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TEXTBOOK OF MEDICAL LABORATORY SCIENCE

(MEDICAL LABORATORY TECHNOLOGY)



Volume 1

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Volume 2

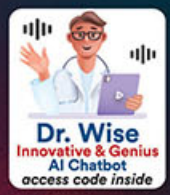
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Ramadas Nayak

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CHAPTER 1

Basic Principles and Applications of Immunohematology

Specific Learning Objectives

After reading this chapter, readers should be able to understand and answer questions related to the following topics:

1. Benefits and Reasons for Transfusion
2. Immune System
3. Immunoglobulins
4. Immune Response
5. Traditional Laboratory Testing Methods
6. Blood Group Antigens
7. Blood Group Alloantibodies and Autoantibodies
8. The Complement System and Blood Banking
9. Major Histocompatibility Complex Molecules
10. Tissue/Organ Transplantation
11. HLA and Transplantation

INTRODUCTION

Transfusion medicine is a multidisciplinary branch consisting of all aspects of blood banking (i.e. blood donation, blood component preparation, blood cell serology, and blood transfusion therapy), immunohematology, transfusion therapy, clinical practice, transplantation science and regenerative medicine. The older term *blood banking* has been replaced by *transfusion medicine* to stress the importance of patient care and clinical outcomes.

Branches

Operationally, transfusion medicine can be divided into blood centers and transfusion services. Blood centers and transfusion services are collectively called *blood establishments*.

- Blood centers collect blood from donors and prepare and distribute blood components.
- Transfusion services perform pretransfusion compatibility testing, select and issue blood components, and provide medical support for blood transfusion.

All blood establishments must be registered with the regulating authority and must have license. Blood cannot be synthesized artificially; therefore, the source of blood is from a healthy human donor.

Blood transfusion is the process of transferring blood/blood products from donor into the circulating system of recipient. It is important to properly collect the blood from donor, prepare its components (if required) and store blood/components in a proper way and transfuse in such a way to avoid any risks or hazards.

- **Immunohematology** deals with the serologic, genetic, biochemical, and molecular study of antigens associated with membrane structures on the cellular constituents of blood (RBCs, WBCs, platelets). It also deals with the immunologic properties and reactions of blood components and constituents.
- **Transfusion medicine** includes the transfusion of blood, its components, and its derivatives.

BENEFITS AND REASONS FOR TRANSFUSION

The indications for the transfusion of RBCs and blood components can be divided into the following four major categories:

1. **Transfusion to restore or maintain oxygen-carrying capacity or hemoglobin** This is done by the transfusion of RBCs with plasma removed, i.e. *packed RBCs*. The most commonly used component is packed RBCs.
2. **Transfusion to restore or maintain blood volume**
   - *Transfusion of whole-blood* is now limited to conditions involving massive resuscitation (severe bleeding during trauma/accidents). This is necessary *to prevent shock in cases of acute blood loss,* as in massive bleeding. May be necessary in pregnancy with bleeding before, during or after delivery. It may be needed during major surgeries (e.g. heart surgery).
   - In **actively bleeding patients** who have *lost more than 25% to 30%* of their blood volume, *RBCs and a volume expander* such as crystalloid (electrolyte) solutions such as 0.9% sodium chloride (isotonic saline) or *thawed plasma* are used.
3. **Transfusion to replace coagulation factors to maintain hemostasis** This is done with a variety of blood components depending on the cause of bleeding. These components include platelet concentrates (platelet disorders) and cryoprecipitate (coagulation factor deficiencies, e.g. hemophilia).

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4. **Transfusion to restore or maintain leukocyte functions** It is rare indication and may be necessary for severely granulocytopenic patients with infections that do not respond to antibiotics.

Immunohematology is the study of blood group antigens and antibodies. Immunohematology involves the immune response to the transfusion of cellular elements that includes red cells, white cells (leukocytes), and platelets. This can potentially initiate immune responses after transfusion. For understanding the principles of immunohematology, it is necessary to know the basic concepts of immunology. These include the antigens, antibodies, antigen-antibody reactions and complement affecting the antigen-antibody reaction. Immunology is an integral part of transfusion medicine.

IMMUNE SYSTEM

Immunity is defined as a resistance (defense mechanism) exhibited by host against invasion by any foreign antigen, including microorganisms.

- The normal immune system is essential for protection against infection. Immune system has an ability to distinguish self from non-self. It rapidly responds to any foreign material or pathogens that invade the body and can initiate a series of events to eliminate these pathogens.
- Immune system is like a double-edged sword. Though it is protective in most of the situations, sometimes a hyperactive immune system may cause fatal diseases.

Types

The immune system consists of two lines of defence, namely innate and adaptive immune response/immunity.

Innate (Natural/Native) Immune Response

Its salient features are:

- *First line of defence present by birth*. It provides immediate initial protection against an invading pathogen. It is triggered by substances which indicate potential danger to a host. These substances common to many pathogens, such as bacterial lipopolysaccharide or viral nucleic acid.
- *Does not depend on the prior contact* with foreign antigen or microbes.
- *Lacks specificity, but highly effective*. No memory, and no self/non-self-recognition.
- *Triggers the adaptive immune response.*
- *No memory* is seen.

Adaptive Immune Response

If the innate immune system fails to provide effective protection against invading microbes, the adaptive immune system is activated. It is characterized by the development of antigen-specific antibody and T-cell responses. Three *characteristic features* are: 1) *specificity, 2) diversity, and 3) memory*. Other salient features are:

- Second line of defense acquired during life
- Capable of recognizing both microbial and nonmicrobial substances
- Takes more time (days to weeks) to develop and is more powerful than innate immunity
- Long-lasting protection
- Prior exposure to antigen is present.

Terminologies used in Immunology

Transfusion medicine needs sound knowledge of antigens and antibodies. For understanding the immune system, it is essential to know some essential terms used in immunology.

