The author presents an in-depth discussion of the immune system and immunohematology. The signs and symptoms of transfusion reactions are given, and steps to avoid and/or treat such reactions are presented.

The complexity of the immune system makes it a very difficult area to study and an even more difficult one to understand. However, the tremendous influence that the immune system has on other body systems makes such an understanding essential. This article presents a review of the components of the immune system and discusses the responsibility of the immune system in transfusion reactions.

The immune system's complexity rivals that of the nervous system. It has a communication system which is, in many respects, more sophisticated than the nervous system's communication network. The immune system functions in a manner very similar to the endocrine system in the sense that it acts by way of circulating components which achieve their goals at sites which may be quite distant from their points of origin. The greatest difference between these two systems is that the immune system's components act on the basis of recognizing their "targets" as foreign substances (antigens). The ability of these circulating components to recognize a substance as foreign, to remember this identification on a later exposure, and to react almost immediately to this second encounter is what makes the immune system such a unique and versatile arrangement. Finally, the immune system's complexity gives it a remarkable degree of flexibility. The system usually has more than one pathway by which it can respond to an antigen.

A great deal of research is being done in all aspects of immunology; this immunologic research is helping to explain and treat many disease states and clinical disorders. One such disorder is the blood transfusion reaction. The anesthetist is frequently consulted on questions regarding blood transfusion and fluid therapy, and is continuously making decisions within these two areas of clinical practice. Therefore, it is especially important that the anesthetist understand the mechanisms involved.

**Blood transfusion reaction**

Transfusion reactions are most likely to occur when a massive transfusion is given. Massive transfusion has been defined as transfusing an adult with 500 ml of blood over a period of five minutes or less, or transfusion of one-half the total blood volume within one hour. One-half the total blood volume of a 70 kg male would be approximately four and a half units of whole blood. Some examples of cases when massive transfusion may be indicated include: extensive trauma, esophageal varices, perforated gastric ulcers, expected surgical loss (such as during a Harrington rod instru-
mentation procedure), and unexpected surgical loss (such as that due to accidental laceration of the aorta).

It should be noted that reactions occurring during massive transfusion are more frequently caused by hypothermia and other problems than to immunologic reactions. However, during massive transfusion, it is occasionally not possible to give properly crossmatched blood, and therefore, an immunologic reaction is an appropriate consideration.

Transfusion reaction is obviously most likely to occur when uncrossmatched blood is given. This would only be done in the gravest emergency. In such a situation, type O Rh negative blood is the safest blood to give. Fortunately, improvements in blood banking and in the collection of donor blood makes these reactions relatively rare occurrences. Even with proper typing and cross-matching, however, reactions can occur. The mechanism for reaction with crossmatched blood will be discussed later in this article.

Overview of the immune system

The immune system is composed of genetic, molecular, and cellular components. Macrophages and lymphocytes are the main cellular components. Macrophages are accessory immune cells. They phagocytize and process antigens, converting them into more immunogenic substances. Macrophages also secrete certain chemical mediators which regulate the response of lymphocytes (both T and B which are the two types of lymphocytes found) by either increasing or decreasing cell division and differentiation. Finally, macrophages determine which T lymphocytes will be stimulated to respond to a particular antigen.

Unlike macrophages, lymphocytes behave in an antigen-specific manner, acting in response to stimulation of specialized receptors on their surfaces. Although B and T lymphocytes arise from stem cells in the bone marrow, B cells develop their characteristics under the influence of the bone marrow and bursa-equivalent structures, and T cells develop under the influence of the thymus.

T lymphocytes may serve in either a regulatory or an effector capacity. Regulatory T cells may either amplify or suppress responses of other T cells or responses of B cells, and are named helper or suppressor cells depending on which function they perform. Effector T lymphocytes may be responsible for delayed cutaneous hypersensitivity responses, rejection of foreign tissue grafts and tumors, and elimination of virus infected cells.

Cytotoxic lymphocytes, or killer cells, are active in these effector responses.

B lymphocytes are the precursors of antibody-forming cells and are responsible for the memory phenomenon of the immune system. The circulating immunoglobulins (IgG, IgA, IgM, IgD, and IgE) are all synthesized and secreted by cells which arise from B cells. Immunoglobulins are humoral mediators for the immune system just as the T lymphocytes are the cellular mediators.

The IgG class of immunoglobulins constitutes approximately 75% of all serum immunoglobulins. Only IgG can cross the placental barrier; and it is the IgG class of immunoglobins which protects the newborn from infection during his first months of life. IgG is also one of the classes of immunoglobins capable of fixing serum complement. (Complement activation will be discussed later in this article.)

