UNIT 19 GENETICS OF BLOOD

19.1 INTRODUCTION

Blood, a "circulating tissue" nurtures the individual cells by supplying nutrients, removing their waste products and regulating their metabolic activities. It consists of red (erythrocytes) white (leukocytes) blood cells and the platelets (thrombqcytes) suspended in a liquid medium, called plasma. Blood and plasma perform many functions that are absolutely necessary for the maintenance of health. The red blood cells are intimately associated with heart, lung and kidney Eunctions. Hemoglobin is the main constitutent of erythrocytes that carries oxygen.

Blood group antigens found on the surface of erythrocytes, are responsible for immunological reactions of red blood cells, At least 20 blood groups have been recognized in man, of which ABO system is an extensively known system. The blood group substances are inherited according to simple Mendelian ratios through multiple alleles representing a single locus. About a dozen set of Rh blood types and a few others are inherited through other loci, independent of ABO system. Blood groups are most readily identified by means of specific antibodies present in the serum. Blood group systems have been used for clarifying disputed paternity. The ABO antigens are considered to be important in organ transplantation and blood transfusion.

Diseases of blood and blood forming organs are like a spectrum, at one end of which are diseases which are entirely genetic in origin such as chromosomal abnormalities due to single gene defects, and hemolytic anemia where' environmental factors play little role. At the other end of the spectrum are those diseases which are entirely environmental in origin, such as infectious and nutritional deficiences and disorders of white blood cells. In the middle of the spectrum are many common disorders which are partly genetic and partly environmental in origin, called multifactorial disorders; for example most anemias are multifactoral. Since there is at present no effective treatment for most genetic disorders, such diseases can be mainly prevented through genetic counselling.

Objectives

After studying this unit you should be able to

- Explain blood group systems and Rh factor
- Describe hemoglobin genes
- 'Describe clinical application of blood groups and some associated disorders
- Explain transfusion reactions, and their hazards.

19.2 CHEMICAL STRUCTURE AND GENETICS OF BLOOD GROUP SYSTEMS

After the discovery of circulatory system in 17th century, the discovery of ABO blood group system that led to immunological basis of transfusion reaction was established for the first time in 1900 by Landsteiner, who was awarded Nobel Prize for his work. He pointed out that blood cells have unique cells surface markers, that function as antigens. The presence of specific antigens on the red blood cells are characteristic of different blood groups as shown in Table 19.1

Table 19.1: Established Blood Group Systems

System	Antigen	Number of antigens for which specific antibody is known	Chromosomal location
ABO	A, B, O	5	9(9)
MNS	M, N, S	30	4
P	P	2	?
Rhesus	Rh	44	1
Lutheran	Lu	16	19
Kell		21	?
Lewis	Le	2	19
Duffy	Fy	5	1
Kidd	Jk	3	2
Diego	Di	2	?
Cartwright	Yt	2	?
Auberger	Au	1	?
Sg		1	X
Scianna	Sc	3	1
Dombrock	Do	2	?
Cotton	Co	3	2
Landsteinei-Weiner	LW	3	19

Antigenic determinants of blood group antigens comprise of polysaccharides and proteins. The polysaccharide antigens occur as complex glycoproteins or glycolipid structures consisting of more than one sugar moiety. Sugars constituting the polysaccharides are glucose, galactose, fucose, N-acetylglucosamine, N-acetylgalactosamine and N-acetyl neuraminic acid (sialic acid) which contribute to the charge on cell surface (Table 19.2). The polysaccharide antigens are synthesised by the enzymes **glycosyl transferases.** These polysaccharides are attached to either proteins or lipids directly which are themselves attached to the membrane. The protein antigens of red blood cells are integral proteins that are

inside the hydrophobic lipid bilayers of the membrane. You have read about the membrane proteins in LSE-01.

Table 19.2: Terminal sugars of the antigenic groups for each blood type.

Blood Group A -N- acetylgalactosamine D- Galactose — N–acetylglucosamine | L–Fucose (Fig. 19.1a)
Blood Group O D Galactose — N–acetylglucosamine | (L) Fucose (Fig. 19.1b)
Blood Group B D- Galactose—D- Galactose —Nacetylglucosamine | (L) Fucose (Fig. 19.1c)

19.2.1: ABO Blood Group System:

Landsteiner divided human red blood cells into four groups designated A, B, AB and O. The four phenotypes are determined by three major alleles situated on chromosome 9 (Table 19.3). The I^A and I^B dominant alleles control the A and B blood group antigens and a third recessive I^O allele does not control synthesis of any antigen. Since then, at least twenty other blood groups have been discovered. But our discussion will be limited only to the well known ABO and Rh system. The ABO blood group system depends on the presence or absence of two polysaccharide antigens located on cell membranes of red blood cells. Those individuals with A type of blood possess antigen A on their red blood surface and type B individuals possess antigen B. Persons with type O blood lack both A and B surface antigens. The serum of persons with A type antigen contains antibodies against type B red cells and type B blood persons have antibodies against type A red cells. Persons with type O blood have antibodies against A and B cells. Individuals with AB type serum contain no antibodies against A and B antigens. Thus if the blood of type B is transfused into a person with type A blood, the antigens on type B blood cell will react with antibodies against B and antigen-antibody reaction will take place.

