

BLOOD: THE ESSENCE OF HUMANITY

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Contents

1. Introduction
2. Blood Composition and Functions
 - 2.1. Red Blood Cells (Erythrocytes)
 - 2.2. White Blood Cells (Leukocytes)
 - 2.3. Platelets (Thrombocytes)
 - 2.4. Plasma
 - 2.5. Blood Components in Diagnosis of Diseases
3. Blood Groups
 - 3.1. Blood group systems
 - 3.2. ABO and Rh Blood Group System
 - 3.3. ABO and Rh Grouping Methods
4. Blood Transfusion: Safety And Transmission Of Diseases
 - 4.1. Safety in Blood Transfusion
 - 4.2. Pre-donation considerations
 - 4.3. Adverse Effects of Blood Transfusion
 - 4.4. Blood Component Therapy
 - 4.5. Blood doping
5. Red Cell Indices And Morphology In Disease Diagnosis
 - 5.1. Red Cell Indices
 - 5.2. Morphology of Red Cells
 - 5.3. Red Cell Indices in Diagnosis
 - 5.4. Reticulocytes and their Importance
6. Anemias
 - 6.1. Iron Deficiency Anemia
 - 6.2. Thalassemias
 - 6.3. Sickle Cell Anemia
 - 6.4. Sideroblastic Anemia
 - 6.5. Megaloblastic Anemia
 - 6.6. Hemolytic Anemias
 - 6.7. G6PD Deficiency
7. Leukemias
 - 7.1. Acute Leukemias

- 7.2. Chronic Leukemias
- 8. Bleeding and Clotting Disorders
 - 8.1. Bleeding Disorders
 - 8.2. Clotting Disorders
- 9. Blood Parasites
 - 9.1. Malaria
 - 9.2. Filariasis
 - 9.3. Kala-Azar
 - 9.4. Trypanosomiasis
- 10. Blood Substitutes
- 11. Blood and the Arts
- 12. Conclusion
- Glossary
- Bibliography
- Biographical Sketches

Summary

Blood is a *mobile biological microprocessor* capable of carrying innumerable messages to every part of the human body via the circulatory system. It is a valuable human resource which is mystifying and dangerous. Blood has captivated mankind since centuries, often regarded as a living substance and the very core of life. The study of blood and diseases of the blood has led to discoveries of great practical importance, that have contributed to the development of knowledge in the vast fields of new sciences such as biochemistry, genetics, molecular biology, stem cell biology and artificial blood substitutes.

The story of blood has been described as a chronicle of a life-sustaining resource, of the researchers who have studied it, the businessmen who have traded it in legal and illegal markets, the doctors who have prescribed it as a remedy for lay people suffering from blood deficiencies and other ailments. This most human of all commodities has often been regarded as a gift of charity or simply as a pharmaceutical accompanied at times, by biosafety and ethical concerns.

Medical terminology associated with blood often begins with *hemo- or hemato-* derived from the Greek word "*haima*" for "blood". Hematology is a multifaceted branch of medicine covering the study of blood, blood constituents, blood groups, blood transfusion, and diseases of the blood, artificial blood substitutes, and its interaction with the arts, culture, and sports.

1. Introduction

Blood, called the "*the river of life*" and described as "*the circulatory computer tape*", carries coded cellular and humoral messages to integrate and serve the intricate demands of the various organs and tissues of the body. The theory of the four humors that includes blood has influenced medical practice from about the time of Galenic medicine up to the early modern period. It also explained the equilibrated balancing of the four elemental fluids: *blood, yellow bile, phlegm, and black bile* and the governance

of the state of health, physiology, and mind, or character.

The discovery of the microscope and pulmonary circulation was followed by the understanding of blood components and their functions, the importance of blood groups in transfusion, the techniques for storage and use of blood and its constituents, and the extensive study of diseases of the blood like anemias, leukemias, bleeding and clotting disorders, and parasitic infections. Furthermore, though no available natural substance can take the place of blood and its many functions there are several blood substitutes. These, however, have been developed for two main functions *i.e.* as plasma volume expanders; and, as substitutes for red blood cells.