IgA is the most common immunoglobin class in body secretions. It primarily serves as a topical defense at certain excretory sites. IgA provides protection for internal body surfaces and cavities by means of its presence in saliva, tears, bronchial secretions, nasal mucosa, prostatic fluid, vaginal secretions and the mucous secretions of the small intestine. IgA comprises approximately 15% of all serum immunoglobulins.

IgM comprises 10% of total immunoglobulins and is probably the most important class of all in terms of blood reactions. IgM is frequently involved in early immune responses and it is predominant in naturally occurring immune reactions. This type of response is usually converted to an IgG class responsiveness within weeks to a few months after exposure. IgM, like IgG, is capable of fixing complement.

IgD is found in serum in only trace amounts (0.2% of total serum immunoglobulins). Although the exact function of IgD is not known, it has been suggested that it may be involved with differentiation of B lymphocytes. Additionally, a relationship has been suggested between IgD and antibody activity toward insulin, penicillin, milk proteins, diphtheria toxoid, nuclear antigens, and thyroid antigens. There are many research projects in progress attempting to relate IgD to immune activity against these antigens; however, the exact purpose and function of IgD remains unknown.

IgE is the smallest class of immunoglobulins, comprising only 0.004% of all serum immunoglobulins. Yet, it has an extremely important function in human immunology. IgE is primarily involved with sensitization reactions of the skin and respiratory tract. When IgE antibodies combine
with certain antigens, subsequently called allergens, these antibodies cause mast cells to release a chemical mediator which then activates the "allergic response." ⁷

The activities of the various cells of the immune system are largely coordinated by cell interaction genes, and a very complicated set of regulatory interactions exists between all components of the immune system. Genes and molecules may act as specific antigen receptors on the surface of lymphocytes. The circulating antibodies perform certain effector functions, exert feedback regulation, and regulate interaction between cells. They also include molecules which enhance or suppress lymphocyte functions.¹

The complement system, mentioned earlier, is the primary humoral mediator of antigen-antibody reactions. This system is composed of a chain of 20 different serum proteins which are able to interact with each other, with antibodies, and with membranes or cell walls of antigenic cells. The end result of a chain of such interactions could be lysis of bacteria or red cells, anaphylaxis, or inflammation. There is a conventional (classic) pathway for such interactions; or, if the classic pathway is blocked, an alternate pathway exists.⁸ The complement system is one of the most outstanding mechanisms the immune system has for achieving its remarkable degree of flexibility.

### Blood groups and blood transfusion

From both an immunologic and infectious standpoint, the hazards of blood transfusion have been greatly reduced in the last decade, due largely to improvements in blood banking and blood collecting procedures. Blood transfusion has, in fact, become a relatively “routine” procedure. However, the immunologic risks cannot be totally eliminated. In order to understand the hazards involved, it is necessary to first understand the various blood groups.

The term blood group refers to a system of red blood cell antigens controlled by a locus, a specific area on a chromosome within the nucleus of the cell. Each locus contains a variable number of allelic genes controlling the antigens which are found on the cell membrane. Human red blood cell membranes contain more than 300 different antigenic determinants.⁷ The chemical structures of some of these antigens are well understood: but the structure of many of the more recently discovered types can only be theorized. The clinical importance of each of these groups depends on the frequency with which the antigen occurs and its relative potency.

**ABO group.** The ABO group was the earliest blood group to be studied. The ability of serum from one human to agglutinate red blood cells of another human was first noted in 1901 by Landsteiner. Shortly thereafter, individual types were identified within the ABO group. It was discovered that the serum from a person with group A blood could agglutinate the cells of a person with group B blood, and vice versa. When red cells from a person with group O blood were given to a person with group A or group B blood, the cells were not agglutinated by either sera. Group O blood was later shown to contain antibodies to both A and B, and, therefore, the serum of a group O person could agglutinate transfused A, B, or AB cells. The last group, AB, has serum which contains no antibodies to A or B.⁹

The antigens which we call A and B are carbohydrates and they are both oligosaccharides. When bound to sphingomyelin, the oligosaccharide forms an essential part of the cell membrane. It is the terminal sugar which determines its antigenic specificity. In the B group, this terminal sugar is galactose; in group A it is N-acetylgalactosamine. In blood group O, no such terminal sugar is present. The group O antigen does not contain a terminal sugar. It has only the last three sugars in the stem (called H substance or H antigen) to which the terminal sugar would be attached (as it is in groups A and B). The H substance consists of N-acetylgalactosamine, galactose, and fucose.⁸

The blood groups themselves are dependent on the presence of allelic genes A, B, and O. These genes are responsible for production of certain transferases which conjugate the terminal sugar to the H substance. In other words, A-gene conjugates N-acetylgalactosamine to H substance and B-gene conjugates galactose to H substance. O gene is unable to produce such a transferase and, therefore, this group has only H antigen. The stem chain is itself dependent on a transferase for its formation. This transferase conjugates fucose to galactose and the production of such a transferase is a genetic trait inherited separately from the ABO system.