Table: 19.3: The genotypes of ABO Blood groups system

Genotype	Antigen	Phenotype
I^AI^A	A	A
I^AI^O	A	A
I^BI^B	B	B
I^BI^O	B	B
I^BI^B	A, B	AB
I^OI^O	Neither	O

I^A and I^B alleles behave dominantly to I^O allele.

Antibodies that agglutinate the cells bearing these antigens are called isohernagglutinins. The IgM antibodies are one of such naturally occurring isohemaplutinins against the red blood cell antigens. The ABO blood groups are presumed to have arisen as a result of immunization by the bacteria in respiratory and gastrointestinal tracts that bear determinants similar to the antigens of ABO groups. Since IgM can not pass through placenta, incompatibility of ABO blood group between fetus and mother does not occur. The ABO blood group antigens are encoded by single gene with three alleles I^A, I^B and I^O. The I^A and I^B alleles are dominant over I^O and codominant with respect to each other.

However, group O individuals have a glycoprotein on the surface of their erythrocytes called the H substance. H substance can be recognised by antisera from different animals. The glycoprotein is not the end product of the gene since it is present on RBC of people who are homozygous for A or B genes. H substance is synthesized just during the synthesis of blood group molecules. Substance H is present in all individuals irrespective of their blood group and no antibodies are produced against it. The sugar moiety contains L-fucose which is recognised by the antibodies. The I^A allele codes for an enzyme that converts the H substance into another glycoprotein i.e. substance A by a adding a terminal N-acetyl galactosamine group that forms the antigenic determinant of blood group A (Fig. 19.1 a).

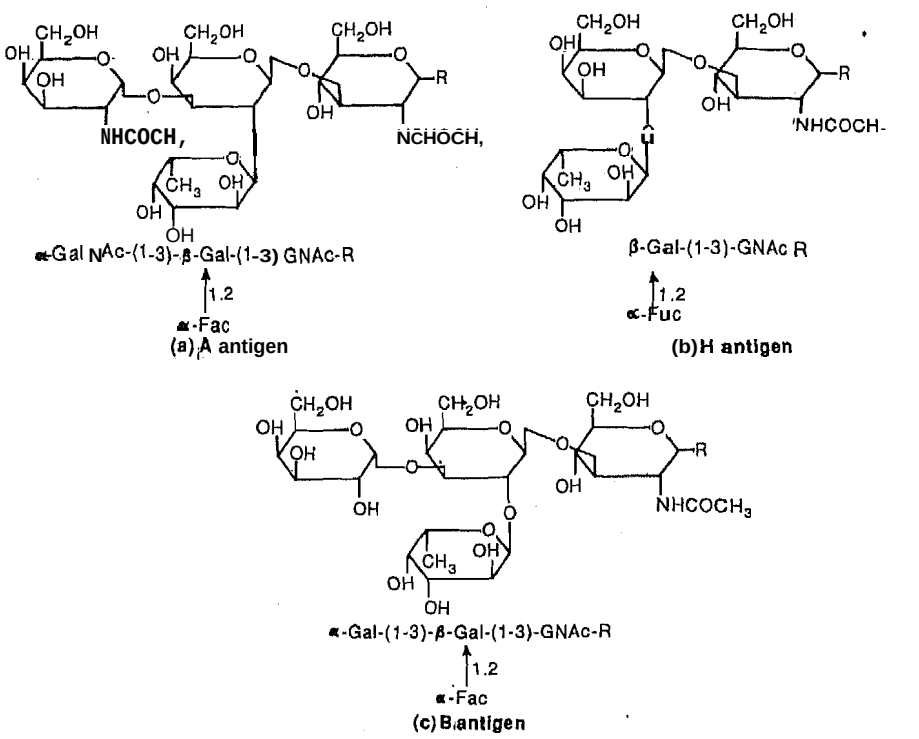

Fig. 19.1 Structure of carbohydrates in ABO Blood group system.

It is now known that the I^A and I^B alleles code for enzymes that attach carbohydrate molecule to the basic glycoprotein called H substance. The carbohydrate group that takes either D galactose or the modified N-acetyl -D-galactosamine at the terminal position is called the H substance and type O individuals (of genotype I^OI^O) possess the H substance on their red blood cell surface. (Fig. 19.1b)

The allele I^A codes for the enzyme N- acetylgalactosaminyl transferase. This enzyme adds -D-N- acetylgalactosamine to the H substance, thereby generating the A type antigenic determinant and A type antigenic structure. The I^B allele codes for the enzyme galactosyltransferase, and converts the H substance similarly into another glycoprotein called the B antigen. Thus the phenotype of a person whose genetic make up is I^AI^O will be group A, but he may pass on the I^O allele to his offspring.

In 1952, a woman in Bombay was found to lack the H substance altogether and she demonstrated a most interesting genetic history and blood type. She was found to lack both A and B antigen and was typed as O blood group. However, as shown in

the partial pedigree (Fig. 19.2) one of her parents was AB and the mother was the obvious donor of I^B allele to two of her offsprings. Thus she was genetically type B but phenotypically type O. She was homozygous for a rare recessive allele h, which prevented her from sysnthesising the complete substance H. The gene responsible for the formation of H-antigen, that serves as a precursor for the A and B antigens was absent in her. As a result the blood group genotypes can not find expression in individuals of hh. To distinguish such types from the rest of the population they were said to demonstrate the Bombay phenomenon. The frequency of the h allele is extremely low, and the vast majority of the human populations is of HH genotype and can synthesize the H substance.

