

1. Nature of the Immune System

I. Historical Concepts

A. Introduction

1. **Immunology** defined as the study of the reaction of a host when foreign substances are introduced into the body.
2. **Immunity** is the condition of being resistant to infection.
3. **Serology** is the study of the noncellular components in the blood.

B. Vaccination

1. Purposeful exposure of individual to infectious material.
2. Edward Jenner in 1700s discovered relationship between exposure to cowpox and immunity to smallpox.
 - a. Example of “*cross reactivity*”
 - b. Cowpox and smallpox so similar in structure that the immune substance produced in response to cowpox was then able to protect against smallpox.
3. “**Vaccination**” = “*vaca*” Latin word for cow.
4. “**Attenuated vaccines**” use actual organisms which have been treated in some manner to prevent infection.
5. Louis Pasteur applied this principle of attenuation to a rabies vaccine.

C. Cellular versus Humoral Immunity

1. Researchers observed that foreign substances were removed by specialized cells in a process known as phagocytosis.
2. Other researchers postulated that substances in the blood provided protection from microorganisms, humoral immunity.

D. Age of Serology

1. Time period from 1900 to 1950 called era of international serology.
2. Immunology is a relatively new science.
3. Tests were developed to detect the presence of immune substances in the blood.

II. Natural (Nonspecific , Innate) Immunity

- A. Non-specific pathway: First line of defense
 - 1. First and most important path, concerned with the body's first line of defense against infection.
 - 2. The following are examples of non-specific defense mechanisms:
 - a. Protective mechanical mechanisms, e.g. coughing sneezing, wafting of the cilia lining the trachea and bronchi.
 - b. The presence of substances in secretions which help destroy bacteria, e.g. hydrochloric acid in the stomach, wax in the ears, enzymes in tears.
 - c. Cells capable of destroying foreign material as soon as it enters the body, e.g. circulating white blood cells such as neutrophils, tissue macrophages.
 - d. Circulating substances, e.g. a group of substances known collectively as complement (to be covered later), a substance known as interferon which is important in the prevention of viral infections.
- B. Mechanisms Involved In Non Specific Immunity: First Line of Defense
 - 1. Physical barriers
 - a. intact skin
 - b. mucous membranes
 - 2. Physiological factors
 - a. Hydrochloric acid in the stomach
 - b. Ciliated epithelium lining the respiratory tract
 - c. Flushing action of urine
 - d. Large amounts of unsaturated fatty acids found in the skin.
 - e. Sweat
 - f. Human tears
 - g. Normal commensal flora
 - h. Susceptibility and nonsusceptibility
 - 3. Factors which may modify these defense mechanisms
 - a. Age
 - b. Hormones
 - c. Drugs and chemicals
 - d. Malnutrition
 - e. Fatigue & stress
 - f. Genetic determinants

C. Nonspecific Immunity: Second line of defense

1. **Inflammatory response** - *classic signs are pain, heat, redness and swelling.*
 - a. local dilation of capillaries (hyperemia)
 - b. slowing of the blood flow
 - c. **chemotaxis** - chemicals released which attract phagocytic cells.
 - d. formation of exudate - same composition as plasma and it contains antibacterial substances, phagocytic cells, and drugs and antibiotics, if present.

2. If bacteria are not successfully killed locally, may further invade the host by way of the lymphatics to the regional lymph nodes.
 - a. within lymph nodes the bacteria meet other phagocytic cells (macrophages).
 - b. bacteria may overcome these and gain access to the bloodstream where they meet circulating phagocytes (neutrophils and monocytes).
 - c. may pass through the bloodstream and reach organs such as the liver and spleen where they come into contact with tissue macrophages.
 - d. although a powerful defense system, this final phagocytic barrier may be overcome, with seeding of the microorganism to organs such as bone, brain, and kidney, terminating in fatal septicemia.

3. Phagocytosis
 - a. **Initiation** is caused by damage to the tissues, either by trauma or as a result of microbial multiplication.
 - b. **Chemotaxis**, attraction of leukocytes or other cells by chemicals.
 - c. **Adherence**, firm contact between phagocyte and microorganism.
 - d. **Engulfment** into cytoplasm and enclosed in a vacuole.
 - e. **Digestion** (degranulation occurs when cytoplasmic granules within phagocyte come into close contact with this vacuole and the granules rupture, discharging their damaging enzymatic contents into the vacuole and destroy the microorganism.
 - f. There are a number of killing mechanisms operating in the vacuoles of phagocytic cells. One of the major mechanisms involves hydrogen peroxide which, acting along with an intracellular enzyme, is rapidly lethal to many bacteria.

4. Many soluble tissue and serum substances help to suppress the grow of or kill microorganisms.
 - a. Interferons - family of proteins which are important non-specific defense mechanisms against viral infections.
 - b. Transferrin - Bacteria do not thrive well in serum that contains low levels of iron but high levels of transferrin.
 - c. Complement - a group of proteins that are essential for bacterial destruction and plays an important role in both non-specific and specific immune mechanisms.

III. Specific Immunity

A. Specific Immune Pathway

1. Concerned with the recognition of certain foreign material known as **antigens** and how the immune system can be stimulated to make a very specific immune response leading to their destruction. This path branches into the **humoral system** and the **cell mediated system**.
2. **Humoral system**
 - a. Concerned with the production of circulating proteins known as **immunoglobulins** or **antibodies**.
 - b. Cells of the humoral system are **B lymphocytes** which, under certain circumstances, become **plasma cell**.
 - c. **Plasma cells** produce and release immunoglobulins into the circulation.
 - d. **B lymphocytes** and **plasma cells** are important in the prevention of bacterial infections.
3. **Cell mediated system**
 - a. Concerned with activity of cells known as **T lymphocytes** which are capable of specifically destroying antigenic material (e.g. foreign material such as microorganisms) which is either fixed in the tissues or inside cells.
 - b. **T lymphocytes** are important in the prevention of many viral infections.

