to microvascular narrowing (e.g. disseminated intravascular coagulation (DIC), hemolytic uremic syndrome (HUS) – both discussed in later chapters)

- *Immune destruction of RBCs*:

- Antibodies bind to RBCs leading to premature destruction
- Two types:
  - Warm antibody disease mediated by IgG
  - Cold antibody disease mediated by IgM

- *Drug induced hemolysis*
- *Chronic inflammation or infection*

- e.g. AIDS, rheumatoid arthritis, SLE
- May occur in malignancies
  - Decreased RBC lifespan, or a failure of compensatory mechanisms related to progression of disease

- *Hemoglobinopathies associated with hemolysis*

- Sickle cell anemia
  - Globin chain deficiency leading to sickle (fragile) RBCs

- Sufficient amounts of hemoglobin is produced, however there is increased destruction of defective (sickled; fragile) cells
- The remaining RBCs being normal in size and structure (hence, normocytic-normochromic classification)

Pathophysiology and manifestations

- The pathophysiology and manifestations vary according to disease conditions
- Underlying diseases causing hemolysis determines the pathophysiology and subsequent symptoms
- For example, a person who has suffered acute hemorrhage and a person with a bone marrow or autoimmune condition will both have normocytic normochromic anemia, however one results from severe blood loss while the other results from an impaired erythropoiesis
- Generally, conditions with increased hemolysis will lead to splenomegaly and bone marrow hyperplasia (if the bone marrow is able to continue to produce cells)

Macrocytic (megaloblasic) Anemia

- MCV >100 + hyper-segmented neutrophils
- Neutrophils are normally bi-lobed, but in macrocytic anemia are multi-lobed due to B12 and B9 deficiency

Cause:

Vitamin B12 (Cobalamin) deficiency

- Synthetic form of Vitamin B12 is Cyanocobalamin
- Can be caused by low levels of intrinsic factor (IF)

1) IF is produced by parietal cells of the stomach lining
2) Cause of Pernicious Anemia (see below)

- Other potential causes include:

1) Insufficient intake (primarily seen in vegans)
2) Malabsorption related to decrease IF follow gastric bypass surgery, autoimmune condition, or other gastric conditions that impact acidity

- The manifestations take a long time to develop and are bad once developed
- B12 deficiency leads to demyelination of nerves resulting in memory loss, ataxia, dementia
- The relationship between B12 and dementia has led to increased attention to B12 supplements in the treatment of Alzheimer's disease

Folic acid (B9) deficiency

- Vitamin B9 = Folic acid (folate)
- More common than B12 deficiency

- This deficiency causes impaired DNA and RNA synthesis in bone marrow (erythropoiesis)
- Symptoms show once stores are depleted (3-4 months) and include:

1) Cheilosis (dry, cracked mouth)
2) Stomatitis (swelling of mouth)
3) Can cause GI disorders
4) Causes no neuropsychiatric symptoms.

- Treatment for deficiency is supplements

Pathophysiology

- Vitamins B12 and B9 are coenzymes required for DNA synthesis
- Impaired metabolic reactions involving homocysteine and methylmalonate, as they require B12 and B9 to complete the reactions

- Levels of homocysteine and methylmalonate increase

- There is impaired DNA synthesis and nuclear maturation

- Inadequate DNA synthesis leads to defective nuclear maturation and rapidly proliferating cells
- The RBC overproduces hemoglobin during a delayed division leading to macrocytosis

(1) Macrocytosis: Disproportionate growth of nucleus & cytoplasm

(2) This results in a large cell with a small nucleus

- Timing of manifestations resulting from B12 and/or B9 deficiency are dependent on body stores.
- It is when body stores are depleted that symptoms begin to manifest

- B12 stores last 3-4 years
- B9 stores last 3-4 months

Table: Summary of B_{12}-deficiency and B_9-Deficiency An

	B_{12}-deficiency Anemia	**Folic Acid (B deficiency Anemia**
Body stores	3-4 years	3-4 months
Lab features	- Elevated homocysteine	- Elevated homocyste

- It is deficiency of both resulting in impaired DNA.

