Hematology

Hematology

Hematology is defined as the science that deals with the: formation, composition, functions and diseases of the blood.

What is Blood?

- Blood is a fluid tissue containing many suspended cells and is found in the circulatory system transporting substances.
- These substances may include the digested food substances like amino acids and glucose, excretory products of the body and tissues and oxygen and carbon dioxide for respiration.
- Blood also serves to protect the body against pathogens.

Blood Composition

Plasma	RBCs
White Blood Cells	Blood Platelets

Sample of whole blood

Contains

Plasma (46–63%)

Formed elements (37–54%)

OTHER SOLUTES

Electrolytes	Normal extracellular fluid ion composition essential for vital cellular activities. Ions contribute to osmotic pressure of body fluids. Major plasma electrolytes are Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, HPO_4^{2-}, SO_4^{2-}
Organic nutrients	Used for ATP production, growth, and maintenance of cells; include lipids (fatty acids, cholesterol, glycerides), carbohydrates (primarily glucose), and amino acids
Organic wastes	Carried to sites of breakdown or excretion; include urea, uric acid, creatinine, bilirubin, ammonium ions

PLASMA PROTEINS

Albumins (60%)	Major contributors to osmotic concentration of plasma; transport lipids, steroid hormones
Globulins (35%)	Transport ions, hormones, lipids; immune function
Fibrinogen (4%)	Essential component of clotting system; can be converted to insoluble fibrin
Regulatory proteins (<1%)	Enzymes, proenzymes, hormones

PLASMA COMPOSITION

Plasma proteins	7%
Other solutes	1%
Water	92%

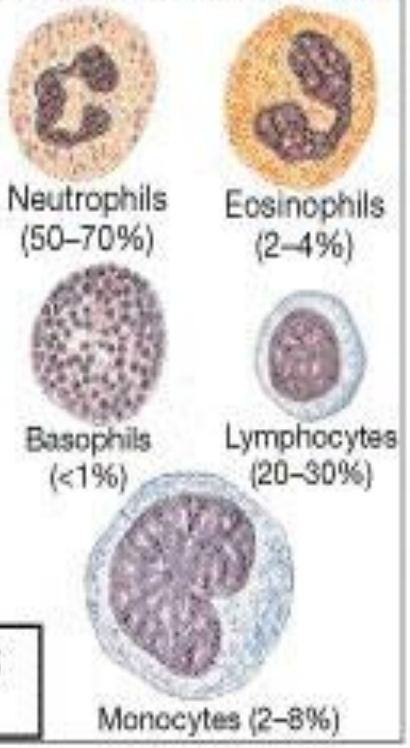
Transports organic and inorganic molecules, formed elements, and heat

FORMED ELEMENTS

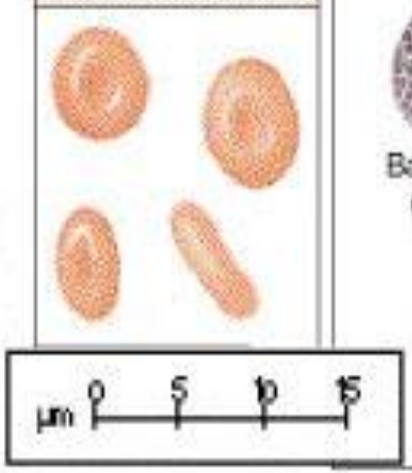
Platelets	0.1%
White blood cells	
Red blood cells	99.9%

PLATELETS

WHITE BLOOD CELLS



RED BLOOD CELLS



Blood components

- Plasma is a pale yellowish fluid with a total volume of 2-3 liters in a normal adult.
- Its contents are :
  - Water **90.0%**
  - Protein **8.0%**
  - Inorganic Ions **0.9%:** Sodium, potassium, calcium, chloride, hydrogen, carbonate and phosphate
  - Organic Substances **1.1%**
- Serum Albumin composed of 60% of the total plasma protein.
- Serum Globulins make up 36% of the total plasma protein. Globulins aid in the inflammatory response of the body.
- Fibrinogen and prothrombin are important in the clotting process of blood.

Blood components

Protein Functions Include:

- Transportation of insoluble substances around the body by allowing them to bind to protein molecules
- Blood clotting
- Responses in accordance to disease (inflammatory response)
- Protection from infection (the gamma globulins function)
- Balance for the pH of the blood

Organic Substances

- Blood plasma carry organic substances such as nutrients (digested food substances like glucose, amino acids, glycerol, triglycerides, cholesterol and vitamins).
- Waste products of the body (urea and cellular waste that will be excreted out of the body).
- Hormones, such as cortisol and thyroxine are also transported around the body in plasma attached to plasma proteins.
- Medicine and drugs also circulate within the plasma.

Blood components

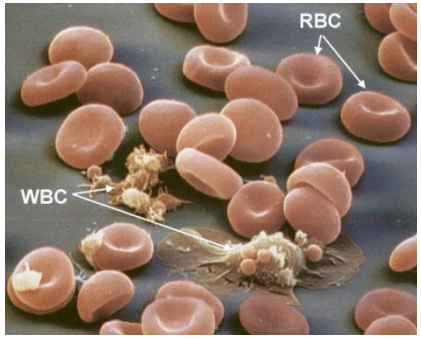
Red Blood Cells (RBC) (Erythrocytes)

- Red blood cells are the most common cells found in blood.
- There are about 5 million RBC in each cubic millimeter of blood
- This number varies with individuals in accordance to heredity, gender and state of health.
- These cells are produced by the bone marrow and have a lifespan of 3-4 months. When they die, they are destroyed by macrophages in the liver and spleen.
- This process releases iron to be stored in the liver, to be recycled and bile pigments to be excreted.

Blood components

Structure of A Red Blood Cell

- Red blood cells have a bi-concave shape with a flattened center.
- It has a diameter less than 0.01 millimeters and do not have a nucleus.
- Haemoglobin gives RBC its red color and Haemoglobin that contains iron, can easily transport gases such as O_2 and CO_2.
- RBCs are highly elastic, rendering it able to squeeze through capillary walls



Functions of Red Blood Cells

- Are important in the process of respiration in carrying O_2 and CO_2

White Blood Cells (Leucocytes)

- White blood cells (WBCs) are responsible for the defense system in the body.
- There are approximately 6,000 white blood cells per millimeter of blood
- WBCs fight infections and protect our body from foreign particles, which includes harmful germs and bacteria.
- WBCs are formed from the stem cell of the bone marrow.
- It has a life-span of a couple of days and when they die, they are destroyed by surrounding white blood cells and replaced with new ones.

