IMMUNOLOGICAL REACTIONS TO BLOOD AND BLOOD PRODUCTS

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It is estimated that approximately one-third of all blood transfusions are given during anaesthesia (Van Dijk and Kleine, 1976), and improved cross-matching techniques have reduced the frequency of adverse reactions to less than 2%. Most of these reactions are caused by immunological phenomena (Ahrons and Kissmeyer-Nielsen, 1968), and their frequency is shown in table I.

TABLE I. Distribution of transfusion reactions according to Ahrons and Kissmeyer-Nielsen (1968)

<table>
<thead>
<tr>
<th>Transfusion reaction</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunological reactions</td>
<td></td>
</tr>
<tr>
<td>Febrile reaction</td>
<td>75.40</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>13.62</td>
</tr>
<tr>
<td>Delayed haemolytic reaction</td>
<td>3.76</td>
</tr>
<tr>
<td>Immediate haemolytic reaction</td>
<td>1.10</td>
</tr>
<tr>
<td>Total</td>
<td>93.88</td>
</tr>
<tr>
<td>Non-immunological reactions</td>
<td></td>
</tr>
<tr>
<td>Overload</td>
<td>1.99</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.55</td>
</tr>
<tr>
<td>Citrate intoxication</td>
<td>0.81</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1.77</td>
</tr>
<tr>
<td>Total</td>
<td>6.12</td>
</tr>
</tbody>
</table>

All blood cells possess inherited antigens; their pattern is specific for any individual or groups of individuals, and remains constant throughout life. Although the majority of the antigens were first recognized in association with blood cells, it is now evident that many of them are also found in other tissues and in body fluids, and specific antigens have been demonstrated in plasma. Antibodies against blood cell or plasma antigens are usually formed when an antigen not present on the cells or in the plasma is introduced parenterally. There are, however, a few naturally occurring antibodies which are regularly found in human serum without any obvious previous exposure to the corresponding antigen. Most of these antibodies, whether naturally occurring or immune, are either IgM or IgG immunoglobulins.

However, occasionally IgA antibodies may be found. Naturally occurring antibodies are "cold" antibodies, the in vitro antigen–antibody reaction being stronger at low temperatures, whereas most immune antibodies are of the "warm" type as they react readily at 37 °C.

RED CELL ANTIGENS AND THEIR ANTIBODIES

Since the discovery in 1901 of the ABO blood group antigens and their corresponding antibodies, numerous other inheritable red cell antigens have been described, and more than a dozen antigen systems have been characterized. There is a very little information about the biochemistry of most of the red cell antigens. The erythrocyte antigen–antibody interaction is usually detected by haemagglutination techniques, whereas soluble blood group antigens in body fluids or tissue extracts are characterized by antibody neutralization tests. Most common blood grouping antisera are derived from human sources. The following description of red cell antigens and antibodies will divide the blood group systems into two major groups: (1) antibodies occurring in the absence of exposure to blood from another person, that is "naturally occurring antibodies" and (2) antibodies that form as the result of blood transfusion or pregnancy, that is "acquired antibodies".

Blood group systems with naturally occurring antibodies

ABO antigens and antibodies. The ABO blood group system was the first to be discovered, and it is still clinically the most important, since all people produce anti-A or anti-B antibodies, or both, when their red cells lack the corresponding antigens. For routine purposes only two antisera, anti-A and anti-B, are sufficient to characterize the ABO antigens. In an AB person neither anti-A nor anti-B is found in the serum, whereas a group O person normally shows anti-A and anti-B activity. A group A person has anti-B antibodies, and a group B person has anti-A antibodies. In some cases it may be useful to distinguish between A₁ and A₂ types and the additional
use of anti-A1 antisera allows further division of the AB blood group into A1B and A2B: thus the classical ABO system consists of six phenotypes: O, A1, A2, B, A1B and A2B. It is now recognized that group O red cells can be agglutinated by a specific antiserum called anti-H. The H antigen is present in the red cells of all blood groups, but there are significant quantitative differences between the different groups and the highest antigenicity is being found in blood group O. Antibodies with H specificity occur as weak cold agglutinins, and they do not normally represent a transfusion hazard. The very rare O_h (Bombay) phenotype lacks the A, B and H antigens, thus a potent anti-H as well as anti-A and anti-B are found in the plasma. If a patient of the Bombay type requires blood transfusion, the only compatible donors are persons of the same rare type.

