physiology

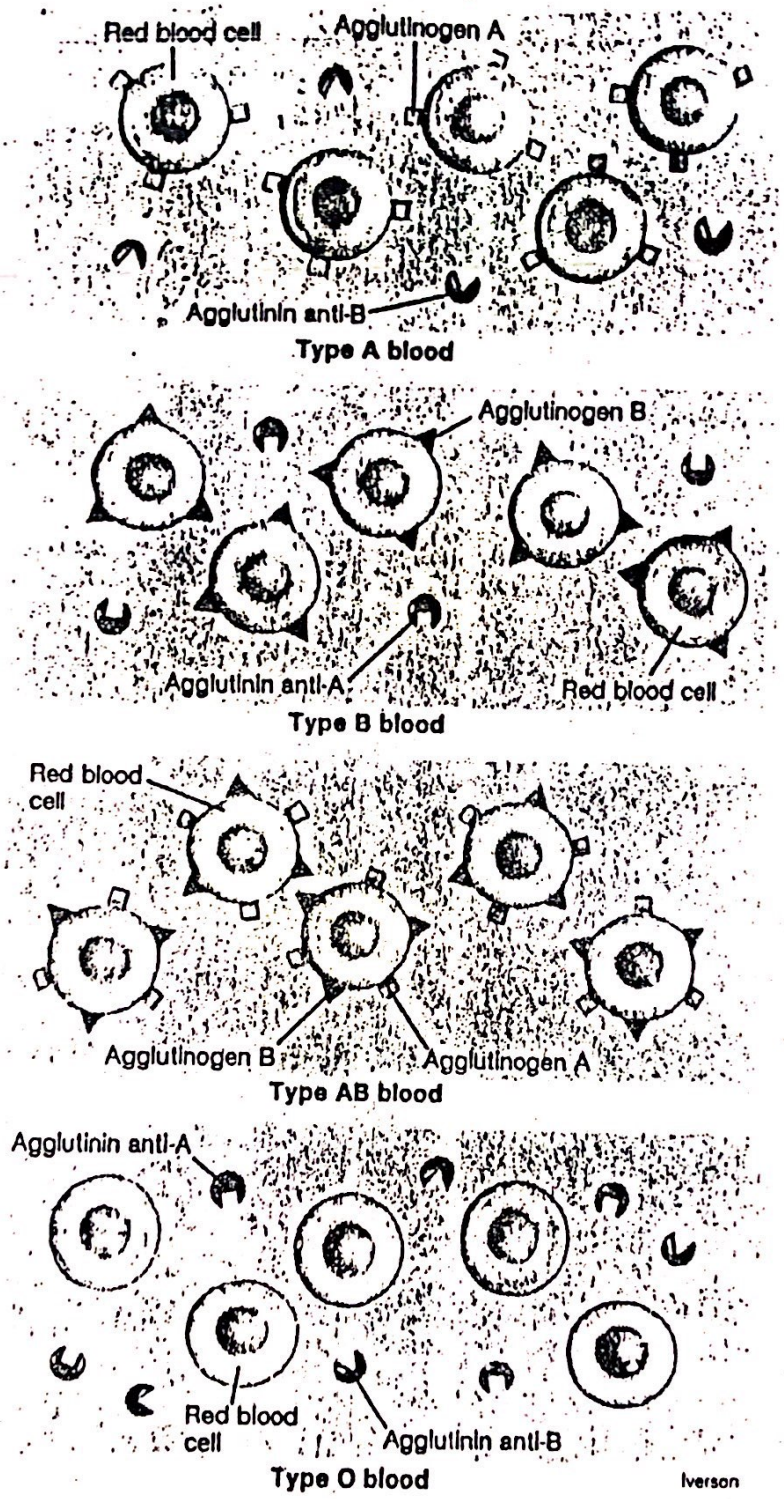

FIGURE 21.16
The antigens and antibodies present in types A, B, AB, and O blood groups.