Structure of White Blood Cells

- WBCs are colorless, because they contain no haemoglobin.
- It contains a nucleus and has an irregular shape.
- Though there are fewer WBCs than RBCs, they are much bigger in size.
- They can change their shape easily and this allows them to squeeze through walls of the blood vessels into the inter-cellular spaces

White Blood Cells (Leucocytes)

Unlike the Red blood cells or platelets, there are 5 different types of white blood cells, each serving a different purpose in our body's immune system.

Neutrophils

- Neutrophils make up 55%-70% of the total white blood count in the blood stream.
- Neutrophils can be most commonly found **near sites of infection or injury** where they will stick to the walls of the blood vessels and engulf any foreign particles that try to enter the bloodstream.
- They can also be found in the **pus of wounds**.

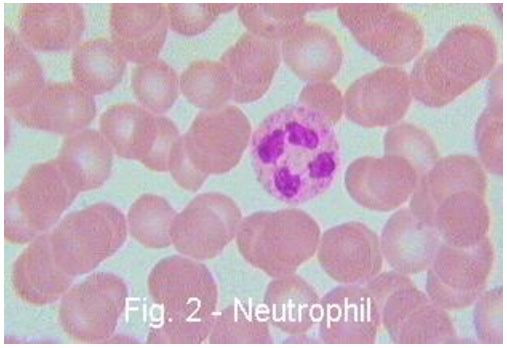
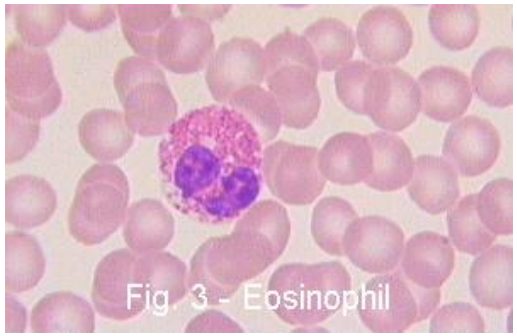


Fig. 2 - Neutrophil

White Blood Cells (Leucocytes)

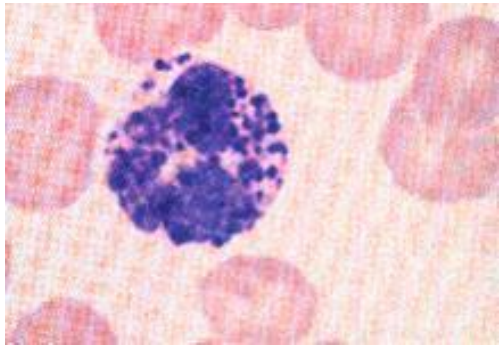
Eosinophils

- ✓ Eosinophils make up 2%-5% of the total blood count and mainly attacks parasites and an antigen complexes.
- ✓ These cells are also responsible for **allergic response** within the blood.



Basophiles

- ✓ Basophiles make up less than 1% of the total white blood count.
- ✓ Upon stimulation, a **massive release of granule contents**. Chemicals released include: heparin, histamine, and other substances which mediate hypersensitivity reactions within the blood.



White Blood Cells (Leucocytes)

Monocytes

- Monocytes 5%-8% of the total white blood count
- Are the largest of the 5 types of white blood cells.
- They act as tissue macrophages and **remove foreign particles** and prevent the invasion of germs which cannot be effectively dealt with by the neutrophils.

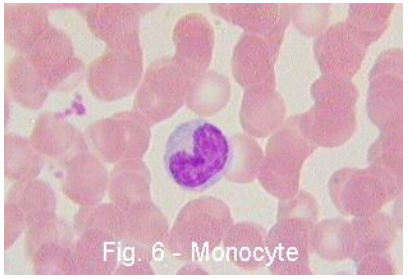


Fig. 6 - Monocyte

Lymphocytes

- Lymphocytes **produce antibodies** against toxins secreted by bacteria and infecting gems.
- These antibodies will be excreted into plasma to kill bacteria in the bloo as well as act antitoxins. In addition, they cause the foreign particles to cluster to be engulfed by phagocytes.
- The nature of lymphocytes is **highly specific** and they can only recognize certain antigens.

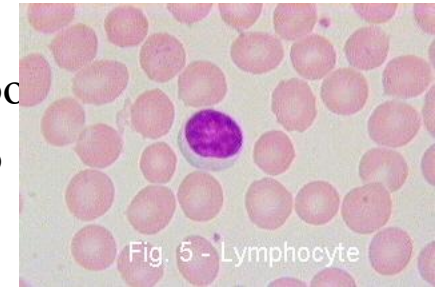


Fig. 5 - Lymphocyte

Blood Platelets

- Blood Platelets are granular non-nucleated fragments of cytoplasm in the form of oval discs.
- A platelet consists of two parts, a clear outer ground substance occupying the greater part of the platelet and a central part that contains granules.

Functions of Blood Platelets

- They secrete a hormone called serotonin which contract blood vessels.
- Have a major role in accumulating at sites of injury sticking together to plug gaps in broken blood vessels.
- They are rich in activators for some proteins, these proteins form a fibers as network ➔ helping in forming the clot➔ bleeding will be stopped.

Laboratory evaluation

- CBC, including RBC indices, a reticulocyte index, examination of a peripheral blood smear

Complete Blood Count (CBC)

- The Complete Blood Count (CBC) test is an automated count of the cells in the blood.
- It provides information about the white blood cell (WBC), red blood cell (RBC), and platelet populations present.
- This information includes the number, type, size, shape, and some of the physical characteristics of the cells. Any abnormalities found are noted.

Hemoglobin (Hgb):

- Very rough estimate of the oxygen-carrying capacity of blood hemoglobin is found within the biconcave red blood cells.
- The normal haemoglobin count is 12-16 g/dl of blood in females and 13-18 g/dl in males.

Hematocrit (Hct):

- PCV is the actual volume of RBCs in a unit volume of whole blood
- It is about three times the Hgb value
- Low Hct indicates a reduction in either the number or size of RBCs, or an increase in plasma volume

Laboratory evaluation

RBC count:

- It is an actual count of RBCs per unit of blood
- RBCs are normally all the same size and shape
- Variations can occur with vitamin B12 and folate deficiencies, iron deficiency, and with a variety of other conditions.