The Lewis blood group system. The Lewis system is a complex blood group system with many obscure features in its genetics and serology.

The presence of these antigens on the erythrocyte is an expression of plasma antigens absorbed by the red cells. The antibody specificity is often complex, and some of the Lewis antibodies can cross-react with antigens of the ABO system. The presence of anti-Le^*^ is an uncommon potential transfusion hazard. Only about 20% of Caucasian donors are Le^a^ (a^+^/b^—^). Not all of these have anti-Le^b^ in their serum, and this antibody is only weakly reactive. About 5–6% of donors are Le (a^—^/b^—^).

The P blood group system. Five phenotypes of the P antigen are known. About 75% of the population possess the antigens P_1^ and P on their red blood cells, thus they do not have serum antibodies against the P system. Twenty-five per cent have only P on their red cells, and correspondingly show anti-P_1^ activity in their serum which is often only detectable at relatively low temperatures and is usually of no clinical importance. The remaining phenotypes of the P system (P_1^k, P_2^k and p) are extremely rare. However, when they are demonstrated, compatible blood donors are difficult to find.

The MNSs blood group system. Nine phenotypes are known (MS, M_Ss, Ms, MNS, MNSs, MNs, NS, N_Ss, Ns). The antibodies anti-M, anti-N and anti-S are usually naturally occurring antibodies; whereas anti-s never occurs without previous sensitization. The frequency of the various phenotypes varies considerably within different racial groups. Transfusion reactions caused by MNSs incompatibility are extremely rare.

Blood group systems associated with acquired antibodies

Allo-antibodies* are formed in response to transfusions or pregnancy. They usually belong to the IgG class. The two major factors determining the frequency of formation of allo-antibodies are the population distribution of the antigens and their immunogenicity.

The Rhesus system. It is now evident that the Rhesus system is a highly complex blood group system with a large number of different antigenic determinants. The present confusion in the nomenclature of the various antigenic determinants reflects ignorance about the biochemistry and physiology of the antigens. In Europe the Fisher–Race nomenclature is currently widely accepted, in which the five major determinants are called D, C, E, c, e. It was suggested that the Rh loci carry three genes, for instance CDe, cde, CDE or other combinations. Since each parent contributes one chromosome, numerous genotypes can be found. The most frequent genotypes are CDe/cde, CDe/CDe, cde/cde, CDe/cDe, cDe/cde, cDe/cde and CDe/cDe (Race et al., 1948).

These combinations represent the gene frequencies in British subjects and are similar for other Western European populations. Other ethnic groups have different frequencies. The D antigen is the most important Rh determinant, since it has the strongest immunogenic capacities. Fifteen per cent of the Caucasian population lack the D antigen on their red cells (Rh negative) and they have a 50% chance of becoming sensitized after a single transfusion of Rh-positive blood. Anti-D antibodies are found in approximately 80% of subjects who have received repeated transfusions of Rh-incompatible blood. The antigens C, c, E, e are far less immunogenic. Blood donors and patients are initially only typed with anti-D, and if found D-negative, they are additionally typed with anti-C and anti-E. There are some quantitative Rh variants that can cause laboratory confusion. The D variant D^null^, often found in black individuals in the complex CD^e/cde, reacts much more weakly with the usual anti-D antiserum. This antigen is best detected by the indirect antiglobulin test. Another variant is the Rh^null^ phenotype which fails to react with any of the antibodies specific for Rh antigens. Rh^null^ red cells usually are associated with

* Allo-antibodies are formed in response to the introduction of a human antigen (allo-antigen) into a recipient. Auto-antibodies occur without obvious exposure to a foreign antigen, that is they are produced in their subject in response to auto-antigens.
membrane defects leading to haemolytic anaemia (Sturgeon, 1970).