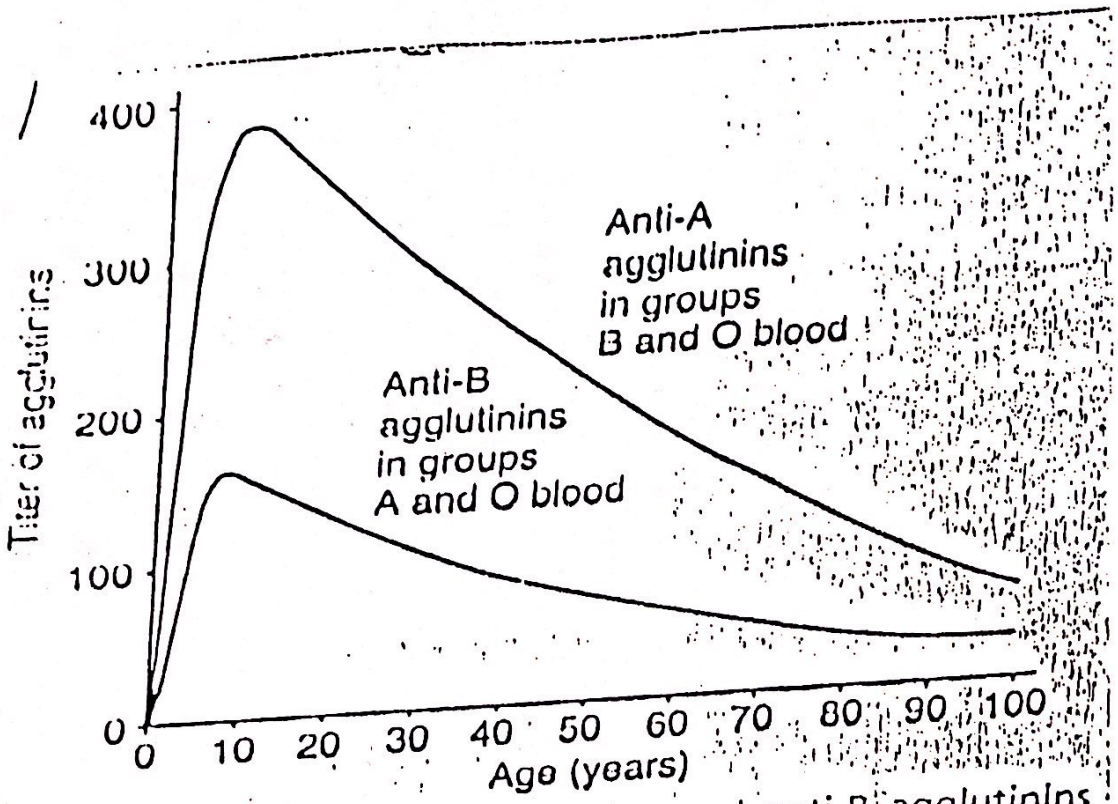

Figure 35–1. Average titers of anti-A and anti-B agglutinins in the blood of people in group B and group A at different ages.

Table 16.1 Racial Distributions of Blood Groups by Percent in the United States*

	A	B	AB	O	Rh+	Rh−
Whites	41	10	4	45	85	15
Blacks	28	20	5	47	90	10
Chinese	28	23	13	36	99	1
Indians (in Utah)	3	0	0	97	100	0
JORDAN*	39	14	8	39	97	3

*Data mainly from A. S. Wiener, *Blood Groups and Transfusion*, 3d ed. Springfield, IL: Charles C. Thomas, 1943.

* Sample of 300 medical Jordanian students.

Fortunately, this disease can be prevented by giving an Rh-negative mother human gamma globulin against Rh-positive erythrocytes within 72 h after she has delivered an Rh-positive infant. These antibodies bind to the antigenic sites on any Rh-positive erythrocytes that might have entered the mother's blood during delivery and prevent them from inducing antibody synthesis by the mother. The administered antibodies are eventually catabolized.

You may be wondering whether ABO incompatibilities are also a cause of hemolytic disease of the newborn. For example, a woman with type O blood has natural antibodies to both the A and B antigens. If her fetus is type A or B, this theoretically should cause a problem. Fortunately, it usually does not, partly because the A and B antigens are not strongly expressed in fetal erythrocytes and partly because the natural antibodies are of the IgM type, which do not readily cross the placenta.

Hemolytic diseases of the newb
incompatibility of Rh blood groups:

Three conditions in which th
develop antibodies:

A. Blood transfusion before
marriage by blood from Rh+
person.

B. leakage during pregnancy of
small amount of fetal blood
(Rh+) into maternal circulation
(placental hemorrhage).

C. during delivery, same blood
squeezed back to maternal
blood.

In these conditions one of the followings hemolytic diseases may occur:

A. erythroblastosis fetalis (mild disease): small amount of RBC,s leak into mother circulation, some mothers develop antibodies against D antigens. These antibodies pass to fetal blood & cause mild hemolysis of the RBC,s of the fetus.

This newborn baby can be rescued by giving him (Rh-) blood, but not from his mother.

Hemolytic diseases of the newborn because the incompatibility of Rh blood groups:

Three conditions in which the mother may develop antibodies:

A. Blood transfusion before marriage by blood from Rh+ person.

B. leakage during pregnancy of small amount of fetal blood (Rh+) into maternal circulation (placental hemorrhage).

C. during delivery, same blood squeezed back to maternal blood.

B. Icterus graves neonatorum (kernicterus) (moderate disease): the infant is born at term, is jaundiced, or becomes so within 24 hours, there may be severe neurological lesions involving the basal ganglia in which the bile pigments deposited.

C. Hydrops fetalis (severe disease). The hemolysis is severe, the infant may die in uterus or may develop severe anemia, Jaundice & edema; dies within few hours.

Blood Transfusion

Indications of blood transfusion:

1. to restore the Blood Volume,
   e.g. in haemorrhage.
2. to provide Red Blood Cells,
   e.g. anaemias.
3. to increase Blood Coagulability in
   haemorrhagic diseases,
   e.g. haemophilia & purpura.
4. to replace infant's blood with Rh.-ve
   blood in erythroblastosis foetalis.
5. to supply antibodies to raise the
   general resistance of the body.
6. to provide White Blood Cells, e.g. in
   leucopenia (= decreased W.B.Cs).
7. to supply plasma proteins in
   hypoproteinaemia.