B. Cells of the Immune System - General information

1. Cells mainly involved in non specific immunity.
 - a. **Phagocytic cells**
 - 1) Mononuclear phagocytes
 - 2) Polymorphonuclear phagocytes (neutrophils)
 - 3) Eosinophils
 - b. **Mediator cells**
 - 1) Basophils and mast cells
 - 2) Platelets
2. Cells mainly involved in specific immunity
 - a. Lymphocytes
 - b. Plasma cells

3. Origin of immune cells
 - a. Origin of all of these cell types are **stem cells** found in the bone marrow. These self replicating cells differentiate into two types of "committed" stem cells.
 - b. One group eventually differentiates further and matures to become **platelets, erythrocytes (red blood cells), monocytes or granulocytes**.
 - c. Second group produces cells of the **lymphoid line** only.
 - d. The lymphoid line will develop into 2 different types, T and B cells, depending upon where they complete their maturation, thymus or bone marrow.

- C. Cells Mainly Involved in Non-Specific Immunity
 1. Phagocytic Cells
 - a. **Mononuclear phagocytes** - include both circulating blood **monocytes** and **macrophages** found in various tissues of the body.
 - 1) Arise from bone marrow stem cells
 - 2) These are not end cells, they may divide.
 - 3) Ingest and destroy material such as bacteria, damaged host cells or tumor cells (non-specific immunity).
 - 4) Stay in peripheral blood 70 hours - migrate to tissues, double in size, then called tissue macrophages.
 - 5) Tissue macrophages named according to tissue location- liver=Kupffer cells, brain-microglial cells, etc.
 - 6) Phagocytosis takes place to a greater degree in tissues.
 - b. **Polymorphonuclear phagocytes (neutrophils)** - characterized by a large nucleus, usually with 3 - 5 lobes, and the presence of numerous, specific granules in the cytoplasm.
 - 1) Arise from bone marrow stem cells.
 - 2) They are end cells.
 - 3) Primary function is ingestion (phagocytosis).
 - 4) Clear body of debris such as dead cells and thrombi.
 - 5) Able to move into tissues by **diapedesis** -wander randomly
 - c. **Eosinophils** - easily distinguished by the presence of large granules in their cytoplasm which appear red when stained by routine hematology stains.
 - 1) Much less phagocytic than macrophages or neutrophils
 - 2) Function is far from clear, however the numbers increase greatly in certain parasitic diseases and allergic diseases.
 - 3) Both **neutrophils** and **eosinophils** contain specific granules, the granules contain various enzymes which are released under certain circumstances.

4. **Mediator Cells** - influence the immune response by releasing various chemical substances into the circulation.
 - a. Have a variety of biological functions
 - 1) Increase vascular permeability
 - 2) Contract smooth muscle
 - 3) Enhance the inflammatory response
 - b. **Basophils and mast cells**
 - 1) Basophils are easily identified due to large numbers of bluish-black granules in the cytoplasm. These granules are a source of mediators such as **histamine** (vasoactive amine that contracts smooth muscle) and **heparin**.
 - 2) Basophils and platelets are found in the circulation, mast cells are situated in the tissues of skin, lung and GI tract.
 - 3) Circulating basophils greatly resemble tissue mast cells and it is likely that they are closely related in function.
 - 4) Both of these cells play a role in hypersensitivity reactions.
 - c. **Platelets**
 - 1) Small non-nucleated cells derived from **megakaryocytes** of the bone marrow.
 - 2) Important in blood clotting.
 - 3) Probably also contribute to the immunological tissue injury occurring in certain types of hypersensitivity reactions by releasing **histamine** and related substances which are contained within specialized granules in their cytoplasm.
- D. Acute Phase Reactants
 1. Defined-normal serum constituents that increase rapidly because of infection, injury, or trauma to tissues.
 2. **C-Reactive Protein**
 - a. Increases rapidly within 4-6 hours of infection or injury.
 - b. Returns to normal rapidly once condition subsides.
 - c. Used to monitor healing and has also increased in usefulness in diagnosing MI.
 3. **Complement** is a series of serum proteins involved in mediation of inflammation but also involved in opsonization, chemotaxis, and cell lysis.

4. ***Alpha-1 Antitrypsin*** plays an important role preventing the breakdown of enzymes in various organs of the body and protects the lungs so they can work normally. When the lungs do not have enough alpha-1 antitrypsin, neutrophil elastase is free to destroy lung tissue. As a result, the lungs lose some of their ability to expand and contract (elasticity). This leads to emphysema and sometimes makes breathing difficult.
5. ***Haptoglobin*** binds irreversibly to free hemoglobin to protect kidneys from damage and prevent loss of iron by urinary excretion.
6. ***Fibrinogen*** is a coagulation factor integral to clot formation which serves as a barrier to prevent spread of microorganisms further in the body.
7. ***Ceruloplasmin*** is the major copper containing protein in plasma, depletion found in Wilson's disease, causes the body to absorb and retain excessive amounts of copper. The copper deposits in the liver, brain, kidneys, and the eyes. The deposits of copper cause tissue damage, necrosis (death of the tissues), and scarring, which causes decreased functioning of the organs affected. Liver failure and damage to the central nervous system (brain, spinal cord) are the most predominant, and the most dangerous, effects of the disorder.
8. ***Alpha-1 Acid Glycoprotein (AGP)*** is an acute phase protein manufactured in the liver and found in the blood of humans and animals. In the simplest form, detection of elevated levels of AGP has been shown to indicate background illness or other stressors when animals appear clinically normal. Acute phase proteins such as AGP are elevated during acute or chronic periods of inflammation or infectious diseases, following surgery, with malignant tumors, in autoimmune diseases, liver cirroses and with all types of stress in general. Other effects related to elevated levels of AGP are immunosuppression, poor response to vaccines, etc.