Pernicious Anemia

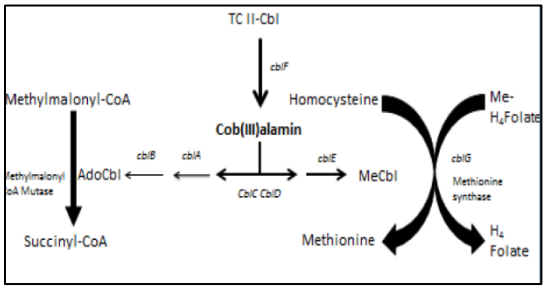

Figure 12: Metabolism of Vitamin B12 (cobalamin)

	- Elevated methylmalonate - Low B_{12} - Normal folate	- Low folate - Normal B_{12}
Clinical features	- *Neuropsychiatric symptoms*: - Memory loss - Dementia - Irritability	- No neuropsyc symptoms

- Autoimmune vitamin B_{12} deficiency (seen with autoimmune thyroiditis, type 1 DM and vitiligo)

Etiology/Patho:

- Lack of intrinsic factor required for B12 absorption (anti-intrinsic factor antibody)

Manifestations:

- General manifestations of anemia
- Dyspnea, weakness, fatigue
- Neurologic manifestations related to demyelination of nerves
- Loss of vibration sense
- Ataxia
- Spasticity
- **Others**:
- Loss of appetite
- Abdominal pain
- Beefy red tongue (atrophic glossitis)
- Icterus (jaundice)
- Splenic enlargement = due to wanting to save RBC

Polycythemia

- Overproduction of RBCs
- Can be classified into:

1. Absolute polycythemia

- **Primary** (Polycythemia Rubra Vera; PRV)
  - Abnormality of stem cells in the bone marrow. High number of RBCs = sticky blood; increase blood viscosity inducing clotting tendency

- **Secondary**
  - Condition of chronic hypoxia:
    - Leading to an increase in erythropoietin (EPO) hormone
    - Increased EPO leads to increased production of RBCs by the bone marrow
    - The body increases RBC production in response to need
  - Potential causes:
    - High altitude
    - Hypoxia associated with respiratory or cardiovascular diseases
    - EPO secreting tumor

2. Relative polycythemia

- Results from dehydration
  - Clinically manifests with an increase in blood viscosity

Leukemia

- Malignant disorder of the blood-forming organs (cancer of white blood cells)
- Neoplasms with widespread involvement of the bone marrow and often, though not always, peripheral blood

Etiology:

- Unknown, chemo, radiotherapy, exposure to chemicals (benzene), genetic (E.g. Down's Syndrome associated with increased risk for AML)

Pathophysiology:

- Replacement of bone marrow (BM) and/or lymphoid organs with leukemic (immature) cells
- There is a depression of normal bone marrow function; red cells, white cells, platelets
- Organomegaly (organs enlarge) of organs related to the immune system
  - E.g. Lymph nodes and spleen

Clinical manifestations

- Anemia (reduced RBCs)
- Increased susceptibility to infection (abnormal WBCs)
- Bleeding manifestations (low platelets)

- Petechiae
- Purpura
- Ecchymosis
- Hemorrhage eg epistaxis, GIT bleeding

- Weight loss
- Lymphadenopathy, hepatosplenomegaly
  - Results from leukemic cells multiplying in organs
- Bony aches
  - The BM hyper activity puts pressure on bones.
- Elevated uric acid
  - As the abnormal cells and their DNA are destroyed, uric acid builds up.
  - Manifests as renal stones, uric acid crystals in urine
    - *LEUKEMIC TRIAD = **ANEMIA + INFECTION + BLEEDING**