- **Antigen (Ag)** Any substance (usually foreign non-self) that is recognized as foreign by the body and *capable of inducing immune response* (antibody formation) in an immunocompetent individual. An antigen molecule binds to an antibody or T-cell receptor.
- **Blood group antigens are present on the surface of red blood cells (RBCs)** There are more than 600 blood group antigens of which only a relatively small number of blood group antigens are clinically important.
  - *Allogenic antigens* Transfused red cells contain antigens and they may be recognized as foreign to the individual receiving the blood and may elicit an immune response in the recipient. These antigens are called *allogeneic* because they are unfamiliar to the individual being transfused but are derived from the same species.
  - *Autologous antigens* Normally, the body's immune system recognizes and tolerates self-antigens. These antigens are called *autologous* because they originate from the individual. When there is failure to tolerate self-antigens, it may produce an immune response against own cells or tissue. This immune response against self is responsible for various forms of autoimmune disease.
- **Immunogen** It is a substance capable of provoking an antibody-mediated immune response when it is introduced in to an immune-competent host to whom it is foreign. The terms antigen and immunogen are often used synonymously. The immune response is initiated by the presentation of an antigen (initiates formation of and reacts with an antibody) or immunogen (initiates an immune response). The term antigen is more commonly used in blood banking because the primary testing is the detection of antibodies to blood group antigens.

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- **Antibody (Ab)** If a foreign antigen is introduced into an immunocompetent individual, a protein produced in response to it is called an antibody. Antibody is an immunoglobulin and is *produced and secreted by activated B lymphocytes (plasma cells derived from B-lymphocytes)* after stimulation by a specific antigen. Immunoglobulin (Ig) proteins consist of two identical heavy chains and two identical light chains. The light chains recognize a particular *epitope* on an antigen and facilitate clearance of that antigen. While all antibodies are immunoglobulins, not all immunoglobulins are antibodies.
  - *Alloantibodies* They are formed in response to antigens from individuals of the same species. These are the type of antibodies involved in transfusion reactions.
  - *Heteroantibodies (xenoantibodies)* They are antibodies produced in response to antigens from another species.
  - *Autoantibodies* They are made in response to the body's own antigens.
- **Immune system** It is a collective term for all the cells and tissues involved in immune activity (host defense system). Included in this system are the cells of the of immune system, the thymus, lymph nodes, spleen, bone marrow, portions of the liver, GI tract and mucosa-associated lymphoid tissue.

Cells of the Immune System

Cells of immune responses (lymphocytes and other cells) migrate among lymphoid and other tissues and the vascular and lymphatic circulations.

1. Lymphocytes are the primary cells involved:
   a. Naïve lymphocytes
   b. T cells
   c. B cells
   d. NK cells
2. Dendritic cells
3. Macrophages

IMMUNOGLOBULINS

Immunoglobulins are a group of serum proteins.

Antibodies

Immunoglobulins for which a corresponding antigen can be identified are called antibodies.

Immunoglobulins which lack corresponding antigen are simply called immunoglobulins and are not antibodies.

Types on Immunoglobulins

There are 5 classes of immunoglobulins designated as IgM, IgG, IgA, IgD and IgE. Of these, IgM, IgG and IgA (rarely) antibodies are produced against RBC antigens and mainly involved in blood group serology.

Structure of Immunoglobulin Molecule (Fig. 1.1)

Immunoglobulin (Ig) consists of amino acid molecules linked by peptide bonds forming amino acid chains.

Heavy and Light Chains

All immunoglobulins share the same basic structure consisting of 4 chain molecules. The basic immunoglobulin unit consist of *two identical heavy chains and two identical light chains* held together by disulfide bonds. Ig molecules

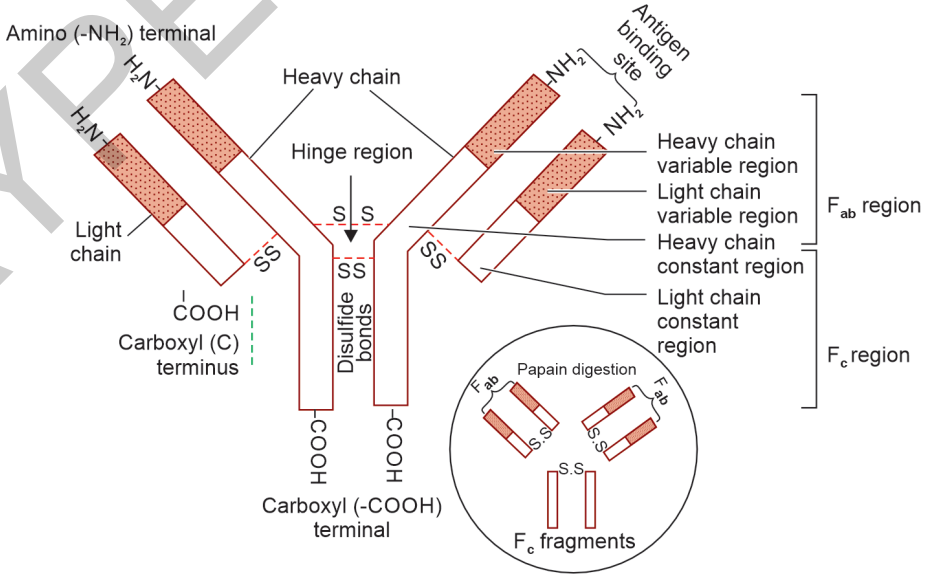


FIG. 1.1 Structure of IgG showing chain structure and interchain disulfide bonds. The inset shows formation of F_{ab} and F_C fragments after enzymatic cleavage of the IgG molecule by papain.

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are proteins and therefore have two terminal regions namely i) the *amino* (-NH_2) terminal and ii) the *carboxyl* (-COOH) terminal.

- **Light chains** The light chains belong to two antigenically different isotypes i.e. Kappa (κ) and Lambda (λ). In any Ig molecule, the two light chains are always identical, being either Kappa or Lambda.
- **Heavy chains** The heavy chains are different for each class **(Table 1.1)**.

