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ZAPORIZHZHYA STATE MEDICAL UNIVERSITY
Department of Normal Physiology

Sukhomlinova I.Ye., Kirsanova E.V., Yeryomina A.K.

PHYSICAL AND CHEMICAL PROPERTIES OF THE BLOOD. PHYSIOLOGY OF RED BLOOD CELLS

EDUCATIONAL MANUAL

for practical lessons on physiology for students on II course of international faculties (specialty “General medicine”)

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Reviewers:

Abramov A.V.

Kolicheva N.L.

AUTHORS:

Sukhomlinova I.Ye.,

Kirsanova E.V

Yeryomina A.K.

Sukhomlinova I.Ye.

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Methodical instructions recommended for the students of “General Medicine” specialty who study Physiology. This educational manual contains plan of study lectures and seminars, the approximate lists of reports and questions to check quality of study. Instructions allows students to acquaint with main definitions of the course “Normal Physiology” and gives a wide list of literature sources for better understanding Normal Physiology during students independent work.

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INTRODUCTION

Students' independent practical work is an important part of the syllabus in the course of Normal Physiology. It helps students to study this fundamental subject.

Systematic independent work enables to reach the final goal in the students' education. It is also important while preparing the students for their future clinical work with patients.

These theoretic materials, questions and tests will help students to get ready for the examination.

CONTENS

Blood, lymph and tissue fluid form the internal environment of the organism. Blood is the fluid constituent of the cardiovascular system, comprising both plasma and cellular components. Fifty-five percent of total blood volume is composed of plasma. Red blood cells, white blood cells and platelets form the cellular component. Blood has many essential homeostatic functions including the transport of oxygen and carbon dioxide, nutrients and waste products, immune function, buffering and hemostasis. As blood has such an important role in the maintenance of homeostasis. Problems with blood composition or circulation can lead to downstream tissue malfunction. Blood is also involved in maintaining homeostasis by acting as a medium for transferring heat to the skin and by acting as a buffer system for bodily pH.

FUNCTIONS OF BLOOD

In our body, the blood performs the following functions :

1. Respiratory.

The hemoglobin of RBC picks up oxygen in the lungs, the oxyhemoglobin now circulates and discharges the oxygen into the tissues which need it. For this purpose, as it will be shown, the RBC and Hb are ideally designed. Further, the CO2 produced in the tissues are discharged into the blood, it is partly carried by the plasma and partly by the Hb; the CO^2 is ultimately disgorged into the lungs.

2. Excretory.

Various waste products of the body are carried by the blood and ultimately removed from the body via the kidneys.

3. Nutritional.

End products of digestion are absorbed from the gastrointestinal tract and transported by the blood to the liver for further processing and then to the tissues who need them.

4. Role of blood in various homeostatic processes.

The term 'homeostasis' has been explained earlier (sec.1, chap.3). Briefly speaking, this is a mechanism, by which the various parameters of our body, like

the internal temperature, pH, the concentrations of various substances (for example, glucose, sodium, potassium etc.) in our body fluids, remain within a narrow range.

(a) Body temperature and blood. The volume of blood is large (around 5 liters in an adult man) and the 'specific heat' of blood is high. Therefore, a good deal amount of heat (calories) can be absorbed or lost by the blood without a great rise or fall in the temperature. It is to be noted that the enzymes in our body operate satisfactorily only in a narrow range of temperature. So either an abnormal rise or an abnormal fall of temperature, damages the enzymes and ultimately stops all biological activities. In this regard blood acts as a part of our body water content.

Moreover, blood has a high conductivity. If an organ becomes hot (eg. liver, due to vigorous metabolic activities) the heat from the organ is taken out by blood and distributed throughout the body.

(b) pH and blood. The enzymes of our body act only within a narrow range of pH. Again, large amount of acids are produced daily, by our body, as a result of metabolism. The blood contains various buffers, which prevent the rise of H+ concentration. Circulation of blood also contributes to the removal of the H^+.

5. Role of blood in various defense mechanism.

The white blood cells of blood act against invading bacteria and virus. The lymphocytes are intimately connected with the immunity of the body. The plasma carries antibodies. These are some examples to show the importance of blood in connection with the defense.

6. Transport of other substances.

Blood also transports various drugs, hormones, etc. to the various tissues.

COMPOSITION OF BLOOD

Blood contains plasma and formed elements. If blood is collected from an individual and its coagulation prevented by adding anticoagulants to it and then centrifuged sufficiently, the blood is separated into two layers, an upper clear (i.e.

free from formed elements) layer, called the plasma and a lower layer, where the formed elements are packed up.

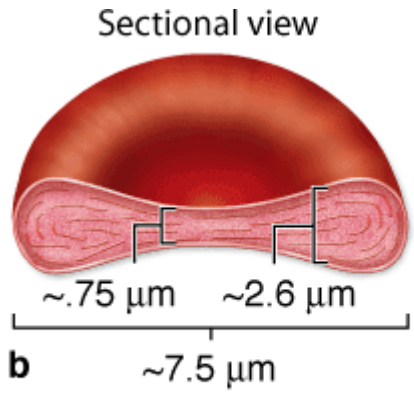
On the other hand, if blood is collected without anticoagulant and is allowed to clot and some further time be allowed so that the clot is allowed to shrink, a fluid separates out. The fluid can be centrifuged further and the clear supernatant part can be collected. This is serum. Basically, serum is plasma minus fibrin.

Formed elements are so called because under microscope they have definite forms. Formed elements are (i) red blood corpuscles (RBC) or erythrocytes, (ii) white blood corpuscle (WBC) or leucocytes (also spelt as leukocytes), (iii) platelets or thrombocytes.

RED BLOOD CORPUSCLES

Human RBC (erythrocyte) is (fig.1) a circular, biconcave cell without a nucleus and with a diameter of about 7.5 μ, (now-a-days written as um). It may be considered as a kind of a living bag containing hemoglobin.

A healthy RBC is very plastic; it can squeeze itself to pass through capillaries whose diameters are very narrow and after coming out of such a capillary it again regains its shape. Compared to its volume (about 80 μ3) it has a very big surface area (135 μ2).



Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com
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Fig.1. Erythrocyte

The biconcavity of RBC has some advantages as mentioned below :

(i) Because of the biconcavity, the thickness of an RBC, in its central part, is not great (about only 1μm), so that oxygen does not have to travel a great distance for the diffusion, (ii) the presence of biconcavity increases the surface area of the RBC, so that oxygen gets a bigger area for diffusion, (iii) because of the biconcavity, the erythrocyte can squeeze itself through a capillary more easily.

Therefore, in diseases where the biconcavity is lost ('spherocytosis') many of the advantages of the erythrocytes are lost.

The RBC is devoid of a nucleus, yet it is alive. It does not contain mitochondria {therefore the tricarboxylic acid cycle of Krebs does not operate within it). It is full of hemoglobin (Hb), but if an RBC is cut, the Hb is not extruded. This is because the Hb is interwoven in the stroma of RBC.

The RBC is also devoid of such structures like ribosomes, endoplasmic reticulum and centriole. Therefore, it does not divide and does not have any nucleic acid in it. Absence of all these structures make it rather a very simple cell. The cell membrane (unit membrane) essentially has the same structure as that of other cell membranes, although some special chemical substances, like blood group antigens, are associated with the RBC cell membrane.

The diameter of an "average" RBC is 7.5 μm and the thickness (mean corpuscular average thickness, MCAT) at the periphery is 2 μm, and at the center it is 1 μm (fig. 1).

As already stated, the RBC contains Hb. About 95% of the dry weight of the RBC is due to Hb. The part of the RBC, which is not Hb, is the erythrocyte cell proper and as already stated it is a very simple cell. It contains no nucleus (therefore, it is unable to divide), no ribosome (therefore, unable to synthesise new protein) and no mitochondria (therefore, Krebs cycle cannot operate within the RBC. The ATP generating machine in the erythrocyte, therefore, is weak).

The cell membrane of the erythrocyte contains the usual materials, lipids and protein. There are channels in the cell membrane, which permits the movements of different ions. Some special features of the cell membrane of an RBC, now may be noted:

The cell membrane contains some protein materials. Some such proteins, e.g. the glycophorin (which extends through and through the membrane) contain the blood group antigens, whereas other proteins like spectrin as well as actin are applied only to the inner side of the cell membrane. Spectrin is contractile and because of this, the RBC membrane is not flat and the red cell as a whole has a biconcave appearance.

Functions. Practically all the functions of the RBCs are due to its content i.e. due to Hb. RBCs pick up, carry and disgorge oxygen as well as CO_2.

However, the fact that Hb is encased within the RBC, is of great importance. Otherwise, there would have been free Hb in our blood causing a great rise in viscosity as well as osmotic tension of the blood. To keep the viscosity or osmotic tension within physiological limits, the volume of the blood would have been great (almost 50 liters or so) and consequently, size of our body would have been unmanageable.

ERYTHROPOIESIS

Introduction

As in our body, normally, loss of huge quantity of RBC occurs daily, to keep the RBC count and Hb% normal, sufficient number of RBCs must be produced daily. This generation of erythrocytes is called 'erythropoiesis'(fig.2), and starts in the 3rd week of intrauterine life and continues as long as the person remains alive.

Blood forming tissues, that is, tissues which produce the RBCs, WBCs and platelets, are usually divided into two great classes, viz. (i) myeloid tissue, and (ii) lymphoid tissue.

Myeloid tissue means the red bone marrow. It produces the RBCs, the granulocytes (= neutrophils, eosinophils and basophils), monocytes and the platelets. In the fetal life, it also produces the precursors of the lymphocytes.

Lymphoid tissue includes the lymph nodes, the thymus and the spleen. They produce the lymphocytes (for further clarification, see chap .4, sec.II, `origin of lymphocytes').

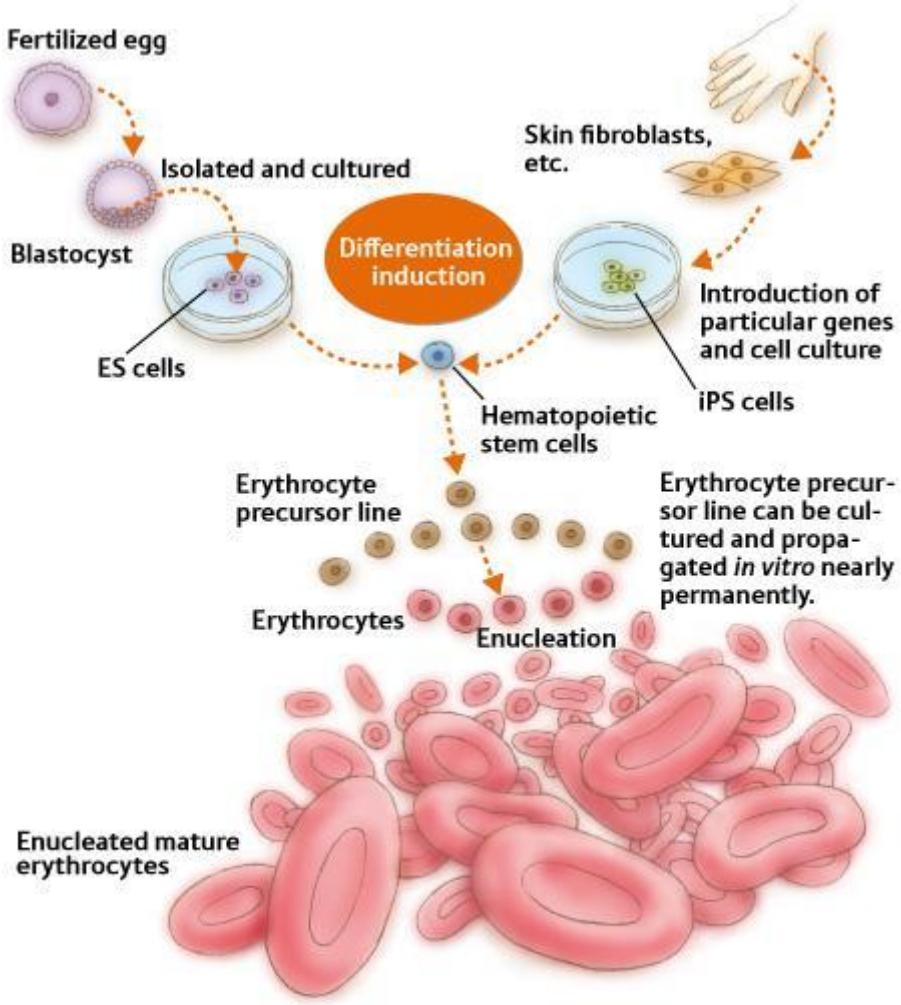

Fig.2. Erythropoiesis

Site of erythropoiesis:

(a) In the intrauterine life :

Formation of blood starts in the 3rd week of intrauterine life.