2. Blood Composition and Functions

Blood, which the ancients believed was at the heart of all emotions, is the red fluid in the body that functions in two directions: arterial and venous, throughout the body by the circulatory system. Arterial blood transports oxygen and nutrients to tissues whereas venous blood is the means by which carbon dioxide and metabolic by-products are transported to the lungs and kidneys, respectively, for removal from the body. About 5 liters of blood (70 ± 10 ml/kg body weight), consisting of about 55% plasma and 45% cells are present in a normal adult. The components of blood - a circulatory tissue circulated by the heart through the vertebrate vascular system - are plasma, blood cells, and platelets. The composition of blood is now a much more complex subject, with each component, their functions and interactions having been studied meticulously up to the molecular level.

2.1. Red Blood Cells (Erythrocytes)

The conception of the red blood cell (RBC), known also as an erythrocyte, has changed from that of an inert corpuscle to that of a “tiny dynamo”. This RBC possesses a pigment called hemoglobin which combines with oxygen to form oxyhemoglobin that coordinates metabolic activity.

Oxyhemoglobin, bright red in color, gives blood its red color. The lifespan of RBCs produced in the red bone marrow of flat bones such as the sternum, skull and ends of the long bones is 120 days. In the bone marrow they pass through various stages of maturation. Immature cells usually do not appear in the peripheral circulation in which only newly released red cells (or reticulocytes), and mature red cells are found. RBCs are destroyed in the spleen. The main function of erythrocytes is to transport oxygen and to a lesser extent, carbon dioxide. RBC counts can increase or decrease in various conditions (Table 1).

a: Causes Of Increased Red Cell Count³

<ol style="list-style-type: none"> 1.Physiological: -In neonates, high altitude, after exercise 2.Hemoconcentration: e.g. burns, dehydration 3.Polycythemia rubra vera (PRV) 4.Secondary polycythemia due to: <ul style="list-style-type: none"> ▪ High altitude hypoxia, heavy smoking ▪ Renal diseases ▪ Central cyanotic states e.g. chronic lung diseases or congenital cyanotic heart diseases ▪ Uterine fibromyomata ▪ Cerebella hemangioblastoma
b: Causes Of Decreased Red Cell Count³
<ol style="list-style-type: none"> 1.Physiological: Old age, pregnancy, hemodilution 2.Anemias 3.Leukemias

Table 1: Red Cell Counts (Mehta 2004)
a) Causes of increased red cell counts
b) Causes of decreased red cell counts

2.2. White Blood Cells (Leukocytes)

White blood cells (WBCs) are nucleated, come in varied shapes, with a normal count between 4.0 and 11.0 X 10⁹ per liter. There are two main groups of white cells – granulocytes containing granules in their cytoplasm and agranulocytes with no granules. Granulocytes consist of neutrophils, eosinophils, and basophils whereas agranulocytes consist of monocytes and lymphocytes. The main function of WBCs is body defense against foreign bodies in different body tissues using blood as a transport system. Granulocytes and monocytes are produced in the bone marrow and lymphocytes are formed in the spleen and lymph nodes.

Abnormalities of WBC counts are leukocytosis *i.e.* increased neutrophil number (>11.0 x 10⁹/L) and leucopenia or decreased neutrophil number (<4.0 x 10⁹/L). Common causes of leukocytosis and leucopenia are listed in Table 2

S.No.	
1	Physiological: Exercise, pregnancy, neonatal period, exposure to cold
2	Drugs: Use of Epinephrine, steroids, GCSF (granulocyte colony stimulating factor)
3	Pathological
	<ol style="list-style-type: none"> a. Infection with pyogenic organisms b. Non-infective inflammations c. Vascular: Myocardial infarction, pulmonary embolism, acute hemorrhage d. Trauma and following surgery e. Toxic: Uremia, hepatic coma, chemicals f. Chronic myeloid leukemia, polycythemia vera, myelofibrosis g. Malignant neoplasms

S.No.	
1	Starvation and debility
2	Overwhelming infections and toxemia in old people
3	Infections like typhoid, measles, malaria, kala-azar, hepatitis, influenza, HIV
4	Hypersplenism, liver failure
5	Bone marrow failure: aplastic anemia, leukemia, chemotherapy, megaloblastic anemia
6	Drugs like antibiotics, bone marrow depressants, analgesics
7	Radiation

Table 2: Neutrophil Counts (Mehta 2004)

- a) Causes of increased neutrophil count
- b) Causes of decreased neutrophil counts

2.3. Platelets (Thrombocytes)

Platelets or thrombocytes, formed in the bone marrow and small fragments of very large cells called megakaryocytes, circulate in blood as small rounded bodies with a normal count between 150 and 450 X 10⁹ per liter. Platelets clump together to form plugs that close any tears in blood vessels; and do play a critical role in hemostasis and in the prevention of blood loss from the body. Increase (thrombocytosis) or decrease (thrombocytopenia) in platelet count can be due to many causes (Table 3, Mehta, 2004).