Complications of Blood Transfusion

Early	Late
Haemolytic reactions immediate delayed. Reactions due to infected blood Allergic reactions to white cells, Platelets or proteins Circulatory overload Air embolism Citrate toxicity Hyperkalaemia Clotting abnormalities (after massive transfusion	Transmission of disease e.g. hepatitis, malaria, syphilis, AIDS. Transfusional iron overload Immune sensitisation, e.g. to rhesus D antigen

Blood transfusion

Blood for transfusion can be kept for several weeks if it is collected from donors under aseptic conditions into sterile plastic packs containing a suitable preservative solution, and it is stored at 4°C. A commonly used preservative, citrate–phosphate–dextrose (CPD) solution, provides citrate as anticoagulant and glucose (dextrose) as metabolic substrate for the red cells. Adequate numbers (i.e. not less than 70%) of red cells remain viable after transfusion when previously stored in CPD solution for 3–4 weeks at 4°C. Adding adenine to the solution can increase this period to 5 weeks.

The plasma may contain antibodies (agglutinins) against the A and B antigens: anti-A or alpha, anti-B or beta. These agglutinins are not present at birth but they appear between the 2nd and 8th month of life, most probably in response to A and/or B antigens taken in food of animal origin, especially meat, and in some bacteria. The anti-A and anti-B antibodies are described as **naturally occurring antibodies**. In the blood of any individual, the antibody present is the reciprocal of the antigen. Therefore, the ABO sys-

Inheritance of blood group: (Table 2.1)

The inheritance of the A and B antigens is dictated by the A and B genes. The O gene does not produce any demonstrable red cell antigen. This is the reason why group A genotype can be AA (homozygous) or AO (heterozygous). Similarly for group B the possible genotype is BB or BO, while for blood group O the only possible genotype is OO. Group AB has both A and B genes and the only possible genotype is AB. Knowledge of these genotypes is useful in working out the probable blood group of an offspring on the basis of the knowledge of the blood genotypes of the father and mother. It is also helpful in sorting out disputed parentage of the child.

The blood groups

On the surface of human red blood cells are found a series of genetically determined glycoproteins and glycolipids that act as blood group antigens. They appear in early fetal life and remain unchanged throughout life. More than 100 blood antigens have been described, out of which at least 15 well-defined red blood cell group systems exist in most racial groups. Of these, only two are of major importance in clinical medicine—the ABO and rhesus (Rh) systems.

MM, MN, NN, PP,

Pp, Kell, Lewis, Kid,

Lutheran, Duffy and many

others.

The rhesus (Rh) blood group system

The Rh system is described on the basis of the presence or absence of the rhesus antigen (D) on the surface of red blood cells. If present, the individual is said to be D-positive or Rh-positive; 85% of Europeans, 90–95% of Arabs and Africans and 98% of Asians are Rh- or D-positive. If absent, the individual is described as D- or Rh-negative.