(i) Between 3rd week to 3rd month of intrauterine life, erythropoiesis occurs in the mesoderm of the yolk sac. This is the only stage, in the entire life span of an individual, when erythropoiesis occurs within the blood vessels (intravascular erythropoiesis). In all other phases described below, that is, in all phases that occur after the 3rd month, the erythropoiesis occurs extravascular. From a clinical point of view, this phase is not important.

(ii) Between the 3rd month to the 5th month of intrauterine life, erythropoiesis occurs in the liver and spleen. This phase is called, the `hepatic phase '.

(iii) From the 5th month onwards, the hepatic phase begins to stop and erythropoiesis starts in the red bone marrow. This phase is thus called, the myeloid phase. By the time, when the baby is born, all erythropoiesis occurs in the red bone marrow.

(b) Post natal erythropoiesis:

As stated already, this occurs, normally, in the red bone marrow.

Distribution of the red bone marrow

Bone marrow is of two types, (i) red (because it has a red color), and (ii) yellow (as it looks yellowish). Blood formation, including erythropoiesis occurs in the red bone marrow (RBM) only.

At birth, all marrows are RBM. As age advances, some of the RBMs are changed into yellow bone marrow. At around 18 to 20 years, the adult pattern becomes fully established. In an adult, over the age of 20 years, RBM can be found only in the (i) flat bones (cranial bones, ribs, sternum, vertebre, pelvic bones) and (ii) in the upper end of the long bones (humerus and femur).

The shafts of the long bones, in fully grown adults, contain only yellow bone marrow (which does not produce blood cells).

Nevertheless, when there is a necessity of increased erythropoiesis, the yellow bone marrow is converted into RBM. If the necessity is still more intense, even the liver and spleen start erythropoiesis in the adult (for some unknown reasons, the thymus never forms blood cells, whatever may be the intensity of the demand). These are instances of extramedullar hemopoiesis (medulla = bone marrow) and may be seen in some diseases.

Histology of the RBM

The RBM consists of — (i) large number of sinusoids, (ii) adventitious cells outside the sinusoids, and (iii) blood forming cells in between the adventitious cells. Sinusoids are basically capillaries with larger diameters. Their walls contain big pores through which big molecules and the blood cells can pass. The sinusoids

criss cross with one another forming a net work. The sinusoids are formed from the nutrient artery of the bone (= the artery that feeds the bone).

The 'adventitious' cells eventually become fat cells. The blood cells are the precursors of the erythrocytes, leucocytes, and platelets.

Normally the fat cells: blood cell ratio is 1 : 1, but in bone marrow depression, the fat cells predominate. Reverse occurs where bone marrow is hyperactive.

The term myeloid in this connection, means the granulocytes and their precursors only. The student should note, that the term 'myeloid' means different things in different contexts. In a previous context, the term v myeloid' meant, granulocytes & monocytes + erythrocytes + platelets together with their precursors, but here it means only the granulocytes and their precursors.

The normal range of myeloid erythroid ratio is between 2.5 to 4.

In case of anemia, the clinical hematologist often has to do a bone marrow examination. For this, in an adult, the sternum is punctured and the RBM aspirated. In children, as sternal puncture is risky, tibia or pelvic bone is usually punctured.

Stages of development

Excepting in the first 3 months of fetal life, all erythroid developments are extravascular. When the erythroid cell is almost completely mature, it enters the sinusoids from the extravascular space.

1. The most primitive cell is called the 'pluripotent stem cell'. This cell divides and differentiates; whereas the pluripotent stem cell can give rise to erythrocyte/granulocyte/ monocyte/lymphocyte and platelets (that is why it is called pluripotent; pluripotent = capable of producing many or different), the daughter cells of the pluripotent are not capable of producing all the types of cells; they can produce either myeloid series or lymphocyte series and so on. More they advance in the lineage, more they become restricted in the plurality of their potency.

2. The pluripotent stem cells give rise to the 'committed stem cells'. One type of committed stem cell gives rise to myeloid series (granulocytes/ monocytes /

platelets and of course the RBCs) but not the lymphocytes, whereas the other type of committed stem cell gives rise to the lymphocytes (both the T and the B varieties) only.

3. Cells committed to produce the myeloid series now divide and differentiate further to produce daughter cells called 'progenitor cells'. Several types of progenitor cells (PC) develop. One type of PC gives rise to cells of erythroid series, another granulocyte-monocyte and so on. However, the PC that is destined to produce RBC can produce RBCs but not any other type of cell, and so on.

Progenitor cells are also called `colony forming unit', CFU and designated as CFU-E (also written as CFUe), CFU - GM (or CFUgm) and so forth, standing for colony forming unit— erythrocyte, colony forming unit — granulocyte monocyte and so on.

4. For RBC, there are two progenitor cells, (i) the first progenitor is called the BFU-E (or BFUe which is "burst forming unit erythrocyte) and (iii) the next is called the CFU -E (or CFUe).

5. From the progenitor CFU - E, the pronormoblast cell, which is the first in the series (lineage) of the morphologically recognizable cell in erythroid series, develops..

6. From pronormoblast, ''`early normoblast' develops. Early normoblast is also called `large basophilic normoblast'. Early normoblast, in turn, gives rise to `intermediate normoblast' (or "polychromatophilic normoblast'). From intermediate normoblast develops the `late normoblast' (or `orthochromatic normoblast').

7. From late normoblast develops the `reticulocyte'. The reticulocyte, in turn, gives rise to the matured RBC. Normally, the reticulocyte matures for one or two days in the bone marrow and then enters the peripheral blood. When the cell enters the peripheral blood it is still not a fully matured RBC, but a reticulocyte in somewhat advanced stage of maturation.

FACTORS INFLUENCING ERYTHROPOIESIS

These are:

(i) Hematopoietic growth factors,

(ii) Some vitamins and

(iii) Iron and copper. For BPA see below.

I. Hematopoietic (also called, hemopoietic) growth factors

By now many such factors are known. More well known among them are : (1) Erythropoietin (2) Interlenkins (ILs) (3) Stem cell factor (SCF) (4) Granulocyte-macrophage colony stimulating factor (GM-CSF) (5) Colony stimulating factor (CSF-V, also called, M-CSF (6) Thrombopoietin.

General features of growth factors:

(1) These factors are produced by various cells, notably the macrophages-monocytes, T lymphocytes and fibroblasts.

(2) Often, one growth factor acts in conjunction with several other growth factors.

(3) They act on the stem cells, pluripotent as well is on their differentiated products, viz, committed stem cells.

(4) Many of these factors can be synthesized by rDNA* technic and are commercially available for therapeutic (= treatment of patients) purposes. (5) These growth factors, are, generally, glycoprotein hormone like substances, ie, .they have polypeptide structures. (6) These factors can be grouped into three classes:

(i) Erythropoietin; which stimulates production of RBCs (erythropoiesis). This has been described in this chapter.

(ii) Myeloid growth factors like SCF, Interleukins, CSF-1, G-CSF etc, which mainly stimulate the production of WBCs (although some of them can stimulate RBC or platelet production). They have been described in p 42.

(iii) Thrombopoietin, a newly discovered factor, stimulates platelet production (thrombopoiesis).

Erythropoietin (EPO)

Erythropoietin is the most important, most well known hemopoietic (hematopoietic) growth factor which causes erythropoiesis. Stimulus for erythropoietin is hypoxia;

details: when tissues of the body become hypoxic (due to any cause), the kidneys produce erythropoietin. It looks that the endothelial cells of the peritubular capillaries of the renal cortex produce erythropoietin.

I

This anoxia (hypoxia) can be due to such causes like —

(i) anemia

(ii) chronic lung disease (COPD),

(iii) high altitude sickness and so on.

Note where kidneys are badly damaged, erythropoietin' production stops. A small quantity of erythropoietin, however, is produced by the liver.

Erythropoietin acts on the stem cells, to be specific, on later order, ie, committed stem cells. Erythropoietin causes increased daughter cell production from such cells.

Applied physiology. (1) In COPD, the high RBC count is due to high erythropoietin production; this high RBC count helps the patient to battle with the disease. Conversely, in gross chronic damage of the kidney, anemia is a feature ("intractable anemia of chronic nephritis" of our forefathers though they did not know anything about erythropoietin).

(2) Erythropoietin is now commercially available (produced by recombinant DNA technique), and is administered in Such patients like (i) chronic renal failure cases undergoing dialysis (ii) patients receiving anticancer chemotherapy which is producing damage of RBM and anemia (iii) in patients of AIDS receiving AIDS chemotherapy.

Healthy persons, in their blood show a small, level of erythropoietin but the level increases in anemia (provided the kidneys are normal).

Note. Apart from erythropoietin, some of the other hemopoietic growth factors (eg. GM-CSF) have some effects on erythropoiesis.

II. Vitamins

For erythropoiesis, (1) vit B_{12} (2) Folic acid (3) Pyridoxine and (4) vit C are particularly important.

Vitamin B_{12}

Source: vit B_{12} cannot be synthesized by the human body. Normally, it is obtained from food.

Bacteria can synthesize vit B_{12}. Thus soil bacteria, bacteria in human intestine contain good amounts of vit B_{12} but human beings cannot utilize the vit B_{12} contained in the bacteria of their own intestinal canal.

Thus grass etc contain good deal of vit B_{12} as they are coated by soil bacteria. Animals feed on grass, thus acquire vit B_{12} and store them (principally in the liver). Rich sources of vit B_{12} for human beings are liver/muscles/egg milk — all animal products. By themselves the vegetables do not contain vit B_{12}. However vegetables are normally contaminated by soil bacteria and thus contain vit B_{12}. Vit B_{12} deficiency in human beings, due to dietary deficiency is very rare. vit B_{12} deficiency, in human being, is for all practical purposes due to fault in the absorption.