E. Cells Involved in Specific Immunity

1. ***Lymphoid cell line*** cells differ from those of the previously described cells in that they have the ability to recognize certain substances (such as proteins) as **foreign** to the host and to eradicate them by means of a ***specific immune response***.
2. ***Lymphocytes*** - several different types and are classified according to function.
 - a. ***B lymphocytes*** are concerned with ***humoral*** immunity, i.e. they recognize certain substances as **foreign**.
 - 1) Transform into ***plasma cells*** and produce a family of proteins known as ***antibodies*** or ***immunoglobulins***.
 - 2) Important in the eradication of circulating foreign material such as bacteria.
 - b. ***T lymphocytes*** are important in recognizing foreign material that is fixed in the tissues of cells.
 - 1) They are not capable of secreting antibody.
 - 2) Examples of foreign materials are transplanted tissue, tumors and organisms causing tuberculosis.

- 3) When stimulated T cells differentiate further into several types of T cells with very different functions. (These will be covered in detail later).
- c. It is not possible to distinguish a T lymphocyte from a B lymphocyte by looking at them on a routine blood smear.

E. Specific Immunity

1. Specific immune response offers no immediate protection on first meeting an antigen, but are effective on second and subsequent exposures (example, measles).
2. Results from activity of cells and organs of the lymphoid system which consists of the following:
 - a. Lymphocytes capable of reacting with antigen.
 - b. Central lymphoid system consists of bone marrow, thymus and component whose identity is known with certainty only in birds-**the bursa of fabricus**. In mammals it is known as bursal equivalent tissue but its site is not clear.
 - c. Peripheral component in which these cells react with antigen and differentiate further. This step is antigen dependent.
 - d. Peripheral lymphoid system consists of lymph nodes, spleen and gut associated lymphoid tissue (Peyer's patches and appendix). These organs are part of the Reticuloendothelial system (RES). Different types of phagocytic cells reside here.
 - e. Two types of lymphocytes (T and B) are found in the peripheral lymphoid tissues. lymphoid compartment.
 - 1) **T lymphocytes** develop in the thymus and are involved in antigen recognition in **cell mediated immunity reactions**.
 - 2) **B lymphocytes** differentiate in the bursa equivalent tissue and are involved in the production of antibody, i.e. **humoral immunity**.

F. Organs of the Immune System

1. Primary lymphoid organs
 - a. Bone Marrow
 - 1) Largest tissue of the body
 - 2) Main source of hematopoietic cells
 - 3) Functions as center for antigen-dependent hematopoiesis
 - 4) Lymphocyte stem cells released from marrow and travel to primary lymphoid organs for maturation: T cells go to Thymus, B cells mature in bone marrow.

- b. **Thymus**
 - 1) Ductless gland-like structure located beneath the sternum (breastbone).
 - 2) Lymphocyte committed stem cells develop into T lymphocytes under the influence of thymic hormones.

 - c. **Bursa of Fabricus**
 - 1) An outgrowth of the cloaca in birds that becomes the site of formation of lymphocytes with B cell characteristics.
 - 2) No equivalent found in man, but thought to be the bone marrow or gut associated lymphoid tissue.
2. Secondary lymphoid tissue
- a. From the primary lymphoid organs, B and T lymphocytes migrate to the peripheral secondary lymphoid organs.
 - 1) They encounter antigens and are transformed into an activated state.
 - 2) They become effectors of the humoral or cell-mediated immunity.

 - b. Spleen
 - 1) A large, gland-like organ located in the upper left quadrant of abdomen under the ribs.
 - 2) It is the body's largest reservoir of mononuclear-phagocytic cells.
 - 3) Both T and B lymphocytes are present but they are segregated.
 - 4) The red pulp of the spleen consists of blood vessels lined with macrophages.
 - 5) White pulp contains lymphoid tissue.
 - 6) T cells and B cells are segregated.
 - 7) Also functions as a filter by removing effete cells from circulation.

 - c. Lymph nodes
 - 1) Located in several areas of the body, including the neck and those points where the arms and legs join the trunk of the body.
 - 2) They serve as a filter for the tissue fluid or lymph.
 - 3) Lymph is a collection of tissue fluid flowing from the limbs and tissues through the lymph nodes on its way to the blood stream.

 - d. Examples of other Secondary Lymphoid Tissue or organs
 - 1) Gut associated lymphoid tissue
 - 2) Tonsils
 - 3) Peyer's patches
 - 4) Bronchus associated lymphoid tissue
 - 5) Mammary glands
 - 6) Salivary glands