IMMUNE RESPONSE

Primary Immune Response

It is the response of the body when first exposed to a foreign antigen. In this, there is a lag period, i.e. the time between exposure to the antigen and appearance of detectable antibody. The antibody that appears in the blood after first contact with an antigen (primary immune response) is always IgM type. After some days IgG becomes detectable. If there is no further exposure to the antigen, the level of circulating IgM antibody peaks and then declines, while IgG antibody persists for longer time.

Anamnestic or secondary immune response Even if the antigen that caused the primary response disappears from the body, circulating T cells and memory B cells continue to persist. When there is a subsequent or second exposure/contact with the same antigen, memory B cells respond more rapidly without any lag period. The memory cells exhibit rapid proliferation of the IgG secreting progeny. This is called anamnestic or secondary response. The IgG response may be as much as 100 times greater than the primary response.

TRADITIONAL LABORATORY TESTING METHODS

Red Cell Antigen-Antibody Reactions

Red cell antigens are located on the red cells and form a part of the cell membrane or protrude from the cell membrane. Red cell antibodies are molecules present in the plasma or serum. The combination of antibody with antigen produces a variety of observable results. Antigen-antibody reactions are important in immunohematology. In blood group serology (immunohematology), the most common reactions are listed in **Box 1.1**.

BOX 1.1 Most common antigen-antibody reaction in blood group serology.

- Agglutination—sensitization and visible agglutination
- Hemolysis
- Neutralization
- Precipitation

Agglutination and Hemagglutination

Hemagglutination is a special type of *agglutination of the RBCs by antibodies*. It produces the clumping of red cells (brings RBCs together and forms a visible aggregate) that results when antibody molecules combine with antigenic determinants on adjacent red cells. Agglutination is the endpoint for most test involving red cells and blood group antibodies. It is the primary and most common reaction

TABLE 1.1 Salient features of antibodies (immunoglobulins).

FEATURES	LGM (MILLIONAIRE ANTIBODY)	LGG (SUBTYPES: LGG1, LGG2, LGG3, LGG4)	LGA	LGE (REAGINIC/ HOMOCYTOTROPIC ANTIBODY)	LGD
Approximately % of total Ig	5%	80% (maximum)	15%	Trace	Trace
Molecular weight	900,000 (maximum)	150,000	150,000–300,000	190,000	180,000
Type of heavy chain	μ	γ	α	ε	δ
Structure	Pentamer (maximum size)	Monomer	Dimer (in glandular secretions), monomer (in serum)	Monomer	Monomer
Complement activation	Yes (classical pathway)	Yes (classical pathway)	Activates alternate complement pathway	No	No
Transport across placenta	No	Yes	No	No	No
Half-life (days)	5	21	6	2	3
Main function	Primary immune response	Secondary immune response Functions as B-cell receptor	Mucosal immunity Highly effective at neutralizing toxins	Allergic diseases, defense against parasite infection and anaphylactic reaction	Unknown

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observed in routine transfusion practice. It occurs in two stages: i) sensitization and ii) agglutination.

- **Sensitization (attachment of antibody)** It is the *simple coating or binding of an antibody on the surface of the red cell antigen* **(Fig. 1.2)**. This does not bring about clumping or agglutination of red cells in saline. Since no visible agglutination is seen, an additional step is needed to produce visible agglutination or to otherwise measure the reaction by the use of i) albumin, ii) proteolytic enzymes, or iii) antihuman globulin reagent.
- **Visible agglutination (due to lattice formation)** It occurs when several RBCs are physically joined together by the union of antigen with antibody **(Fig. 1.3)**. This stage depends on factors (e.g. pH, temperature, and ionic strength of the suspension medium).
- **Enhancement of contact** The use of *proteolytic enzymes (e.g. papain or ficin)* can increase cell-to cell contact of RBCs.
- **Adding antiserum** RBCs sensitized by *incomplete antibodies* (antibodies that will not react in saline) agglutinate when antiserum against human IgG is added (Coombs test).

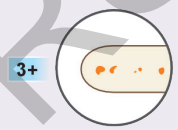
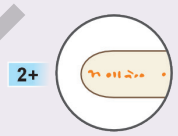
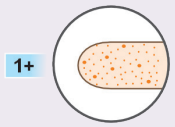
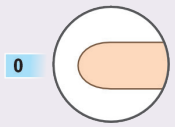
Grading Agglutination Reactions

In immunohematology, antigen-antibody reactions forming red cell agglutination are measured qualitatively. Red cell antigen and antibody reactions may be performed in test tubes, in microplate wells and in microtubes filled with gel particles. An agglutination viewer lamp with a magnifying mirror is usually used for checking the agglutination reactions. Grading and scoring of hemagglutination is presented in **Table 1.2**.

Hemolysis as an Indicator of Antigen-Antibody Reactions

In immunohematology apart from agglutination as an indicator of an antigen-antibody reaction, red cell hemolysis observed in the tube is also indicates the reactivity of an antigen and antibody. Hemolysis is the rupture or breakdown of red cells with release of intracellular hemoglobin **(Fig. 1.4)**. In vitro hemolysis *requires activation of complement cascade.*

TABLE 1.2 Grading and scoring of hemagglutination.

GRADE	APPEARANCE	SCORE	
H	Hemolysis—presence of free hemoglobin in the serum	10	
4+	One solid RBC aggregate	10	
3+	Several medium to large RBC aggregates	8	
2+	Many small to medium RBC aggregates with a clear background	5	
1+	Many small aggregates with a turbid background	3	
+ or w	Few small aggregates with many unagglutinated cells	2	
$+^{-m}$ or $+^{m}$	Aggregates visible only under microscope	1	
0	Negative—absence of aggregates	0	
Mf	Mixed-field agglutination—presence of minor population of agglutinated cells superimposed on a negative background	NA	
R	Rouleaux—nonspecific aggregation appearing like a stack of coins. It disappears when saline is added	NA	

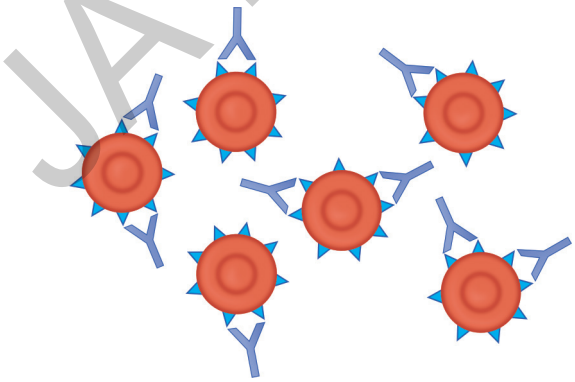


FIG. 1.2 Sensitization of RBCs with IgG.