S.No.	
1.	During infections, at high altitudes, after severe muscular exercise
2.	Immediately after surgery and following bleeding
3.	Iron deficiency anemia
4.	Chronic myeloid leukemia
5.	Polycythemia vera
6.	Myelofibrosis
7.	Idiopathic thrombocytosis
S.No.	
1	Congenital (rare):
	<ul style="list-style-type: none"> ▪ Congenital aplastic anemia, congenital CMV or rubella infection ▪ TAR (thrombocytopenia with absent radii) syndrome ▪ Wiskott Aldrich syndrome
2	Acquired:
	<ul style="list-style-type: none"> ▪ Aplastic anemia, megaloblastic anemia, viral infections, drugs (e.g. sulphonamides, thiazides, NSAIDs), chemotherapy, radiotherapy, myelodysplasia ▪ Immune Thrombocytopenia: Autoimmune thrombocytopenia (AITP) or Drug-induced immune thrombocytopenia (e.g. heparin, quinine) caused by platelets being coated with antibodies & destroyed by macrophages. AITP includes: <ul style="list-style-type: none"> ▪ <i>ITP</i>: Idiopathic thrombocytopenic purpura (acute/chronic) ▪ <i>Secondary AITP</i> (chronic lymphocytic leukemia, lymphomas, solid tumors, HIV infection, chemo/radiotherapy, bone marrow transplant, systemic lupus erythematosus, Evan's syndrome)

	<ul style="list-style-type: none"> ▪ <i>Acute post-viral AITP</i> (e.g. malaria, HIV, EBV) ▪ DIC (Thrombotic Thrombocytopenia (TTP), hemolytic uremic syndrome (HUS)) ▪ Vasculitis due to thrombosis in small vessels
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Table 3: Platelet counts
 a) Causes of increased platelet count
 b) Causes of decreased platelet count

2.4. Plasma

Plasma is a straw-colored watery fluid portion of blood that serves as the liquid medium in which the corpuscular elements of blood are suspended; and, which comprises the major portion of whole blood. Plasma, composed of 92% water, 7% protein and 1% minerals, contains 6.5-8.0 grams of protein per deciliter of blood. The main proteins in plasma are: albumin (60%), globulins such as alpha-1, alpha-2, beta and gamma globulins (immunoglobulins), and clotting proteins (especially fibrinogen).

Serum is plasma from which fibrinogen has been removed by allowing the blood to clot naturally. Serum has no fibrinogen or clotting factors. It is the clot that makes the difference between serum and plasma. The term "serum", a Latin word, is also used to designate any normal or pathological fluid that resembles serum as, for example, the fluid in a blister or the "whey", the watery liquid that separates from the curds in the process of cheese making.

Functions of plasma are to:

- maintain blood volume and viscosity
- serve as a transport medium for glucose, lipids, amino acids, hormones, minerals, metabolic end products, carbon dioxide and oxygen
- store and transport clotting factors and plasma proteins

2.5. Blood Components in Diagnosis of Diseases

Blood components function as important diagnostic tools for various disorders like anemias (Refer to Table 10), leukemias, bleeding and clotting disorders, platelet disorders, etc

3. Blood Groups

3.1. Blood group systems

The term *blood group* or blood type is a classification of blood applied to any well-defined system of red blood cell surface antigens which are genetically controlled. There are 29 blood group systems with about 600 such antigens (International Society of Blood Transfusion, 2006). Clinically, the ABO and rhesus (Rh) groups are the most important. Other clinically less important blood group systems are Kell, Duffy, Kidd, Lutheran, P, MNS, Li, etc.

Blood groups or types have been used in forensic science and in paternity testing. Today, both of these uses are being replaced by DNA analysis, which provides greater certitude. It is worth noting that ABO blood types are also present in apes, chimpanzees, bonobos and gorillas.