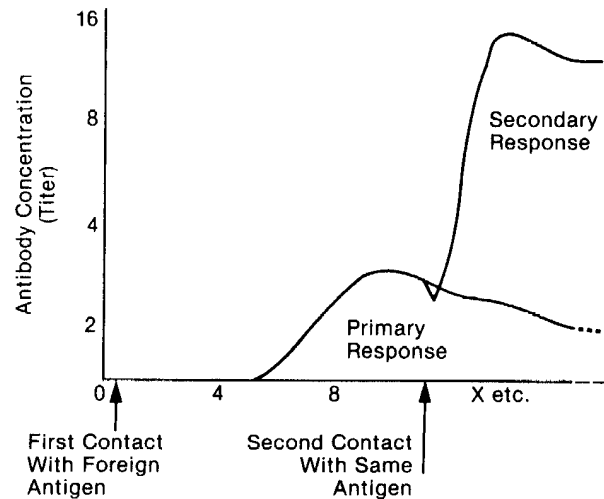
IV. The Immune Response

A. Antigens and Antigen/Antibody Binding

1. An **antigen** is any substance which is recognized as foreign by the body and is capable, under appropriate conditions, of provoking a specific immune response. It is capable of:
 - a. Stimulating the formation of **antibody** and the development of cell-mediated immunity.
 - b. Reacting specifically with the antibodies or T lymphocytes produced.
2. Physical nature of antigens
 - a. **Foreign nature**
 - 1) The immune system of an individual can normally distinguish between body components ("self") and foreign substances ("non-self").
 - 2) The body is tolerant of its own components and does not initiate immune response against these.
 - 3) Under certain circumstances this natural tolerance may be disturbed, permitting the individual to react against himself, as is seen in **autoimmune disease**.
 - 4) The greater the "foreignness" or difference from self, the greater the immune response.
 - b. **Molecular size**
 - 1) The higher the molecular weight, the better the molecule will function as an antigen.
 - 2) The larger the size, the greater the number of antigenic sites and the greater the variety and amount of antibody production.
 - 3) Molecules with a molecular weight of less than 10,000 daltons have no or weak antigenicity.
 - c. **Molecular complexity and rigidity**
 - 1) The more complex an antigen is, the more effective it will be.
 - 2) Complex proteins are better antigen than large repeating polymers such as lipids, carbohydrates, and nucleic acids, which are relatively poor antigens.
 - 3) specific regions of limited size function at antigenic sites, it's thought that 2 antigenic determinants per molecule are required to stimulate antibody production.
 - 3) **Haptens** are substances, usually of low molecular weight, that can combine with antibody but cannot initiate an immune response unless it is coupled to a larger carrier molecule.
 - d. **Genetic factors**
 - 1) Not all individuals within a species will show the same response to a substance - some are **responders** and some **non-responders**.
 - 2) There is also a wide variation between species.

- e. **Route of administration and dose**
 - 1) Route of administration (oral, skin, intramuscular, IV, peritoneal, etc.) for stimulation of the immune response is very important.
 - 2) Recognition may not occur if the dose is too small.
 - 3) If the dose is too large it may cause "immune paralysis" and also fail to elicit an immune response.
- 3. Antigenic Determinants
 - a. Structures on antigens that are recognized as foreign by the immune system.
 - b. Number of antigenic determinants on a molecule varies with molecular size.
 - c. An immune response is directed against specific determinants, and resultant antibodies will specifically bind to them.
- 4. Antigen-Antibody Binding
 - a. Binding of antigenic determinant to the antibody binding can be likened to a "lock and key". Antibodies of different degrees of specificity may be produced in the immune response to a given antigen.
 - b. "Poor fit" of an antigen with an antibody is in response to the antigen reacting with an antibody produced in response to an entirely different antigen. This phenomenon is called **cross reactivity**.
- B. The Humoral Immune Response
 - 1. Humoral immunity has to do with the production of antibodies induced when the host's immune system comes into contact with foreign antigenic substance and reacts to this antigenic stimulation.
 - 2. Dynamics of antibody production
 - a. Exposure to antigen is followed by a latent or lag period during which there is no detectable antibody.
 - b. On first exposure to antigen the latent period of 2-4 days is followed by the **primary immune response**.
 - 1) Gradual rise in plasma antibody for over a period of a few days to a few weeks.
 - 2) Specific antibody concentrations reach a plateau and over the succeeding weeks diminish to very low or undetectable levels.
 - 3) In the primary response the initial antibody produced is **IgM** and its production lasts 10-12 days. This is followed by an **IgG** response with the production of large quantities of **IgG** antibody for the next 4-5 days.
 - 4) In the absence of continued antigenic stimulus, IgM antibody disappears, IgG antibodies may continue to be produced for several months.

- 5) After the primary response there is a phase of **immunological memory** during which, there is enhanced secondary response to the administration of antigen.
- c. The **secondary response** is characterized by a shorter latent period, faster production and higher concentrations of antibody.
- 1) When an individual is exposed to the same antigen again there is minimal production of IgM and the bulk of the antibody production is **IgG**.
 - 2) Involves immunological memory.

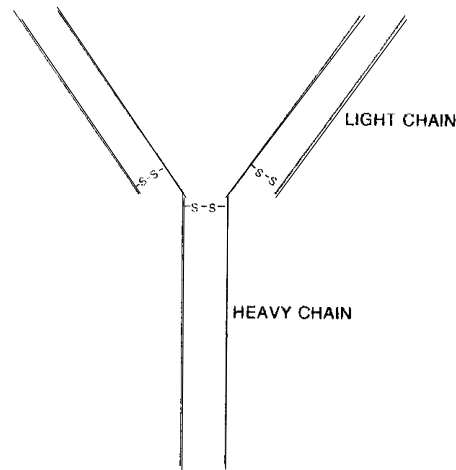


Primary and secondary response to foreign antigen.

3. Cellular events in antibody production.
 - a. Antigen is first "processed" by T lymphocytes and macrophages so that it can be presented to the circulating pool of B lymphocytes.
 - b. Small number of cells in this pool have specific receptors on their surface for the antigen.
 - c. Reaction between receptor and antigen stimulates the B cell to divide and differentiate into plasma cells.
 - d. Initially, the receptors on the surface of the plasma cells are IgM and the cell produces and secretes IgM antibody. There is a switch in production from IgM to IgG.
 - e. When the antigenic stimulus is removed, cell division and differentiation stop but the circulating pool of lymphocytes now contains a larger population of memory cells to that particular antigen.
 - f. When re-exposure to that antigen occurs there is a more immediate and more extensive division and differentiation of cell that have IgG receptors and produce and secrete IgG antibody.