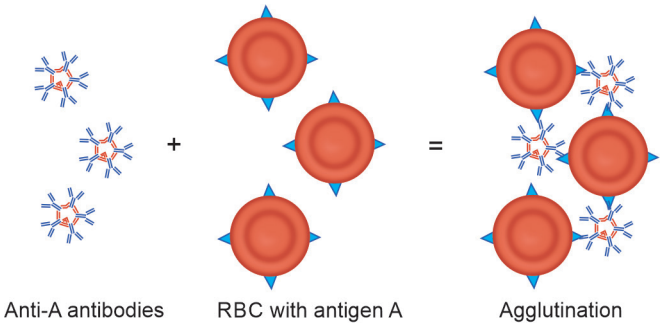


FIG. 1.3 Agglutination is the clumping of red cells together because of interactions with specific antibodies.

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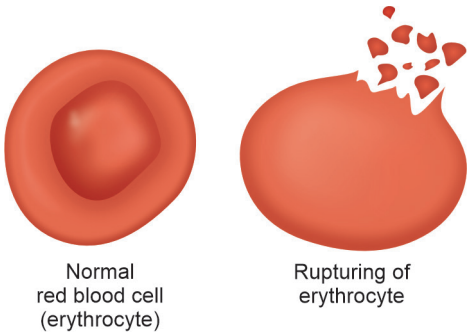


FIG. 1.4 Hemolysis.

The final steps in the process of complement activation initiate the membrane attack complex which produces damage to the RBC membrane. Hemolysis does not occur if the antigen antibody reaction takes place in serum that lacks complement (stored blood) or in anticoagulant that chelates Ca^{++} and Mg^{++} (both Ca^{++} and Mg^{++} necessary for complement activation). Many blood group antibodies on reacting with the antigens on red cells activate the complement and causes destruction of red blood cells.

Hemolysin Antibodies that have the capacity to activate complement on reacting with antigens on red cells are called hemolysins. They cause hemolysis.

Identification In the test system, hemolysis is identified by the *pink or red supernatant fluid after centrifugation of the test mixtures.* IgM antibodies predominantly activate complement while IgG rarely does so.

Note: Testing for hemolysin is mandatory prior to release of the so called universal red cells/whole blood of group 'O' to a recipient with non-O (A, B, AB) group.

Neutralization (Inhibition)

Soluble form of blood group antigens can also combine with soluble blood group antibody. It will result in full or partial neutralization (inhibition) of antibody. There is *no formation of a visible precipitate*. In this reaction, if the strength of the antibody diminishes or if it disappears completely, an antigen antibody reaction can be assumed to have taken place. Missing or weak antigens/antibodies can often be detected with the help of neutralization reactions.

Precipitation

When soluble antibody reacts with soluble antigen and forms an insoluble, usually visible complex, the reaction is called as precipitation. Such complexes are seen in test tubes as a sediment or ring and in agar gels as a white line **(Fig. 1.5)**. Precipitation is the endpoint of procedures such as immunodiffusion and immunoelectrophoresis. Examples for precipitation reactions are VDRL and RPR (rapid plasma regain) tests performed in the blood bank to screen for syphilis.

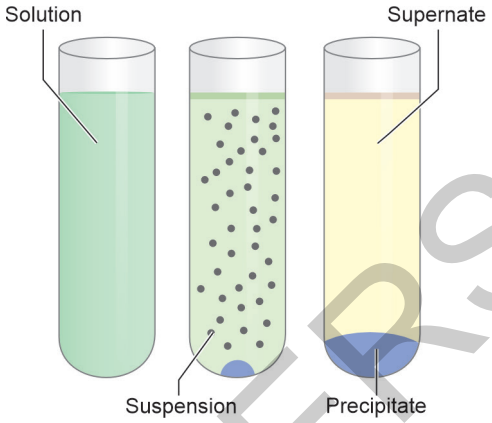


FIG. 1.5 Diagrammatic appearance of suspension and precipitation.

- Antigen and antibody should be present in optimal proportions for the occurrence of precipitation. In ideal reactive conditions, an equivalent amount of antigen and antibody binds.
- **Prozone phenomenon** If there is excess of unbound Ab (immunoglobulin), there will be very few Ag sites to combine with the molecules and the lattice structure is not formed. Ag-Ab complexes are formed but do not accumulate sufficiently to form a visible lattice. An excess of antibody leads to a phenomenon called a prozone. It is important to rule out prozone phenomenon while screening for atypical antibodies like anti-D in a woman giving a sample for indirect antiglobulin test, during antenatal check-up.
- A surplus of antigen leads to a *postzone effect*.

Other techniques which are used to quantify antigen or antibody with the use of a radioisotope, enzyme, or fluorescent label—such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA) or enzyme immunoassay (EIA), Western blotting (WB), and immunofluorescence (IF).

BLOOD GROUP ANTIGENS

The term blood group is not only used for genetically encoded *red cell antigens* but also to the immunologic diversity expressed by *other blood constituents, including leukocytes, platelets, and plasma.*

Location of gene and mode of inheritance Most blood group genes (few exceptions) are located on the *autosomal chromosomes* and their inheritance follows Mendelian laws of inheritance. Majority of blood group alleles also demonstrate *codominance*. In codominance, the products of *both alleles of a gene pair exert* an observable effect and are thus equally dominant (e.g. the alleles A and B of the blood group system ABO; O is recessive to A and B). That means genetic heterozygotes at a particular locus will express both gene.