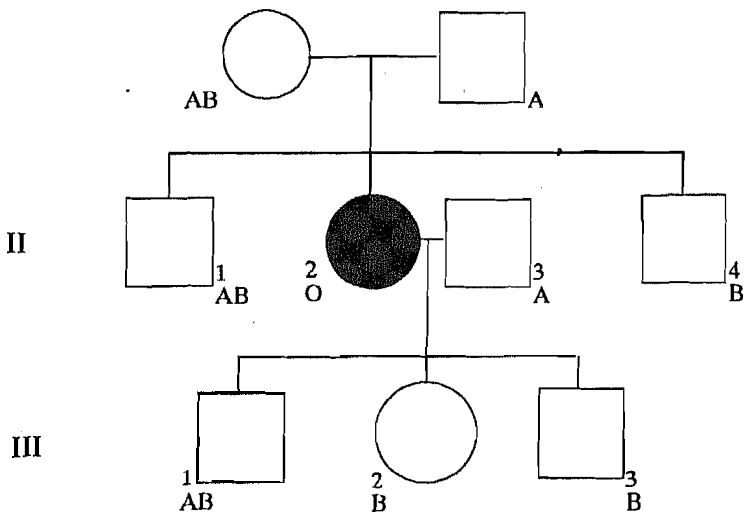

Fig.19.2: Partial pedigree that explains Bombay phenomenon.

Blood group **A** is further divided into sub groups A_1 and A_2, A_3, and **Am** on the basis of number of antigenic sites (epitopes) on the cell. The A_1 cells have **high** antigenic density. Table 19.4 summarises ABO blood group systems.

Table 19.4: Antigens and antibodies of ABO blood group system.

Group	Specific antigen	Quantity of H-antigen	Antibodies in serum	May receive blood from	May give blood to
O	None	High	Anti-A Anti-B	**O**	O,A,B,AB
A	A, A_1	Low	Anti-B	A,O	A, A_2, AB
A_2	A_2	More than A	Anti-B Anti-A_1	A (usually) A_2O (occasionally)	A, A_2, AB
B	B	Like A	Anti-A	B,O	B,AB
AB	A, A_1, B	Less than A or B	None'	AB,A,B,O	AB
A_2B	A_2,B	More than AB	None	AB,A,B,O	AB

SAQ1:

a) Fill in the blanks with appropriate words.

1). **ABO** blood group systems were discovered by ---------- in the year 1904.

2). The polysaccharide antigens are generated by ----------.

3). ---------- does not code for any enzyme in the ABO system.

4). Bombay phenomen is a unique case where mother's blood lacked antigens and two of her offsprings belonged to B blood group; genetically her blood group was ---------- but phenotypically .....

b) Match the terminal sugars with the blood groups in column-I

	Sugars		Column-I
1)	D-galactose-(L)-fucose	(i)	Blood group B
2)	Nactyl glactosamino — D-galactose -L-fucose	(ii)	Blood group A
3)	D-galactose-D galacrose-(L)-fucose	(iii)	Blood group O

19.2.2 The Rh System

The Rh system was discovered by K. Landsteiner and A.S.Weiner from rabbits immunized with the blood of monkey Macaca rhesus. This blood group antigen is also found on the surface of human erythrocytes. About 85% of the population possesses Rh antigen on the surface of their red blood cells and are called Rh positive persons. Those individuals who do not possess Rh factor on their red blood cells are called Rh negative. The plasma of Rh negative persons does not contain antibodies (agglutinins) against Rh positive factor but such persons can produce antibodies if blood of Rh positive persons is transferred to them.

The Rh antigens are proteins and are of common occurrence in humans and so preformed antibodies are rare. They are the product of immunization either through pregnancy or by transfusion. The original antigen (D) now designated as Rh^o is present in about 85% of whites which means that they have antigen D on the surface of their red blood cells. In the remaining 15%Rh negative individuals who have no antigen D, will produce antibodies against that antigen when they are exposed to Rh positive blood. At least eight different kinds of Rh antigens each referred to as an Rh factor is present in Rh system. Only three genes residing at three separate but closely linked loci regulate the synthesis of Rh antigen. These exist as the allelic pair Cc, Dd and Ee. By far the most important of these is the allele coding for antigen D.

19.2.3 Secretors and Lewis Blood Group System

The ABO blood group substances are present as glycoproteins on the surface of erythrocytes and on the surface of many endothelial and epithelial cells. The genetically controlled A, B and H substances are present in about 80% humans as mucopolysaccharides in body secrations such as saliva, sweat, urine, seminal fluid and gastric juices. Such prople are termed as secretors. The secreted substances are immunologically identical to those present on their red blood cells. The inherited characteristics are controlled by allelic gene pairs denoted by *Sc* and sc. Both homozygous (*ScSc*) and heterozygous (Scsc) are secretors and sc gene is recessive; non-secretors possess scsc alleles.

In the Lewis (Le) system, there are two substances Lewis a(Le^a) and Lewis b(Le^b). These antigens are complex glycoproteins or glycolipds that are found free in serum and have a natural ability to be adsorbed on RBC surfaces. The Lewis antigen is produced from the same precursor as those of ABO(H) antigens. The H substance is a key intermediate in the pathway to the A,B and Le^b antigens synthesis. The Le^a gene activates fucosyl transferase which adds fucosyl residue to the precursor moiety and produces a Le antigen. The precursor substance is operated upon by the H gene which controls the fucosyl transferase. The Le^a and H genes are structural genes for transferase that have slightly different functions. To generate b(Le^b) antigen, a third type of fucosyl transferase adds a fucose molecule to precursor

substance. Thus, the structure of ABO(H) and Lewis antigens are closely related to one another.