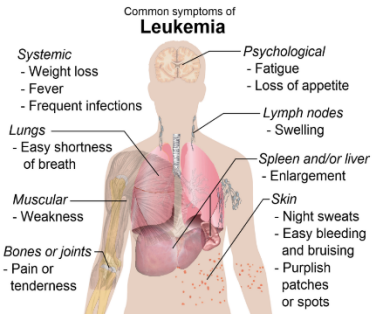

Figure 13: Classic symptoms of leukemia

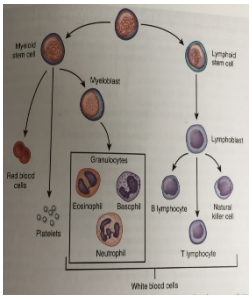

Figure 14: Lymphoid and myeloid stem cell maturation

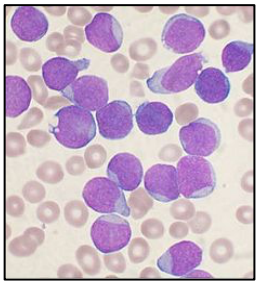

Figure 15: Lymphoblasts in blood smear

Table: Summary Classification of Leukemias		
	Acute	**Chronic**
Lymphoid Stem Cell Precursor	ALL	CLL

Classification/Types of Leukemia

Myeloid Stem Cell Precursor	AML	CML

Acute Leukemia

- Immature cells (blast cells)
- Blasts leak from the bone marrow to cause acute disease
- *Acute Lymphoid leukemia (ALL)*
- More common in children
- *Acute Myeloid leukemia (AML)*
- More common in adults
- Also, more serious in adults too

Chronic Leukemia

- Mature cells, but abnormal function
- Cells are more differentiated and cause disease over a longer period of time
- *Chronic lymphoid leukemia (CLL)*
- More common in adults
- *Chronic myeloid leukemia (CML)*
- More common in adults

Stem Cell Classification

- ALL and CLL come from the lymphoid stem cell
- AML and CML come from the myeloid stem cell

ALL

- Most common childhood leukemia

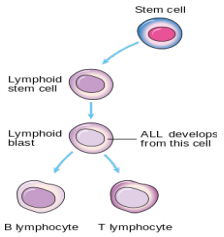

Figure 16: Development of ALL from lymphoid stem cell

Pathological features:

- Marked leukocytosis
- Lymphoblasts in peripheral blood and bone marrow

Cytogenetics:

- T(4;11) (q21;q23)
- T(8;14)(q24;q32)
- T(11;14)(p13;q11)
- Note: When reading translocation mutations:
- E.g. T(**4**;11)(**q21**;q23)
- **chromosome 4**, **band 21** is translocated with chromosome 11's band 23"

AML

- Most common adulthood acute leukemia
- Down syndrome and Fanconi anemia are known to increase the risk for AML

Pathological features:

- Marked leukocytosis
- Myeloblasts in peripheral blood and bone marrow

Cytogenetics

- T(8;21)(q22;q22)
- Inv (16)(p13.1;q22)
- T(16;16)(p13.1;q22)

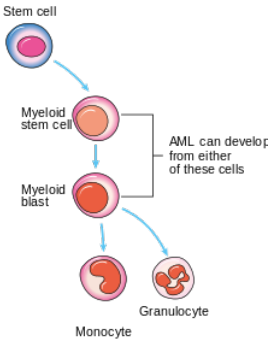

Figure 17: Development of AML from myeloid stem cell

CML

Most common adulthood chronic leukemia

Pathological features:

- Marked leukocytosis
- Present in terminal phase of CML
- Myeloblasts in the peripheral blood and bone marrow
- Peripheral blood look like bone marrow!!
- Basophilia
- Basophilia present in terminal, final stage of CML
- Splenomegaly
- Blastic crisis
- Occurs in stage 2, the acute/ accelerative phase
- Very painful
- Lymphadenopathy
- Usually only found in the acute phase of the disease

Cytogenic

- Philadelphia chromosome:
- T(9;22)(q34;q11) that creates the BCR-ABL fusion gene (oncogene)

Lymphomas

- Malignant transformation and proliferation of lymphocytes and their precursors/derivatives in lymphoid tissues

- A cancer of both the blood (lymphocytes) and lymphatic system (lymphoma)
- Lymphomas primarily affect the lymph nodes
- The patient usually presents with a mass

2 major categories of lymphoma:

- *Hodgkin lymphoma*
- Neoplasm of Reed-Sternberg cells
- *Non-Hodgkin lymphoma*
- Includes 4 cell-types as classified by WHO
  - Precursor (immature) B-cell neoplasms
  - Peripheral (mature) B-cell neoplasms
  - Precursor (immature) T-cell neoplasms
  - Peripheral (mature) T-cell neoplasms