RBC indices:

- Wintrobe indices describe the size and Hgb content of the RBCs and are calculated from Hgb, Hct and RBC count
- MCV, MCH and MCHC
- Mean corpuscular volume (MCV)
  - Hct/RBC count
  - The average volume of RBCs
  - Micro-, normo- and macrocytic
  - Reticulocytosis
- Mean corpuscular hemoglobin (MCH)
  - Hgb/RBC count
  - The percent volume of Hgb in an RBC
  - Microcytosis or hypochromia can reduce the MCH
  - Elevated MCH is macrocytosis

Laboratory evaluation

Mean corpuscular hemoglobin concentration (MCHC)

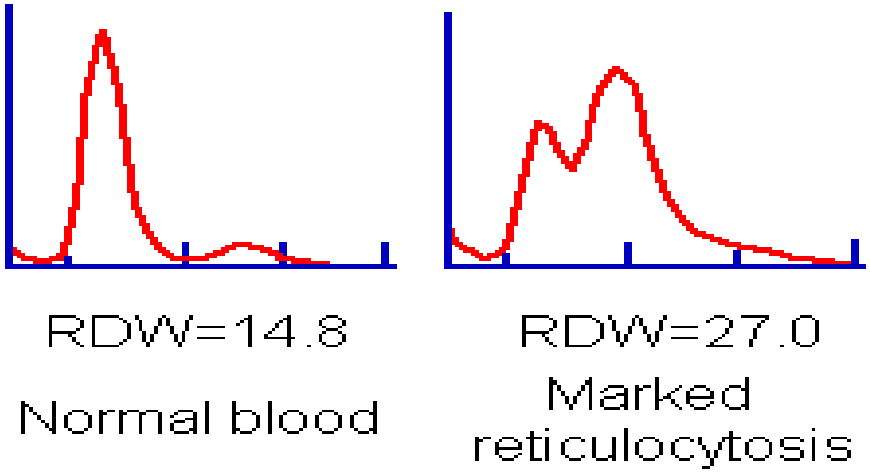
- Hgb/Hct
- The weight of Hgb per volume of cells
- It is independent of cell size
- It can differentiate between microcytosis and hypochromia
- A low MCHC always indicates hypochromia

Total reticulocyte count:

- Indicates new RBC production
- Normal is 1%

Laboratory evaluation

- **RBC distribution width (RDW)**
- **RDW = (Standard deviation of red cell volume ÷ mean cell volume) x 100**
- The higher the RDW, the more variable the size of RBCs
- Helpful in the diagnosis of mixed anemia



- **Peripheral smear**:
- Complements other clinical data
- It provide information on the variation in cell size and shape

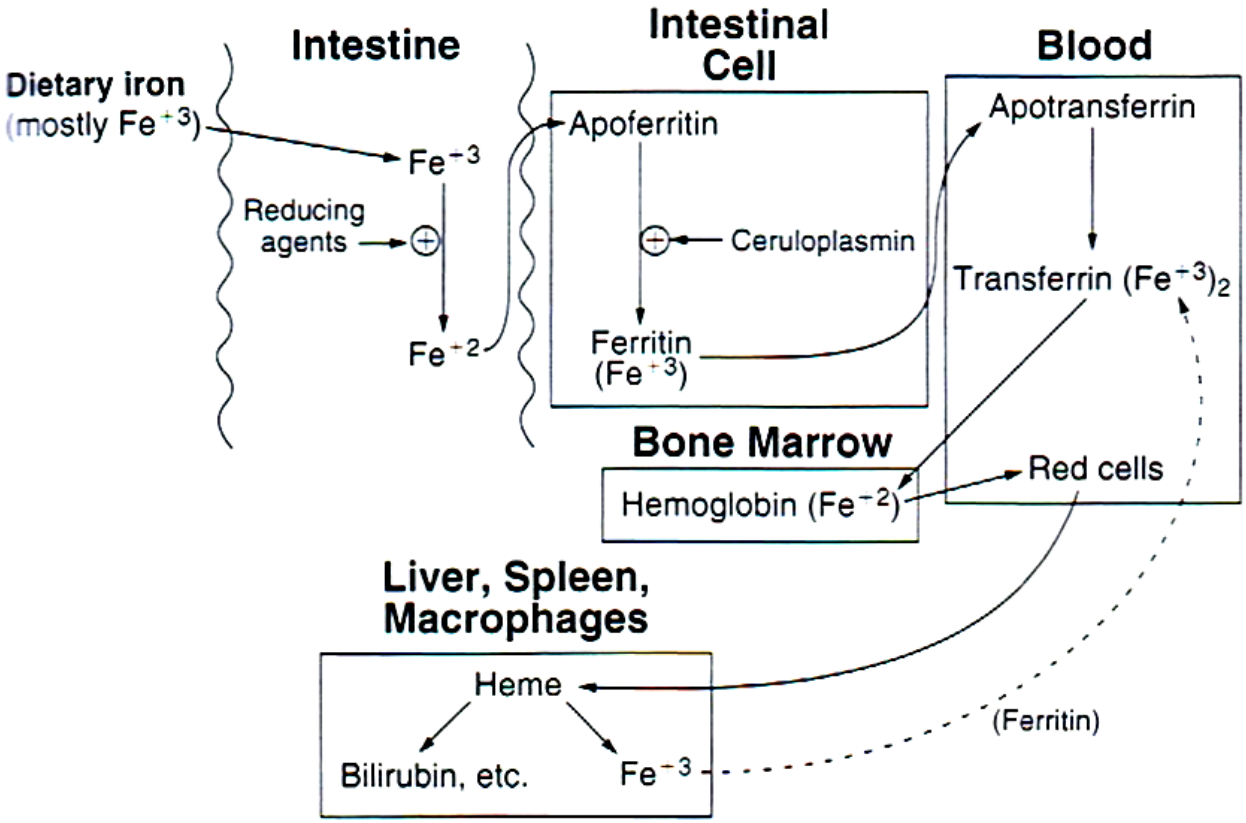
Iron

- The total iron content of the adult body is approximately 4g (70mmol), of which some two-thirds is in haemoglobin. Iron stores (mainly spleen, liver and bone marrow) contain about one-quarter of the body's iron.
- Most of the reminder is in myoglobin and other haemoproteins; only 0.1% of the total body iron in the plasma where it is almost all bound to a transport protein, transferrin.
- The mean daily intake of iron is about 20 mg but less than 10% of this is absorbed.
- Iron absorption is determined by the state of the body's iron stores, being increased when they are depleted and decreased when they are adequate. It is also increased when erythropoiesis is increased (irrespective of the state of iron stores).
- Iron is more readily absorbed in the Fe^{2+} form but dietary iron is mainly in the Fe^{3+} form. **Gastric secretions** are important in iron absorption in that they liberate iron from food (although haem can be absorbed intact) and promote the conversion of Fe^{3+} ions to Fe^{2+}.