19.2.4 MN Blood Groups

The MN System under the control of a locus on chromosome 4, consists of three blood groups M,N and MN phenotypes. Genotype L^ML^M represents blood group M. L^ML^N blood group MN and L^NL^N blood group N (see table 19.5). (L represents the name of the discoverer Lewis)

Table 19.5. Inheritance of MN blood groups.

Parental Phenotypes	Offspring Phenotypes
M × M	All *M*
N × N	All N
M × N	All MN
M × MN	1/2 M: 1/2 MN
N × MN	1/2 N: 1/2 MN
MN *x* MN	1/4 *M:* 1/2 *MN: 114 N.*

The M type elicits antibodies (anti M.serum) for M, which could agglutinate M antigens, while N red blood cells caused the production of antibodiesspecific for N (anti N serum). Both type of antibodies however could agglutinate the MN red blood cells. It is known now that MN system is inherited as a result of two alleles of a gene.

19.2.5 The Kelly & Duffy Systems

The Kelly and Duffy blood groups are minor blood groups, but can cause haemolysis in transfusion reactions. The kelly system consist of two allelic forms as K and k. The K antigens are found on the RBCs of about 10% of the Georgian population and are highly immunogenic. Exposure of K antigen during pregnancy or transfusion may lead to the formation of anti-K IgG which causes agglntination reactions. There are a number of other antigens belonging to Kell system (Kpa, Kpb, Jsa, Jsb, Uia)but antibodies other than anti-K are rare. About two thirds of the white population have the antigen Fya in Duffy system. Compared to other antigens in this system, anti-Fya is a relatively common cause of hemolytic transfusion reactions. The allelic form was named as Fyb . Approximately 60% of all black population lacks Fy antigens and lacks receptor for the malarial parasite Plasmodium vivax, hence resistant to P.vivax malaria. In another minor system called Kidd (JK) system two antigens have been described - JKa and JKb . The antibodies to these antigens are particularly unstable on storage and do not remain in the serum of sensitised patients.

SAQ *2:*

1 a) Tick (√) the correct statement.

An individual is said to be a secretor when

a) soluble form of blood group antigens are found in body secretions.

b) 'insoluble form of blood group antigens are found in blood.

c) soluble form of blood group antigens are found in saliva.

d) soluble form of blood group antigens are found in urine.

b) Briefly describe the following.

Kelly System:

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Duffy System:

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19.3 HEMOGLOBIN GENE IN EUKARYOTES

Human hemoglobins are conjugated proteins in which a prosthetic group, heme, is attached to each of four polypeptide subunits. Adult hemoglobin (HbA) consists of two a and two β polypeptide chains The peptide chain of hemoglobin is responsible for the species specificity. The pigmentary property and respiratory functions are associated with heme, the iron containing pigment; but the globin fraction of hemoglobin functions to transport carbon dioxide. Hemoglobin has the property of combining reversibly with atmospheric oxygen, forming oxyhemoglobin. This occurs in the capillaries surrounding the alveoli of the lungs. The oxygen is then transported by the arterial blood to tissues and the blood depleted of its oxygen returns to lungs for oxygenation.

19.3.1 Chemistry of hemoglobin

As you know that in a complete hemoglobin molecule there are four individual polypeptide chains divided into two identical alpha (a) chains and two identical beta (β) chains. The alpha and beta chains are almost of the same chain length and of similar structural conformations but different in chemical and electrophoretic properties.

The four polypeptide chains of mammalian hemoglobin are individually linked with one heme group. Hemoglobin exists in several forms, made up of various combinations of six different peptide chains, designated as a, β, gamma (y), delta (δ) and zeta (ζ) and epsilon (ε).

About 90%of the normal adult hemoglobin (HbA) consists of two a and two β chains and is designated as HbA. The subunits of various human hemoglobins are given in Table 19.6.

Table 19.6: Subunit composition of human hemoglobins.

Embryonic hemoglobin	Subunits
Hb Gower 1	$\zeta_2 \varepsilon_2$
Hb Gower 2	$\alpha_2 \varepsilon_2$
Hb Portland	$\zeta_2 \varepsilon_2$
Fetal hemoglobins	
HbF	$\alpha_2 \gamma_2$
Adult hemoglobins	
HbA	$\alpha_2 \beta_2$
HbA_2	$\alpha_2 \delta_2$ (a minor variant of adult-hemoglobin).

19.3.2 Hemoglobin gene Clusters

Different hemoglobins are synthesized in different stages of development: embryonic hemoglobins are followed by fetal hemoglobin present in the developing foetus and is normally displaced by adult haemoglobin within six months after birth.

Each of these hemoglobins consists of two alpha type (a) and two beta (β) type of chains. The a type genes are clustered on chromosome 16 in human and the β-type genes on chromosome 11 (Figure 19.3).