**The Kell system.** In approximately 9% of Western Europeans the Kell antigen can be found in the red cells (K-positive). The K-antigen, which has several phenotypes and variants, is highly immunogenic in the 91% of the people who lack the K determining gene. Anti-Kell can cause severe transfusion reactions as well as haemolytic disease of the newborn. The Kell blood group system is very complex, and contains a large number of antigens (for example Kp\textsuperscript{a}, Kp\textsuperscript{b}, Js\textsuperscript{a}, Js\textsuperscript{b}).

**Other blood group systems.** Many other blood group systems have been described. In routine laboratory practice the Duffy and the Kidd systems are important because severe transfusion reactions can occur, and yet the antibodies may be difficult to detect. The I\textsubscript{i}, Lutheran and the Xg systems as well as the so-called “private blood group antigens” are further examples of the serological complexity of the human blood groups.

**LEUCOCYTE AND PLATELET ANTIGENS AND ANTIBODIES**

Antibodies against antigens present on leucocytes and platelets are of clinical interest when they develop in patients after multiple blood transfusions, since they can give rise to transfusion reactions, even causing a fatal outcome (Felbo and Jensen, 1962). It is now well established that leucocytes contain antigens, the most important belonging to the HLA system. At present more than 40 HLA antigens with different antigenic specificities have been characterized showing considerable differences in their racial distribution. The HLA antigens form the major human histocompatibility system, since they have been found on a wide variety of tissues, as well as blood cells. Besides the HLA system, B lymphocyte and neutrophil specific antigens have been described (Lalezari and Radel, 1974; Winchester et al., 1975). A more detailed description of the HLA system and other white cell antigens is far beyond the scope of the present review, and the interested reader is referred to a more recent review on this subject (Bodmer, 1978).

Platelets possess most of the HLA antigens, and clinically these are the most important in antiplatelet transfusion reactions. Antibodies against platelet-specific antigenic determinants are occasionally demonstrated in mothers of infants with neonatal thrombocytopenia and in patients after multiple transfusions. These antibodies can sometimes be the cause for unexplained transfusion reactions. Sensitization to leucocyte and platelet antigens during pregnancy explains why transfusion reactions occur more frequently in women (Hattler et al., 1966; Pineda, Taswell and Brzica, 1978).

**PLASMA ANTIGENS AND ANTIBODIES**

Since a considerable polymorphism of some of the plasma proteins exists, it is possible that a recipient of a blood transfusion develops allo-antibodies against antigenic determinants of plasma proteins which are not present on his own proteins. Antibodies with immunoglobulin and \(\beta\)-lipoprotein specificities have been identified in patients after multiple blood transfusions. Occasionally febrile transfusion reactions have been attributed to incompatibility of plasma antigens. It appears that these reactions are rare and normally only of minor severity. An important exception is the presence of anti-IgA antibodies in patients with either a lack or severe deficiency of IgA. It has been calculated that the prevalence of total IgA deficiency in a normal population is between 1 in 500 and 1 in 700 (Bachmann, 1965). Thus, the chance of sensitization in these individuals by multiple transfusions is appreciable and severe anaphylactoid reactions have been observed. Antibodies against clotting factors may be found in patients with congenital coagulation disorders. Approximately 10% of haemophiliacs and patients with Christmas Disease develop inhibitors to Factor VIII or IX after transfusion of plasma or clotting factor concentrates.