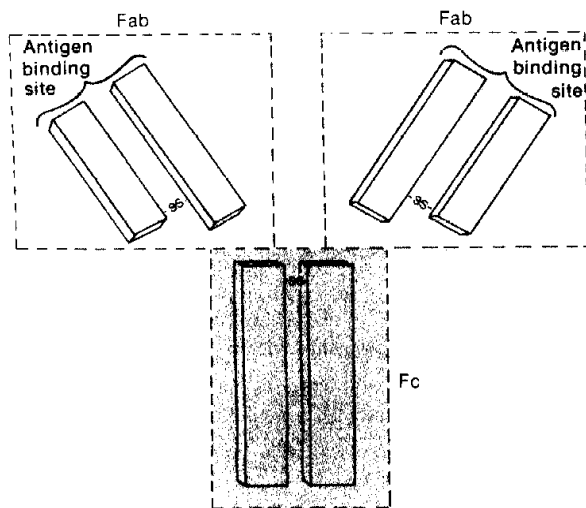
C. Basic Structure of Immunoglobulins

1. Basic Structure consists of two identical heavy chains and two light chains held together by a chemical link (disulfide bonds).
 - a. Light chains are named by the Greek letters **kappa** and **lambda**.
 - b. Heavy chains by the Greek letters: **gamma (G), alpha (A), mu (M), delta (D), and epsilon (E)**.

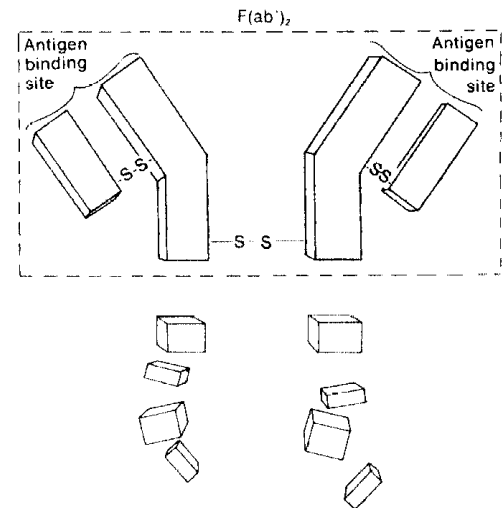


2. Antibodies are treated with enzymes to determine structure and activity of the various areas of the antibody molecule.
 - a. **Papain** will split the antibody into three fragments.
 - 1) **Two Fab** (fragment antigen binding) is composed of the entire light chain and about half of the heavy chain linked to each other by a disulfide bond.
 - a) The Fab portions contain what is known as the **variable regions** of the molecule in which the amino acid sequence is very different from molecule to molecule.
 - b) The variable region provides the "lock" of the antibody molecule which causes it to be highly specific for the binding of one particular antibody to an antigen.
 - c) These fragments are not capable of causing agglutination.
 - 2) The third fragment is the **Fc fragment** (fragment crystalline) which plays no part in combining with the antigen but determines the biological functions of the antibody.

- b. Treatment with **pepsin**
- 1) Results in two slightly different Fab fragments known as F(ab')₂.
 - 2) Has ability to bind with antigen **and** is also capable of causing agglutination or precipitation reactions.



Cleavage of antibody molecule by papain.



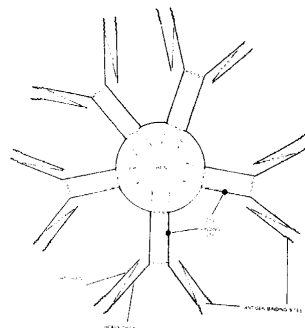
Cleavage of antibody molecule by pepsin.

D. Structure and Function of the Five Immunoglobulin Classes

1. **IgG**

- a. Most abundant of the immunoglobulins in the plasma (accounts for 70 to 75% of the total immunoglobulin pool) and because of its very small molecular weight it can diffuse into the interstitial fluid.
- b. Consists of one basic structural unit, i.e. Y-shaped molecule having 2 light chains and 2 Gamma heavy chains.
- c. Found in significant concentrations in both vascular and extra vascular spaces.
- d. Neutralizes toxins and binds to microorganisms in extra vascular spaces which attracts polymorphs to site of infection.
- e. IgG can coat organisms and this enhances their phagocytosis by neutrophils and macrophages.
- f. **Through its ability to cross the placenta, maternal IgG provides the major line of defense against infection for the first few weeks of a baby's life.**
- g. **It is the predominant antibody produced in the secondary response.**
- h. **(Capable of binding complement)**
- i. Four subclasses which differ in their heavy chain composition and in some of their characteristics such as biologic activities. IgG1, IgG2, IgG3 and IgG4.

2. **IgA**
- As well as being in the plasma, IgA is the **major immunoglobulin of the external secretory system and is found in saliva, tears, colostrum breast milk and in nasal, bronchial and intestinal secretions.**
 - It is produced in high concentrations by lymphoid tissues lining the gastro-intestinal, respiratory and genitourinary tracts.
 - It plays an important role in protection against respiratory, urinary tract and bowel infections.
 - It is probably also important in preventing absorption of potential antigens in the food we eat.
 - IgA represents 15 to 20% of the total circulatory immunoglobulin pool.
 - In plasma IgA exists as a single basic structural unit or as two or three basic units joined together.
 - The IgA present in secretions exists as two basic units (a dimer) attached to another molecule known as **secretory component**.
 - This substance is produced by the cells lining the mucous membranes.
 - It is thought to protect the IgA in secretions from destruction by digestive enzymes.
 - IgA does not cross the placenta and does not bind complement.**
 - IgA is present in large quantities in colostrum and breast milk and can be transferred across the gut mucosa in the neonate. It probably plays an important role in protecting the neonate from infection - hence the importance of breast feeding.
 - Plasma IgA is the last immunoglobulin to develop in childhood, although secretory IgA tends to appear early.
3. **IgM**
- Largest of all the antibody molecules and the structure consists of five of the basic units (**pentamer**) joined together by a structure known as **J-chain**.
 - Accounts for about 10% of the immunoglobulin pool.
 - IgM is restricted almost entirely to the intravascular space due to its large size.
 - IgM fixes complement** and is much more efficient than IgG in the activation of complement and agglutination
 - It is the first antibody to be produced and is of greatest importance in the first few days of a **primary immune response** to an infecting organism. Thus it acts as an effective first line of defense against bacteria.
 - IgM does not cross the placenta.**