Table 16.1 Racial Distributions of Blood Groups by Percent in the United States*

	A	B	AB	O	Rh+	Rh−
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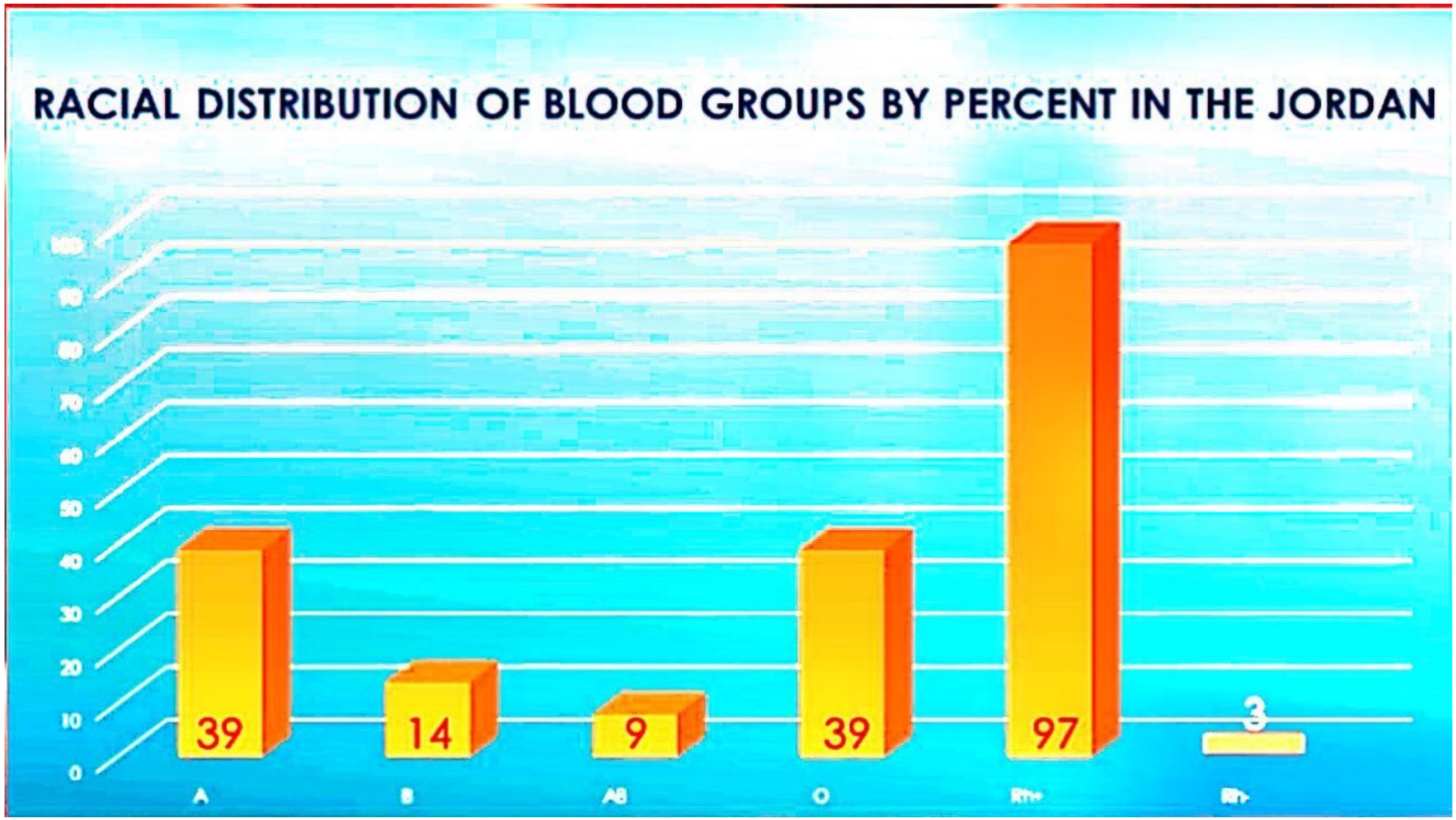


(2) During storage at 4°C, the red cells show a progressive decrease in content of adenosine triphosphate and 2,3-BPG, while with decreased activity of the Na^+–K^+ pump, the cells gradually lose K^+ to the surrounding plasma and gain Na^+ from it. The concentration of K^+ in the plasma may reach values as high as 30 mmol L^{-1} after storage of blood for 4 weeks. The pH of the plasma also decreases with time of storage and its concentration of ammonia rises. These changes can make stored blood dangerous for transfusion in certain patients, e.g. those with renal or hepatic failure. The decline in Na^+–K^+ pump activity makes some red cells spherocytic, with loss of deformability. These effects may be irreversible and after transfusion the abnormal red cells are destroyed very rapidly by macrophages in the spleen and elsewhere. Other constituents of blood do not withstand prolonged storage. Granulocytes begin to lose their phagocytic capacity within 6 h of collection and they are functionally inert after 24 h. Platelets lose their haemostatic effect (p. 310) within 48 h at 4°C, while the labile coagulation factors, V and VIII (p. 314), also rapidly deteriorate in chilled blood.

(2) Before donated blood is made available for issue from a blood-bank, the ABO and rhesus groups of the cells are determined and commonly the serum is screened for atypical antibodies. Serological tests are also done for syphilis, hepatitis and human immunodeficiency virus (HIV). Before transfusion, the ABO and rhesus groups of the patient's red cells are determined, the serum is checked for unexpected antibodies and red cells from the donor are tested against the patient's serum by **cross-matching** tests (compatibility tests). These cross-matching tests are essential for checking that there has been no error in ABO grouping of donor and recipient, and for ensuring that the recipient's serum does not contain naturally occurring or immune antibodies active against the donor's cells.

Transfusion of whole blood is sometimes necessary but, over recent years, the use of cell-separator machines and large-scale production of plasma constituents have made it increasingly possible to transfuse specific components of blood which the patient lacks. Thus **red-cell concentrates**, often resuspended in a small volume of electrolyte solution, are used to restore the haemoglobin concentration in an anaemic patient in whom the plasma volume may already be expanded. **Platelet concentrates** are of use in patients with severe thrombocytopenia (p. 317). A variety of plasma fractions is also available to supply coagulation factors, e.g. **cryoprecipitate**, which is rich in factor VIII and fibrinogen, and for expanding plasma volume, e.g. **stable plasma protein solution**. A useful source of antibodies against common viruses is **pooled normal immunoglobulin** and various specific immunoglobulins are also available, e.g. anti-D and antibodies against tetanus, hepatitis B and diphtheria.