3.2 ABO and Rh Blood Group System

The A, B and O blood groups involve the interaction between enzymes which are the product of two genes:

- The H gene on chromosome 19 codes for a fucosyl transferase (FUT1) that synthesizes the precursor H substance.
- The genes for the A, B or O are located on chromosome 9. The A and B genes are responsible for adding single carbohydrate residues to the H substance giving the A and B blood antigens respectively. The O gene enzyme is non-functional and does not transform the H substance giving the O group.

Blood Group	Antigen on red cell	Naturally-occurring plasma antibodies*	Genotype
O	O	anti-A, anti-B	OO
A	A	anti-B	AA or AO
B	B	anti-A	BB or BO
AB	AB	None	AB

* *Naturally occurring antibodies* are found in the plasma of individuals who lack the corresponding antigen and who have not been transfused or been pregnant. The most important are anti-A and anti-B antibodies, usually immunoglobulin M (IgM) class and cold antibodies reacting optimally at 4°C.

Table 4: ABO Blood Group System

Prevalence of the ABO Blood Groups

Type O blood is the most common blood type in the United Kingdom and the Americas. Type A blood is more prevalent in Central and Eastern Europe countries. Type B blood is most prevalent in Chinese/Asian communities when compared to other races. Type AB blood is easier to find in China, Korea, Japan, and Pakistan.

Rhesus system

The Rhesus system is named after the Rhesus monkey (*Macaca mulatta*) one of the best known species of Old World monkeys which is common throughout Afghanistan, northern India and southern China. Karl Landsteiner and Alexander S. Wiener discovered this factor in 1937. Dr. Phillip Levine working at the Newark Beth Israel Hospital made a connection between the Rh factor and the incidence of erythroblastosis fetalis. Alexander S. Wiener discovered this factor in 1937 and pioneered the exchange transfusion to combat erythroblastosis fetalis in newborn infants.

Hemolytic disease of the newborn

Immune antibodies develop in response to transfusion or by trans-placental passage during pregnancy. These are usually warm antibodies (react at 37⁰C) of the immunoglobulin G (IgG) class. They can cross the placental barrier and can result in hemolytic disease of the newborn. This is also known as erythroblastosis fetalis and occurs when there is an incompatibility between the blood types of the mother and the baby. Hemolytic originates from two words: *hemo* (blood) and *lysis* (destruction) or breaking down of red blood cells; *erythroblastosis* refers to the making of immature red blood cells; and *fetalis* refers to the foetus. When the condition is caused by the RhD antigen-antibody incompatibility, it is called RhD Hemolytic disease of the newborn (or often called *Rhesus disease* or *Rh disease* for brevity). The incidence of Rhesus disease is mathematically related to the frequency of RhD negative individuals in a population, so Rhesus disease is rare in East Asians and Africans, but more common in Caucasians.

3.3. ABO and Rh Grouping Methods

The traditional means of determining an individuals' ABO phenotype is via the reaction of immune antibodies with the carbohydrate A, B and H antigen. This involves two processes:

3.3.1. Forward Grouping

This uses an antibody of known specificity to detect the presence or absence of the corresponding antigen on the surface of an individual's red cells. The monoclonal antibodies routinely used are: Anti-A, Anti-B, Anti-AB and anti-D (Rh). If the antibody detects the presence of its corresponding antigen it will cause the red cells possessing this antigen to agglutinate. Agglutination signifies a positive reaction.

3.3.2. Reverse Grouping

The reverse group uses cells with known ABO blood group antigens on their surface. These are reacted with the individual's serum.

An individual's serum possesses *naturally occurring antibodies* to the A, B, H antigens that their cells lack. If the naturally occurring antibodies recognize the corresponding antigens on the cells with the known ABO antigen they will agglutinate these cells.

The reverse and forward groups are performed together as each method is used to check the validity of the other result.

3.3.3. Cross Matching

Cross matching is an important test to be carried out after the ABO and Rh blood group is determined and prior to blood transfusion. This is to ensure that compatible blood is given to the patient. The saline, albumin or Coomb's cross match can be carried out. No agglutination indicates compatibility. Agglutination indicates incompatibility.

3.3.4. Direct Coombs (Antiglobulin) Test (DCT)

DCT is used to detect antibody or complement system factors on the red cell surface where sensitization has occurred *in vivo*. A positive test occurs in hemolytic disease of the newborn, autoimmune or drug-induced immune hemolytic anemia and hemolytic transfusion reactions.

3.3.5. Indirect Coombs (Antiglobulin) Test (ICT)

ICT is used to detect antibodies that have coated the red cells *in vitro*. A positive test indicates that the original serum contained antibody which has coated the red cells *in vitro*.