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Many *membrane-associated structures on blood cells act as antigens* because they are capable of reacting with a complementary antibody or cell receptor. A majority of these antigens are capable of eliciting an antibody-mediated immunologic response and thus are immunogenic (*refer* below). Each antigen can have a variety of different epitopes or specific antigenic determinants. Epitopes are discrete, immunologically active regions of the antigen. The epitopes can interact with specific lymphocyte membrane receptors or secreted complementary antibody.

About a **dozen of antigen systems** are significant and are commonly important in the transfusion medicine. Individuals who lack certain antigens, when exposed to them may form antibodies. These antibodies may be detected on routine testing in the blood bank products.

Immunogenicity

An antigen capable of eliciting an immune response is called *immunogenic*. Blood group antigens greatly vary in their capability to elicit an immune response. The most immunogenic are A, B, and Rh or D antigens. Hence, all blood to be transfused must be matched for these antigens between the blood donor and the recipient. About 50–75% of D-negative individuals would produce anti-D if transfused with only one unit of D-positive blood. Apart from AB and D antigen, K followed by Fy_a antigens is also immunogenic.

BLOOD GROUP ALLOANTIBODIES AND AUTOANTIBODIES

Majority of clinically significant blood group antibodies are IgG or IgM type and occasionally an IgA type.

Classification of Blood Group Antibodies

Blood group antibodies can be classified as:

- **Alloantibody** This reacts with a foreign antigen not present on the patient's own RBCs. Identification of alloantibodies and selection of compatible blood components is the most important functions of a transfusion medicine service.
  - *Naturally-occurring antibodies* These antibodies that are present in our body in the absence of an apparent stimulus. Some alloantibodies to RBC antigens are called naturally occurring. The antigenic stimulus for this is unknown and these antibodies may appear regularly in the serum of persons who lack the corresponding antigen (the ABO blood group system). These antibodies are commonly of IgM type and occur in serum without any specific red cell antigenic stimulus (e.g. anti-A, anti-B, anti-P).
  - *Acquired antibodies* Most blood group alloantibodies are produced as the result of immunization to foreign RBC antigens. The immunization may occur either during previous transfusion of blood components or following pregnancy. These antibodies are usually IgG type. Example include Rh antibodies like anti-D and anti-Kell produced by external sensitization.
- **Autoantibody** It reacts with an antigen on the patient's own cells.

THE COMPLEMENT SYSTEM AND BLOOD BANKING

The complement system, or complement, is a complex group of over 20 circulating serum and cell membrane proteins that play a number of biologic roles. They play most important role in immunohematology in that they are able to lyse the cell membranes of antibody-coated RBCs. They have a multiple function within the immune response. Their primary roles include immune adherence; phagocytosis; direct lysis of cells, bacteria, as well as assisting with opsonization to facilitate phagocytosis. Their peptide fragment split products play roles in inflammatory responses such as increased vascular permeability, smooth muscle contraction, chemotaxis, migration, and adherence. It is often involved in blood group reactions and immunological disorders. Complement plays an important role in the sensitization and destruction of transfused RBCs by alloantibody or the destruction of autologous RBCs by autoantibody. Complement is also important in immunohematologic testing. The complement components are unstable and heat liable. Hence, it is important for serum specimens to be fresh for blood bank testing.

The complement system is a group of plasma proteins synthesized in the liver, and are native precursor components. They are sequentially numbered from C1 to C9. The number refers to their discovery date, not to their activation sequence. The four unique serum proteins of the alternative pathway are designated by letters: factor B, factor D, factor P (properdin), and IF (initiating factor). Complement components circulate in inactive form as proenzymes, with the exception of factor D of the alternate pathway. The cleavage products of complement proteins are distinguished from parent molecules by adding suffixes to their cleaved product (e.g. C3a and C3b).

Pathways of complement system activation (Fig. 1.6)
The complement proteins may be activated in a *cascade of events*. The decisive step in complement activation is the proteolysis of the third component, C3. Cleavage of C3 can occur by any one of the three pathways: the classical, alternative, and lectin pathways.

1. **Classical pathway** It is activated by *antigen-antibody (Ag-Ab) complexes*. The antibodies involved are IgM, IgG1, or IgG3 antibody and gets activated when the

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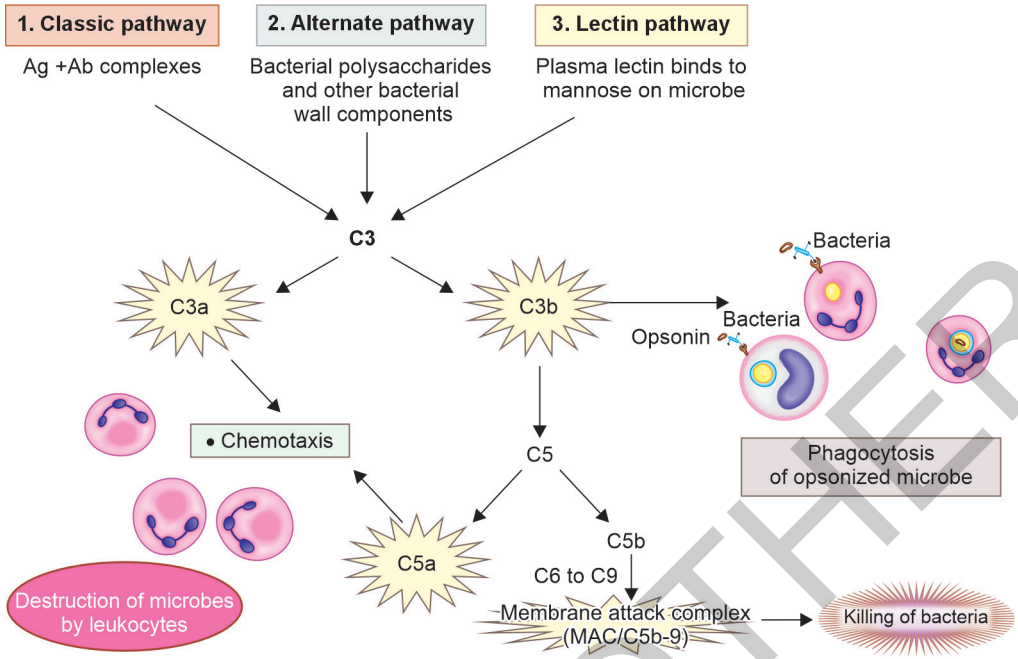


FIG. 1.6 Different pathways of activation and functions of the complement system. All pathways of activation lead to cleavage of C3.