- b. **IgE**
 - a. Trace plasma protein (0.01-0.05 mg/dl) in the plasma of non-parasitized individuals.
 - b. It is of major importance because it mediates some types of allergic reactions, allergies and anaphylaxis and is generally responsible for an individual's immunity to invading parasites.
 - c. IgE is unique in that its Fc region binds strongly to a receptor on mast cells and basophils and, together with antigen, mediates the release of histamines and heparin from these cells, resulting in allergic symptoms.
 - d. Not much else is known about its biologic role but it is believed that the ability to produce IgE evolved mainly for the purpose of dealing with parasitic infections.
 - e. ***IgE does not fix complement.***
 - f. ***IgE does not cross the placenta.***

5. **IgD**

- a. IgD occurs in minute quantities in the serum (3 mg/dl) and accounts for less than 1% of the total immunoglobulin pool.
- b. This is primarily a cell membrane immunoglobulin found on the surface of B lymphocytes.
- c. IgD does not fix complement.
- d. IgD does not cross the placenta.
- e. Little is known about the function of this class of antibody.

E. The Cellular Immune Response

- 1. Important defense mechanism against viral infections, some fungal infections, parasitic disease and against some bacteria, particularly those inside cells.
- 2. Responsible for delayed hypersensitivity, transplant rejection and possibly tumor surveillance.
- 3. This branch of the immune system depends on the presence of thymus-derived lymphocytes (T lymphocytes).
- 4. Cell-mediated reaction is initiated by the binding of the antigen with an antigen receptor on the surface of the sensitized T lymphocyte, causes stimulation of the T lymphocyte into differentiation into two main groups of cells.
 - a. **Helper and suppressor T cells** that regulate the intensity of the body's immune response.
 - b. T cells capable of **direct interaction** with the antigen. This group can be divided further.
 - 1) T cells which, on contact with the specific antigen, liberate substances called **lymphokines**.
 - 2) **Cytotoxic T cells** which directly attack antigen on the surface of foreign cells.

5. **Lymphokines** are a mixed group of proteins. None have been identified chemically, and they can only be classified in terms of their biological activities. They have diverse properties.
 - a. Macrophages are probably the primary target cells. Some lymphokines will aggregate macrophages at the site of the infection, while others activate macrophages, inducing them to phagocytose and destroy foreign antigens more vigorously.
 - b. Another important function is the attraction of neutrophils and monocytes to the site of infection.
 - c. The end result of their combined action is an amplification of the local inflammatory reaction with recruitment of circulating cells of the immune system.
 - d. Contact between antigen and **specific** sensitized T lymphocytes is necessary to cause release of lymphokines, but once released the lymphokine action is **not antigen specific**; for example, an immune reaction to the tubercle bacillus may protect an animal against simultaneous challenge by brucella organisms.

6. Cytotoxic T cells
 - a. Attach directly to the target cell via specific receptors.
 - b. The target cell is lysed; the cytotoxic cell is not destroyed and may move on and kill additional targets.
 - c. T cell of this kind develop with specificities against antigens on grafted tissues and they are important in the rejection of such grafts. Until recently this type of immunity was considered to be mediated only by T lymphocytes, but would now appear that other cell types play a part.
 - 1) **Killer** or **Killer T cells** - their precise identity and site of origin are unknown, but they can recognize and destroy antibody-coated target cells. Unlike the situation with T lymphocytes, these reactions occur with non-sensitized Killer cells.
 - 2) **Macrophages**, which are probably important in the processing of the antigen before presentation to the T lymphocytes, as with B lymphocytes. Moreover, they may take part directly in the destruction of target cells by phagocytosis and by direct cytotoxic effects on antibody-coated target cells in a manner similar to Killer cells.

7. Control of the immune response is very complex.
 - a. Genetic control
 - 1) Rabbits usually produce high levels of antibodies to soluble proteins, while mice respond poorly to such antigens.

- 2) Within a species it has been found that some genetic types are good antibody producers, while others are poor **responders** and **non-responders**.
- b. Cellular control
- 1) Specific immune response is classically divided into two branches, antibody mediated immunity of B lymphocytes and cell mediated immunity of T lymphocytes.
 - 2) T cells play an important role in regulating the production of antibodies by B cells. T - B cell cooperation is necessary for antibody production to take place.
 - 3) **Helper T cell** - upon interaction with an antigenic molecule they release substances which help B lymphocytes to produce antibodies against this antigen.
 - 4) **Suppressor T cell** are thought to "turn off" B cells so that they can no longer cooperate with normal T cells to induce an immune response.
 - 5) Normal immune response probably represents a very fine balance between the action of **helper** and **suppressor** T cells.

F. Hypersensitivity Reactions

1. Introduction

- a. When the immune system "goes wrong" it can cause a whole spectrum of disease states affecting any organs of the body.
- b. Hypersensitivity denotes a state of increased reactivity of the host to an antigen and implies that the reaction is damaging to the host.
- c. The individual must first have become **sensitized** by previous exposure to the antigen.
- d. On second and subsequent exposures, symptoms and signs of a hypersensitivity state can occur immediately or be delayed until several days later.
- e. **Immediate hypersensitivity** refers to antibody mediated reactions, while **delayed hypersensitivity** refers to cell mediated immunity.

2. Type I (*Immediate*) Hypersensitivity

- a. Reactions range from mild manifestations associated with food allergies to life-threatening anaphylactic shock.
- b. **Atopic allergies** include hay fever, asthma, food allergies and eczema.
- c. Exposure to allergens can be through inhalation, absorption from the digestive tract or direct skin contact.
- d. Extent of allergic response related to port of entry, IE, bee sting introduces allergen directly into the circulation.
- e. Caused by inappropriate IgE production
 - 1) This antibody has an affinity for mast cells or basophils and attach to them.