Absorption. In the food vit B_{12} remains bound to enzymes (ie, proteins) -⟶ in the stomach the binding enzyme (protein) is digested and removed and now the vit B12 binds with a protein from saliva called "R binder protein" -⟶ this complex enters duodenum where proteolytic enzymes of the pancreatic juice digest and remove the R binder protein -»the free Vit B_{12} binds with **the intrinsic factor**, IF. IF is produced by the parietal cells of the gastric glands.

Vit B_{12}- IF complex proceeds onwards via the intestinal canal (without being digested) -⟶ reaches the terminal part of the ileum where it binds with its receptor present on the membrane of the cells of the epithelium of the mucosa -» here the two components of complex, IF and vit B_{12} separate -⟶ vitamin B12 absorbed by endocytosis but the IF cannot be absorbed and is destroyed.

Chemically, IF is a protein. Note that presence of IF, ie, the formation of vit B12 - IF complex prevents digestion of Vit B_{12} itself by the pancreatic juice.

Applied physiology. Absorption of vit B_{12} can be deficient leading to defective formation of RBC. Clinically, the condition is called megaloblastic anemia. Fault in absorption of Vit B_{12} can be due to :

(1) Lack of IF. This condition, when it develops due to an immune disorder, clinically, produces 'pernicious anemia' or 'Addisonian anemia'. This disease is rare in India.

(2) Severe pancreatic deficiency leading to non-freeing of vit B12 from R binder protein.

(3) Severe disorders of small intestinal epithelium, eg. Malabsorption syndrome, sprue (p 104) or severe bacterial invasion of small intestine. Therefore, vit B_{12} deficiency anemia can be due to (A) Addisonian pernicious anemia or (B) causes other than Addisonian pernicious anemia.

Transport of vit B12- After absorption from the intestine vit B_{12} is transported (via portal venous blood) to the liver being bound by a (3 globulin type of protein called transco-balamin II (ie, an agent which can transport cobalamin. Incidentally, vit B_{12} is also called cobalamin). In the liver vit B12 is deposited in the hepatocytes (= liver cells). An adult (healthy) human being stores about 5 mg of vit B_{12} in his liver. This 5 mg is enough to act as reserve which can prevent any vit B_{12} deficiency syndrome in complete absence of Vit B12 '" the food for 5 years.

Daily requirement: 3 to 5 μg.

Clinical features of vit B12 deficiency

(1) Recall, in the bone marrow, normally, precursors of RBC, viz, normoblasts, are found. In vit B12 deficiency instead of normoblasts, megaloblasts which are abnormal cells, are found. Megaloblasts are not found in normal RBM. Under microscope, megaloblasts appear different from normoblasts. Normoblasts when mature become normocyte or normal RBC but megaloblasts when mature become macrocyte (which are abnormal RBCs. Macrocyte is a much bigger cell than the normocyte).

(2) In the peripheral blood, therefore, vit B_{12} deficiency produces presence of macrocytic anemia, ie, there is anemia + RBCs are macrocytic.

Explanation. Lack of vit B_{12} causes some abnormality of DNA -» therefore chromosomes of the nuclei of the precursors of RBCs which are about to divide, show abnormality. The results of this abnormality is twofold : one, there is no cell division but cytoplasmic accumulation remains unhampered leading to bigger sized abnormal cells called megaloblasts; two, many of these precursor cells die leading to anemia. These two, taken together, constitute "defective hemopoiesis'. Vit B12 deficiency thus causes defective hemopoiesis.

Vit B_{12} deficiency also causes some neurological disorders. Demyelination and death of neurons occur in spinal cord and brain leading to paralysis and/or sensory disturbances and/or insanity. These neurological changes reuslt from abnormal fatty acid metabolism.

Conclusion. Vit B_{12} is an erythropoietic vitamin whose lack is not uncommon. Lack of vit B_{12} produces megaloblastic macrocytic anemia.

Therapeutic uses : vit B_{12} is given where there is vit B_{12} deficiency anemia, eg. pernicious anemia (rare in India), sprue (common in India), malabsorption syndrome.

Folic acid

Folic acid and their chemically related compounds are collectively known as "folates". Folic acid has three components :

(i) a pterine nucleus; (ii) para amino benzoic acid; (iii) glutamic acid. Folic acid therefore is a pterolyl glutamic acid.

Several forms of pteroyl glutamates are known, eg : (1) monoglutamate form which occurs in blood, (2) polyglutamate form which is present in the food. In monoglutamate form, in the folic acid nucleus, only one glutamic acid is present whereas in the polyglutamate form, several (upto 7) glutamic acid radicals are present.

Folic acid is an erythropoietic vitamin. For our folic acid, we depend on external sources like food or medicinal form. Folates are obtainable from vegetable foods. Liver is also a good source.

Digestion, absorption and metabolism. Food folates are of polyglutamate form. In the intestine, polyglutamates are converted into monoglutamates; these monoglutamates are converted into methyl monoglutamates by intestinal mucosal cells -⟶ now, they are absorbed (from upper part of small intestine) -⟶ they now enter blood.

The mode of action of folic acid and the vit B12 — folic acid interrelationship

In the blood they are reduced to become methyl tetrahydrofolate (CH_3 FH_4 also written as CH_3 THF) -> they in this form, reach the tissues —> in the tissues, they lose the methyl (CH_3-) group and become tetrahy-drofolate (THF or FH_4). The CH3~ group is accepted by vit g12 (vit B_{12} is also called cobalamin). Vit B_{12} thus becomes methyl cobalamin. THF then becomes formyl THF better known as 'folinic acid' —» folinic acid becomes, then 5, 10 methylene THF which is the active form of folate for DNA synthesis. 5,10, methylene THF is required for DNA synthesis. (Hence no 5, 10, methylene THF, no mitosis).

5, 10, methylene THF is then converted into dihydrofolate (FH2)- FH2 is converted back into THF by dihydrofolate reductase enzyme, DHFR.

The FH2 is inactive material but FH2, thus can again be converted into the active material, viz, 5, 10, methylene THF, provided DHFR is available. DHFR thus greatly reduces the food requirement of folic acid.

Applied physiology

Note, no 5, 10, methylene THF -» no DNA synthesis -> no chromosome division -» no mitosis. Also note, DHFR helps to regenerate 5, 10, methylene THF from FH2.

(1) Methotrexate, MTX, inhibits DHFR, leading to lack of 5, 10 methylene THF -» stops mitosis. Hence MTX is an extremely popular anticancer drug. But MTX will also stop mitosis in the stem cells of RBM or intestinal

mucosa. Hence anemia and gastrointestinal erosions are well known side effects of MTX.

(2) Pyrimethamine inhibits DHFR of malarial parasite but not that of man. Hence pyrimethamine (present in CROYDOXIN-FM) is a popular antimalarial.

(3) Trimethoprim (TMP) inhibits, bacterial (but not human) DHFR. Hence TMP (present in SEPTRAN) is an antibacterial drug.

Vit B12 -folate interrelationship

Note, vit B12 causes conversion of CH3THF into THF. Therefore, no vit B12 no formation of active form of folate in the tissues. In short, vit B12 deficiency produces a 'metabolic block' of folic acid metabolism.

Causes of folate deficiency

Folate deficiency can reusult in (i) destruction of small intestinal mucosa, as in sprue/celiac disease etc. (p 104 for details), (2) in pregnancy (folate requirement increases in pregnancy), (3) in MTX therapy, and in (4) nutritional megaloblastic anemia.

Clinical features of folate deficiency

Microscopic studies of peripheral blood or RBM reveals macrocytic, megaloblastic anemia — just as in vit B12 deficiency anemia. How then to distinguish between anemia due to vit B12 deficiency and that due to folate deficiency?

In folate deficiency anemia, serum folate level will be very low whereas in vit B\i deficiency anemia serum level of vit B12 will be very low.

Folic acid is available commercially. In the past it was very expensive. In 1944, Yallapragadha Subbarao* and his colleagues synthesized folic acid in Lederle laboratories and since then folic acid has become very cheap.

Daily requirement, in non pregnant persons, of folic acid is 50 ugms but in pregnancy the requirement rises. Total body reserve of folic acid is between 5 to 20 mg which can last for only few months in total stoppage of exogenous folic acid supply.

Note. In vit B12 deficiency, both (1) megaloblastic anemia, plus (ii) neurological disorder (see above) can occur but in folic acid deficiency neurological disorder does not occur. Vit B12 deficiency induced neurological disorder is due to a defect in fatty acid metabolism which is independent of any erythropoietic connection.

Pyridoxine. Vit C

These vitamins have been discussed in details in sec VII. Spontaneously occuring pure pyridoxine deficiency anemia must be very rare in man. Vit C deficiency can lead to anemia.

Iron. Copper

Iron has been described in p 33. After intestinal by pass surgery or in persons kept alive by chronic parenteral fluid therapy, copper deficiency can develop but otherwise copper deficiency must be very rare.

Applied physiology

I. Common conditions where erythropoiesis is deficient:

(1) Bone marrow hypofunction (= bone marrow hypoplasia or aplasia). Here not only the erythropoiesis but the entire hemopoiesis suffers. (2) Lack of erythropoietic factors like vit Bi2-folate-Vit C-iron. See above. (3) Excessive blood transfusion.

II. Common-conditions where erythropoiesis becomes excessive:

(1) Anemia (provided the RBM is healthy) (2) Where there is excessive erythropoietin generation, eg, COPD-high

altitude (see above).

III. A simple way to judge the intensity of erythropoiesis : Note the reticulocyte count. A high reticulocyte count (> 3%) indicates stepped up erythropoiesis while a low reticulocyte count (< 0.5%) indicates suppression of RBM. Reticulocyte count is made by assessing the number of reticulocytes per every 100 RBCs in peripheral blood.

RBC INDICES

An 'average' matured RBC has a standard — (1) volume (2) hemoglobin (Hb) content (3) Hb saturation. For diagnosis of type as well as the assessment of the intensity, response to treatment etc. of anemia these values should be estimated. To understand them, first, PCV (packed corpuscular volume) should be understood.

PCV: Whole blood, mixed with a suitable anticoagulant is centrifuged in Wintrobe's hematocrit tube for a long time -> all the blood cells now become packed at the bottom of Wintrobe's tube, thus PCV can be obtained. PCV is also called hematocrit value (hct). Normally PCV is about 45, that is, in 100 ml blood, packed cells account for 45 ml of volume.

MCV means mean corpuscular volume, ie, volume of an average RBC.

MCH = the quantity of hemoglobin (Hb) in 'average' RBC.

MCHC = quantity of Hb present in 100 ml of RBC (not 100 ml of blood).

Color index (CI):

14.5 gm of Hb is regarded as 100% Hb. Similarly, 5 million/µl is 100% RBC. Therefore, if a person has 14.5 gm% Hb and 5 x 10(6)/µl RBC, his CI will be 1 (one). Range of CI is 0.9 to 1%. Low CIs are seen in microcytic anemias and high CIs are seen in macrocytic anemias (Table 2.2.3). In short, CI = percentage of Hb (14.5 being 100 per cent) divided by percentage of RBC (5 million being 100 per cent). All said, color index determination is no longer popular.

Normal values

MCV : 90 cubic micron (cub m). Values higher than 100 = big volumed RBC = macrocyte (seen typically in vit B12 -folate deficiency anemia). Values less than 80 = small volu¬med RBC = microcyte (seen typically in iron deficiency anemia). Values between 80 to 90 = normal = normocytosis (Note: cyte = cell; macro = large; micro = small).

