Immunization and Hypersensitivity

As explained earlier, **Louis Pasteur's** discovery of immunization was serendipitous, i.e., occurred through chance. It involved knowledge provided by other individuals (**Robert Koch**, **Edward Jenner**, **Joseph Lister**, etc.), during a period when immune system physiology and the antigenic properties of microorganisms were not yet recognized. Fortunately, current information available on immune system function has greatly improved our understanding of how immunization works and why it provides protection. Adaptive immunity involves the production of **memory cells**, both B-cells and T-cells, and these allow the body to respond quickly when challenged by a previously encountered pathogen. The effectiveness of immunization is dependent on proper immune function, and the body's ability to launch an **anamnestic response**.

Immunization:

Immunization is the process of conferring **specific immunity** by **artificial means**. As described earlier adaptive immunity acquired through artificial means may be either **active** or **passive**, depending on if or not the body is induced to produce its own immune cells and substances. Therefore, immunization may involve one or more of the following:

1. **Vaccination** – Vaccination is the process of inducing **active immunity** by introducing killed or attenuated microorganisms, components of these or their products into the body. The term **vaccine**, as initially used by Louis Pasteur, applied to a substance containing **killed or attenuated microorganisms**. Attenuated forms were weakened in some manner, so that although they could initiate an immune response, they did not cause disease (or at least not in most individuals). Currently vaccines may contain genetically modified microorganisms, or components of microorganisms. Vaccines containing microbial parts rather than whole organisms are called **sub-unit vaccines**.

   Since the toxic by-products of microorganisms are often responsible for causing disease symptoms, vaccination can often be accomplished by inducing immunity against these substances. **Toxoids** are detoxified microbial toxins, and are often included in combined vaccines such as the DPT vaccine. In this case toxoids induce immunity to the toxins of *Corynebacterium diphtheriae* and *Clostridium tetani*, while a vaccine provides protection against *Bordetella pertussis*, the causative agent of whooping cough.

   In either case, vaccination will provide protection only if the individual receiving it has a fully functional immune system capable of producing B-cells, antibodies, T-cells and lymphokines.

2. **Administration of immune serum** – Immune serum or **anti-serum** is a substance containing a high antibody titer, and capable of providing protection against a specific pathogen. Antibody in the isotype IgG (gamma-globulin) is most commonly used, but other types could be.

Historically, immune serum was produced by inoculating various types of animals (horses, goats, pigs, etc.) with specific antigens, allowing them to produce antibodies against these antigens, and then harvesting their serum (blood plasma with clotting factors removed). Unfortunately, anti-serum produced by non-human animals will trigger potentially deadly hypersensitivity reactions if used more than once on the same individual. To avoid the potential damage resulting from this practice, anti-serum is now made using cells in tissue culture or **monoclonal antibody** techniques. This technique involves fusing B-cell myoloma cells (cancer cells with indefinite life spans) with plasma cells capable of secreting a specific type of antibody. Once such a cell line is established, it can theoretically continue producing human antibody indefinitely.

When a patient is receiving immune serum, his/her body is not required to produce any immune cells or substances, so immunity is passively acquired.

Trends in Immunization:

Although immunization has become a topic of some controversy of late (for a variety of reasons), it remains the method of choice for preventing disease and avoiding epidemics. Immunization is considered appropriate for the mass of a population, i.e., everyone present only under specific circumstances as indicated below.

1. The disease in question is one that will spread rapidly and affect a large number of people (most of the population).
2. The risk of contracting the disease outweighs the risk of being immunized, i.e., the consequences of becoming infected with the disease-causing agent are likely to be life threatening or otherwise damaging.

Currently, recommendations provided through the Centers for Disease Control and Prevention (CDC) indicate that all persons living in this country should be immunized against measles, mumps, rubella (German measles), diphtheria, tetanus, whooping cough (*Bordetella pertussis*), poliomyelitis, hepatitis A and B, meningitis and chicken pox. Adult individuals are also encouraged to be immunized against influenza and pneumococcal pneumonia. The Hib vaccine, providing immunity to *Haemophilous influenzae* strain b, bacteria causing meningitis and pneumonia is also recommended for children.