C1 component binds to the F_c portion of the antibody molecule.

2. **Alternate pathway or properdin system** It is triggered by microbial surface molecules (e.g. endotoxin, or lipopolysaccharides/LPS), complex polysaccharides, cobra venom, and other substances and does not require specific antibody for activation. Thus, they get activated *in the absence of antibody*.
3. **Lectin pathway** It directly activates C1 when plasma mannose-binding lectin (MBL) binds to mannose on microbes. MBL in turn activates proteins of the classical pathway.

Binding of Complement by RBC Antibodies

Role of Complement in Erythrocyte Destruction

The reactions that take place from *C5 to C9 are termed the membrane attack complex* and result in lesions on the RBC surface. These lesions allow the rapid passage of ions, and the cell lyses from osmotic pressure changes. When antibody binds to *intrinsic (self) RBC antigens* on the RBC membrane, it activates the complement by classic pathway. Complement may also be activated on RBCs when an *exogenous antigen* (nonself, e.g. drugs like penicillin which acts as hapten) *adsorbed to its cell surface*. For example, penicillin coated RBCs and forms anti-penicillin antibodies.

RBC antigen–antibody complexes usually activate complement by the classical pathway. Antibody-coated RBCs, are removed by cells of the mononuclear phagocyte system.

Intravascular Hemolysis (Fig. 1.7)

Intravascular RBC hemolysis is usually caused by antibodies directed against the ABO antigens. Rarely, hemolysis may be due to other IgM blood group antibodies or some complement-fixing IgG antibodies (e.g. anti-Kidd

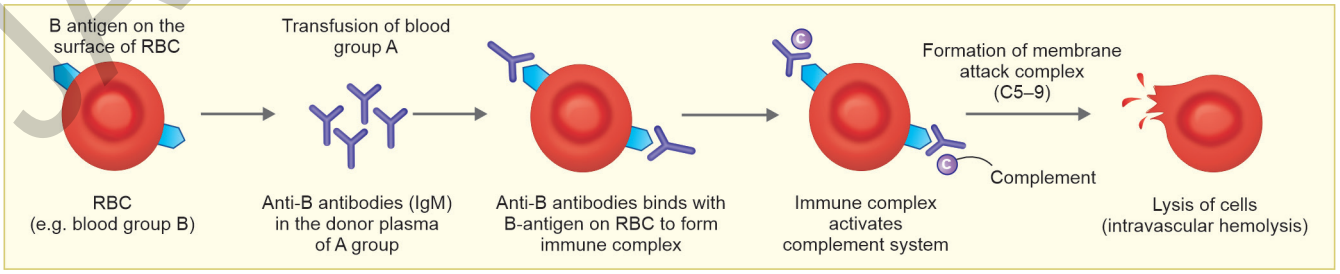


FIG. 1.7 Type II hypersensitivity reaction: Cell lysis through MAC. Binding of IgG or IgM antibody to an antigen promotes complement fixation. Activation of complement leads to formation of membrane attack complex (MAC) which causes cell lysis. Example—transfusion of A group blood to individual with B group.

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antibodies). Intravascular lysis occurs when large amounts of complement are rapidly activated. It results in complete activation of complement cascade and generation of the terminal membrane attack complex (C5–9). This complex polymerizes to form pores in the RBC membrane and the extracellular fluid enters the cell. The RBCs swell and burst by osmotic lysis.

Extravascular Hemolysis

Majority of extravascular hemolysis is due to IgG antibodies against RBC antigen. When IgG antibodies bind RBCs, it activates the complement and the complement-coated RBCs are removed from the circulation and are destroyed in the RE (reticuloendothelial) system such as spleen.

MAJOR HISTOCOMPATIBILITY COMPLEX MOLECULES

Introduction

Survival of an individual depends on defense mechanism consisting of immune system. The immune system recognizes and responds to a various microorganisms and foreign substances (antigens). However, the same defense system has a negative impact when tissue is transplanted from one individual to another, or its malfunctioning may trigger auto-aggressive reactions.

All human cells have a series of molecules on their surfaces that are recognized by other individuals as foreign antigens. The surface antigens or receptors responsible for the recognition and elimination of foreign tissues are *coded by genes in the human leukocyte antigen (HLA) region /complex*. HLA system is composed of a complex array or series of closely linked genes located within the major histocompatibility complex (MHC). Hence, the HLA system (region/complex) is also referred to as the major histocompatibility complex (MHC). It was named HLA because in humans, MHC-encoded proteins were initially detected on leukocytes by the binding of antibodies.

Classification

Protein products of HLA system consists of HLA antigens (MHC molecules). The HLA complex contains about 35 to 40 genes physically densely clustered/grouped/packed into three regions located on small segment on the short arm of chromosome 6 (6p21.3).

HLA/ MHC gene product is classified based on their structure, cellular distribution, and function into *three groups: class I, class II, and class III regions* **(Fig. 1.8)**.

MHC class I and class II gene products are critical for immunologic specificity and transplantation histocompatibility, and they play a major role in susceptibility to a number of autoimmune diseases.

Class I MHC Molecules (HLA Antigens)

Expression of class I antigens Class I MHC molecules are the products of MHC class I genes and are *expressed on all nucleated cells and platelets* (neurons, corneal epithelial cells, and trophoblasts). On mature red cells, only vestigial amounts remain, with certain allotypes better expressed than others.