However much care is taken in cross-matching and administering blood, transfusion carries definite risks of unpleasant or even fatal complications. Major red-cell incompatibility can lead to lethal intravascular haemolysis or delayed extravascular breakdown of donor cells. Transfusion of blood contaminated with bacteria can cause profound shock with hyperpyrexia, while allergic reactions to transfused white cells, platelets and plasma proteins can also be severe. Circulatory overload, air embolism and changes in plasma electrolyte concentrations (e.g. hyperkalaemia) may occur and there may be direct transmission of disease, e.g. HIV and cytomegalovirus infections, hepatitis and malaria.

13.9 Blood transfusions and the ABO system of blood groups

Early attempts to restore heavy loss of blood by transfusion of blood from another person were frequently disastrous. The transfused cells aggregated together in clumps which were sufficiently large to block minor blood vessels. This clumping is known as *agglutination*. Following the agglutination reaction, the red cell membranes broke down and hemoglobin was liberated into the plasma (this is known as *hemolysis*). The liberated hemoglobin was converted to bilirubin by the liver and this resulted in jaundice (yellowish skin coloration). In addition, the high plasma levels of bilirubin adversely affected urine production by the kidney. When such clinical signs follow the transfusion of blood the transfused blood is said to be *incompatible* with that of the recipient. Death frequently occurred as a result of the transfusion of incompatible blood.

(2)

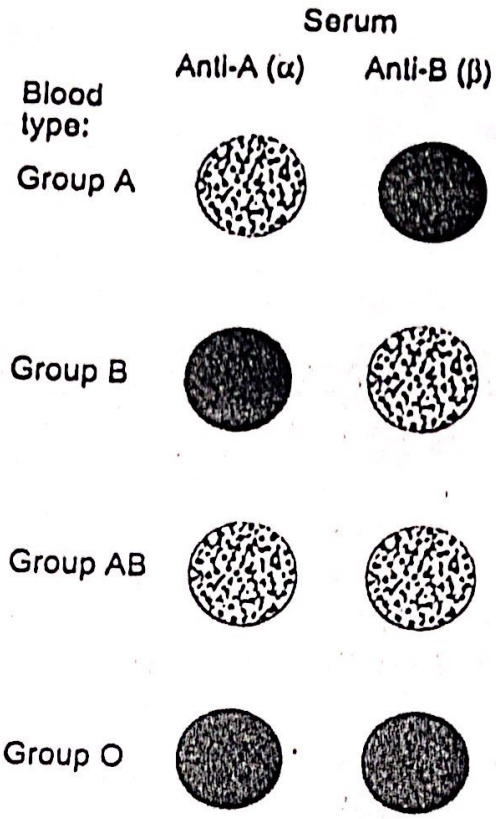


Fig. 13.12 The agglutination reaction of incompatible blood types. Drops of anti-A and anti-B serum are placed in shallow wells on a porcelain plate as shown in the figure. A drop of the test sample of blood is added to each well and mixed. If the blood is compatible, the mixed blood sample appears uniform but, if the blood is incompatible with the serum, it aggregates and precipitates as shown.

(3) What is the basis of this incompatibility and why is some blood compatible while other blood is not? It is now known that agglutination results from an antibody–antigen interaction. Normal human plasma (and the corresponding serum) may contain antibodies that cause red cells to stick together in large clumps (i.e. to agglutinate; Fig. 13.12). The antibodies that cause the reaction are known as *agglutinins*. Unlike most other antibodies, the agglutinins have not arisen as a result of a specific antibody reaction. They occur naturally and are inherited by mendelian laws. Clearly, if red cells agglutinate in response to a particular kind of plasma or serum, they must possess the corresponding antigen, which is known as an *agglutinogen*.

(41)

To account for the known cross-reactivity of blood from different people, Landsteiner proposed that two kinds of agglutinogen are present on human red cells. These agglutinogens are called A and B and they may be present separately, together, or be completely absent, so giving rise to four groups: A, B, AB and O (Table 13.5). In addition, human plasma may contain antibodies to one or both agglutinogens. The plasma antibodies are known as anti-A and anti-B or as agglutinins α and β. Where the blood contains red cells with a particular agglutinogen, the corresponding agglutinin is absent from the plasma. Thus people with agglutinogen A on their red cells do not have anti-A in their plasma as they do not agglutinate their own blood. Nevertheless, this group of people do have anti-B in their plasma. Conversely, group B have agglutinogen B on their red cells but anti-A in their plasma. Group AB have both agglutinogens A and B on their red cells but no agglutinins in their plasma and group O have neither agglutinogen but both anti-A and anti-B agglutinins. Table 13.5 gives the relationships between the different groups and their approximate frequency of occurrence in the general population of the United Kingdom and United Sates.

(5) The rhesus blood group system

In 1940 Landsteiner and Wiener found that the serum of rabbits that had been immunized against the blood of rhesus monkeys could agglutinate human blood. Using this antibody they identified two groups in the general population. Those whose blood could be agglutinated by this serum, now known as rhesus (or Rh) positive (about 85 per cent of the population), and those whose blood could not be agglutinated—Rh-negative. Rh-positive persons have a specific antigen on their red cells known as the D-antigen (also known as the rhesus factor).