**TRANSFUSION REACTIONS**

As indicated in table I, immunological mechanisms underlie most reactions, which can be either the immediate or the delayed type. In anaesthetic practice the immediate transfusion reactions are most important since they occur during administration of the blood or shortly thereafter. Delayed reactions usually develop days or weeks following the transfusion. The clinical features of the immediate transfusion reaction may range from a febrile response to anaphylactic shock. They may be a result of a haemolytic reaction or sensitivity to leucocytes or platelets. Pyrexia during blood transfusion may be caused by a variety of other unidentifiable factors and the clinical decision to discontinue a blood transfusion may be difficult. Allergic reactions are considered to be mainly caused by incompatibility of plasma proteins, and the clinical picture may range from urticaria to anaphylaxis.

In anaesthetic practice a generalized bleeding tendency and the inability to improve a shock syndrome by further blood transfusion frequently represent the
clinical signs of a severe immediate transfusion reaction caused by haemolysis. If a haemolytic reaction is suspected, it is essential to stop the transfusion immediately, because the severity of the reaction is proportional to the amount of incompatible blood given. Haemorrhage and renal failure are predominant features of the haemolytic transfusion reaction. Disseminated intravascular clotting (DIC) is considered to be the major pathogenic mechanism; clot-promoting material derived from the lysed red cells as well as antigen–antibody complexes are the possible triggers for DIC (Goldfinger, 1977). The diagnosis of intravascular haemolysis is invariably based on the appropriate laboratory tests, which should include a clotting screen as well as a repeat cross-match.

**Haemorrhagic diathesis associated with transfusion reactions**

As outlined above, haemorrhage is one of the symptoms of the acute haemolytic reaction, and may be the result of a consumption coagulopathy caused by the intravascular activation of the clotting mechanism. Thrombocytopenia, abnormal clotting screening tests and fibrin degradation products in the serum are predominant laboratory findings. However, there are other mechanisms leading to haemorrhage during blood transfusion, and an accurate laboratory diagnosis is essential for correct therapeutic measures. The anaesthesit should be aware of the fact that the most common cause of local bleeding is improper surgical haemostasis. Post-transfusion purpura is also a rare complication and occurs exclusively as a delayed transfusion reaction. Antibodies to transfused platelets may occasionally cause thrombocytopenia by interaction of the patient’s own platelets with antigen–antibody complexes. Stored blood contains only trace amounts of Factor V and VIII. Thus deficiencies of these clotting factors may be encountered after massive transfusion.

**Prevention of transfusion reactions**

Despite the enormous increase of our knowledge about immunological mechanisms in blood transfusion and advances in laboratory techniques, the use of blood or blood products still carries a risk for the recipient. The hazards of transfusion therapy could certainly be minimized if clerical errors or incorrect identification of the patient were ruled out. Anyone involved with the preparation or administration of blood or blood products has to pay attention to minute detail. In addition, there are a few basic practices which should be observed:

1. To avoid bacterial contamination, the blood should always be stored in controlled refrigerators with an outside temperature recorder and an alarm system.
2. Before requesting blood, the history of past transfusions, pregnancies, previous transfusion reactions and drug intake should be given.
3. Whenever possible, adequate time must be allowed for screening of the patient’s serum for antibodies.
4. Non-cross-matched blood should only be requested if essential. The patient’s own group should preferably be used rather than blood of the group O Rh-negative. However, if there is any doubt about the patient’s group or history of transfusions, O-negative blood should be used until the patient is retyped and compatible blood is available.
5. Some antibodies are detected by complement fixation tests (for example, anti-Lewis), therefore fresh serum, in which the serum complement concentration is adequate, should be sent to the laboratory. Patients receiving regular blood transfusions should be carefully screened for antibodies at 2–3-day intervals. Some laboratory problems may be encountered if serum from patients receiving certain types of dextran is used.

It is evident that knowledge of blood group serology and the use of various blood products has made major surgical procedures easier. However, as there are still problems arising out of the extensive use of these products, they should not be used indiscriminately.

**ACKNOWLEDGEMENT**

The advice and criticism of E. Lloyd, F.I.M.L.S., in preparing this manuscript is gratefully acknowledged.

**REFERENCES**