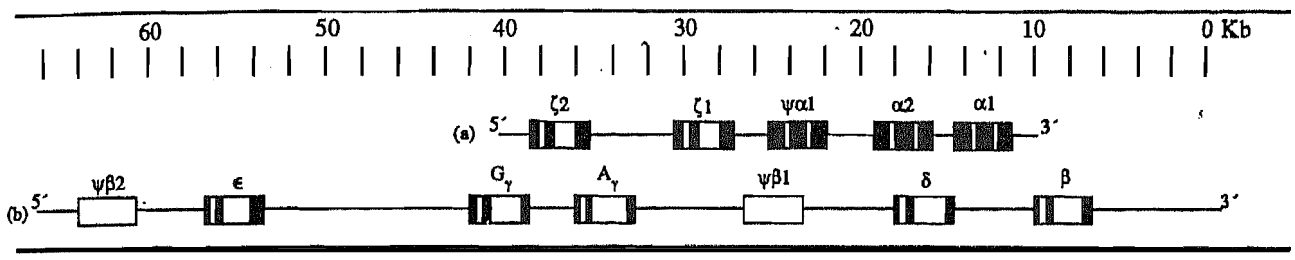

Fig. 19.3: Gene clusters of different chains of haemoglobin.

In the a - cluster, the gene for embryonic zeta(ζ) chain appears before two genes for a-chains, which are components of both fetal and adult hemoglobins. Both the a and β gene clusters contain pseudogenes represented by symbol psi (ψ). These sequences are homologous to adjoining genes but they do not code for functional products.

In the β - cluster, the gene for the embryonic epsilon (∈) chain is followed by two genes for fetal β chains, and then by the genes for the adult chains. Thus, the sequence of the human globin genes matches the order in which they are expressed during development.

A single pair of genes code for a chains and another pair for β chains. There are at least 2 different copies of the genes. One codes for a chain with glycine at position 136 while the other codes for a chain having alanine in the same position.

As is true of various other proteins, all the four hemoglobin polypeptide chains are synthesized separately prior to their union as tetramer. Generally, proteins formed from two or more polypeptide chains are controlled by adjacent genes. This is not the case with hemoglobins, since the two genes are not even on the same chromosomes. As noted earlier, the duplicate pair of alpha genes is on chromosome 16, and the beta gene cluster is on chromosome 11.

SAQ 3:

i) State whether the following statements are True (T) or False (F).

a) Human hemoglobins are proteins with'four subunits. [ ]

b) Heme contributes to the pigmentary property and performs chief respiratory functions. [ ]

c) The a - type genes are clustered on chromosome 16 and β -type gene on chromosome10. [ ]

d) The sequence of the human globin genes does not match the order in which they are expressed during development. [ ]

ii) Match the items in column I with those in column II

Column I		Column II	
a}	HbA	i)	$\alpha_2 \gamma_2$
b)	HbA_2	ii)	$\zeta_2 \varepsilon_2$
c)	Hb portland	iii)	$\alpha_2 \beta_2$
9	HbF	iv)	$\alpha_2 \delta_2$

iii) Hemoglobin exists in several forms made out of six different peptide chains. The six different types of polypephide chains that go to form different forms of haemoglobin are:

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19.4 BLOOD GROUPS AND MEDICINE

There are many applications of blood groups in medicine. Their involvement in blood transfusion and organ/tissue transplanlation is well documented. Blood group markers in conjunction with other parameters are being emplolyed in paternity disputes. The complications of pregnancy and blood group-related disorders are some of the other examples of the role of blood groups in clinical sciences.

19.4.1 Blood transfusion

The discovery of blood types (A, B and O) and Rh factor along with many advances in immunohematology provided the immunological understanding required for modern and safe transfusion of blood. Parallel advances in the techniques of drawing, storage and administration of blood have also helped in the transfusion process.

Ideally a recipient should be transfused with exactly the same type of blood as his own. Table 19.4 shows the interchangeability of the blood groups in transfusion indicating clearly that group O persons are universal donors due to the absence of A and B antigens on their erythrocyte surface which could react with anti A or anti B antibodies in the serum of the recipient. Since both the A and B antigens are present as surface antigens and no antibody against A or B in their serum, the group AB persons are the universal recipients for blood group A, B, O. Similarly a person with blood type B could receive blood from O or B individual but would react to A or AB donor type blood as a consequence of circulating anti-A antibodies. Table 19.4. shows all the possible donor recipient relationships in blood transfusion reactions for ABO antibody system. One of the most important factors for transfusion therapy is choosing the right material. The development of blood banks has made available the stored whole blood. Its usefulness is limited because of changes that occur on storage. Most blood banks set a limit of 21 days storage for RBC, after which blood is considered unsuitable for transfusion. Leucocytes start

disintegrating even earlier and show very little bactericidal activity by the end of 4th day. Similar is the case with blood platelets unless special precaution is taken in drawing blood. If platelets are required'it is best to administer blood within 24 hours after it is withdrawn.

Fresh whole blood is generally used when the recipient needs RBC in addition to platelets, leucocytes or labile coagulation factors. Plasma is used when the patient does not require any of the formed elements. Stored plasma is most useful in the treatment of shock and hypoproteinemia.

Recently plasma extenders and substitutes like dextran and methyl cellulose have been tried but each has its disadvantages. Also autologous (predonated) transfusion, the process of returning to a person his own blood when needed has been practiced. This has many advantages and eliminates transfusion hazards and possibility of transmitting disease.