Iron

- **Ascorbic acid** and other reducing substances facilitate iron absorption while **phytic acid** (in cereals), **phosphates and oxalates** form insoluble complexes with iron and decrease its absorption.
- Once absorbed into the intestinal mucosal cells, iron is either transported directly into the blood stream, or else combines with apoferritin, a complex iron-binding protein, to form ferritin. This iron is lost into the lumen of the gut when mucosal cells are shed. In iron deficiency, the apoferritin content of mucosal cells decreases and a greater proportion of absorbed iron reaches the blood stream.
- In the blood, iron is transported bound mainly to transferrin. Transferrin is normally about one-third saturated with iron. In tissues, iron is bound in ferritin and haemosiderin. **Free iron is very toxic and protein binding allows iron to be transported and stored in a non-toxic form**
- It is rarely necessary to use biochemical tests merely to substantiate a diagnosis of iron deficiency, since this by far the commonest cause of microcytic (any anaemia in which the average size of circulating erythrocytes is smaller than normal), hypochromic anaemia, and the diagnosis is confirmed by a response to iron therapy.

Transport of iron



Plasma iron

- The plasma iron concentration is of little value in the investigation of iron metabolism, except in relation to **haemochromatosis** and in the diagnosis and management of **iron poisoning**.

- A fall in plasma iron concentration is a late feature of iron deficiency, although a raised plasma iron is usually present in iron overload.

- The concentration of iron in the plasma of normal individuals fluctuates considerably; differences of more than 20% can occur within a few minutes, and of 100% from one day to the next.

Plasma ferritin

- Although plasma ferritin concentration is more difficult to measure than iron or iron-binding capacity, it is by far superior to them for the assessment of body iron stores.

- **The only known cause of low plasma ferritin concentration is a decrease in body iron stores;** concentration below 20 μg/L indicate depletion, and below 12 μg/L suggests a complete absence of stored iron.

- However, ferritin is an **acute phase protein** and patients with iron deficiency may have plasma ferritin concentrations within the reference range when they are acutely ill.

Iron overload

- This can occur with increased intestinal absorption of iron: either acutely, as in iron poisoning, or chronically, as is seen in people who traditionally cook their food in iron pots.
- Increased parentral iron administration occurs unavoidably in patients given repeated blood transfusions for the treatment of refractory anaemias and can also lead to overloading of the body's iron stores (**haemosiderosis** or acquired **haemochromatosis**).
- The excess iron is deposited mainly as haemosiderin in reticuloendothelial cells in the liver and spleen where it is relatively innocuous, but with time parenchymal deposition may lead to hepatic fibrosis and myocardial damage.

Tests for Iron

- Serum iron: is the concentration of iron bound to transferrin
- Total iron binding capacity (TIBC)
- Percentage transferrin saturation
- % Transferrin saturation=(Serum iron/TIBC) × 100

Folic acid

- Folate coenzymes are essential for the transfer of a single carbon units. A derivative of folic acid is vital to purine and pyrimidine (and hence nucleic acid) synthesis.
- Folate is absorbed from dietary sources such as green leafy vegetable.
- Dietary sources provide approximately 500 μg of folate per day. The human daily requirement for folate is approximately 50 μg. Body stores of folate amount approximately 5 mg. Interruption of absorption of folate may therefore result in deficiency within a few months.
- Folic acid deficiency is relatively common; its manifestation is as a macrocytic anaemia:
  - Inadequate intake, decreased absorption, hyperutilization (during pregnancy, malignancy), and inadequate utilization
- It is destroyed by cooking or processing.

Vitamin B_{12}

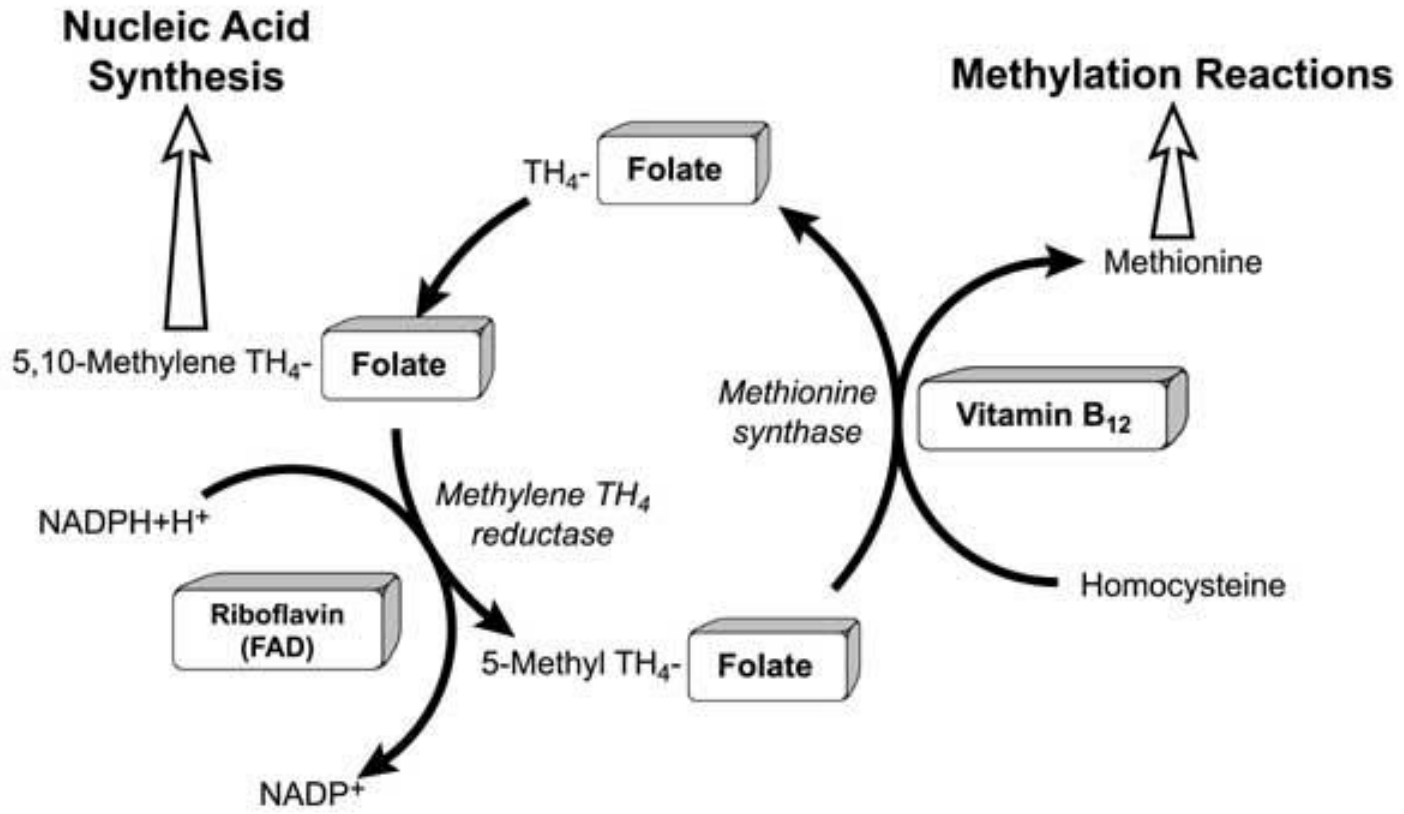
- Vitamin B_{12} refers to a group of physiologically active substances chemically classified as cobalamins.
- In humans, the daily requirement is 0.5 μg. The only significant dietary sources of vitamin B_{12} are meat, milk or milk products and eggs.
- It is stored within the liver and released to plasma to meet physiological demands. If the quantity of vitamin B_{12} exceeds the capacity of hepatocyte receptors, most of the excess is excreted by the kidneys. Normally, approximately 1 mg of vitamin B_{12} is stored in the liver, a quantity equivalent to the daily metabolic requirement for 2000 days; **thus dietary deficiency or impaired absorption of vitamin B_{12} does not become evident for 5 years or more.**
- In the stomach, vitamin B_{12} forms a complex with intrinsic factor (IF). When the vitamin B_{12}-IF complex reaches the distal ileum, it is bound by receptors on the surface of mucosal epithelial cells and then enters the cells. Within the mucosal epithelial cells, the vitamin B_{12}-IF complex is dissociated, and the vitamin then passes into the plasma. The gastric secretion of IF is stimulated by food, histamine and gastrin; it is inhibited by vagal blockade.