Since the D-antigen is inherited like the AB agglutinogens, anti-Rh antibody can occur in the serum of Rh-negative mothers who have had Rh-positive children. During pregnancy a Rh-negative mother may form anti-Rh antibodies in response to the leakage of fetal red cells into her circulation. This immunization of the mother by the baby's red cells may occur at any time during pregnancy but is most likely to occur when the placenta is separating from the wall of the uterus while the mother is giving birth. For this reason anti-Rh antibodies generally arise

(6)

after the first or second pregnancy. The anti-Rh antibodies are IgG antibodies of about 150 kDa and are sufficiently small to pass across the placenta into the fetal circulation. If this happens, they may cause a severe agglutination reaction. The resulting disorder is known as hemolytic disease of the newborn and, in the absence of suitable preventative measures, it occurs about 1 in every 160 births. As indicated above, this problem usually arises during a woman's second or third pregnancy. About half of the affected babies will require a partial replacement of their blood by transfusion. This problem can be avoided by injecting Rhesus negative mothers with anti-D immunoglobulin immediately after delivery. This neutralizes any Rhesus positive fetal red cells that may be present in the maternal circulation.

Although hemolytic disease can occur as a result of an anti-A antibody in the blood of group O mothers, ABO blood group incompatibility generally causes no problems during pregnancy. This reflects the fact that the plasma agglutinins are IgM antibodies of high molecular weight (about 900 kDa) and proteins of this size do not readily cross the placenta.

7

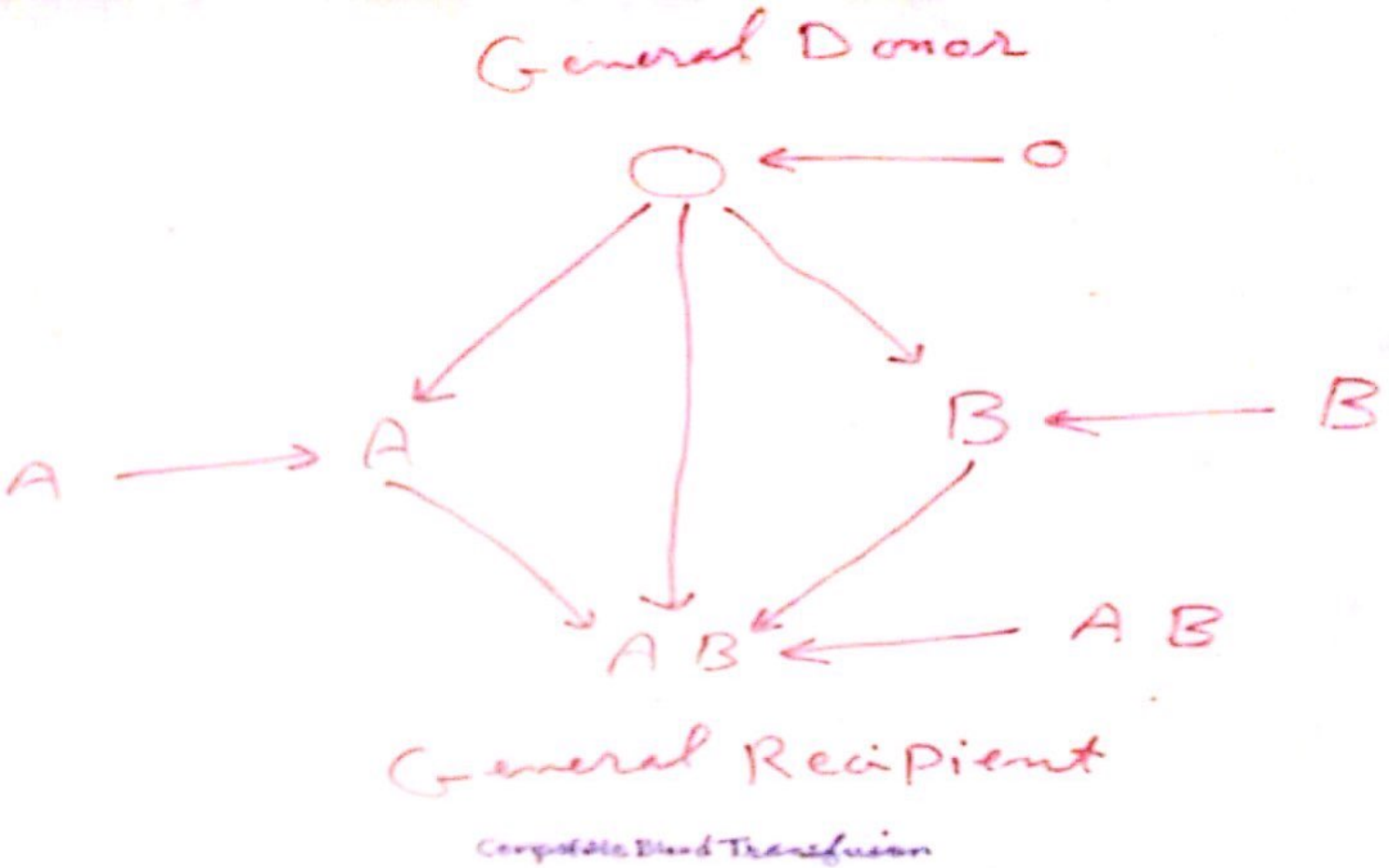
Other blood group types

The blood group antigens (agglutinogens) are found on the surface of the red cell membrane and many kinds of antigen have been discovered in addition to the fundamental ABO system. For example, soon after the original description of the ABO system of blood groups it was discovered that group A could be further subdivided into two groups: A_1 and A_2. Other blood groups such as the M, N, P, and Lewis groups are also known. Nevertheless, the A_1 and A_2 subdivisions and other blood groups are not generally of significance in blood transfusion.