MCH : 28 - 30 pg. MCHC : 34%. MCHC cannot be > than 34% because, in normal persons an RBC holds near maximum amount of Hb which can be held (ie, speaking loosely, a normal RBC is nearly saturated by Hb; therefore, MCHC value cannot be more than normal).

MCD: 7,5µ

History: In 1824 Thomas Addison of USA and his colleague Combe described for the first time, megaloblastic anemia, which we understand was due to IF deficiency. Incidentally, Addison subsequently also described Addison's disease. In the 1920s, Richard Minot's and his associate Murphy introduced liver therapy (Murphy-Minot's liver therapy) for remission of Addisonian anemia. It was Castle, who afterwards, demonstrated that there shall have to be an IF for absorption of the "extrinsic factor". The extrinsic factor was vit B12, first isolated by Smith & Parker in the 1940s; subsequently chemistry of vit B12 was established by Dorothy Hodgkin. Incidentally, Richard Minot, a Canadian, was a juvenile diabetic and was one of the first few volunteers who submitted himself for clinical trial of the recently discovered insulin in the 1920s by Banting and Best. Some of these workers (MurphyMinot, Hodgkin) were awarded Nobel Prize.

Wills while working in Madras (Chennai) of India in the 1930s discovered a factor, which was first named after her, "Wills' factor" but subsequently Wills' factor was renamed as folic acid. The contribution of Subbarao has already been mentioned.

Metabolism of RBC. Because of absence of such structures in the mature erythrocyte, like mitochondria, ribosome, rough endoplasmic reticulum, nucleus etc., many metabolic processes are absent. Thus, tricarboxylic acid cycle of Krebs is absent in the RBC and generation of ATP is poor.

Nevertheless, glucose is metabolized within the RBC and energy in the form of ATP are present. Metabolism in the RBC is needed for the following reasons :

(i) For maintaining the sodium potassium pump. Like all normal cells the erythrocyte has to pump out sodium to the ECF and pump in K+ from ECF, a process which requires energy.

Further, it is also known that lack of energy in the RBCs cause them to become rigid, fragile and spheroidal in shape, all leading to their lysis as they pass through the spleen.

(ii) The iron of the Hb, even after taking up the oxygen, remains in the ferrous state. If it is converted into ferric state, an abnormality, called methemoglobinemia results. Again, the exposure to oxygen, which an erythrocyte is always having, may damage the Hb.

To prevent these above mentioned oxidative injuries (ie, methemoglobinemia, injury to Hb, rigidity of the RBC membrane, etc), various enzymes and reducing agents must be present in the RBC. The enzyme methemoglobin reductase together with NADH prevents the iron to become ferric iron, whereas glutathione (GSH) which is a strongly redu-cing agent prevents damage of the Hb.

To keep glutathione in reduced state, the activity of an enzyme, glucose-6-phosphate dehydrogenase (G-6-PD), which is normally found in RBC, is necessary.

In an inborn error of metabolism, G-6-PD deficiency, (which is sex linked) develops; therefore, the RBCs become susceptible to the damages due to oxidation. These people become especially vulnerable to oxidative damage after taking some types of antimalarial drugs. The symptoms include hemolysis, jaundice and anemia. These people are, however, somewhat immune against malaria (the explanation of the resistance will not, however, be discussed here).

Erythrocyte sedimentation rate (ESR). If blood is mixed suitably with an anticoagulant (sodium citrate in the popular Westergren method) and allowed to stand vertically in a special tube (e.g. Westergren tube, the erythrocytes, because they have a higher specific gravity than plasma, begin to settle down, leaving a clear supernatant plasma above.

The length of the column of this clear supernatant plasma in mm after the end of first hour is the erythrocyte sedimentation rate (ESR). The tendency of the RBCs to settle down increases when they form rouleaux*. In rouleaux, RBCs pile one over another like a pile of coin.

Rouleaux formation increases when there is increase of plasma fibrinogen and y globulin. Most infections, inflammations and destructive diseases cause increase of y globulins (including fibrinogen). Therefore, ESR increases in most acute as well as in chronic infections, collagenous disease (eg. rheumatoid arthritis), tuberculosis etc. It also increases in cancers,

Normal values of ESR in male, by the Westergren method, is about 5 mm and in female about 10 mm in the 1st hour. A rise in ESR indicates the presence of infective/ inflammatory/destructive disease but does not help in specific diagnosis. However, ESR values are important for prognostication as well as for assessment of progress in a person under treatment.

Life span and fate of RBC. Normally the life span of RBC is about 120 days.

The process of ageing and death of an erythrocyte is as follows:

As age of the RBC increases, the enzymes which protect the erythrocyte from the damaging effects of oxygen (see above) begin to lose their efficiency, therefore oxidative damages begin to appear and the RBC becomes rather rigid, spheroidal and fragile. During circulation, the erythrocytes pass through the spleen where the anatomical structure is such that RBCs have to pass through vessels whose diameters are very narrow and the fragile RBCs, as a result, are ruptured. Only the comparatively young and healthy RBCs with a sufficient degree of biconcavity ("discocyte") can survive.

In diseases like spherocytosis and G-6-PD deficiency states, etc. the erythrocytes become prematurely senile and their life span is reduced.

Normally spleen is the important slaughter house for the RBCs. But when the erythrocytes are diseased so that their fragility increases, they break down when passing through other structures also, particularly liver.

If the life span of RBCs are reduced, the erythropoiesis is stepped up in the bone marrow, which therefore compensates the increased loss of RBCs to some extent.

Fragility of RBC. Recall that, if erythrocytes are suspended in an isotonic saline solution (0.85% or 0.9% NaCl solution) the erythrocytes neither swell nor shrink. If, however, the erythrocytes are suspended in a very dilute saline solution or plain distilled water, they swell by taking up extracellular water and eventually burst, a phenomenon called hemolysis.

If the fragility of RBCs are increased due to disease, they burst more readily than normal erythrocyte.

If normal erythrocytes are suspended in NaCl solutions of various strengths, it will be seen that hemolysis starts* when the strength of the saline solution is about 0.5% and is complete** when it is about 0.3%. In conditions, where the erythrocyte fragility is increased (eg., spherocytosis) the hemolysis starts earlier than 0.5% saline solutions, and completes before the strength 0.3% is reached. This is because, the increased fragility makes the RBC more susceptible to lysis.

HEMOGLOBIN

FUNCTIONS, CONCENTRATION AND PRINCIPLES OF ESTIMATION

Hemoglobin (also spelt, haemoglobin) is present inside the RBCs. It is required for

(i) transport of oxygen as well as (fig. 3)

(ii) transport of carbon dioxide and

(iii) it also behaves as a blood buffer.

The iron in the Hb is in ferrous state (Fe++) and even after the combination with oxygen it remains ferrous. The Hb, in health, after catching oxygen, is called oxyHb (Hb02). The combination of oxygen and Hb is loose and reversible so that in the capillaries of the tissues, oxygen can leave the Hb02 and migrate to the tissues (where the 02 tension is low). Reduced hemoglobin can combine with oxygen very speedily and that is why, although the transit time of RBC through a pulmonary capillary may be very short, the uptake of the 02 by Hb is complete. In some diseased states, the iron of Hb is oxidized and converted into ferric (Fe+++) iron. The condition is called methemoglobinemia and oxygen cannot be released easily from such Hb. Normally, the presence of an enzyme, methemoglobin reductase keeps the iron in ferrous state.

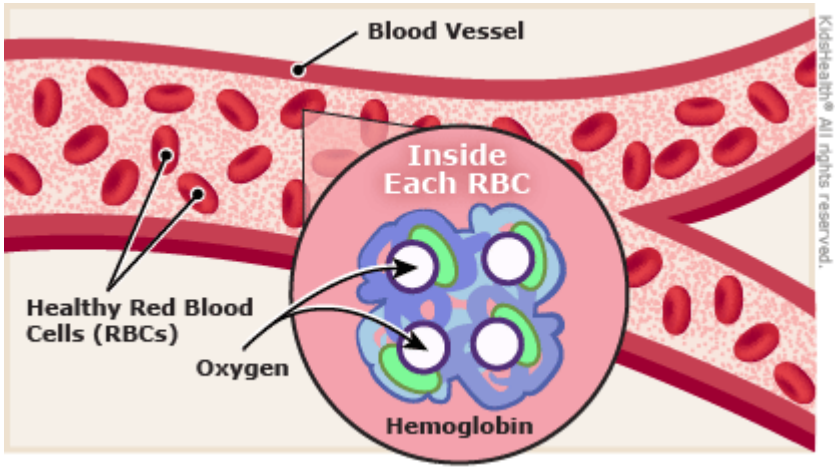

Fig.3 Transport of oxygen

Hb also normally carries C02. It also acts as a blood buffer. Normal values for the concentration of Hb is around 15 gm per 100 ml, but the range is somewhat wide; for males it is between 14 to 17 gms/100 ml and for females between 12 to 16 gms/100 ml.

As a bedside method, Hb is commonly estimated by converting it into acid hematin by adding N/10 HC1 and diluting with water (Sahli's method) and matching with the standard. In clinical laboratories, cyanmethemoglobin method is

very popular; in this method, Hb is converted into cyanmethemoglobin and the color developed is compared against a standard in a suitable colorimeter.

Hemoglobin chemistry and synthesis. A hemoglobin molecule contains two ingredients, viz. haem (also spelt as heme) and globin.

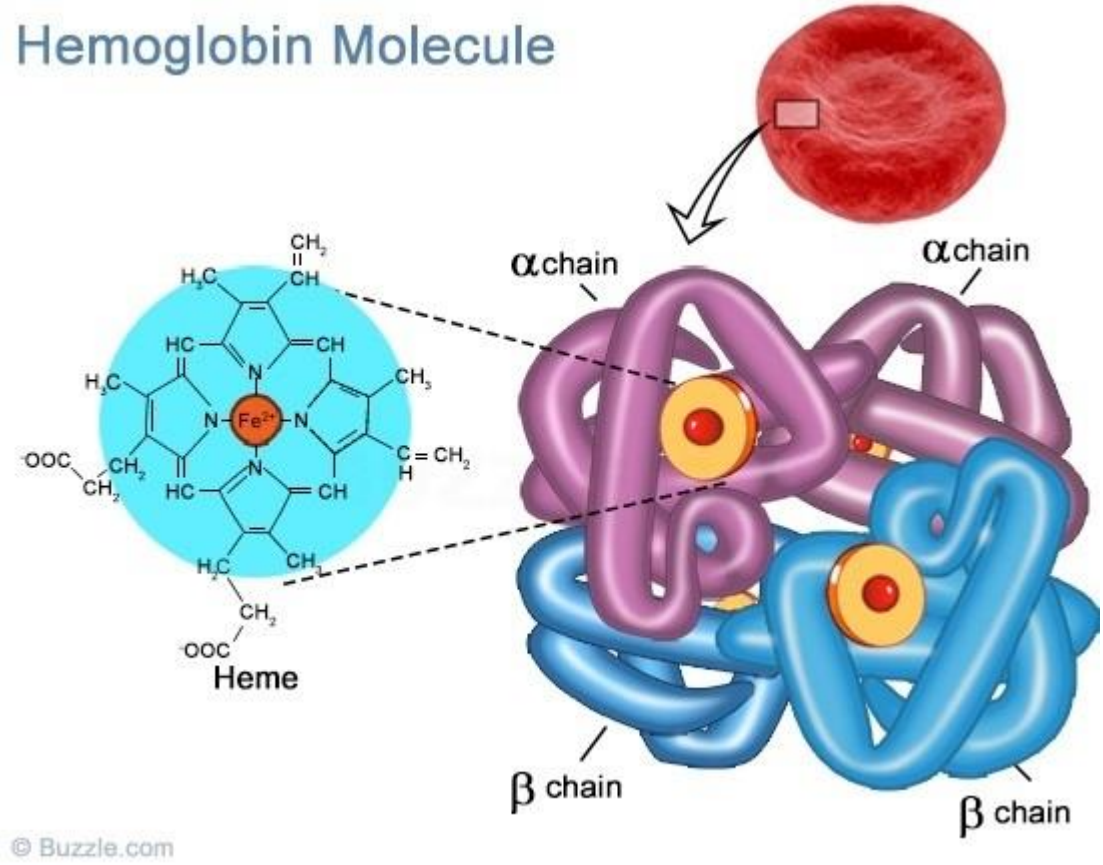

Fig. 4. Hemoglobin

The haem is an iron containing compound belonging to the class of compounds called protoporphyrins. Globin belongs to the class of protein called globulins. Hemoglobin thus is a conjugated protein.