Transfusion of blood and blood products represents one of the major advances in medicine. In spite of tremendous progress, a small but significant number of side reactions can be expected in transfusion. If a person whose blood belongs to one of the groups receives a blood transfusion from a donor of another group a hemolytic transfusion reaction can occur. This is due to the serum of the recipient that may agglutinate the cells of the donor or vice versa, which results in hemolysis of erythrocytes and liberation of free hemoglobin from the lysed red cells. Liberation of hemoglobin may cause secondary complications such as jaundice, fever and kidney function impairment. The most important causes of death related to blood transfusion before the advent of AIDS were hemolysis and hepatitis.

SAQ 4

a) Tick mark the correct answer from the alternatives provided:

(1) The Universal blood donor is

i) blood group A,

ii) blood group B,

iii) blood group AB,

iv) blood group Rh,

v) blood group O.

(2) The universal recipient is

i) AB blood group

ii) A blood group

iii) O blood group

iv) B blood group

b) Maternal antibodies capable of crossing the placenta are: (Indicate by (√) mark)

a)	IgA	[ ]
b)	IgG	[ ]
c)	IgD	[ ]
d)	IgE	[ ]
e)	IgM	[ ]

c) Fill in the blanks with appropriate words.

1) The Rh locus is located on ----------.

2) Isoantibody present in type O individuals are predominantly ----------.

3) Group B and O persons contain ---------- antibodies in their sera.

d) Tick mark the correct answers:

Fresh blood is generally used to suply,

1) White blood cells

2) Red blood cells

3) Platelets

4) Complements

19.4.2 Acquired Immune Deficiency Syndrome (AIDS)

Acquired immune deficiency syndorme or AIDS was first recognised in 1981 as a deadly disease and is spreading throughout the world at an alarming rate. The causative agent is human immunodeficiency virus (HTLV-III) that rapidly infects helper T cells resulting in irreversible defects in immune response. You may recall that helper T-cells stimulate the proliferation of B and T cells and as well as macrophages. Anti-HTLV III antibodies can be effectively measured by ELISA technique and hence screening of blood donors can be done, It is important that higher risk population groups (homo/bisexual men and drug addicts) should refrain from blood donation even if blood tested is anti- HTLV-III negative. The virus may circulate in blood in the absence of antibodies. Testing of blood before transfusion for other disease like syphilis, cytomegalovirus (CMV), malaria and other such infections have also been recommended.

19.4.3: Paternity Exclusion

A blood group antigen cannot be inherited by the child unless it is present in either of the parents. This is the basis of blood group tests in paternity disputes. The genotypes and phenotypes of the ABO system are given in Table.

Table 19.7: Inheritance of the ABO blood groups

Allele from one parent	Allele from other Parent	Genotypoe	Phenotype
I^A	I^B	I^AI^B	AB
I^A	I^A	I^AI^A	A
I^A	I^O	I^AI^O	A
I^B	I^B	I^BI^B	B
I^B	I^O	I^BI^O	B
I^O	I^O	I^OI^O	O

From the above table it is evident that an AB man cannot father a group O child. Similarly A group parenfs can not produce a B group child. An AB woman and an A_1 man can not give beirth to a A2 child. Also O-Rh negative parents can not produce O-Rh positive chid. Testing of blood group can only exclude a putative father from fatherhood. This is now generally accepted in courts of law. Testing of

polymorphic antigens, such as HLA antigens is considered usually superior to blood group antigen in paternity disputes.

19.4.4: Maternal - foetal incompatibility and its prevention

Hemolytic disease of newborn (hemolytic anemia) results from the mother's antibodies against fetal red blood cells. Formation of Rh antibodies and antibodies to blood groups A and B may also cause hemolysis of fetal cells due to the maternal antibodies that are of IgG class and thus capable of crossing the placenta. You have read in Unit 18 of this course about the nature and functions of antibodies. In fact ABO immunization during pregnancy occurs more often than Rh immunization, but it seldom results in serious problems. This is because the maternal antibodies are neutralized before they can cause damage to red cells as A and B substances are present in the tissues of the mother including the placental endothelium.

Several types of maternal–fetal blood incompatibilities are known. Among them Rh incompatibility is the most important. If the mother is Rh negative and the father of the fetus is Rh positive, the child may also be positive having inherited the D-antigen from father. Ordinarily there is no mixing of maternal and fetal blood molecules and no exchange between the two circulatory systems by the placenta. However, late in pregnancy or during the birth at the time of parturition, a small quantity of blood from the fetus may pass through placenta. The fetal RBCs which bear antigen D sensitize the mother's WBCs inducing them to form antibodies against antigen D. When this mother becomes pregnant again, the anti Rh bodies in her may cross the placenta and enter the fetal blood causing the cells to clump together. In the extreme case of this situation, known as **erythroblastosis foetalis** the fetal red blood cells are destroyed and the fetus dies before birth. .

The Rh locus is situated on chromosome 1. Rh antigenic determinants may be dependent on interaction between RBC membrane proteins and phospholipid molecule. Rh antigens are controlled by three closely linked allelic pairs of gene, which produce the antigenic determinants C or c, D or d, E or e respectively. The most important is the D atnigen, and RBCs possessing this antigen are Rh positive. Individuals with DD or Dd are Rh positive, whereas dd are Rh negative.