Class II MHC Molecules

Expression of class II antigens Their expression is more restricted than that of Class I antigens. Class II antigens (HLA-D and -DR, D-related) *are expressed only on professional antigen-presenting cells (B lymphocytes, monocytes/ macrophages, Langerhans cells, dendritic cells), intestinal epithelium and early hematopoietic cells.*

Class III MHC Molecules

Their gene *encode* components of the complement system C2, C4, and Bf), 21-hydroxylase (CYP21), cytokines, heat-shock protein (HSP)70, and tumor necrosis factor (TNF), lymphotoxin and some proteins without apparent role in the immune system.

TISSUE/ORGAN TRANSPLANTATION

The donor HLA class I and class II molecules are recognized by the recipient's immune system as foreign antigens. Hence, it is beneficial to ensure that donor and recipient are histo- (i.e. tissue) compatible (i.e. HLA matched). To increase success rates of transplant, **histocompatibility testing or HLA typing or tissue typing** is done to identify alleles

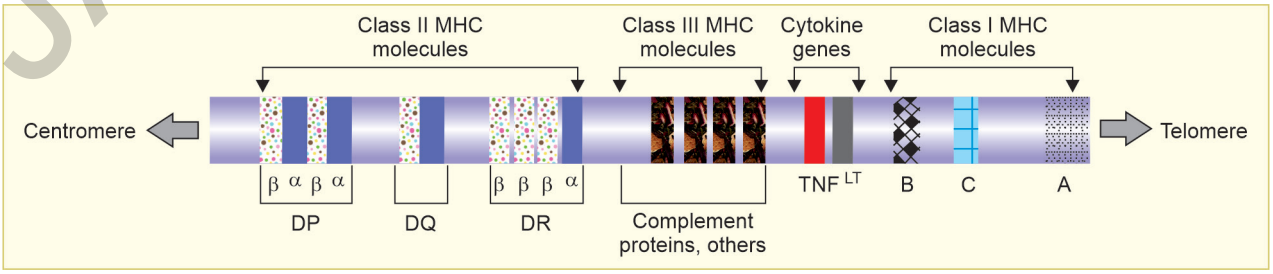


FIG. 1.8 Major histocompatibility complex (human leukocyte antigen complex) showing location of genes.

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at important MHC loci (in lymphocytes) so that potential donors can be sought with a closely matching MHC profile, and drugs are administered that can suppress immune responses. However, MHC polymorphism (i.e. having two or more common distinct genotypes maintained in a population) remains a challenge for successful transplantation.

Transplantation mainly is consisting of solid organ (e.g. renal, heart, lung, liver, and pancreas) and hematopoietic progenitor cell (HPC) transplants. Long-term survival of transplants/grafts is one of the most challenging goals in medical science. Renal transplantation is the therapy of choice for most patients with end-stage renal disease.

Rejection of transplant A major barrier for transplantation in both solid organ and hematopoietic progenitor cell transplantation is immunologically mediated rejection of the foreign tissue. This is because the recipient's immune system recognizes the graft as being foreign and mounts the immunological reactions against it. Hence, the success of allografting depends on the ability to deter the immune reaction.

HLA AND TRANSPLANTATION

HLA and Solid Organ Transplantation

- An important factor that determines the *outcome of solid organ transplantation* (particularly renal transplants) is the *matching for HLA-A, -B and -DR antigens between donor and recipient*. PCR-based techniques can identify the molecular differences between otherwise serologically identical HLA types of donor and recipient pairs (especially in the HLA-DRβ1 chain).
- The graft survival rate is higher in kidney graft survival when recipients and donors are *HLA-DR identical by serological and molecular techniques*, compared to HLA-DR identical by serological but not molecular methods.
- In renal and cardiac recipients, the presence of *circulating HLA-specific antibodies* directed against donor antigens will produce *hyperacute rejection of the graft*. Hence, these antibodies should be detected and identified to ensure that incompatible donors are not considered for transplantation.
- The development of donor-specific antibodies after transplantation is associated with graft rejection. This indicates the importance of post-transplant antibody monitoring for some groups of patients.

HLA and Hematopoietic Stem Cell Transplantation

Acute Graft-Versus-Host Disease (aGVHD)

- One of the main factors associated with the *development of acute graft-versus-host disease (aGVHD) is HLA incompatibility*. This is particularly important when using matched unrelated donors.
- **HLA-identical siblings** HSC transplantation between HLA-identical siblings ensures matching for all HLA-A, -B, -C, -DRB1 and -DQB1genes. However, *acute GVHD still develops in about 20–30% of these patients*. This may be due to the effect of untested HLA antigens, such as DP, or minor histocompatibility antigens which activate donor T-cells. However, there is higher risk of developing GVHD patients receiving grafts from HLA-matched unrelated donors than those transplanted using an HLA-identical sibling.
  HLA matching by DNA-based techniques of patients and unrelated donors has reduced the development of GVHD.

HLA and Blood Transfusion

White cells and platelets present in transfused products express high concentration of HLA antigens. Hence, transfusion of platelets or leukocytes is associated with the risk of immunizing the patient. If patients with intact immune system, need multiple transfusions of whole blood, platelets or leukocytes concentrates, they develop antibodies to HLA antigens. This risk can be minimized by washing or filtering the red cell preparations and by reducing leukocyte contamination as far is possible.

Transfusion Reaction in Recipients

- *Due to activation of T cells in recipient* When HLA antigens of blood donor are not identical to those antigens expressed by the recipient, the donor HLA antigens can *activate T-cells in the recipient*. This in turn may lead to the development of *antibodies and/or effector cells in the recipient against donor HLA antigens*. These can result in some of the serious complications of blood transfusion.
- *Due to antibodies and T cells in donor blood product* The antibodies (and T-cells) present in the transfused (donor) blood product may react directly with the relevant HLA antigens in the recipient. This also can lead to the development of a transfusion reaction.