The globin molecule contains four polypeptide chains. Two of them have identical amino acid number and sequence and are designated as a chains (each containing 141 amino acids) whereas the other two, called (3 chains have 146 amino acids each and have identical amino acid sequence. The formula of globin of normal adult hemoglobin, that is HbA.

With each polypeptide chain, one molecule of haem is attached. A Hb molecule, therefore, has four haem molecules. As the iron of each haem molecule

can combine with one molecule (2 atoms) of oxygen, each Hb molecule can combine with four molecules of oxygen. The molecular weight of Hb is 64500 (= 64.5 KD*).

Properties of Hb

1. Oxygen affinity. The affinity of Hb, for oxygen, is ideal, it is neither excessive nor too little. If the affinity were too little, the Hb within the RBC would have failed to combine with the O_2 of the alveoli of the lung. Had it been excessive, in the peripheral tissues (eg. working muscles), where the oxyHb is supposed to release its O_2 , the Hb would have retained its 0_2.

Further, this type of affinity of Hb for O_2, produces the sigmoid shape of the O_2 dissociation curve.

This affinity decreases in (a) hot and/or (b) acid environment. This is ideologically desirable. The working muscles are hot as well as their pH is low; in these conditions the affinity for O_2 is low and the O_2 is released vigorously. Another compound, 2,3 DPG (2,3 diphosphoglycerate), which accumulates during metabolism, also causes loss of affinity. This results in rapid and easy release of O2 in exercising muscles.

2. Haem-haem interaction. In the initial phase (of oxygenation), the combination of haem and O_2 is a bit slow, but once a little of O2 has combined with haem, further combi nations are facilitated. This is called 'haem-haem interaction'. This explains the steeper part of the sigmoid shaped graph of O_2 dissociation curve.

Structure of Haem

In a haem molecule, there are four pyrrole structures.

The four pyrroles are linked up with one another by methine (= CH -) bridges, to form, what is known as porphyrin.

There are various types of porphyrins. The particular type of porphyrin found in hemoglobin is called protoporphyrin III and as it contains an iron in the central part of the molecule, it is called iron protoporphyrin. Haem is iron protoporphyrin.

Synthesis of Hb

Hb is synthesized by the cells of erythroid series in the RBM (red bone marrow). Hb first appears at the stage of intermediate normoblast. The protoporphyrin can be synthesised by the normoblasts from products of metabolism, and amino acids, like succinyl CoA, glycine etc. Iron has to be obtained from food or iron contained in the Hb of dead RBCs. Important factor for Hb synthesis which is clinically important is iron (food must contain iron). Copper and cobalt are also necessary but they are more of academic interest only.

IRON METABOLISM

Iron containing substances in our body

Two sets of iron containing compounds are found in our body:

(1) Essential iron containing compounds. These are essential compounds in our body (ie, they must be present in our body so that we remain alive and in health) and they have irpn as one of the component parts. Examples : Hb, some enzymes like cytochrome catalse, peroxidase, xanthine oxidase and soon.

(2) Storage iron, (a) Ferritin is iron + apoferritin. Apoferritin is a protein, (b) Hemosiderin, which resembles ferritin, is another storage form of iron. But in hemosiderin, the proportion of iron is much more.

Hb is a very important iron containing compound of our body. In an adult, the total body iron content is about 4 gm of which iron in Hb alone accounts for nearly 70%.

Why iron is needed?

Life span of RBC, normally, is about 120 days. After 120 days, the RBC dies and iron of the Hb, within the RBC, is ultimately extracted > stored> reutilised to form Hb (recycling of iron). Viewed in this way, iron, apparently need not be supplied through food because iron is preserved. But this is not so because:

(1) Some iron is lost through desquamation of epithelial cells of the intestine in the feces. These epithelial cells contain iron. (2) In women additional loss of iron occurs through menstrual flow/drainage by the fetus during pregnancy/even drainage via breast milk during lactation. (3) Additional iron is required during growth.

Conclusion is some iron is required by adult male. Women particularly pregnant women require more. Growing infants, children also require more.

In the infant of about 3 months age and in the pregnants, body store of Iron (eg. ferritin) may be nil.

Source, daily requirement, absorption, transport and intake regulation of iron

Liver, heart, kidney, egg yolk (all animal foods) are excellent sources. Meat and fish also are also good sources. Milk, particularly cow's milk is well known for its iron deficiency. Green vegetables are good sources but non-green vegetables are deficient in iron. Vegetables contain phytic acid and phosphates which retard iron absorption.

. Food iron are divided into — (i) haem and (ii) non-haem (= inorganic) iron. Haem iron is the one which is present in the RBC, rather, in the Hb. Vast majority of food iron is non-haem iron. Most poor Indians depend only on non-haem iron from the green vegetables for their iron supply. However, commercial bread and powdered milk are usually fortified by iron by the manufacturer.

Absorption. Ease with which this varies depends upon whether the iron is haem iron or non-haem iron. Haem iron is easily absorbed. Most of the non haem iron is ferric (Fe+++) iron and is insoluble. For absorption, it has to become soluble and ferrous (Fe++) iron. Gastric HC1 makes the iron soluble and vit C (a strongly reducing agent) converts ferric into ferrous iron. Thus, persons whose

stomach has been removed or persons deficient in vit C suffer from iron deficiency.

The non-haem iron after becoming soluble and ferrous iron enters within the epithelium of the intestinal mucosa -> here (1) a part of this iron binds with apoferritin and becomes ferritin which may be lost via feces or may be absorbed in future, (ii) Another part of iron enters plasma and is transported being bound with a protein called 'transferrin'. Iron is delivered from this transferrin (rather, iron-transferrin complex) to the various cells which utilise the iron (eg. RBM and others).

Haem iron absorption : Hb enters the within of the intestinal mucosal cell and for this neither vit C nor HC1 is required. Within the cell the iron comes out of the Hb.

Daily requirement. In adult males, it is about 1 mg/day. In the non-pregnant non-lactating women of reproducing age, it is 1.5 to 2 mg/day. In pregnancy it is more.

In an affluent (= well to do) person's daily meal, the total iron content is about 20 mg, about 5% of which is haem iron. In a poor man, the daily meal contains much less iron.

Not only the conent of iron in the daily meal, but the bioavailability of iron is also very important. In usual meals containing 20 mg of iron per day, not more than 5% (ie, 1 mg/day) of the food iron is absorbed. But in the severely anemic/pregnant, 20% (ie, 4 mg/day) of the food iron is absorbed.

Regulation

If the iron store of the body (ferritin)is nil or low, in presenc of severe anemia/pregnancy, the fraction of food iron absorbed rises from 5% to 20% or even 30%. Conversely, in iron overload states, the iron absorption from intestine becomes nearly nil (despite normal iron intake). This is the major mechanism to safeguard that the absorption of iron can be varied according to the need of the body and the mechanism is called "mucosal block" mechanism. Another

mechanism is : from transferrin, delivery of iron is increased to the cells when the need of the body is great (iron deficiency states) and,vice versa.

Iron absorption occurs from duodenum and upper part of jejunum.

TIBC

Iron is carried by transferrin of blood plasma. Normally, only about 30% of transferrin is saturated by iron, that is, only 30% of the TIBC (total iron binding capacity, fig. 2.2.4) of the blood is saturated. When TIBC saturation becomes very low (say < 20%), there is iron deficiency anemia or when TIBC saturation becomes > 45% iron overload state is reached. Clinically, iron overload state is dangerous and can result when excessive iron therapy by IV (intravenous) route is employed.

An important cause of iron overload is too frequent blood transfusion.

Kinetics of iron absorption

Iron is absorbed from the duodenum and upper part of the jejunum -» enters blood -» from the blood it goes to the different cells which produce (i) Hb (erythroblasts), (ii) myoglobin, Mgb (muscle cells), (iii) enzymes like peroxidase/ catatase etc (liver cells etc).

from dead RBCs, Hb is relased —> iron is extracted from this Hb —> this iron is stored as ferritin, usually in the macrophages of the reticuloendothelial system, RES —> from this ferritin iron again comes back to the blood —» goes to form Hb; thus iron is recycled.

How to diagnose iron deficiency ?

(i) In iron deficiency state there will be 'iron deficiency anemia' characterized by microcytic hypochromic RBCs

which can be diagnosed by ordinary blood film staining and examining under ordinary microscope, (ii) A superior method is to estimate bone marrow iron

content by aspirating the RBM. (iii) Plasma iron, TIBC saturation can be measured.

FATE OF HEMOGLOBIN

As stated previously, when the erythrocytes become old, they rupture, mostly in spleen (as well as in the liver and bone marrow). The Hb is liberated from the ruptured RBC and phagocytozed by the phagocytes of reticulo endothelial system.

Within the phagocytes, the tetrapyrrole ring is opened up, that is, the haem is converted into a compound where the four pyrrole rings lie side by side, as shown in.

The iron is still attached with the tetrapyrrole straight chain compound and probably the globin also remains attached with it. Subsequently both globin and" iron are removed. The tetrapyrrole straight chain compound thus formed (free from iron and globin) is called biliverdin. Biliverdin is oxidized to form bilirubin. All these changes occur within the phagocyte of the reticuloendothelial system.

Bilirubin now comes out of the phagocyte and in the plasma, combines with albumin and is transported in the plasma as bilirubin-albiimin complex. This complex is frequently called "free bilirubin" by the clinicians and clinical biochemists.

The free bilirubin ultimately enters the liver and here the albumin is removed from the free bilirubin and most of the bilirubin is conjugated with glucuronic acid (a derivative of glucose), to form bilirubin glucuronides, which is water soluble. A small amount of bilirubin is conjugated with sulphate radicals to form bilirubin sulphate. The conjugated water soluble bilirubin is called "conjugated bilirubin".

The conjugated bilirubin is discharged into the biliary canaliculi and gets mixed up with bile. This is the main coloring matter of the bile.