Vitamin B_{12}

- The deficiency of vitamin B_{12} in humans is associated with megaloblastic anaemia.
- Pernicious anaemia: the most important disorder of vitamin B_{12} metabolism, is due to decreased secretion of IF. It is an autoimmune disease. Deficiency of vitamin B_{12} causes serious and often irreversible neurological disorders such as burning pain or loss of sensation in the extremities, weakness, spasticity and paralysis, confusion, disorientation and dementia.

Tests for vitamin B_{12}

1. Vitamin B12: serum values are maintained at the expense of vitamin B_{12} tissue stores.
2. Homocysteine: vitamin B_{12} and folate are required for conversion of homocysteine to methionine. It can be also elevated in B_6 deficiency.
3. Methylmalonic acid (MMA): a vitamin B_{12}coenzyme is needed to convert methylmalonyl coA to succinyl coA. Increased urinary excretion of MMA is a more specific marker of vitamin B_{12} deficiency


Nucleic Acid Synthesis
Methylation Reactions
TH4- Folate
5,10-Methylene TH4- Folate
Methionine
Methionine synthase
Vitamin B12
Methylene TH4 reductase
NADPH+H+
Riboflavin (FAD)
5-Methyl TH4- Folate
Homocysteine
NADP+

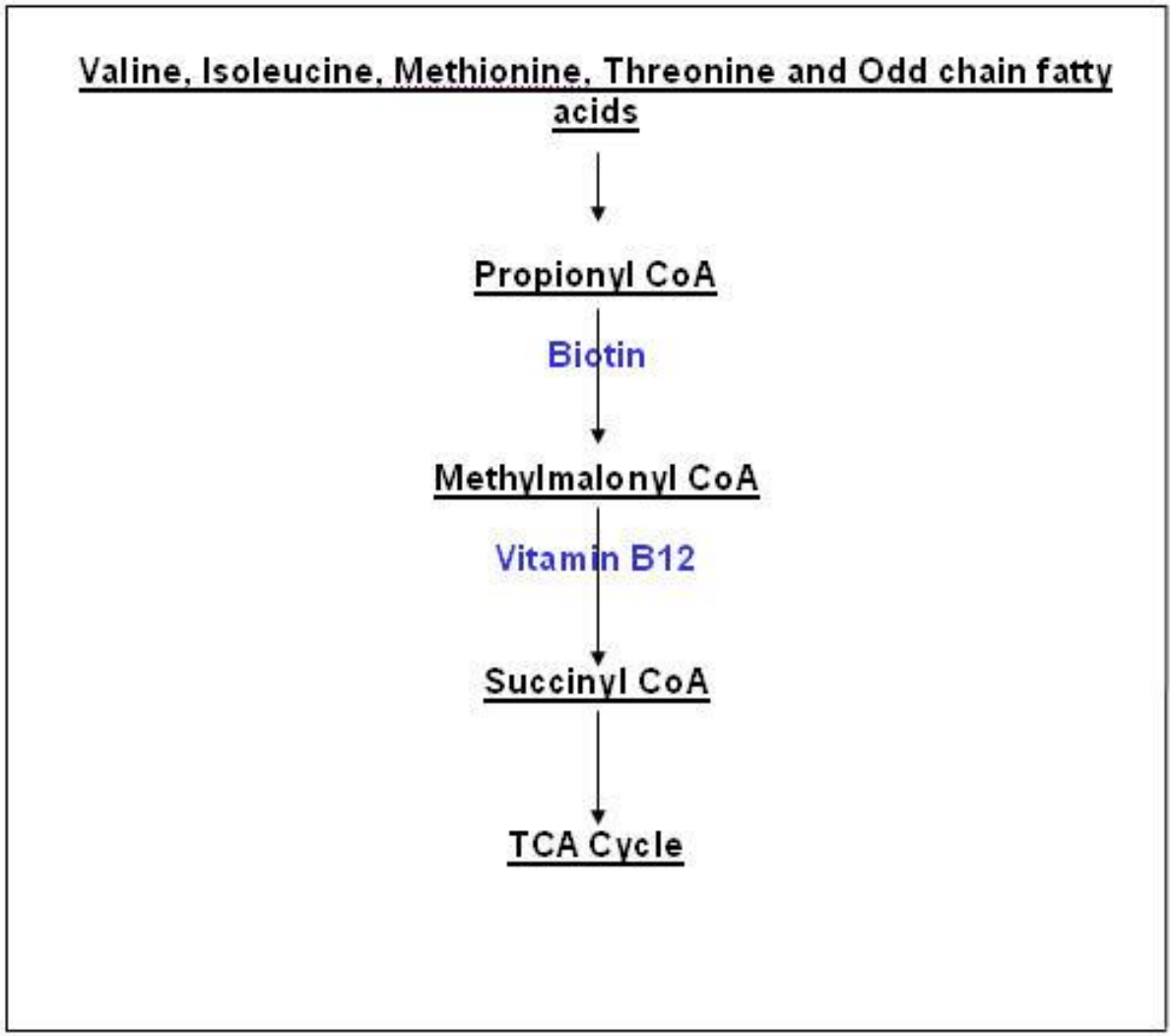

Valine, Isoleucine, Methionine, Threonine and Odd chain fatty acids
Propionyl CoA
Biotin
Methylmalonyl CoA
Vitamin B12
Succinyl CoA
TCA Cycle