(8)

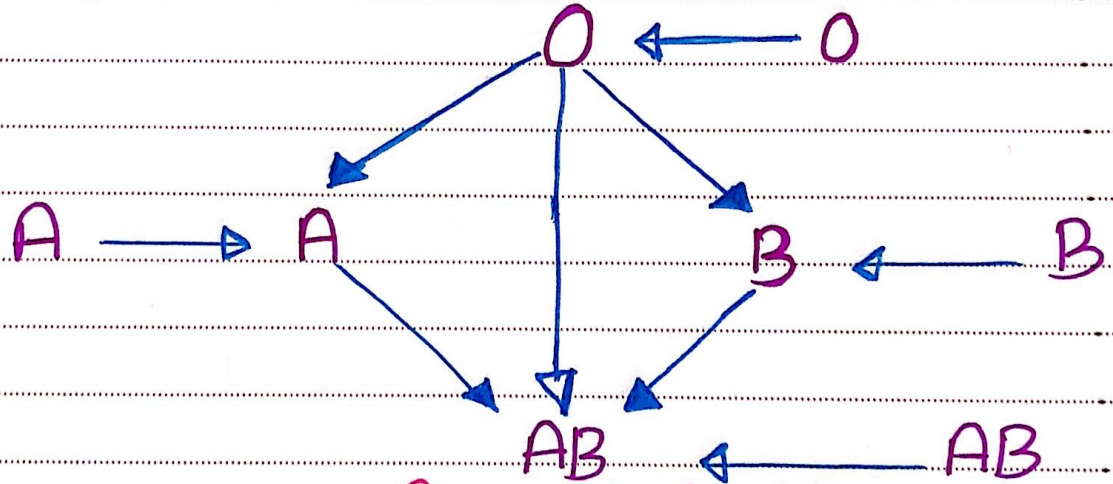
Blood must be cross-matched for safe transfusions

To prevent the problems of blood group incompatibility, blood for transfusion is *cross-matched* to that of the recipient. In this process, serum from the recipient is tested against the donor's cells. If there is no reaction to the cross-match test, the transfusion will be safe. Note that *this test screens for all serum agglutinins and not just those of the ABO system.* Although correct matching of blood groups of both donor and recipient is preferable, in emergencies group O blood can be transfused into people of other groups because group O red cells have neither A nor B antigens. For this reason a group O person is sometimes called a *universal donor.* As the plasma of group AB has neither anti-A nor anti-B antibodies other blood groups can be transfused into a group AB patient. Such a patient is known as a *universal recipient.* The plasma agglutinins present in the blood of a donor do not generally cause adverse reactions because they become diluted in the recipient's circulation.