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KEY POINTS

- When the immune system comes across a foreign substance or antigen for the first time, the innate immune system responds quickly to get rid of the offending organism or toxin.
- The adaptive immune system also called acquired immunity takes longer time to respond to antigen. The adaptive immune system has the additional feature of memory.
- Antigens are foreign molecules that combine with an antibody or immunoglobulin. Red cells, white cells, and platelets have numerous antigens and they can elicit an immune response after exposure from transfusions, pregnancy, and transplantation.
- Immunoglobulins are a group of serum proteins. Immunoglobulins for which a corresponding antigen can be identified are called antibodies. There are 5 classes of immunoglobulins designated as IgM, IgG, IgA, IgD and IgE.
- Traditional methods of detecting antigen-antibody reaction includes agglutination and hemolysis, neutralization.
- Agglutination is the aggregation of particulate matter and is the endpoint of antigen–antibody reactions for blood bank testing. Agglutination is a reaction between antigen and antibody and is a two-step process. The first step is characterized by initial binding of antibody with antigen and is also known as sensitization. During sensitization, antibody binds to antigen on a red blood cell membrane, but agglutination is not observable. Lattice formation is the second step of the agglutination process.
- Hemolysis is the destruction of red blood cells with release of intracellular hemoglobin.
- Genes encoding the expression of the HLAs are part of the MHC found on chromosome 6. There are three classes of MHC namely class I (A, B, C), class II (DR, DQ, DP), and class III complement proteins.
- HLA antigens are inherited as haplotype. They are important in recognition of self and non-self, coordination of cellular and humoral immunity, and the immune response to antigens.

KEY QUESTIONS

REVIEW QUESTIONS

1. Define transfusion and write a note on its benefits and reasons.
2. Discuss immune system in detail.
3. Write a note on immunoglobulins and draw its labeled diagram.
4. Write a note on define and grading and scoring of hemagglutination.
5. Discuss blood group antigens in detail.
6. Write classification of blood group antibodies.
7. Write a note on pathways of complement system activation.
8. Discuss major histocompatibility complex molecules in detail with classification.
9. Write a note on HLA and transplantation.

MULTIPLE CHOICE QUESTIONS (MCQs)

1. *What is a primary benefit of blood transfusion in patients with severe anemia?*
   a. Improvement in bone marrow function
   b. Immediate increase in red blood cell count and oxygen-carrying capacity
   c. Reduction in blood pressure
   d. Enhancement of kidney function
2. *One of the key benefits of transfusing cryoprecipitate is:*
   a. Increasing platelet count
   b. Providing high levels of clotting factors, especially factor VIII and fibrinogen
   c. Treating anemia
   d. Enhancing kidney function
3. *Which type of blood transfusion is most likely to be required in a patient with severe bleeding from trauma?*
   a. Platelet transfusion
   b. Red blood cell transfusion
   c. Plasma transfusion
   d. White blood cell transfusion
4. *Which patient condition is commonly associated with the need for granulocyte transfusions?*
   a. Severe anemia
   b. Neutropenia with infection
   c. Hemophilia
   d. Liver failure
5. *What is one of the main reasons for transfusing plasma in patients with bleeding disorders?*
   a. To provide a source of iron
   b. To replenish blood volume
   c. To replace clotting factors and correct coagulopathy
   d. To reduce blood pressure
6. *Which of the following conditions is a common indication for transfusing platelets?*

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a. Acute myeloid leukemia with thrombocytopenia
b. Chronic kidney disease
c. Diabetes mellitus
d. Severe anemia

7. *Why irradiated blood products be used in certain patients?*
a. To prevent allergic reactions
b. To reduce the risk of transfusion-related acute lung injury (TRALI)
c. To prevent transfusion-associated graft-versus-host disease (TA-GVHD)
d. To increase the shelf-life of the blood

8. *In which situation might a patient require a granulocyte transfusion?*
a. For severe anemia
b. For neutropenia with a high risk of infection
c. For coagulopathy
d. For acute bleeding

9. *What is the necessity of transfusion in a patients on chemotherapy?*
a. To increase platelet production
b. To treat anemia caused by bone marrow suppression
c. To correct electrolyte imbalances
d. To reduce the risk of thrombosis

10. *Which type of transfusion is often used to prevent or treat bleeding in patients with a deficiency of specific clotting factors?*
a. Cryoprecipitate transfusion
b. Red blood cell transfusion
c. Platelet transfusion
d. Granulocyte transfusion

11. *What are the primary functions of major histocompatibility complex (MHC) molecules?*
a. To transport oxygen in the blood
b. To present antigens to T cells and initiate immune responses
c. To regulate blood clotting
d. To synthesize hormones

12. *Which MHC class is primarily involved in presenting endogenous antigens to cytotoxic T lymphocytes (CTLs)?*
a. MHC class I
b. MHC class II
c. MHC class III
d. MHC class IV

13. *Which cells primarily express MHC class II molecules?*
a. All nucleated cells
b. Erythrocytes
c. Professional antigen-presenting cells (APCs) like macrophages, dendritic cells, and B cells
d. Platelets

14. *What is the role of the antigen-binding groove in MHC molecules?*
a. To bind to antibodies
b. To bind to and present specific peptides to T cells
c. To mediate cell-cell adhesion
d. To transport peptides across the cell membrane

15. *Which HLA molecules are most crucial for matching in organ transplantation?*
a. HLA class I molecules
b. HLA class II molecules
c. Both HLA class I and class II molecules
d. HLA class III molecules

16. *What type of immune response is primarily involved in acute rejection of transplanted organs?*
a. Humoral response
b. Delayed-type hypersensitivity (cell-mediated) response
c. Immediate-type hypersensitivity (IgE-mediated) response
d. Complement-mediated lysis

17. *Which cells are primarily responsible for recognizing foreign HLA molecules in a transplanted organ?*
a. B cells
b. Cytotoxic T lymphocytes (CTLs)
c. Erythrocytes
d. Neutrophils

ANSWERS

1. b	2. b	3. b	4. b	5. c
6. a	7. c	8. b	9. b	10. a
11. b	12. a	13. c	14. b	15. c
16. b	17. b			

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