Since one of the factors determining if or not immunization is appropriate is weighing the risk of contracting a disease against the risk of receiving immunization; there must be some risks involved, or at least the potential for risks. Not surprisingly, there are potential risks associated with immunization as indicated below.

a. **Vaccine failure –** Vaccine failure may leave individuals unprotected and potentially expose them to virulent pathogens they would otherwise seek to avoid. Vaccine failure is uncommon in this country, but can occur if vaccines, toxoids, serum samples, etc. are improperly stored, e.g., not maintained at the proper temperature, or have been stored too long, i.e., beyond a given expiration date.
b. **Infection** – Vaccines containing attenuated microorganisms can sometimes cause disease when used under certain circumstances. Live viral vaccines can sometimes result in fetal infection if the virions involved can cross the placenta. Although the live viral vaccine used to immunize adult individuals against rubella does not harm adults, it can cross the placenta and cause severe damage to a developing fetus. Live vaccines

may also cause infection in immunocompromised individuals living with those receiving vaccines.

c. **Contamination** – Although contamination is rarely a problem in facilities where needles are used only once, and where vaccines, toxoids, serum samples, etc. are provided in single-use containers, contamination is a serious problem in some regions of the world. Reusing syringes and containers without means for sterilization can result in serious contamination problems.
d. **Toxicity** – Vaccines made with Gram-negative bacteria can cause toxic side effects because the lipopolysaccharide (LPS) associated with the outer membrane of the Gram-negative cell wall is highly toxic to humans and other mammals. Preservatives added to vaccines, e.g., mercury compounds, can also have toxic side effects.
e. **Hypersensitivity** – Hypersensitivity or allergic reactions can be initiated by immunizations; however, this is not the most common cause.

Various individuals and organizations suggest that immunization is unwarranted in this country, and that the risks far outweigh the benefits. These individuals argue that the risk of contracting diphtheria, poliomyelitis, whooping cough, measles and other potentially life-threatening diseases is low in this country, and that immunization poses a far greater threat. This is only true because most of the population is already immunized, and the disease-causing agents are unlikely to be encountered. If the majority of individuals chose to refuse immunization, the risk of contracting disease would increase significantly.

Hypersensitivity:

Hypersensitivity is listed above as one of the risks associated with immunization, but is more commonly initiated by other factors. Like immunization, hypersensitivity involves the immune system, so familiarity with immune system physiology is essential to understanding it.

Hypersensitivity can be defined as an abnormal physiological state during which an immune reaction causes tissue damage or malfunction within the body. Commonly referred to as **allergic reactions**, hypersensitivity reactions can involve either **humoral** or **cell-mediated** immune responses and can be categorized as immediate or delayed as indicated below.

1. **Immediate hypersensitivity** reactions involve B-lymphocytes and antibodies and typically occur within minutes of exposure to a specific antigen or **allergen**. There are at least three different types of immediate hypersentivity reactions (sometimes categorized as type I, type II and type III) involving different types of antibodies and other immune substances.

2. **Delayed hypersensitivity** reactions involve T-lymphocytes and cytokines and occur 24-48 hours or more after exposure to a specific antigen or allergen. Sometimes categorized as type IV, delayed hypersensitivity reactions involve Killer T-cells and can result in severe tissue damage.

A somewhat simplified explanation for each type of hypersensitivity reaction is presented below. Note that allergic reactions involving the same types of antibodies are sometimes

given different names based on whether they are **localized**, i.e., restricted to specific areas or occur body wide.

Type 1 hypersensitivity – Type 1 hypersensitivity reactions are the most common, and involve antibodies in the isotype **IgE** and **mast cells**. Mast cells (mastocytes) are common throughout the body in association with loose connective tissues and near blood vessels. They are similar to basophils (granular leukocytes), containing granules rich in **histamine** and heparin. They also have receptors with high affinity for IgE, so tend to bind irreversibly with these antibodies. Type 1 hypersensitivity reactions can be localized (atopy) or involve most of the body (anaphylaxis) and vary considerably in their severity.

a. **Atopy or atopic allergy** – Type 1 hypersensitivity reactions involving specific regions of the body, e.g., the eyes, nasal passages, patches of skin, etc. are examples of atopy or atopic allergy. During such reactions, IgE binding with antigens at the surfaces of mast cells cause them to degranulate, i.e., release their granules. Heparin is an anticoagulant, while **histamine** causes relaxation of precapillary sphincters, increased blood flow into capillaries and increased permeability of blood vessel walls. Localized increases in blood flow and the movement of fluid into tissue spaces putting pressure on receptors cause symptoms common to type 1 hypersensitivity reactions, e.g., redness, swelling, itching and sometimes pain. The red, watery eyes, runny nose, and itching sensation commonly referred to as hay fever, is an example of atopic allergy, often stimulated by exposure to pollen grains, fungus spores, dust mites, cat hair, and other allergens. Localized redness, swelling and itching of the skin following a mosquito bite, or due to hives is another example.

b. **Anaphylaxis** – Type 1 hypersensitivity reactions involving the release of histamine and other inflammatory substances body wide are called **anaphylactic reactions** or **anaphylaxis**. In this case, the binding of IgE with antigen at the surfaces of mast cells occurs throughout the body due to the presence of an allergen within the circulation. The human body contains around 70,000 miles of blood vessels, most of which are capillaries, and during an anaphylactic reaction, blood flow into capillary beds is increased body wide. Since under normal circumstances most capillary beds are closed, the pooling of blood in capillaries and venules has seriously detrimental effects. Without sufficient blood returning to the heart, there is insufficient outflow and the body begins to experience **circulatory shock** due to low venous return. Tissues become oxygen deficient, and metabolic wastes begin to accumulate, causing additional disturbances in blood flow. If not corrected, the situation can rapidly progress to circulatory failure and death.