Via the bile, the conjugated bilirubin ultimately enters the duodenum. In the intestine, when it comes in contact with the intestinal bacteria, bilirubin glucuronide is hydrolyzed by bacterial enzymes and non-conjugated bilirubin, which also is, unfortunately, called free bilirubin, is formed (unfortunate, because the term 'free', can create a confusion; whether it means bilirubin albumin complex or it is bilirubin obtained by unconjugation of the glucuronides). This free bilirubin is reduced to form urobilinogens and stereo bilinogens. Part of the urobilinogens and stercobilino-gens are absorbed by blood which then circulate in the blood and is excreted via the urine. The rest (ie. that part which was not absorbed from the gut) is excreted via stool. Golden yellow color of the stool is due to these pigments (stercobilinogen), and if the stool be kept exposed to the sun and air.

The conjugation (with glucuronic acid) of bilirubin in liver is catalyzed by the enzyme glucuronyl transferase. Many drugs, especially some steroids [for example, 'methandrostenolone' ('Dianabol'), a compound with androgenic activity, used clinically for its protein anabolic effects] compete with bilirubin for conjugating with glucuronic acid. Unless bilirubin conjugates with glucuronic acid it cannot be excreted via bile. So excessive use of these drugs often lead to accummulation of "free bilirubin" in the plasma (jaundice).

In the rare clinical condition known as "Crigler-Najjar disease" glucuronyl transferase is absent. As a result , the patients develop severe jaundice.

Glucuronyl transferase activity can be increased by the drug phenobarbitone. Hyperbilirubinemia and kernicterus in the neonates (in Rh incompatibility) can thus be successfully treated by phenobarbitone.

All conditions which produce excessive erythrocyte destruction, eg., malaria, mismatched blood transfusion, erythroblastosis fetalis, bites by some types of poisonous snakes, thus lead to excessive "free bilirubin" (ie, bilirubin-albumin complex) formation, and jaundice, clinically called, hemolytic jaundice, develops. But the urine does not contain free bilirubin in hemolytic jaundice, as the compound (ie, bilirubin-albumin complex) cannot pass the renal filter (omng to its big size). Instead, the urine contains excessive urobilinogen. The normal bilirubin

concentration of plasma is between 0.5 to 1.0 mg/100 ml, which rises greatly in hemolytic jaundice. The clinical and related biochemical features of different types of jaundice have been discussed later.

Hb. APPLIED PHYSIOLOGY

From what has been stated, it should be clear that for a smooth functioning of RBC, there must be :

(1) Proper erythropoiesis. For this, erythropoietic factors are necessary. They have been discussed earlier.

(2) Proper synthesis of haem as well as globin is necessary, (i) For haem synthesis, iron must be present in the food, (ii) Other raw materials for haem synthesis can be picked up from the intermediate metabolites. However, there may be defects in the synthesizing machinery of haem, resulting in porphyrias, (iii) The synthesis of globin can be defective due to hereditary disorders (abnormality in

chromosomes : such disorders are of two major kinds, viz, (a) haemoglobinopathies and (b) thalassemia). Besides, there can be abnormalities of globin due to acquired conditions like carboxyhaemoglobinemia, methemoglobinemia. Table 2.2.1 summarises the position.

Hemoglobinopathies

(1) Globin of normal Hb in the adult contains 2 a chains and 2 B chains, consequently adult Hb, that is, HbA, is written as a2 B2 Hb. (2) In the fetus, Hb is fetal Hb, that is, HbF and is written as oc2 Y2. This means, normally, in the fetus, a chains are like those of the adult but they (= the fetus) have y chains instead of the B chains. Sequence of amino acids in y chain is different from B chain. Normally, after birth HbF is spontaneously replaced by HbA.

(3) In the condition, clinically called "sickle cell anemia", the Hb is of the variety of HbS. In HbS, there are 2a chains as usual but the B chains contains, in position 6, valine instead of glutamic acid (as in normal B chains in HbA). Consequently HbS is written as oc2B2s. When exposed to hypoxic condition, this abnormal Hb tends to produce crystals, called, 'tectoids', within the RBC. Tectoid formation leads to increased fragility of RBC leading to susceptibility to hemolysis. West Africans, North American blacks are particularly susceptible to this disease.

Porphyrias

Although, this author is not aware of any serious study, porphyrias must be very "rare in the Indians. In the porphyrias, there is overproduction of porphyrins, which are intermediate compounds of haem biosynthesis. The over production is due to over activity of an enzyme, necessary in haem biosynthesis, viz, δALA synthase. Symptoms include psychosis, photosensitivity of skin to sunlight. The symptoms are often precipitated by alcohol or some particular drugs.

Thalassemias

a thalassemia major cases usually do not survive while a thalassemia minor is virtually symptomless. In P thalassemia major (Cooley's anemia) there is insufficient production of p chains, although once the chains are synthesized, they (= the P chains) are normal. There is no deficiency of a chain synthesis and hence there is excess of a chains not paired by p chains. These excess a chains cling to the membrane of RBC causing damage of the RBC membrane -» hemolysis. Patients are usually severely anemic, have signs of hemolysis in addition and are dependent on blood transfusion.

Repeated blood transfusions can lead to iron overload.

ANEMIA

Anemia is a condition where either the RBC count or the Hb concentration or both are deficient.

Cut off values

Females : In adult female, Hb below 11.8 gms/100 ml, RBC count < 3.8 m/ul, hematocrit value < 37 are usually regarded as anemia. In adult males, Hb < 13.2 gm/lOO ml, RBC < 4.5 m/ul and hematocrit < 40 are the cut off values.

Note, androgenic hormones, particularly testosterone is responsible for the higher Hb%, RBC count and hematocrit values in the males.

Terms

Such terms like microcytosis, macrocytosis have already been described earlier. Hypochromia means when the RBCs are pale, ie, they have less Hb.

Anisocytosis. Even in normal blood film, some variations between the size of the RBCs do occur but if the variation is too great, then the condition is called anisocytosis.

Target cells. Normally, the central part of the RBC does not take stain,, or stains poorly while the peripheral part takes stain so that the central part looks vacuolated. But, under some abnormal conditions, the central part takes stain but the peripheral part stains poorly — such cells are called 'target cells'.

Burr cells are characteristic of hemolytic, anemia. Bun-cells are RBCs in whom there are spiky projections.

Spherocytes = round RBCs.

Causes of vit B^ folate deficiency have already been .described (in chap 1 sec II). Iron deficiency anemia : occurs typically in chronic bleeders (eg, menorrhagic women/ sufferers of pile, hookworm infestation, chronic NSAID intakers) whose diet contains poor amount of iron. Women are particularly susceptible. Infants on breast/cow's milk are also prone to iron deficiency anemia.

Hemolytic anemias. Excessive hemolysis, producing ane-mia, may be due to (1) causes outside the RBC (hypersensi-tivity against some drugs/malaria/bites of

snakes* like viper) or (ii) due to causes residing within the RBC, like, , GI-6-PD deficiency, spherocytosis, sickle cell anemia and so orb-

Bone marrow aplasia or hypoplasia may be (i) due to the actions of known destructive agents (eg, x-ray irradiation/ use of some drugs in susceptible persons) or (ii) due to no known causes; when the hypoplasia/aplasia is due to no known cause then it is called 'primary' or 'idiopathic' aplasia, while others are 2ndary bone marrow aplasia. Recall, the RBM produces, RBCs, granulocytes (neutrophil/basophil/ eosinophil), monocytes, platelets — hence a CBC will reveal fall of all these cells, but there will be a relative lymphocytosis. In particular reticulocyte count (p 28) will be nil (0).

Some of the important features (which, help to diagnose the nature of anemia) which can be deter-mined by simple procedures like CBC and other simple blood tests.

Note. In some of the anemias, RBM activity increases as a compensatory mechanism and in aplastic anemia this does not occur. This (ie, increase or decrease of RBM activity) can be determined by reticulocyte count.

POLYCYTHEMIA

Polycythemia is, roughly speaking, opposite of anemia. In polycythemia, Hb concentration and RBC count, both rise. [However, there is a rare variety of polycythemia, called 'low plasma volume polycythemia' where Hb% rises but the RBC count remains normal or becomes even less than normal. This low plasma volume polycythemia will not be discussed further].

Polycythemia can be (i) secondary or (ii) primary which is also called 'polycythemia vera', PV.

PV is a member of the group of diseases, collectively known as 'myeloproliferative syndrome' or MPS, a term introduced by Damschek in the 1970s. In MPS, a stem cell becomes cancerous. If the stem cell that becomes cancerous, is of the variety of 'pluripo.tent stem cell', then the counts of RBC-

WBC-platelets all rise, but if the cancer afflicts only a committed stem cell, committed to produce only RBC,. PV develops.

Note, MPS developing in a committed stem cell, committed to develop granulocyte will produce chronic myeloid leukemia (CML). CML, thus, like PV, is a member of MPS.

[MPS is also called MPD — myeloproliferative disease. Incidentally, syndrome means disease]. In PV, erythropoietin concentration in plasma is very low or nil (ve feed back).

Note. The cancerous change in MPS occurs only in one stem cell -» therefore daughter cells of this cancerous cell alone increase in number. Ultimately the heavy cell count (produced by this cancerous clone cell), by -ve feed back, causes inhibition of the multiplication of all other (healthy) stem cells. But this -ve feed back cannot stop the multiplication of the cancerous stem cell as because it is a cancer cell. Ultimately, in PV, all RBCs are monoclonal.

Secondary polycythemia develops where there is need of excess erythropoietin to produce more RBC for survival of the person. Secondary polycythemia is thus seen in, high altitude sickness, emphysema, COPD and cyanotic heart diseases.

STUDY QUESTIONS:

1. What do you know about the physiological functions of the blood .

2. What elements make up blood?

3. What is hematopoiesis?

4. Where does hematopoiesis occur?

5. What are blood stem cells?

6. Describe the morphological structure of erythrocytes.

7. What are the other names for erythrocytes?

8. What is the function of these cells?

9. What is the name of the molecule in red blood cells that transports oxygen?

10. What is the molecular composition of hemoglobin?

11. Does the functionality of hemoglobin as a protein depend on its tertiary or quaternary structure?

12. Describe the morphological structure of hemoglobin. the colour test of the red cell.

13. The reactions of hemoglobin.

14. The hemoglobin in the fetus.

15. Explain the abnormalities of hemoglobin production.

16. The synthesis and catabolism of hemoglobin.

17. The red cell fragility.

18. The sedimentation rate

15. On average, what is the lifespan of a red blood cell? Where do heme groups go after the destruction of hemoglobin molecules?

16. Explain the role of the spleen for the red cells. Why can people still live after a total splenectomy (surgical removal of the spleen)?

17. What do you know about the physiological functions of the plasma.

18. The plasma proteins and its function.

19. The origin of plasma proteins.the hypoproteinemia

20. What do you know about the anemias and the polycythemia?

MULTIPLE CHOICE QUESTIONS (Select the single best answer)

1. How many Blood is on the Human body?

A. 1/5 of body's weight

B. 4 - 5% of body's weight

C. 13 - 14% of body's weight

D. 6 - 8% of body's weight

E. 1/2 of body's weight

#

2. What kind of Hemolysis can be at the person after a sting of the snake?

A .Osmotic

B. Oncotic

C. Biological

D. Mechanical

E. Physical

#

3. The pigment in red blood cells that carries oxygen is

A. erythropoietin.

B. melatonin.

C. urobilinogen.

D. Erythropoietin and hemoglobin

E. hemoglobin

#

4. The Patient A. has 90 g/l, of common proteins, 35 g/l of albumins, 31 g/l of globulins and 24 g/l of fibrinogens in the analysis of blood. What can happen with sedimentation rate at the patient and Why?