TABLE 17-3 REFERENCE INTERVALS FOR PARAMETERS USED TO ASSESS IRON STATUS[47,84]

PATIENT POPULATION	SERUM IRON (mg/dL)	TRANSFERRIN (mg/dL)	FERRITIN (mg/dL)	PERCENT SATURATION	TIBC (μg/DL)
Newborn	100–250	130–275	25–200	12–50	100–400
Infant	40–100	200–360	200–600	12–50	100–400
Child	50–120	200–360	7–140	12–50	100–400
Male, adult	50–160	200–380	20–250	20–55	250–425
Female, 16–40 years	45–150	200–380	10–120	15–50	250–425
Female, >40 years					10–250

TABLE 17-4 LABORATORY MARKERS OF IRON STATUS IN SEVERAL DISEASE STATES

CONDITION	SERUM IRON	TRANSFERRIN	FERRITIN	PERCENT SATURATION	TIBS
Normal intervals	50–160 μg/dL	200–400 mg/dL	20–250 μg/L	20%–50%	250–350 μg/dL
Iron deficiency	Decreased	Increased	Decreased	Decreased	Increased
Iron overdose	Increased	Decreased	Increased	Increased	Decreased
Hematochromatosis	Increased	Slightly decreased	Increased	Increased	Slightly decreased
Malnutrition	Decreased	Decreased	Decreased	Variable	Decreased
Malignancy	Decreased	Decreased	Increased	Decreased	Decreased
Chronic infection	Decreased	Decreased	Increased	Decreased	Decreased
Viral hepatitis	Increased	Increased	Increased	Normal/ increased	Increased
Acute liver disease	Increased	Variable/increased	Increased	Increased	Variable/increase
Chronic anemia	Decreased	Normal/decreased	Normal/ increased	Decreased	Normal/decreased
Sideroblastic anemia	Increased	Normal/decreased	Increased	Increased	Normal/decreased

Source: Adapted with permission from Jacobs DS, ed. Laboratory test handbook. Boca Raton, Fla.: Lexi-Comp Inc, 1996.

White Blood Cell Count

- It is a count of the actual number of white blood cells per volume of blood.
- An unusually high white blood cell count can lead to leukemia and infection within the organs.
- Low white blood cell count will make the individual susceptible and vulnerable to diseases and foreign invasive organism.

Differential Blood Count of WBCs

- The differential blood count is done to calculate the percentage of each type of WBCs
- It also gives a clearer picture in a diagnosis for the cause of a disease. These may temporarily shift higher or lower depending on what is going on in the body.
- A high neutrophil count would suggest infection/cancer/physical stress.
- High monocyte and eosinophil count usually points at bacterial infection.
- With allergies, there may be an increased number of eosinophils
- With leukemia, there may be a much higher percentage of a single type of cell, such as a lymphocyte. In this case, the cell may be present in large numbers, in a mature form and in a variety of immature forms.

Platelet Count

Thrombocyte count:

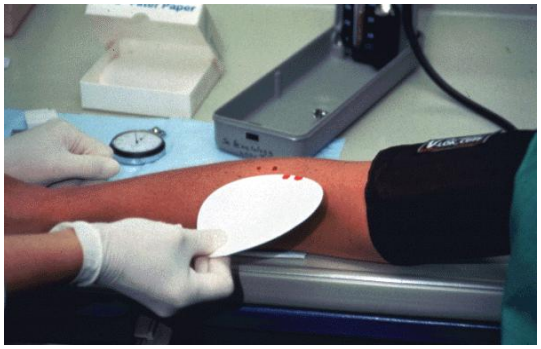
- Platelets are essential in the coagulation
- If there are insufficient platelets ➔ **hemophilia**
- Hence platelet counts are usually done before an operation.
- The platelet count is the number of platelets in a given volume of blood.

Simple laboratory tests

- Bleeding time, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), D-dimer, mixing test, antiphospholipid antibodies

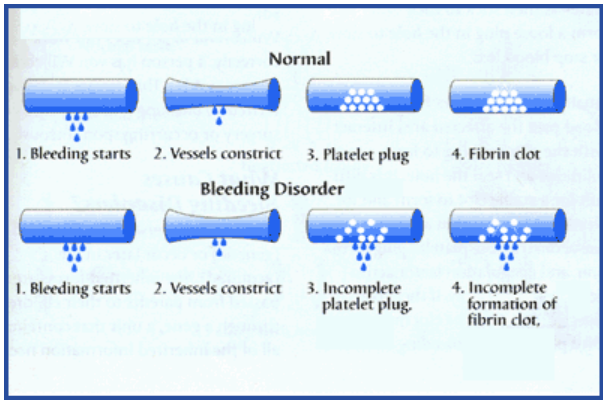
Bleeding time

- It assess platelet and capillary function
- It reflects the time to cessation of bleeding following a standardized skin cut
- Normal Values: the bleeding stops within 1 to 9 minutes
- Quantitative and qualitative platelets



Formation of a blood clot

When a blood vessel is damaged, there are four stages in the normal formation of a clot



Stage 1: The blood vessels is damaged and the bleedings starts.

Stage 2: The blood vessels constrict to slow the flow of blood to the injured area.

Stage 3: Platelets stick to, and spread on, the walls of damaged blood vessels. This is called platelet adhesion. These spreading platelets release substances that activate other nearby platelets which clump at the site of injury to form a platelet plug. This called platelet aggregation