The risk of initial sensitization of Rh negative mothers has been reduced from 10-20% to less than 1% by intramuscular injection of human anti-D globulins within 72 hours of delivery or abortion. This destroys any Rh positive cells that have entered the mother's circulation, well before her own white blood cells could be sensetized. Also the antibodies that have been introduced are also soon eliminated from her body. As a result, when she becomes pregnant again her blood will not contain the anti-D that could harm her baby.

Hemolysis associated with ABO incompatibility is similar to Rh diseases wherein the maternal antibody enters fetal circulation and reacts with A or B antigen on erythrocyte surface. In type A and B individuals, naturally occurring anti-B and anti-A isoantibody are largely IgM, that do not cross placenta. In contrast, isoantibody present in type O individuals are predominantally IgG type and for this reason, ABO incompatibility is largely limited to type O mothers with type A or B fetus. The presence of IgG anti-A or anti-B in type O mothers frequently explains why hemolysis due to ABO incompatibility occurs in first pregnancy without prior sensitization. Incompatibility may also occur due to other minor blood groups.

SAQ 5:

a) Tick (√) the most appropriate answer.

i) Hemolytic disease of the new born occurs when

a) father is Rh-negative and mother is Rh-positive [ ]

b) both the parents are Rh-positive [ ]

c) both the parents are Rh-negative [ ]

d) mother is Rh-negative and father is Rh-positive [ ]

ii) Tick the most appropriate statement

i) The causative agent of **AIDS** is

a) HLV antigens [ ]

b) HTLV-III virus [ ]

c) EBV [ ]

d) Herpes simplex virus [ ]

b) Four babies were born in nursing home at one time. They had the blood groups B, **AB,** O and **A.** The four parents were B and **B, AB** and **O , O** and O ,A and B. Assign the four babies to their correct parents.

	Babies		Parents	
1)	B	(A)	AB and O	( )
2)	AB	(B)	B and B	( )
3)	**0**	(C)	A and B	( )
4)	A	(D)	O and **0.**	( )

c) Which of the following stalements relating to newborn hemolytic disease is/are irrelevant.

1) Injection of anti Rh globulins to an Rh mother soon after delivery of an Rh baby can suppress the formation of anti Rh globulins by the mother.

2) If mother is Rh^+ and newborn is Rh^-, the child becomes toleranl to Rh antigen.

3) The mother forms antibodies against Rh antigen of the foetus if D-antigen is not administered with in 72 hours of the birth of the first child.

19.4.5: Blood groups and diseases

Many years of extensive investigations to ascertain whether a person with a particular blood group is more likely to develop a particular disease has indicated some relationship between blood groups and diseases. The evidence have not been conclusive in view of the multifactorial origin of human ailments. The relationship could be summarized as follows:

1. Group A persons are more likely than those of group B or O to develop carcinoma of the stomach or pernicious anemia. Group A persons are more liable to thromboembolic disease. Such persons tend to have higher levels of anti-haemophilicglobulin than others. Anti-A1 in the serum of A_{2a} or A_{2b} persons can cause haemolytic transfusion reactions.

2. Group B or O persons whose sera normally contain anti-A antibodies would tend to have milder small pox than A or AB persons.

3. Non-secretors of group O are more likely to develop duodenal ulcer with increased liability to haemorrhage.

4. An association has been observed between rare Kell groups and some patients with chronic granulomatosus disease (CGD). It is an inherited X-linked defect in neutrophil function, in which there is a higher susceptibility Io infection even by a low grade pathogen. Blood transfusion in CGD patients is a potential hazard since Kell system antibodies react with red cells of almost everyone else. Anti-Kidd antibodies may cause immediate or delayed haemolytic transfusion reactions or hemolytic disease of the newborn.

5. A possible relationship between Duffy groups and malaria has been observed. Persons of group Fy(a^-, b^-) appear to be resistant to *Plasmodium vivax* malaria. This accounts for evaluation of higher incidence of Fy (a^-b^-) in West Africa and resistance of its people to P. *vivax* malaria.

19.5 RACIAL DIFFERENCES

The incidence of blood group antigens varies from one race to another. Most of the surveys have been conducted on ABO system. Their distribution in some selected populations is shown in Table **19.8.**

Table 19.8: Distribution of ABO blood group In selected populations.

Population	Blood group			
	O	A	B	AB
U.K	47	42	8	3
European Gypsies	31	27	35	7
Asiatic Indians	33	24	34	9
Japanese	30	39	22	9
Polynesians	40	56	3	1
Some South American Tribes	100	0	0	0

European gypsies have a blood distribution similar to that of Asiatic Indians, from whom they appear to have originated. Negroid and Mongoloid races have a very high incidence of Rh-positives, whereas Basques have an unusually higher incidence of Rh-negatives. At least three theories have been put forward to explain the racial differences in blood group distribution. These are:

1 Originally there are three human races of groups A, B and O. The present distribution is a consequence of migration and intermarriage.

2. Blood groups arose by mutation from one group, probably O. The exclusive O group of many south American tribes support this hypothesis. The origin of A and B gene has probably been from Europe and Asia respectively.

3. It is a reversal of the second hypothesis and speculates that the original blood group was AB and that A, B and eventually O arose from mutations.

SAQ 6:

i) Fill in the blanks:

1 Population having highest incidence of blood group O is ---- ----------,

2) Origin of A and B genes is probably from ---------- and ---- ----------.

3) Blood groups A, B and O probably arose from ----------.