A. increase, because the high molecular proteins increase too

B. increase, because the high molecular proteins decrease

C. decrease, because the low molecular proteins increase

D. decrease, because the high molecular proteins increase

E. increase, because the low molecular proteins increase

#

5. The percentage of blood cells in whole blood is called _____.

A. plasma

B. plasma and erythrocytes

C. hematocrit

D. erythrocytes

E. serum

#

6. Two days ago Tom had Bleeding. Now there are some Reticulocyts in a patient's Blood. Where do Reticulocyts synthesize?

A. the Liver

B. the Kidneys

C. the Bone Marrow

D. the Spleen

E. the Kidneys and the Liver

#

7. Iron is stored in the liver in the form of _____.

A. hemoglobin

B. plasmine

C. transferrin

D. bilirubin

E. ferritin

#

8. What endocrinology glands take place in regulation of Erythropoesis?

A. the Thymus

B. the Thyroid

C. the Pineal gland

D. the Adrenal gland

E. the Thyroid, the Pituitary gland, the Adrenal gland, the Gonads

#

9. Red blood cells live around _____ before they disintegrate.

A. one month

B. 120 days

C. 21 days

D. three months

E. seven months

#

10. Which of the following are functions of the blood?

A. transportation

B. regulation

C. protection

D. regulation and protection

E. all of the above

#

11. How many Proteins are there in the Human Blood?

A. 2-3%

B. 90-92%.

C. 18-10%

D. 0,4%

E. 7-8%

#

12. Which blood components transport most of the gases?

A. erythrocytes

B. platelets

C. leukocytes

D. granulocytes

E. plasma

#

13. What kind of Hemolysis can be after shakeing a bottle with the tinned blood?

A. Osmotic

B. Onkotic

C. Biological

D. Mechanical

E. Termical

#

14. Which of the following cells do NOT have a nucleus?

A. erythrocytes

B. granulocytes

C. granulocytes and erythrocytes

D. leukocytes

E. agranulocytes

#

15. The Patient B. has 57 g/l, of common proteins, 35 g/l of albumins, 21 g/l of globulins and 0,5 g/l of fibrinogens in the analysis of blood. What can happen with sedimentation rate at the patient and Why?

A. decrease, because the high molecular proteins decrease

B. increase, because the high molecular proteins decrease

C. decrease, because the low molecular proteins increase

D. increase, because the high molecular proteins increase too

E. increase, because the low molecular proteins increase

#

16. Damaged or old red blood cells are removed by the liver and

A. kidney

B. skeletal muscle

C. bone marrow

D. spleen

E. intestine

#

17. What pathological form of Hemoglobin forms has this worker? The man works with aniline paints a lot .

A. Desoxyhemoglobin

B. Carbhemoglobin

C. Ca rboxyhemoglobin

D. Methemoglobin

E. Oxyhemoglobin

#

18. The blood volume of an averaged sized male is

A. 1 to 2 liters

B. 3 to 4 liters.

C. 4 to 5 liters.

D. 5 to 6 liters.

E. 6 to 7 liters.

#

19. Where does Erythropoetin produce?

A. the Liver

B. the Kidneys

C. the Spleen

D. the Bone Marrow

E. the Kidneys and the Liver

#

20. Which of these factors will increase the RBC or RCC?

A. sleeping

B. decreased altitudes

C. low body temperature

D. dieting

E. exercise

#

21. The relatively clear liquid medium which carries the other cells of blood is called:

A. lipid

B. antibody

C. plasma

D. defense system

E. all of the above

#

22. Which of the following are likely to increase in quantities when the body is under attack from bacteria?

A. erythrocytes
B. leukocytes
C. thrombocytes
D. erythroblasts
E. thromboblasts

#

23. Most of the volume of normal human blood is composed of:

A. red cells
B. hemoglobin
C. plasma
D. white cells
E. hemoglobin and red cells

#

24. Which of the following are functions of the blood?

A. transportation
B. regulation
C. protection
D. all of the above
E. all are incorrect

#

25. The blood volume of an averaged sized male is

A. 3 to 4 liters
B. 4 to 5 liters
C. 5 to 6 liters
D. 6 to 7 liters.

E. 7 to 8 liters.

#

26. Which of the following belongs to agranular leukocytes?

A. neutrophil

B. Basophile

C. Platelet

D. Monocyte

E. all are incorrect

#

27. Which of the following cells do NOT have a nucleus?

A. erythrocytes

B. Granulocytes

C. leukocytes

D. agranulocytes

E. all are incorrect

#

28. The patient with chronik renal insufficiency has the decreased general protein of the blood? How will the oncotic blood pressure and water metabolism between blood and tissues change?

A. the oncotic pressure will increase; dehydration of tissues

B. the oncotic pressure will decrease; dehydration of tissues

C. the oncotic pressure will decrease; edema of tissues

D. the oncotic pressure will increase; edema of tissues

E. no change

#

29. The blood serum of patient C. was received in the laboratory. What components may be found in it?

A. albumen, globulin, calcium

B. albumen, fibrinogen, ferum

C. complex of fibrin-monomer with products of fibrin decomposition

D. factor XIII, albumen, sodium ions

E. globulin, ferum

#

30. The blood viscosity of the patient was 7,0. What factor has changed the blood viscosity?

A. dehydratation of organism

B. physical overstrain

C. over dosage (superfluous dose) of liquid

D. food

E. hypodynamia

#

31. _____ is(are) the most numerous cellular element in blood.

A. Leukocytes

B. Erythrocytes

C. Plasma

D. Electrolytes

E. Platelets

#

32. The most abundant plasma protein in the blood is _____ and is synthesized by the _____.

A. albumin : spleen

B. albumin : liver

C. alpha globulins : B-lymphocytes c. beta globulins : liver

D. fibrinogen : kidney

E. gamma globulins : B-lymphocytes

#

33. Which of the following is a function of plasma proteins?

A. create colloid osmotic pressure

B. help buffer blood pH

C. transport hydrophobic substances in the blood

D. all of the above are functions of plasma proteins

E. none of the above are functions of plasma proteins

#

34. Which of the following feature(s) of red blood cells help(s) to increase the diffusion rate of oxygen into them at the pulmonary capillaries?

A. A thin plasma membrane that decreases the diffusion distance for oxygen.

B. A biconcave shape that increases the diffusion area for oxygen.

C. The presence of hemoglobin that binds oxygen and maintains the large

D. concentration gradient for oxygen between the alveoli and the red blood cells.

E. All of the above.

#

35. Which of the following enzymes is found only in red blood cells and is critical for carbon dioxide transport?

A. lactate dehydrogenase

B. carbonic anhydrase

C. peroxidase

D. sucrase

E. ATP synthase

#

36. The _____ detects a reduction in oxygen carry capacity of the blood and releases _____ that increases red blood cell production in the _____.

A. spleen : thrombopoietin : bone marrow

B. kidney : erythropoietin : spleen

C. spleen : erythropoietin : liver

D. kidney : erythropoietin : bone marrow

E. Liver : thrombopoietin : bone marrow

#

37. A deficiency in _____ can cause anemia.

A. sodium

B. Potassium

C. iron

D. vitamin C

E. vitamin A

#

38. Plasma

A. contains about 50% water.

B. contains about 40% plasma proteins.

C. volume changes considerably from moment to moment.

D. is a colloidal solution.

E. all of these

#

39. The liquid portion of the blood with fibrinogen and some of the clotting proteins removed is

A. plasma.

B. platelets.

C. plasma proteins.

D. formed elements.

E. serum.

#

40. Albumin, globulins, and fibrinogen are examples of

A. formed elements.

B. platelets.

C. plasma proteins.

D. granulocytes.

E. agranulocytes.

#

41. A 40-year-old female says she feels tired all the time. On exam, you note that she is tachycardic and pale. You order a CBC, which shows the following: Hgb 10 g/dL (12-16), MCV 75 (80-100). Her reticulocyte count is not increased. Which of the following is most likely?

A. She has iron-deficiency anemia

B. She has megaloblastic anemia, probably due to folate deficiency

C. She has megaloblastic anemia, probably due to B12 deficiency

D. She has a hemolytic anemia

E. She has NOT anemia

#

42. Select the statement about red blood cells that is incorrect.

A. Mature red blood cells lack nuclei.

B. Red blood cells contain hemoglobin.

C. Deoxyhemoglobin carries oxygen.

D. Red blood cells lack mitochondria.

E. Red blood cells are the non-nucleated formed elements

#

43. When red blood cells are worn out, part of their components are recycled while others are disposed. Select the incorrect statement about destruction of red blood cells.

A. The greenish pigment, biliverdin, is recycled to the bone marrow.

B. Iron is carried to the bone marrow by a protein called transferrin.

C. Biliverdin and bilirubin impart color to bile.

D. Macrophages in the liver and spleen destroy worn out red blood cells.

E. Daily 10% red blood cells, which are senile, get destroyed in normal young healthy adults

#

44. Which dietary component(s) is/are needed for DNA synthesis, and thus greatly influence the production of red blood cells?

A. calcium

B. iron

C. vitamin B12 and folic acid

D. protein

E. Cl^-

#

45. The type of anemia that is fairly common and caused by insufficient dietary iron is _____.

A. aplastic anemia

B. pernicious anemia

C. hemolytic anemia

D. iron deficiency anemia

E. aplastic anemia

#

46. Solutes that cannot pass through a semipermeable membrane are said to be. This is the correct answer.

A. osmotically active

B. osmotically inert

C. isotonic

D. isosmotic

E.

#

47. Water passes from the tissue fluids into the blood capillaries mainly because the

A. blood has a lower protein concentration than the tissue fluids

B. blood has a higher protein concentration than the tissue fluids

C. blood contains more salt than the tissue fluids

D. blood has a lower mineral concentration than the tissue fluids

E. blood has a higher mineral concentration than the tissue fluids

#

48. A deficiency of protein in the blood caused by liver disease such as cirrhosis, where the damaged liver is unable to produce adequate amounts of the protein albumin, leads to

A. edema

B. high blood volume

C. high blood pressure

D. high ECF volume

E. high ICF volume

#

49. Plant cells have a tough, fibrous cell wall that can push against the expanding cell membrane and prevent the uptake of excess water. The pressure that the cell wall must generate to oppose the uptake of water is called (p. 131)

A. osmotic pressure

B. hydrostatic pressure

C. osmolality

D. tonicity

E. hydrostatic pressure

#

50. Which of the following solutions is isotonic relative to blood plasma?

A. 0.15 m NaCl

B. 0.9% NaCl

C. 5% dextrose

D. all of these are isotonic to plasma

E. physiological solution

#

51. Two solutions are said to differ in ____ if they have different effects on the osmosis of water.

A. tonicity

B. molarity

C. molality

D. osmolality

E.