Certain rare individuals lack H gene and are thus unable to synthesize H antigen. To further complicate matters, some individuals are homozgyously A, while others are heterozgyous with one A gene and one H gene. It is important that this difference is understood, since individuals in homozygous group A (A₁) produce only anti-B antibodies but individuals in heterozygous group B (A₂) produce both anti-B and anti-A₁.

The chemical structure of these oligosaccharides occurs commonly in nature (such as in substances
derived from intestinal bacteria and some vegetables). By exposure to these naturally occurring carbohydrates, an immune response may be triggered. This initial response is probably responsible for production of anti-A or anti-B in the individual. The isoagglutinins, as anti-A and anti-B are collectively called, are produced by infants within the first few months of life.

Certain individuals, such as those with hypogammaglobulinemia, may have extremely low levels of anti-A or anti-B. Additionally, those individuals who are genetically unable to produce H substance develop anti-H. This means that they are also anti-A\(_1\), anti-A\(_2\), and anti-B, since H is the stem for A and B. If this individual requires transfusion, therefore, it must be of this same very rare type. Absence of H substance is called O\(_b\) or Bombay phenotype.

Since we have established that IgM is the class of immunoglobins most commonly involved with blood reactions per se, it should not be surprising to discover that the isoagglutinins are usually of the IgM class. In cases where a sufficient immunologic stimulus exists, anti-A and anti-B may be produced which is of the IgG class. As mentioned earlier, IgG is capable of crossing the placenta; so a very strong maternal immune response could theoretically cause fetal red blood cell hemolysis. This is but one example of the many areas of immunology currently undergoing research.

Both anti-A and anti-B may cause erythrocyte hemolysis. It is important to remember that these isoagglutinins tend to be stronger in type O persons than in A or B persons. Therefore, it is recommended that minimal amounts of type O plasma be transfused into A, B, and AB individuals. In such instances, an acceptable alternative is the use of type O packed red cells. This is usually only done in an emergency situation when there is not adequate time for crossmatching or when blood of a person's specific type is not available.

The last point which must be made in regard to the ABO group is the Se gene. This gene does not affect antigen formation but it does stimulate the H gene to produce fucosyltransferase in secretory tissues. Eighty percent of the world's population are heterozygously or homozygously Se and are therefore "secretors." Those who are homozygously Se are called nonsecretors because their secretory cells cannot produce H transferase, which means that their body fluids lack H, A, and B antigen activities. In secretors, soluble blood group antigens may be found in saliva, milk, and other body fluids. It is by means of these antigens that proof of blood type can be established in criminal cases where the only evidence may be cigarettes, sweat spots, etc. The only other blood groups which secrete products into saliva are the Lewis and Sd\(_b\) antigens.

**Rh groups.** Most of the early Rh factor research was done on rhesus monkeys, and the name Rh was given in recognition of these early studies. However, the primary researchers were Landsteiner and Wiener and the antigen was later renamed LW, although it is still more popularly called Rh. This particular group is so complex and contains so many different specificities that it is impossible to discuss it in any depth in this article.

In distinguishing the characteristics of blood groups, much depends on whether the individual is homozygously or heterozygously Rh negative or positive. The strongest of these Rh antigens is called D. It is 50 times more likely to produce a response if transfused into a susceptible Rh negative person than either C or E. About 15% of Caucasians lack the D (Rh\(_d\)) antigen and are therefore Rh negative. When transfused with Rh-positive blood just once, the Rh-negative person has a 50% chance of forming antibodies which will cause hemolysis on a second exposure.

Rh antigens only appear on red cells, therefore, sensitization can only occur by exposure to incompatible blood. Anti-D is the most common and the strongest of the Rh antibodies. It may be possible to induce antibody formation by infusing as little as 0.01 ml of Rh positive blood into an Rh negative individual. In contrast to anti-A and anti-B, these antibodies are usually IgG, but an exceptionally strong immunization may induce formation of IgM class antibodies. It is possible to prevent Rh immunization by passive administration of anti-D antibody to Rh negative persons within 72 hours after exposure to Rh positive blood.