4) Negroid and Mongoloid races have a high incidence of ----------

ii) Fill in the blanks:

1) Persons with blood groups ------- are more likely to suffer from carcinoma of stomach, pernicious anemia and thromboembolic diseases.

2) Persons of group Fy (a^-, b^-) are resistant to ---- ----------malaria.

3) Non-secretors of group O are more likely to develop ---- ----------.

4) Group B and O persons suffer mildly from small-pox due to ----------.

19.6 SUMMARY

- Blood consists of solid elements suspended in the plasma. Hemoglobin is the main functioning constituent of the erythrocytes. **A** group of antigenic substances responsible for major immunological reactions are found on the surface of the erythrocytes. There are at least twenty established blood group systems in man, the so called types.
- Genes coding for hemoglobin a and β chains are clustered on chromosomes 16 and 11 respectively.
- The clinical significance of a blood group system depends on two factors: the frequency of antibodies in the population and their relative potency. The antigens of the blood cells and their antibodies are important in transfusion of blood. Great care is to be taken to be certain that antibodies are not present in the serum of the recipient that might react with the antigens on the red cells of the donors, which would result in the destruction of the transfused cells.,
- The emergence of AIDS as a dreadful disease in transfusion of blood, blood components and coagulation factor emphasizes that the infectious diseases are still the main cause of transfusion complications. Hemolysis and transfusion hepatitis were the most important causes of deaths related to blood transfusion before **AIDS** was discovered.
- The inheritance of a blood group by a child occurs only if it is present in either of the parents and that is the basis of blood group tests in paternity disputes generally accepted in courts of law. **Hemolytic** disease of the new born may be due to incompatibility of Rh, ABO and other minor blood groups.
- The most common cause of hemolysis of new born is transplacental transfer of maternal antibodies that destory fetal erythrocytes. Surveys conducted on the ABO system reveal that the distribution of blood group antigens varies from one race to another.

19.7 TERMINAL QUESTIONS

1. What is hemoglobin and what are its functions?
2. On which chromosome are the hemoglobin genes located?
3. What is autologous transfusion?
4. How will you detect severe hemolysis?
5. What will be the genotype and phenotype of a child with one parent having I^AI^A genotype and the other I^BI^B genotype?
6. What is ABO incompatibility?
7. What are the theories put forward to explain the racial differences in blood group distribution?

19.8 ANSWERS

SAQ 1:

a) 1) Landsteiner

2) Glycosyl-transferases

3) O allele

4) O group

b) (1) -iii; (2) - ii; (3) - i;

SAQ 2:

a) a.

b). i) Kelly system is one of the minor blood groups, sometime associated with transfusion risk and consists of two allelic forms K and k.

ii) Duffy System: **Anti-Fy^a** is a relatively of common cause of hemolytic transfusion reactions. The allelic form was named as Fy^b. Approximately 60% of West African population lacks Fy(a ,b) and receptor for malarial parasite Plasmodium ***vivax,*** hence resistant to **P. *vivax*** malaria.

SAQ 3:

i) a-F, b-T, c-F, d-F.

ii) a-iii, b-iv, c-ii, d-i

iii) α, β, γ, ∂, ε, ζ

SAQ 4:

a) 1) blood group **O,** 2) AB blood group.

b) **IgG;** c- (1), chromosome **1,** (2). Anti-A

3) anti A and anti AB

d) 2 and 3

SAQ 5:

a) (i) d (ii) b

b) **1-B,** 2-C, 3-D, 4-A.

c) **2.**

SAQ 6:

i) 1- South American tribes, 2- Europe and Asia, 3 4- **Rh^+ groups.**

ii) 1-A, 2- ***P.vivax,*** 3-duodenal ulcer and haemorrhage 4- Antibody A.

Answers to Terminal Questions:

1 Hemoglobins are conjugated proteins in which a prosthetic group, heme, is attached to each of four subunits. The **peptide** chain of hemoglobin is responsible for the species specificity of the hemoglobin. Hence, the iron-containing pigment performs the chief respiratory functions and exhibits pigmentary property, but the **globin** fraction plays a role in carrying carbon dioxide.

2. Hemoglobin consists of two ***a-*** type chains and two β- type chains. The ***a-*** type genes are clustered on chromosome 16 and the @- type genes on chromosome 11.

3. It is the process of returning to a person his own blood when needed and is also known as predonated transfusion.

4. In severe transfusion reaction, billirubin, the breakdown product of heme, appears in the plasma, a few hours after the reaction. In acute hemolysis, hemoglobin is bound to albumin to make methemoglobin, which is brown in colour. The hemolysis could be detected by the colour of plasma and urine, determination of hemoglobin in plasma and urine and quantitation of billirubin, LDH and methemoglobin in plasma.

5.

Genotype	Phenotype
I^AI^B	AB

6. In type A and B individuals, naturally occurring anti-A and anti-B isoantibody are largely IgM, that does not cross placenta. Whereas, type O individuals predominately have IgG molecule. For this reason, ABO incompatibility is largely limited to'type O mothers with type A or B fetus. The presence of IgG anti-A or anti-B in type O mothers causes hemolysis in first pregnancy without prior sensitization.

7. Theories are:

   1. The present distribution is the consequence of migration and intermarriage of the original human races of groups A,B and O.
   2. Mutation from one group, probably O, gave rise to other blood groups.
   3. The original blood group was AB and that A,B and O arose from mutation.