#

52. Red blood cells placed in Ringer's lactate solution will exhibit

A. swelling

B. no change

C. crenation

D. hemolysis

E. shrinkage

#

53. Red blood cells placed in a 0.2% NaCl solution will exhibit

A. shrinkage

B. no change

C. crenation

D. hemolysis

E. swollen

#

54. When the body loses water and the blood becomes too concentrated, it is detected by osmoreceptors located in the

A. brain

B. heart

C. blood vessels

D. blood cells

E. tissue

#

55. The primary effect of antidiuretic hormone (ADH), is to

A. lower the osmolality of the blood

B. raise the osmolality of the blood

C. prevent unnecessary loss of water

D. inhibit the sense of thirst

E. rise loss of water

#

56. A cell whose internal osmotic concentration is 0.3 osmoles/liter is placed in a solution that is 0.5 osmoles/liter. The solution is:

A. Isoosmotic to the cell
B. Hypoosmotic to the cell
C. Hyperosmotic to the cell
D. Isotonic to the cell
E. Hypertonic to the cell f

#

57. A cell is placed in a solution and swells. The solution is:

A. Isoosmotic to the cell
B. Hypoosmotic to the cell
C. Hyperosmotic to the cell
D. Isotonic to the cell
E. Hypertonic to the cell

#

58. The waste product bilirubin is formed from

A. transferrin.
B. globin.
C. heme.
D. hemosiderin.
E. ferritin.

#

59. Erythropoietin directly stimulates RBC formation by

A. increasing rates of mitotic divisions in erythroblasts.
B. speeding up the maturation of red blood cells.
C. accelerating the rate of hemoglobin synthesis.
D. accelerating production of proerythroblasts from the stem cells in

CFU-E of the bone marrow.

E. all of these

#

60. Dehydration would

A. cause an increase in the hematocrit.

B. cause a decrease in the hematocrit.

C. have no effect on the hematocrit.

D. cause an increase in plasma volume.

E. cause an increase ECF volume.

#

61. What four conditions cause the release of erythropoietin?

A. During anemia

B. When blood flow to the kidney declines

C. When oxygen content of the air in the lungs decline

D. When the respiratory surfaces of the lungs are damaged

E. All of the above

#

62. What five major functions are performed by blood?

A. transports dissolved gases, nutrients, hormones, and metabolic wastes;

B. regulates pH and electrolyte composition of interstitial fluids throughout the body;

C. restricts fluid losses through damaged vessels or at other injury sites;

D. defends against toxins and pathogens; and (5) stabilizes body temperature.

#

63. A hemoglobin molecule is composed of

A. two protein chains.

B. three protein chains.

C. four protein chains and nothing else.

D. four protein chains and four heme groups.

(e) four heme groups but no protein.

#

64. Serum is

A. the same as blood plasma.

B. plasma minus the formed elements.

C. plasma minus the proteins.

D. plasma minus fibrinogen.

(e) plasma minus the electrolytes.

#

65. Plasma contributes approximately _____ percent of the volume of whole blood, and water accounts for _____ percent of the plasma volume.

A. 55, 92

B. 25, 55

C. 92, 55

D. 35, 72

#

66. Blood temperature is approximately _____, and blood pH averages _____.

A. 36˚C, 7.0

B. 39˚C, 7.8

C. 38˚C, 7.4

D. 37˚C, 7.0

E. 40˚C, 7.0

#

67. The formed elements of the blood include

A. plasma, fibrin, and serum.

B. albumins, globulins, and fibrinogen.

C. WBCs, RBCs, and platelets.

D. a, b, and c.

#

68. A decrease in plasma proteins results in

A. decreased colloid osmotic pressure.

B. increased colloid osmotic pressure.

C. increased glomerular capillary pressure.

D. decreased filtration pressure.

E) increased tubular reabsorption.

#

69. Blood helps to maintain homeostasis by

A. transporting materials between the tissue fluid and the external environment

B. ridding the body of wastes

C. breaking down nutrients

D. coordinating metabolic reactions

E. controlling activity of enzymes

#

70. The average blood volume for an adult is about

A. 45 liters

B. 450 ml

C. 5 gallons

D. 5 liters

E. 8 liters

#

71. Each body function on the left is correctly matched with the corresponding function of the blood on the right EXCEPT

A. respiration - transports oxygen and carbon dioxide

B. immune defense - platelet factors initiate clotting

C. acid-base balance - buffers acids and bases

D. thermoregulation - allows heat to escape from the body at the skin

E. humoral function – transport of hormones

#

72. Which statement concerning blood viscosity is correct?

A. The viscosity of blood is 4.5 to 5.5 higher than the viscosity of water.

B. Blood viscosity is due to the presence of the plasma proteins and erythrocytes.

C. The higher the blood viscosity the harder the heart has to work to move blood through the vessels.

D. Anemia increases blood viscosity.

E. Erythrocytosis increases blood viscosity.

#

73. Plasma is:

A. Intracellular fluid found in red blood cells.

B. Interstitial fluid that surrounds tissue cells.

C. Extracellular fluid that is within the circulatory system.

D. Intracellular fluid found in white blood cells.

E. Interstitial fluid found in lymphatic vessels.

#

74. A(n) _____ solution would make your red blood cells shrink.

A. Hypotonic

B. Hypertonic

C. Isotonic

D. Isometric

E. Hypoplasia

#

75. _____ is(are) the most numerous cellular element in blood.

A. Leukocytes

B. Erythrocytes

C. Plasma

D. Electrolytes

E. Platelets

#

76. The most abundant plasma protein in the blood is _____ and is synthesized by the _____.

A. Albumin : spleen

B. Albumin : liver

C. Alpha globulins : B-lymphocytes c. beta globulins : liver

D. Fibrinogen : kidney

E. Gamma globulins : B-lymphocytes

#

77. Which of the following is a function of plasma proteins?

A. Create colloid osmotic pressure

B. Help buffer blood pH

C. Transport hydrophobic substances in the blood

D. All of the above are functions of plasma proteins

E. None of the above are functions of plasma proteins

#

78. Which of the following feature(s) of red blood cells help(s) to increase the diffusion rate of oxygen into them at the pulmonary capillaries?

A. A thin plasma membrane that decreases the diffusion distance for oxygen.

B. A biconcave shape that increases the diffusion area for oxygen.

C. The presence of hemoglobin that binds oxygen and maintains the large concentration gradient for oxygen between the alveoli and the red blood cells.

D. All of the above.

#

79. Which of the following enzymes is found only in red blood cells and is critical for carbon dioxide transport?

A. Lactate dehydrogenase

B. Carbonic anhydrase

C. Peroxidase

D. Sucrase

E. ATP synthase

#

80. _____ accounts for about 40% of the total body weight.

A. Extracellular fluid

B. Interstitial fluid

C. Intracellular fluid

D. Plasma

E.

#

81. Intracellular fluid

A. comprises a smaller percentage of body weight than extracellular fluid.

B. has a lower concentration of sodium ions than extracellular fluid.

C. has a lower concentration of potassium ions than extracellular fluid.

D. has a higher concentration of calcium ions than extracellular fluid.

E. all of these

#

82. If the solute concentration in the extracellular fluid decreases, water

A. moves into the cells.

B. moves out of the cells.

C. moves out of the blood.

D. will not move

E.

#

83. Approximately 90-95% of the osmotic pressure of the extracellular fluid is caused by and the negative ions associated with them.

A. Ca^{2+} ions

B. K^{+} ions

C. Mg^{2+} ions

D. Na+ ions

#

84. In the body, the dominant extracellular cations are

A. Ca^{2+} ions.

B. K^{+} ions.

C. Mg^{2+} ions.

D. Na^{+} ions.

E. Cl^{-} ions.

#

85. Which of these is NOT one of the major buffer systems in the body?

A. lactic acid buffer system

B. carbonic acid/bicarbonate buffer system

C. phosphate buffer system

D. protein buffer system

#

86. Buffers

A. bind to excess H^+ ions that are added to a solution.

B. prevent large changes in body fluid pH.

C. may involve weak acids.

D. release H+ ions when H+ ion concentration in a solution falls.

E. all of these

#

87. Respiratory regulation of pH depends upon the

A. carbonic acid/bicarbonate buffer system.

B. phosphate buffer system.

C. protein buffer system.

D. hemoglobin buffer system

E. chlorine buffer system

#

88. The reaction between CO2 and H2O is catalyzed by

A. angiotensin-converting enzyme.

B. carbonic anhydrase.

C. sodium bicarbonate.

D. phosphate.

E. carbonic acid.

#

89. Alkalosis

A. occurs when the pH of the body fluids is less than 7.35.

B. can be caused by hyperventilation.

C. can occur as a result of anaerobic respiration.

D. can result from production of urine that has a high pH.

E. all of these

#

90. When an acid reacts with the bicarbonate buffer system, _____ is formed as an end product.

A. NaCl

B. water

C. carbonic acid

D. bicarbonate ion

E. K ion

#

91. As total body water decreases, the _____ of the extracellular fluid increases.

A. amount of sodium

B. osmotic pressure

C. hydrostatic pressure

D. protein level

E. transmural pressure

#

92. Which of the following acts as a base in body fluids?

A. H^+

B. HCl^-

C. H_2CO_3

D. HCO_3^-

E. K^+

#

93. Which of the following does not play a significant role in maintaining acid-base balance?

A. blood buffers

B. stomach

C. kidney

D. respiration

#

94. The purpose of a buffer system is to _____.

A. prevent pH changes

B. increase acidity

C. decrease pH

D. maintain a pH range

E. increase alkalinity

#

95. In the bicarbonate buffer system, _____ reacts with bases.

A. carbon dioxide

B. carbonic acid

C. bicarbonate ion

D. water

E. chloric acid

#

96. When a strong base reacts with the bicarbonate buffer system, _____ is formed from the base.

A. water
B. carbon dioxide
C. bicarbonate ion
D. carbonic acid
E. chloric acid

#

97. When an acid reacts with the bicarbonate buffer system, _____ is formed as an end product.

A. NaCl
B. water
C. carbonic acid
D. bicarbonate ion
E. chloric acid

#

98. What happens to HCl in the phosphate buffer reaction?

A. ionizes
B. forms water
C. forms H_2PO_4
D. forms a weak acid and salt
E. no change

#

99. What reacts with excess acids in protein buffers?

A. carboxyl group
B. amino group
C. CO_2

D. $NH3^{+}$

E. $COOH^{-}$

#

100. What reacts with the excess bases in protein buffers?

A. NH_2

B. carbon dioxide

C. NH_3^{+}

D. carboxyl group

E. $COOH^{-}$

ANSWERS

1. D	26. D	51. A	76. B
2. C	27. A	52. B	77. D
3. E	28. C	53. D	78. D
4. A	29. A	54. A	79. B
5. C	30. A	55. C	80. C
6. C	31. B	56. C	81. B
7. E	32. B	57. B	82. A
8. E	33. D	58. C	83. D
9. B	34. E	59. E	84. D
10. E	35. B	60. A	85. A
11. E	36. D	61. E	86. E
12. A	37. C	62. C	87. A
13. D	38. D	63. D	88. B
14. A	39. E	64. D	89. B
15. A	40. C	65. A	90. C
16. D	41. A	66. C	91. B
17. D	42. C	67. B	92. D
18. D	43. A	68. A	93. B
19. E	44. C	69. A	94. A
20. E	45. B	70. D	95. B
21. C	46. A	71. B	96. A
22. B	47. B	72. E	97. C
23. C	48. A	73. C	98. D
24. D	49. A	74. B	99. B
25. C	50. D	75. B	100. C

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