- 2) When IgE meets its specific allergen it causes the mast cell to discharge its contents of vasoactive substances into the circulation.
 - 3) This release leads to symptoms of sneezing, runny noses, red watery eyes and wheezing.
 - 4) Symptoms subside when allergen is gone.
- f. **The most common immunological abnormality seen in medical practice.** As much as 10% of the population suffers from this but the symptoms are usually more irritating than serious.
- g. **Anaphylactic shock** is the most serious and fortunately the rarest form of this Type I hypersensitivity.
- 1) Symptoms are directly related to the massive release of vasoactive substances leading to fall in blood pressure, shock, difficulty in breathing and even death.
 - 2) It can be due to the following:
 - a) Horse gamma globulin given to patients who are sensitized to horse protein.
 - b) Injection of a drug that is capable of acting as a hapten into a patient who is sensitive.
 - c) Following a wasp or bee sting in highly sensitive individuals.
3. **Type II (cytotoxic) hypersensitivity**
- a. Manifested by the production of IgG or IgM antibodies which are capable of destroying cells surface molecules or tissue components.
 - b. Binding of antigen and antibody result in the activation of complement and destruction of cell to which the antigen is bound.
 - c. Well known common example of this type of hypersensitivity is the transfusion reaction due to ABO incompatibility.
 - d. In addition to hemolytic reaction to blood the following types of reactions are included in this category:
 - 1) Non-hemolytic reaction to platelets and plasma constituents.
 - 2) Immune hemolytic anemias
 - 3) Hemolytic disease of the newborn
 - 4) Anaphylactic reactions
 - e. Some individuals make antibody which cross reacts with self antigens found in both the lung and kidney, this leads to a serious but uncommon condition known as Goodpasture syndrome associated with symptoms of both hemoptysis and hematuria.
 - f. Some drugs may act as haptens, attach to the RBC membrane causing antibodies to be formed that react with the penicillin and lead to red cell damage and even hemolysis of the coated cells.

4. **Type III (*immune complex mediated*) hypersensitivity**
- a. During the normal immune response antibody is produced in response to exposure to antigen, forms immune complexes of antigen and antibody which may circulate. These complexes cause no symptoms and quickly disappear from the circulation.
 - b. In some individuals these immune complexes can persist in the circulation and may cause clinical symptoms, some of them serious. The size of the complexes produced seems important in determining whether they will be eliminated quickly from the body or retained long enough to cause damage.
 - c. Classical clinical symptoms of immune complex disease are due to blood vessel involvement, i.e., vasculitis. The blood vessels of joints and the kidney are most frequently affected, giving rise to symptoms of arthritis and glomerulonephritis.
 - d. Mechanisms are as follows:
 - 1) ***Soluble immune complexes*** which contain a greater proportion of antigen than antibody penetrate blood vessels and lodge on the basement membrane (Complexes that are larger and insoluble are easily removed by polymorphs and macrophages and do no harm).
 - 2) At the basement membrane site, these complexes activate the complement cascade.
 - 3) During complement activation, certain products of the cascade are produced. These are able to attract neutrophils to the area. Such substances are known as chemotactic substances.
 - 4) Once the polymorphs reach the basement membrane they release their granules, which contain lysosomal enzymes which are damaging to the blood vessel.
 - 5) This total process leads to the condition recognized histologically as vasculitis. When it occurs locally (in the skin) it is known as an ***Arthus Reaction***, when it occurs systemically as a result of circulating immune complexes it is known as ***serum sickness***.
 - e. Chronic immune complex diseases are naturally occurring diseases believed to be caused by deposits of immune complex and complement in the tissues.
 - 1) Systemic Lupus Erythematosus (SLE)
 - 2) Acute glomerulonephritis
 - 3) Rheumatic fever
 - 4) Rheumatoid arthritis

5. Type IV (*delayed*) hypersensitivity

- a. Used to describe the signs and symptoms associated with a cell mediated immune response.
- b. Results from reactions involving T lymphocytes.
- c. Koch Phenomenon caused by injection of tuberculo-protein (PPD test) intradermally resulting in an area of induration of 5 mm or more in diameter and surrounded by erythema within 48 hours is a positive.
- d. Characteristics of this phenomenon are:
 - 1) Delayed, taking 12 hours to develop.
 - 2) Causes accumulation of lymphs and macrophages.
 - 3) Reaction is not mediated by histamine.
 - 4) Antibodies are not involved in the reaction.
- e. Cell mediated reactions in certain circumstances are wholly damaging and may be seen in the following conditions:
 - 1) Drug allergy and allergic response to insect bites and stings.
 - 2) Contact dermatitis.
 - 3) Rejection of grafts.
 - 4) Autoimmune disease.

G. Immunoglobulin Deficiency Diseases**1. Primary immunodeficiency syndrome**

- a. Due to a primary hereditary condition the cellular, humoral or both immune mechanisms are deficient.
- b. At one extreme there may be agammaglobulinemia or dysgammaglobulinemia in which one or several immunoglobulins are absent because of B cell deficiency.
- c. Thymic dysplasia will result in a T cell deficiency.
- d. Wiskott-Aldrich syndrome involves combined deficiencies.

2. Secondary immunodeficiency syndrome.

- a. Results from involvement of the immunogenetic system in the course of another disease.
- b. Tumors of the lymphoid system.
- c. Hematologic disorders involving phagocytes.
- d. Protein losing conditions like the nephrotic syndrome.
- e. Other mechanisms occur which are not well understood which affect patients with diabetes mellitus and renal failure.
- f. Drugs and irradiation for cancer therapy may affect immunologic functions.
- g. Many drugs used therapeutically as immunosuppressive particularly after transplant surgery.

3. Acquired Immunodeficiency Syndrome (AIDS)
 - a. A condition in which T cell dysfunction results from a viral agent.
 - b. Loss of T cell activity renders the patient susceptible to a wide variety of rare or unusual infections.