ICT is used as part of the routine antibody screening of the recipient's serum with donor's red cells prior to transfusion. In hemolytic disease of newborn, the mother's serum is tested to detect anti-Rh antibodies.

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Visit: <http://www.eolss.net/Eolss-sampleAllChapter.aspx>

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Biographical Sketches

Shilpa P. Mehta obtained her Bachelor's Degrees (1971) and Master's degree (1973) in Microbiology of the University of Bombay with First class Honours. In 1977 she was awarded the Ph.D. Degree of the University of Bombay in Applied Biology following successful conclusion of her research at the nationally specialized research facility - Tata Cancer Research Institute, on Human Breast Cancer. During the period 1969 – 1977 she was awarded the National Science Talent Search Scholarship granted by the National Council of Educational Research and Training, Ministry of Education, GOI, New Delhi, India.

Lecturer at two Universities in Bombay in microbiology, author of a textbook on Practical Pathology and editor of several texts dealing with practical medicine, common medical symptoms and Electrocardiography, Shilpa Mehta has "hands-on" experience with coagulation and thalassemias studies, polymerase chain reaction (PCR), platelet function studies, lupus anticoagulant studies, and currently involved in projects dealing with the diagnosis and monitoring of chronic myeloproliferative disorders using QR-PCR. Furthermore, she possesses the experience and skills in setting up a Molecular Diagnostics (PCR) Laboratory. Currently Research Scientist at the Hematology Laboratory.

Sunil J. Parekh obtained his MBBS and MD (Internal Medicine) degrees from the University of Bombay. He received sub-specialty hematology training at the Christian Medical College, Vellore (India), the State University of New York and the University of Utah (USA) in the fields of laboratory and clinical hematology, blood banking and blood transfusion. He has been associated with several institutions and hospitals in Mumbai and is a member of several Indian, European and American hematology societies. He is currently India's representative in the International Members Committee of the American Society of Hematology. He has been practicing medicine for almost 40 years and believes that the needs of poor patients are being overlooked in the current debate about patent rights and protection of intellectual property in India.

Edgar DaSilva, a graduate of the University of Bombay in microbiology and chemistry, was awarded, in 1962, the Bachelor of Science Degree (First Class with Honours). In 1966, he obtained the Master of Science Degree, and in 1969 his Doctoral Degree for research studies on the cyanobacteria. As a NORAD Fellow, his research study, on the marine algae at the Norwegian Seaweed Research Institute, Trondheim, Norway, in 1970, was followed by a teaching assignment at the University of Helsinki, Helsinki, Finland. Two years later, he joined the Institute of Physiology, University of Uppsala, Uppsala, Sweden as a UNESCO fellow. A former Vice-President of the World Federation for Culture Collections (WFCC),

author of several scientific publications, and member of well-known microbiological societies. Moreover, he has also been a keynote plenary speaker at several international events in, Argentina, China, Kuwait, Nigeria, South Africa, Sweden, Thailand, USA, etc. on biopolicy issues in regional co-operation, microbiological education, and on globalization and sustainable development.

At UNESCO since 1974 in various capacities within the Division of Scientific Research and Higher Education and the Division of the Basic Science Dr. DaSilva has been instrumental in the planning and implementation of several UNESCO regional and international programmes in applied microbiology as well as in the development of the global networks dealing with management and use of microbial resources and training opportunities in the fields of marine and plant biotechnology. Moreover he mobilized several extrabudgetary programmes in close cooperation with UNEP and UNDP and Donor Member States for activities in national development in biotechnology and regional cooperation in microbiology.

He also was the Director, Division of Life Sciences that was subsequently transformed into a Section of the Life Sciences within a new Division of the Basic and Engineering Sciences prior to his retirement from UNESCO.

Currently Dr. DaSilva has had teaching assignments as Visiting Professor at the International Centre for Biotechnology (ICBiotech) in Osaka University and its outreach station, and teaching assignments at the UFS, and at the Outreach station of ICBiotech at Mahidol University, Thailand and at the University of the Free State, Republic of South Africa

A fellow of the World Academy of Art and Science and following a keynote lecture to the Biotechnology Division of the Royal Swedish Academy of Engineering Sciences and the Biofocus Foundation, Dr. DaSilva was awarded the Biopolicy Award in 2003