**Lewis groups.** The Lewis antigen (Le) contains a stem carbohydrate which is nearly identical to that of the ABH antigens. The presence of the Le gene causes the synthesis of a transferase which conjugates a fucose to N-acetylglucosamine. If a Lewis blood group substance is secreted into saliva or plasma, the antigen formed by the transferase-induced conjugation is Le\(^a\). If the substance is not secreted into saliva or plasma, the antigen is Le\(^b\). Strong anti-Le\(^a\) may cause transfusion problems but anti-Le\(^b\) usually does not. Lewis antibodies are nearly always of the IgM class. Anti-Le\(^a\) and anti-Le\(^b\) are fairly common naturally occurring antibodies, and they are seen most frequently in those who are blood type O.
**Kell system.** The Kell antigen (K) occurs in only 8% of the Caucasian population, but anti-K induced transfusion reactions are still possible. If this antibody is present, it is usually strong and may be detected by Coomb’s technique. In certain situations, however, the Kell antigen may be weakly expressed on red blood cells; in such cases, it may be difficult to detect.9

**Duffy system.** The antigen Fy' is seen in approximately 2% of the Caucasian population. The antibodies to Fy' can only be detected by Coomb’s technique. Anti-Fy' is considered to be a fairly common cause of hemolytic transfusion reactions. This antibody is relatively weak in vitro, and it may be completely missed in compatibility testing. It is interesting to note that 70% of African blacks are Fy' (a+b+) and these same individuals are resistant to the parasitic infection malaria. This is another area of immunology which is currently receiving a great deal of clinical and laboratory attention.9

**Kidd system.** The Kidd antigens are known as Jk" and Jk". Anti-Jk" and anti-Jk" are uncommon, but they do activate complement and in vivo hemolysis of red cells may be very rapid. In the laboratory, anti-Jk" may be very weak and can be detected only by using anti-complement in the Coomb’s test reagent. It has been suggested that whenever hemolytic transfusion reaction occurs after transfusion of blood properly crossmatched using the routine tests, the most likely cause is anti-Jk".7

The blood group antibodies described above are certainly not responsible for all complications of transfusion reaction. In fact, there are many other complications which are overwhelmingly more common. Contamination of blood products resulting in infection, circulatory overload, air embolism, hypothermia, bleeding, and metabolic problems related to massive transfusion occur far more frequently than immunologic reactions.9 However, when immunologic reactions do occur, they can be devastating, and when this occurs during general anesthesia the clinical symptoms may be masked.

**Recognition and treatment of reaction**

The first signs of transfusion reaction in the anesthetized patient may be hypotension, tachycardia, general oozing from the wound and mucous membranes, and urticarial rash. Later, jaundice and oliguria may occur in 5-10% of these patients.8 In the awake patient, the initial signs and symptoms include: fullness of the head, tingling of the limbs, precordial pain, lumbar pain, dyspnea, restlessness, nausea and vomiting, pyrexia, circulatory collapse, tachycardia, bronchospasm and profuse sputum secretion. Later, hemoglobinemia, hemo- globinuria, and oliguria may occur. These symptoms will begin to occur early in the transfusion.9

The first step in treatment of a reaction is obviously to stop the transfusion immediately. After that, maintaining adequate kidney function should be the primary goal of therapy. The renal failure associated with transfusion reactions seems to be due to ischemia, so improving renal blood flow is probably more important than just increasing urinary output. Therefore, replacement of volume with saline solutions, plasma fractions, or albumin will be necessary.9 Furosemide is the diuretic of choice. Dialysis or exchange transfusions may be necessary in more severe cases. Acid/base status should be monitored and corrected, as necessary. Antihistamines may be necessary, but they may aggravate hypotension.9

In cases of anaphylactoid reaction, more rapid measures will be necessary to correct hypotension and bronchospasm. Steroids may also be useful. Symptomatic treatment then remains the proper course of treatment.9

If the reaction is due to leukocyte antibodies, it will usually not occur until after a considerable amount of blood has been transfused. Chills and fever may be the only notable symptomatology. If it is definitely established that the reaction is non-hemolytic, the transfusion may be completed at a slow rate of infusion; however, it is probably wiser to give leukocyte-poor blood.9

**Investigation and treatment.** Once a reaction has occurred, laboratory investigation is essential. For detection of hemolysis the following tests should be made: inspection of color of plasma and urine, plasma and urine hemoglobin, and plasma levels of bilirubin, haptoglobin, lactate dehydrogenase (LDH), and methemalbumin. The tests to detect antibodies include: retyping both the patient’s and the donor’s blood, repeating crossmatches, antibody screening of the patient’s serum, direct antiglobulin on the patient’s cells, tests for cytotoxic white cell antibodies, and determination of the IgA level and tests for anti-IgA antibodies.