H. The Immune Response, Functional Aspects

1. Recognition
 - a. An individual does not generally produce antibodies to antigens regarded as "self".
 - b. The system must have a memory so that the same antigen can be recognized after re-exposure.
 - c. Lymphocytes are the recognition cells which initiate the immune response.
2. Processing
 - a. Subsequent to recognition as foreign, an antigen's determinants must be processed in such a way that a specific antibody can be produced.
 - b. Macrophages are believed to perform this function because they ingest the antigen.
3. Production
 - a. The final phase of the immune response is the production of antibody.
 - b. This manufacturing system must be regulated in some way so that the immune response can be discontinued when the antigen stimulation is withdrawn.

I. Terms Used to Describe Immunity

1. **Active immunity** - two types
 - a. Naturally from disease
 - b. Artificially such as from injection or purposeful exposure to antigen, i.e., measles.
2. **Passive immunity** involves receiving antibody or antibody protection produced by another.
 - a. Naturally such as the transfer of maternal antibody across the placenta to the fetus or by colostrum.
 - b. Artificially such as Hepatitis B Immune Globulin (also known as gamma globulin) given after exposure to Hepatitis B.

V. COMPLEMENT

A. Introduction

1. Complement refers to a complex set of 14 distinct serum proteins (nine components) that are involved in two separate pathways of activation.
 - a. Components numbered in order of discovery.
 - b. Sequence of activation is not in numerical order.
 - c. Components circulate in inactive precursor form, develop activity upon activation.
 - d. Complement proteins designated by "C" followed by numbers and letters.
2. Two major functions:
 - a. Promote the inflammatory response.
 - b. Alter biological membranes to cause direct cell lysis or enhanced susceptibility to phagocytosis.
3. General properties of complement:
 - a. Primary role is cell lysis.
 - b. Activity of complement destroyed by heating sera to 56 C for 30 minutes.
 - c. IgM and IgG are the only immunoglobulin capable of activating complement (classical pathway).
 - d. Complement activation can be initiated by complex polysaccharides or enzymes (alternative or properdin pathway).
 - e. Portions of the complement system contribute to chemotaxis, opsonization, immune adherence, anaphylatoxin formation, virus neutralization, and other physiologic functions.
4. Sequential interaction of complement components.
 - a. Cleavage of components generates a small fragment which is released, and a larger molecule which attaches to cell surface and continues in reaction sequence.
 - b. Sequence of activation referred to as a cascade reaction.

B. Classical Pathway

1. **C1: *The Recognition Unit***
 - a. C1 consists of 3 subunits: C1q, C1r, and C1s.
 - b. C1q molecule consists of a collagenous region with six globular head groups (flower pot with flowers), globe end serves as recognition unit.
 - c. When antibody binds to antigen, binding sites for the globular head groups of C1q are exposed on the Fc region of the antibody.
 - d. For C1q to initiate the cascade it must attach to at least 2 Fc fragments, requires at least 2 molecules of IgG or one molecule of IgM.
 - e. C1q binding causes C1r to enzymatically activate C1s.

2. ***The Activation Unit (C4b2a3b)***
 - a. C1s cleaves C4 into C4a and C4b.
 - 1) C4a released into plasma (anaphylotoxic).
 - 2) C4b binds to antigen surface.
 - b. C1s cleaves C2 into C2a and C2b
 - 1) C2b released into plasma
 - 2) C2a binds to C4b to form C3 convertase.
 - c. C4b2a (C4b2b in some texts) is enzymatically active and can cleave many molecules of C3 into C3a and C3b.
 - 1) C3a released into plasma (anaphylotoxin).
 - 2) Some C3b binds to the cell membrane.
 - 3) Binding of C3b greatly enhances susceptibility to phagocytosis (IE, acts as an opsonin).
 - 4) Some C3b binds to C4b2a to form next catalytic unit C4b2a3b (C5 convertase).
 - 5) C5 convertase cleaves C5 into C5a (released to plasma and is an anaphylotoxic and chemotactic) and C5b.

3. ***Membrane Attack Unit***

- a. In the presence of C5b, molecules of C6, C7, C8 and a variable number of C9 molecules assemble themselves into aggregates.
 - b. This molecular complex causes a change in membrane permeability.
 - c. Exact cause of lysis unknown.
 - d. One theory is change in lipid membrane causes exchange of ions and water molecules across membrane.
 - e. Cells can lyse without C9 but it's slower.
 - f. In presence of C9 holes are observed on cell surface.
4. Order of activation in classical pathway is:

C1, C4, C2, C3, C5, C6, C7, C8, C9

- C. ***Alternative Pathway (Properdin Pathway)***

1. Cleavage of C3 and activation of the remainder of the complement cascade **occurs independently of antibody.**
2. Triggers for the alternative pathway include:
 - a. bacterial cell walls
 - b. bacterial lipopolysaccharide
 - c. fungal cell walls
 - d. some virus infected cells
 - e. and rabbit erythrocytes
3. Molecules of C3 undergo cleavage at continuous low level in normal plasma.

4. At least 4 serum proteins (factor B, factor D, properdin (P), and initiating factor (IF) function in this pathway.
 5. C3b attaches to appropriate site (activating surface) which is actually a protective surface.
 6. Action by the 4 serum proteins on C3b proceeds to the C3 activator stage without participation of C1, C4 or C2.
 7. Activation sequence: C3, C5, C6, C7, C8, C9.
- D. Regulation of the Complement Cascade
1. Modulating mechanisms are necessary to regulate complement activation and control production of biologically active split products.
 2. First means of control is extreme lability of activated complement.
 - a. If activated complement does not combine within milliseconds the activity is lost or decreased.
 - b. Active fragments rapidly cleared from the body.
 3. Second type of control involves specific control proteins.
 - a. C1 inhibitor blocks activity of C1r and C1s.
 - b. Factor I in activator in the presence of certain cofactors inactivates C3b and C4b.
 - c. A number of proteins act to control membrane attack unit.