Pathophysiology & manifestations (for both Hodgkin and Non-Hodgkin Lymphoma):

- Main pathophysiological feature is lymphadenopathy
- Weight loss and night sweats
- Fever, mediastinal mass, splenomegaly, abdominal mass, pruritus

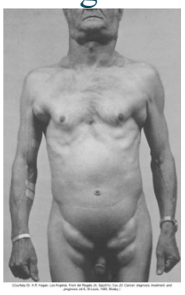

Figure 18: Lymphadenopathy (visible in groin and axilla)

Diagnostic Testing and Staging

- Anemia, leukocytosis, eosinophilia
- Elevated ESR and ALP
- LN biopsy and staging
- Histopathology: Reed-Sternberg cells; essential for diagnosis
- **Ann-Arbor staging (see Table below)**
- Staging classification used for Hodgkin lymphoma

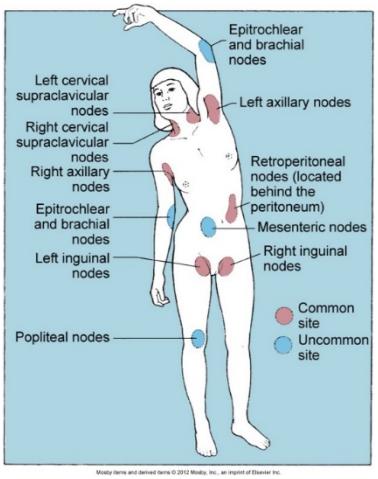

Figure 19: Body lymph node sites

Hodgkin Lymphoma

- HL affects people aged 20-40 and 60-80
- Typical cases associated with infectious mononucleosis (EBV is oncogenic virus)
- Presence of abnormal B cells called *Reed-Sternberg cells (RS)*
- RS cells are usually infected with EBV which is likely linked to the cause

- The cells are large and binucleate, they are necessary for diagnosis but are not specific to HL

- Curable disease

Table 4. Ann Arbor Staging Classification for Hodgkin Lymphoma[a]

Stage	Description
I	Involvement of a single lymphatic site (i.e., nodal region, Waldeyer's ring, thymus, or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE).
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.
Designations applicable to any stage	
A	No symptoms.
B	Fever (temperature >38.0°C), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 months.
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site.
S	Splenic involvement.

[a]Reprinted with permission from AJCC: Hodgkin and non-Hodgkin lymphomas. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 607-11.[21]

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Non-Hodgkin Lymphoma

- Lymphoma from either B cell, T cell and/or NK cell neoplasms

- Proliferation occurs through lymphoid tissue with differing patterns and responses to treatment

- Able to spread throughout body

- In contrast HL is usually localized, affecting a certain chain of lymph nodes

- Median age for diagnosis is 67 years

Multiple Myeloma (MM)

- Malignant proliferation of plasma cells

Pathophysiology:

- Proliferation of plasma cells
- These cells infiltrate bone marrow and aggregate creating tumor masses in bone
- Myeloma cells produce monoclonal immunoglobulins (antibodies) which are proteins
- High levels of these proteins in the blood leads to increased blood viscosity

Clinical and lab manifestations:

- Anemia
- Depressed bone marrow so can't make RBCs
- Bone lesions
- Lead to bone aches
- Prone to bone fractures
- Bence-Jones protein
- The plasma cells can make a "free immunoglobulin light chain" (the Bence-Jones protein)
- Circulate in blood and kindey, can cause renal failure
- Hypercalcemia
- From bone break down
- Leads to reduced bone density
- Renal failure
- BJ protein buildup can block kidney tubules

Disorders Related to Alterations of the Clotting System (Bleeding Defects)

- Disorders that lead to an inability to form fibrin at an injured site

Pathophysiology:

- 3 potential causes leading to development of clotting system disorder:
- Clotting factor defects
- Platelet defects
- Vascular (blood vessel) issues
  - Impaired myogenic effect
  - Impaired endothelium (vasculitis)