Type 1 hypersensitivity reactions range in severity, and are not necessarily restricted to the examples described above. **Asthma**, a chronic disease of the respiratory system can involve type 1 hypersensitivity, and anaphylaxis typically involves respiratory as well as circulatory symptoms.

Type 2 hypersensitivity – Type 2 hypersensitivity reactions involve antibodies in the isotype **IgG** (sometimes IgM) and the activation of **complement** factors on the surfaces of cells. **Hemolytic disease of the newborn (HDN)**, sometimes called a **cytotoxic response** is one example.

a. During a **cytotoxic response**, a mother carrying a fetus with Rh-positive blood produces anti-Rh antibodies. Antibodies in the isotype IgG cross the placenta (IgM antibodies cannot because they are too large), and bind with Rh epitopes on the surfaces of the fetal RBCs. The binding of antibody and antigen causes complement factors to be activated and the resulting complement cascade causes destruction of the fetal RBCs. Hemolytic disease of the newborn varies in severity, but sometimes results in fetal death.
   Since people rarely check blood type before choosing a mate, and because Rhesus factors are abundant within the population, it is not uncommon for women with Rh-negative blood to carry offspring with Rh-positive blood. Blood exchange is generally minimal during pregnancy, but occurs often during delivery, so it is the second or subsequent Rh-positive fetus that is most likely to be damaged by a cytotoxic response. Women with Rh-negative blood and Rh-positive mates can avoid the problems associated with type 2 hypersensitivity by receiving RhoGAM or Rho(D) immune globulin. The anti-Rh antibodies (IgG) present in this substance bind with any fetal RBCs entering the mother's circulation and prevent the activation of B-lymphocytes capable of binding with these. Thus the mother is prevented from forming anti-Rh antibodies of her own.

b. Type 2 hypersensitivity is also involved when antibodies bind with transfused RBCs, as can occur if transfusion donors and recipients are incorrectly matched. A patient with type O-positive blood cannot receive RBCs from a donor with type A-positive blood because he/she will be carrying anti-A antibodies (potentially both IgG and IgM) that can bind with epitopes on the donated RBCs and activate complement factors. These will destroy the donated cells.

Type 3 hypersensitivity – Type 3 hypersensitivity reactions, sometimes referred to as **immune complex disease**, involve antibodies in the isotypes IgG and IgM complexing with antigens and the activation of complement factors resulting in cellular damage. Like type 1 reactions, these can be either localized or can occur body wide.

a. **Serum sickness** is a body wide reaction involving IgG and IgM binding with soluble antigens and forming complexes throughout the circulation. These complexes are eventually deposited in tissues where they activate complement factors and cause tissue damage. Serum sickness was a common occurrence when anti-serum from animal sources was used to prevent disease. People could be given horse antibodies to prevent tetanus, but only once, because the second time they received such antibodies, they could experience potentially deadly serum sickness.

b. An **Arthus reaction** is a localized type 3 hypersensitivity reaction caused by the binding of circulating antibody with antigens introduced into a localized area. The complexing of antibodies with antigen causes activation of complement factors and can result in cell damage and inflammation. Arthus reactions are sometimes stimulated by tetanus and diphtheria vaccinations.

Type 4 hypersensitivity – Type 4 hypersensitivity also called **delayed hypersensitivity** reactions involve the **cell-mediated** portion of the immune system and often occur 48 hours or more after exposure to an antigen. Allergic reactions to poison oak, ivy, etc., and graft rejection fall into this category.

a. **Contact dermatitis** can result from exposure to allergenic plants such as poison oak and poison ivy, and is one example of delayed hypersensitivity. In this case, oil from the plant becomes associated with skin cells, and they are then recognized as antigens by T-lymphocytes. **Killer T-cells** can respond to antigen in combination with MHC class I membrane markers, which skin cells carry, and can begin to attack and kill epithelial cells with perforin and granzymes. The extent of tissue damage is variable, but in severe cases may involve epithelial surfaces within the mouth and respiratory tract as well as external surfaces.

b. **Transplant rejection** can also involve T-cells and delayed hypersensitivity. In the case of **acute rejection**, T-cells recognize the transplanted tissue or organ as foreign, and begin to destroy the foreign cells just as they would eukaryotic pathogens. Transplant rejection is reduced by matching the MHC proteins of donors and recipients and by treating recipients with immunosuppressant drugs.

Numerous other conditions including rheumatoid arthritis, glomerulonephritis, endocarditis, rheumatic fever, scarlet fever and damage associated with tuberculosis and leprosy are due to hypersensitivity reactions. Though immune responses are for the most part protective in nature, they can sometimes cause considerable damage.