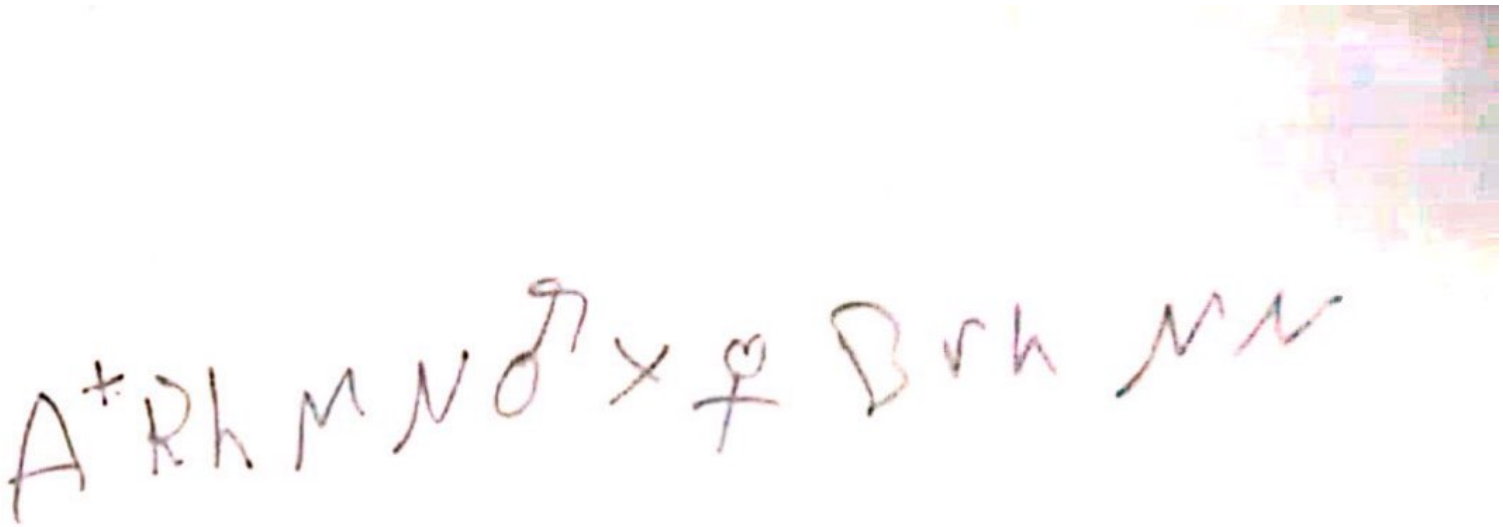
Compatible Blood Transfusion

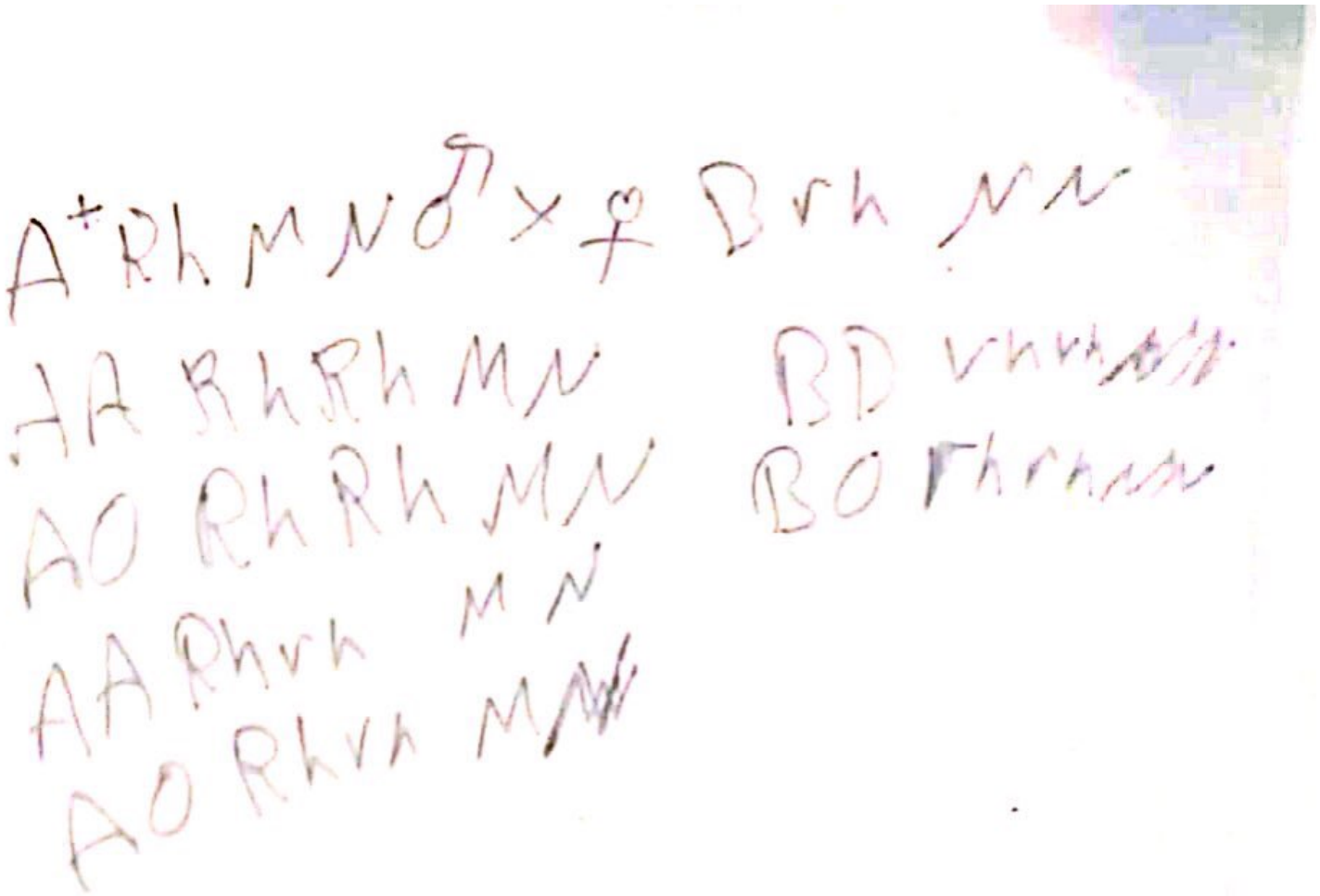
General Donor



General Recipient

* Compatable Blood Transfusion.





♂ X ♀

A^+ Rh MN B rh NN

AA Rh Rh MN
AO Rh Rh MN
AA Rh rh MN
AO Rh rh MN

BD rh rh NN
BO rh rh NN