Diagnostics Used for Diagnosis and Treatment

- *Should know the normal CBC*
- PT (Prothrombin time)/ INR
  - The length of time it takes make prothrombin (a clot)
  - Normal range is 10-14 seconds
  - Longer times indicate bleeding issues
    - Potential cause from vitamin K deficiency
    - Oral anticoagulants (warfarin); titrated according to INR
  - Shorter times indicate clotting issues
- aPTT (Activated partial thromboplastin time)
  - A substance is added to the blood sample to make it clot faster
  - Normal range is 30-40 seconds
  - If you take heparin, your result would be higher.
    - Heparin is titrated according to aPTT

Selected Disorders Related to Clotting factors

Hereditary:

- Haemophilia A (deficiency of coagulation protein VIII)
- Von Willebrand disease (vWD) (vWF protein defects)
  - The most common mild bleeding disorder
  - Impaired VWF dependent platelet functions
- Both Haemophilia and Von Willebrand disease are very common

Acquired:

- Vitamin K deficiency
- Liver disease
  - Due to defective synthesis of coagulation factors
  - Impaired synthesis of vitamin k dependent factors (II,VII,IX,X) and proteins C and S (natural anticoagulants)

Platelet Disorders

Thrombocytopenia

- Platelet count <150,000/mm3

Selected Causes for Thrombocytopenia:

- Hypersplenism

- Overactive spleen that destroys RBCs and platelets

▪ DIC (disseminated intravascular coagulation)

- Excessive generation of thrombin and fibrin, usually from exposure to tissue factor in the circulation, leading to activation of the coagulation cascade
- Platelet aggregation combined with consumption of coagulation factors leads to a combination of clot formation and bleeding
- Thrombocytopenia resulting from platelet consumption in formation of clots

▪ HIT (heparin induced thrombocytopenia)

- Within 7-10 days of heparin use
- Abnormal antibodies against heparin; bound to a protein called platelet factor 4
- Bleeding due to low platelets
- Thrombosis may result from activated platelet

▪ ITP (idiopathic/immune thrombocytopenia purpura)

- Mainly children
- IgG against platelets
- Antibody-coated platelets are sequestered and removed from the circulation
- Leads to splenomegaly

Manifestations

▪ Petechiae, purpura

▪ Major bleeds

Thrombocytosis

▪ Elevated platelet production

▪ Platelet count >500,000/mm3

Selected causes:

▪ Essential thrombocythemia

▪ Myeloproliferative disorder affecting all lineage or just platelet precursor cells

Manifestations

▪ Microvascular thrombosis (blockages in small blood vessels)

- Symptoms depend on vessels affected
- Primarily occurs in hands and feet, lead to:

o Redness

o Warm to touch

o Feel burning sensations in affected digits and/or limbs

o Standing and warmth make it worse and relief from elevation and cooling

- May develop erythromyalgia secondary to microvascular thrombosis
- This is the paroxysmal vasodilation of small arteries (most often in hands and feet but can include face, ears and knees)
- Causes burning pain, redness, and localized warmth
- Microvascular thrombosis in other areas with associated symptoms include:
- Eye (ocular migraines)
- CNS (transient ischemic attacks)
- Chest (pulmonary embolism)
- Bleeding events associated with thrombocytosis include easy bruising, GI bleeds, and epistaxis

Thrombophilia conditions

- Hypercoaguability of the blood
- Causes:
- AT-III (antithrombin III) deficiency
- Protein C deficiency and factor V Leiden (protein C resistance)
- Protein S deficiency
- Prothrombin gene mutations
- Antiphospholipid syndrome

Thrombosis

- Blood clot forms inside vessel
- 3 conditions (*Virchow's triad*) together increase risk/ can lead to thrombosis
- Hypercoagulability of blood
- Vessel wall injury

Stasis of blood

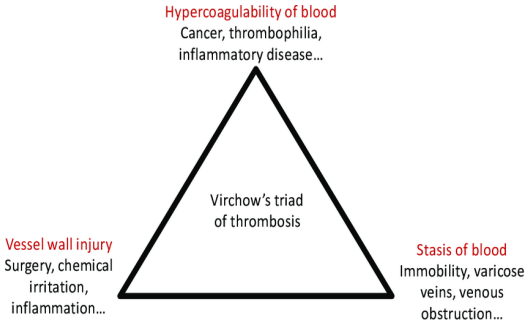

Figure 20: Virchow's Triad of thrombosis