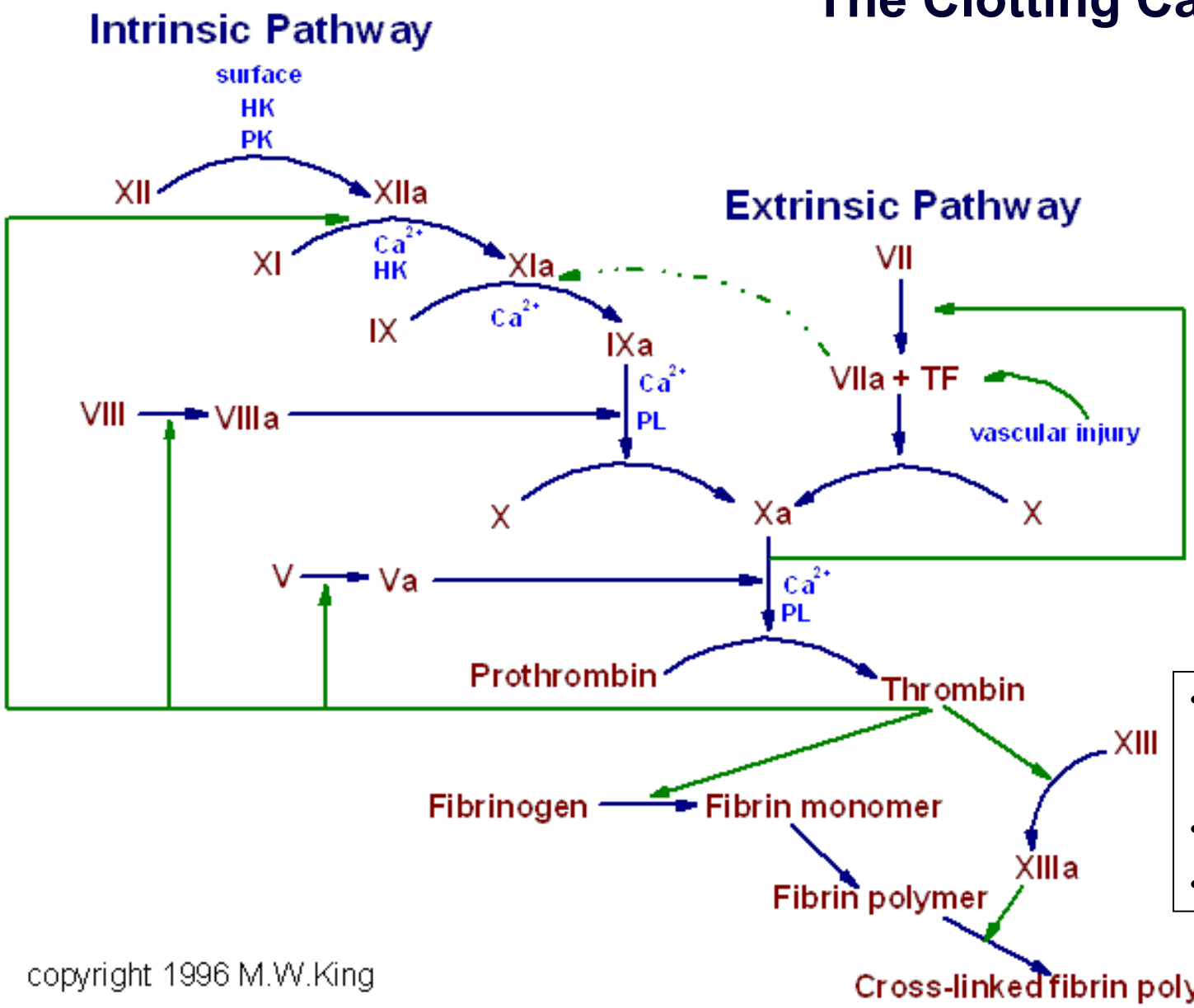
Stage 4: The surface of these activated platelets then provides a site for blood clotting to occur. Clotting proteins like Factor VIII and IX circulating in the blood are activated on the surface of the platelets to form a mesh-like fibrin clot

These proteins (Factors I, II, V, VII, VIII, IX, X, XI, XII AND XIII and Von Willebrand Factor) work like dominos, in a chain reaction. This is called the coagulation cascade.

The Clotting Cascades

- Two pathways lead to the formation of a fibrin clot: the intrinsic and extrinsic pathway. Although they are initiated by distinct mechanisms, the two converge on a common pathway that leads to clot formation.
- The formation of a red thrombus or a clot in response to an abnormal vessel wall in the absence of tissue injury is the result of the **intrinsic pathway**.
- Fibrin clot formation in response to tissue injury is the result of the **extrinsic pathway**.
- Both pathways are complex and involve numerous different proteins termed clotting factors.

The Clotting Cascades



- HK = high molecular weight kininogen.
- PK = prekallikrein.
- PL = phospholipid

The clotting cascades

- The intrinsic cascade is initiated when contact is made between blood and exposed endothelial cell surfaces.
- The extrinsic pathway is initiated upon vascular injury which leads to exposure of **tissue factor (TF)** (also identified as **factor III**), a subendothelial cell-surface glycoprotein that binds phospholipid.
- The dotted arrow represents a point of cross-over between the extrinsic and intrinsic pathways. The two pathways converge at the activation of factor X to Xa. Factor Xa has a role in the further activation of factor VII to VIIa as depicted by the arrow. Active factor Xa hydrolyzes and activates prothrombin to thrombin. Thrombin can then activate factors XI, VIII and V furthering the cascade.
- Ultimately the role of thrombin is to convert fribrinogen to fibrin and to activate factor XIII to XIIIa. Factor XIIIa cross links fibrin polymers solidifying the clot.

Platelet Activation and von Willebrand Factor (vWF)

- In order for hemostasis to occur, platelets must adhere to exposed collagen, release the contents of their granules, and aggregate. The adhesion of platelets to the collagen exposed on endothelial cell surfaces is mediated by **von Willebrand factor (vWF)**.

- The function of vWF is to act as a bridge between a specific glycoprotein on the surface of platelets and collagen fibrils. In addition to it binds to and **stabilizes coagulation factor VIII**. Binding of factor VIII by vWF is required for normal survival of factor VIII in the circulation.

Prothrombin time (PT)

- It assess the function of **extrinsic** and the common pathways
- It measures the activity of vitamin K dependent proteins (factors II, VII, IX, and X and proteins C and S)
- It reflects the time required for fibrin strands to appear after the addition of tissue thromboplastin to a patient's plasma
- Plasma obtained from blood to which a calcium-binding anticoagulant (citrate or oxalate) has been added, will clot in a few seconds when recalcified in the presence of tissue factor (obtained from animals)
- The elapsed time between the addition of calcium-tissue factor mixture and the presence of a detectable clot is the prothrombin time
- PT yield evidence about: current synthetic capacity of the liver, vitamin K absorption, the inhibition of clotting factor synthesis by **warfarin**
- **Reference Range**: 10-12 seconds

Prothrombin time (PT), INR

- PT is expressed as an International Normalized Ratio (INR) to normalize the values due to the wide variation among reagent and instrument systems
- The sensitivity of a reagent used with an instrument is compared to an international standard
- Each manufacturer gives an ISI (International Sensitivity Index) for any tissue factor they make. The ISI value indicates how the particular batch of tissue factor compares to an internationally standardized sample.
- The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the control sample used.
- The INR of the patient can then be calculated by the formula:

$$INR = (PTpat/PTcont)^{ISI}$$

- Where PTpat is the prothrombin time of the patient and PTcont is the mean of 20 normal patient prothrombin times