All of these tests and observations are directed toward demonstrating hemolysis and identifying antibodies incompatible with the transfused blood. The color of the urine and plasma are examined since the color will change during a severe hemolytic reaction due to free hemoglobin. Plasma hemoglobin must be at least 200 mg/L to be grossly visible (normal is 20-30 mg/L). In severe
hemolysis, hemoglobin binds to methemalbumin, which has a characteristic brownish color. Hemoglobin binds to haptoglobin, reducing haptoglobin levels nearly to zero.9

The serologic tests are also important. It is important to retest pre-infusion samples since the reaction may consume all of the antibodies. The samples should be re-examined for irregular antibodies, and a direct Coombs test should be done on the post-transfusion sample.9

The best way to prevent problems is to carefully check and recheck blood before transfusing it. The patient should be positively identified according to hospital identification procedures. The donor's blood type should be compared to the patient's blood type, and close attention should be paid to the expiration date. The older the blood, the greater the likelihood of transfusion problems. It should be noted, however, that these problems are more apt to be due to acid-base imbalance than to immunologic reactions.

Warming blood, especially when multiple units will be given or when blood is pumped, will reduce transfusion complications.3 Also, the judicious use of blood components, rather than haphazard administration of whatever blood products are available, will greatly reduce the incidence of transfusion complications.9

One of the best methods for reducing the likelihood of transfusion reaction is through the use of autotransfusion. This is only useful in certain limited cases; but, in surgical cases where excessive blood loss is anticipated, the use of a cell-saver type of device intraoperatively or collection of some of the patient's own blood preoperatively can greatly reduce the amount of donor blood required. Transfusion of autologous blood virtually excludes the possibility of immunologic reaction. The only drawback to autologous collection devices is that only cells can be salvaged. Therefore, an appropriate amount of plasma must be transfused in order to prevent hemorrhagic problems.

Identification of high risk patients. One last consideration with regard to prevention of immunologic reactions is recognition of patients who are particularly at risk for transfusion problems. Those individuals with selective IgA deficiency are probably the highest risk group, followed by those with hypogammaglobulinemia and patients who have received multiple blood or plasma transfusions.10

Selective IgA deficiency (serum IgA 0.50 mg/L with normal or increased serum IgG and IgM) occurs more often in those with repeated sinopulmonary infections, some autoimmune diseases (particularly rheumatoid arthritis and systemic lupus erythematosus), or gastrointestinal malabsorption. There seems to be a rather striking geographical distribution of individuals with selective IgA deficiency. The incidence of this disorder is 0.15% in the United States which is an intermediate figure in relation to other countries in the world.10

The greatest problem is the tendency of these people to develop antibodies to human immunoglobins. Antibodies to both IgG and IgM have been reported, but are not as serious as are antibodies to IgA. Severe anaphylactic reactions may occur in patients with anti-IgA when they are given blood products. The anti-IgA antibodies are complement-fixing and may cause serum component levels to fall drastically. The activation of the complement system causes release of vasoactive substances (such as histamine) from basophils and/or mast cells which leads to symptomatology. The classic symptoms of anaphylaxis are then seen: apprehension: chest, abdominal, or lumbar pain; hypotension; marked flushing of the face and neck; dyspnea; cyanosis and wheezing.10

Such problems can be avoided once these patients are detected by screening them thoroughly and by transfusing them only with blood which contains no IgA. Autologous blood may be stored for subsequent administration. Other alternatives include administration of red cells after freezing (washing and deglycerolisation removes residual IgA), and consulting rare donor files in blood banks for donors who also have selective IgA deficiency.10

Conclusion

In conclusion, the blood transfusion reaction is an occurrence which has become relatively uncommon. However, there are some immunohematologic problems that will require more time and research to understand. And, there still exist certain immune reactions due to transfusion which simply cannot be prevented at the present time with current cross-matching techniques. The anesthetist must be aware of the possibility of such reactions and closely monitor all patients receiving transfusions. Studies involving the immune response are still in their infancy, and much remains unknown about all areas of immunology—including that area related to transfusion therapy.

REFERENCES

AUTHOR

Mary F. Jocius, CRNA, received her associate degree in nursing from North Central Technical Institute in Wausau, Wisconsin. She wrote this article while a senior student at the Wausau Hospital School of Anesthesia in Wausau, Wisconsin. Mrs. Jocius is currently a member of the Marshfield Clinic Anesthesia Department and an affiliate to the anesthesia staff of St. Joseph’s Hospital in Marshfield, Wisconsin.