Activated Partial thromboplastin time (aPTT) and thrombin time (TT)

Activated Partial thromboplastin time (aPTT)

- It measures the activity of the **intrinsic** and common pathways
- It reflects the time required for a fibrin clot to form after a **partial thromboplastin, calcium and an activating agent** are added to the patient's plasma
- The PTT is measured by using a citrated sample, in order to activate the intrinsic pathway, phospholipid and another activator are mixed into the plasma sample (such as silica or kaolin), and calcium, the time is measured until a clot forms
- The test is termed "partial" due to the absence of tissue factor from the reaction mixture
- **Reference Range: 25-35 seconds**
- aPTT is widely used for monitoring **heparin therapy**

Thrombin time (TT, TCT)

- It measures the conversion of fibrinogen to fibrin
- It is affected by quantitative and qualitative **abnormalities of fibrinogen**
- It measures the time required for the formation and the appearance of the fibrin clot after thrombin is added to plasma
- **Reference Range: 18-22 seconds**
- It is unaffected by Vitamin K antagonist therapy
- TT is unaffected by most drugs that alter platelet function

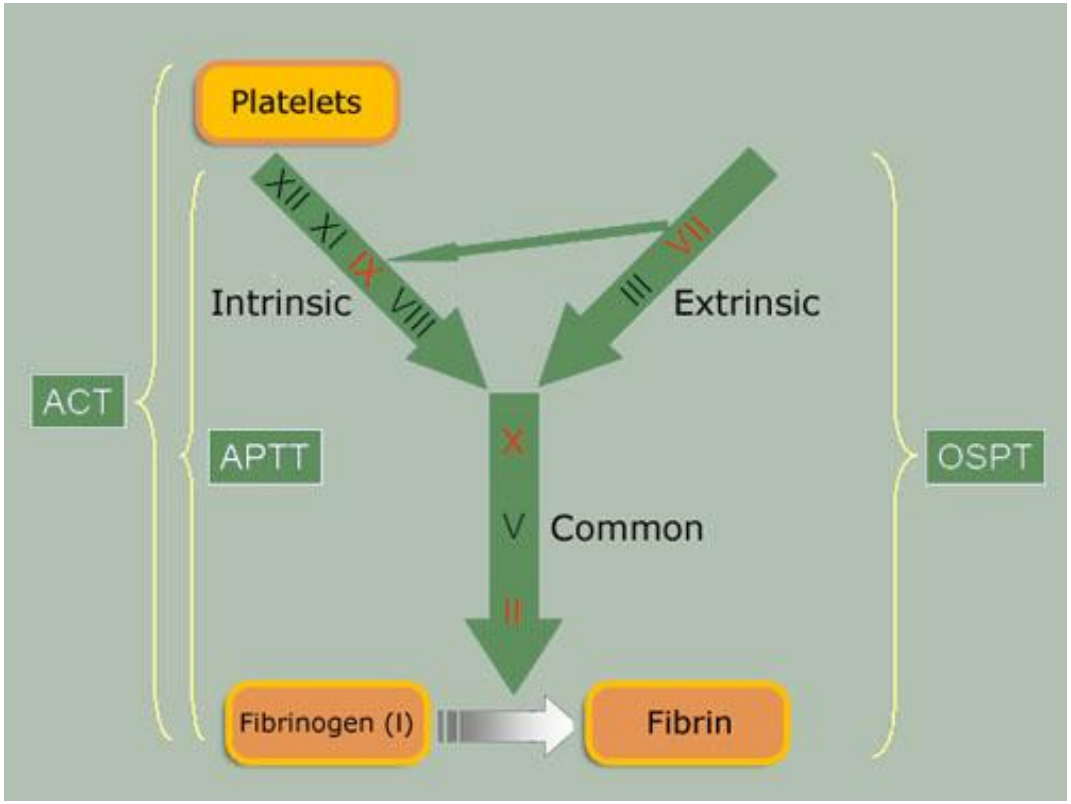


Figure 2. Schematic diagram of the intrinsic, extrinsic, and common pathways of coagulation. The vitamin K-dependent clotting factors (II, VII, IX, and X) are shown in red. Factor IX is in the intrinsic pathway, factor VII is in the extrinsic pathway, and factors X and II are in the common pathway. These four clotting factors are not activated if the function of vitamin K_1 is inhibited.

(One-stage prothrombin time [OSPT or PT], activated partial thromboplastin time [APTT or PTT], thrombin time [TT], and activated clotting time [ACT])

CASE STUDY 17-3

A 65-year-old woman with a history of diabetes was seen by her physician for weight loss, anorexia, and general fatigue. As part of the physical examination, both "bronze" skin pigmentation (hyperpigmentation) and enlarged liver were noted. Her initial chemistry panel showed the following relevant results:

Albumin	3.7 g/dL (3.8–5.0)
A LP	180 U/L (30–135)
A LT	200 U/L (10–60)
Total bilirubin	2.5 mg/dL (0.2–1.2)
Serum iron	180 μg/dL (45–150)

Further testing for the elevated iron showed the following:

Serum iron	170 μg/dL (45–150)
Transferrin	210 mg/dL (200–380)
Ferritin	300 μg/L (10–250)
% Transferrin saturation	80

The patient was diagnosed with hemochromatosis that caused iron overload.

Questions

1. What happens to serum ferritin in this condition?
2. Are this patient's conditions and symptoms typical of hemochromatosis?
3. What is a treatment plan for iron overload, and what is the main goal?

- Mariah is a 17-year-old student who has recently migrated to Australia from Malta with her parents. She comes to you complaining of general fatigue and occasional dizziness.
- Mariah has no significant past medical history and is not on any regular medicines. She does not drink alcohol or smoke. Her parents are both healthy.
- On examination, she has strong peripheral pulses, and her cardiovascular system examination is normal. BP is 115/75 mmHg, pulse 90 / minute, and BMI 19.5 kg/m2.
- Mariah has pale skin, conjunctiva and nail beds. Given her clinical symptoms, age and the findings on physical examination, you suspect that Mariah may have iron deficiency anaemia.

Q.1. To assist you in establishing a diagnosis of iron-deficiency anaemia, what additional questions would you ask Mariah?

Q.2

a) Would you recommend any investigations to assist you in confirming Mariah's iron deficiency anaemia?

b) The most reliable marker of early iron deficiency is:

Q.3 Would you recommend drug therapy for Mariah? Why/why not?

Q.4. Regardless of your answer in Q3, if Mariah were to be prescribed oral iron, list 2 strategies or tips you would recommend for Mariah to maximize iron absorption.