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Review Article

Immunological Diseases: Physiology to Classification Part I

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Abstract

The immune system is comprised of biological structures and processes within an organism that protects against diseases. This system has been discussed extensively since the introduction of medicine and yet has remained the most enigmatic. Continuous research in the field has yielded better but not complete understanding of concepts of immunity and related disorders. Although researchers have learned much about the immune system, new technologies for identification of individual immune cells are now allowing scientists to determine which targets are triggering immune response against healthy self. The detailed understanding of immunological tolerance, its regulatory network, combination of new technologies and expanded genetic information may increase the awareness to make it possible to control degree of auto reactivity in the immune system and lay down new hope for treatment of autoimmune diseases in the future.

Key words: Immunology, antibodies, auoimmune.

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INTRODUCTION

When we consider how animals defend themselves, it is natural to think of turtles, armadillos, and other animals covered like tanks with heavy plates of armour[1]. However, armour offers no protection against the greatest dangers vertebrates face—microorganisms and viruses. We live in a world awash with attackers too tiny to see with the naked eye, and no vertebrate could long withstand their onslaught unprotected[1]. Some 22 million Americans and Europeans died from influenza over an 18-month period in 1918–1919. Attempts to improve our defences against infection are among the most active areas of scientific research today.

Immunology is the study of the physiological mechanisms that humans and other animals use to defend their bodies from invasion by other organisms. The origin of the subject lie in the practice of medicine and in historical observations that people who survived the ravages of epidemic disease were untouched when faced with that same disease again—they had become immune to infection [2]. Infectious diseases are caused by microorganisms, which have the advantage of reproducing and evolving much more rapidly than their human hosts.

In medicine the greatest triumph of immunology has been vaccination, or immunization, a procedure whereby severe disease is prevented by prior exposure to the infectious agent in a form that cannot cause disease[3]. Vaccination was first used against smallpox, a viral scourge that once ravaged populations and disfigured the survivors[2].

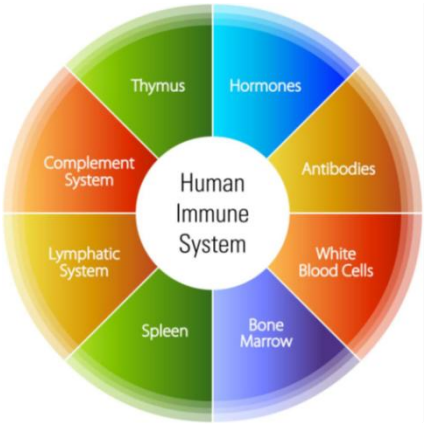
Skin: The First Line of Defence

The vertebrate is defended from infection the same way knights defended medieval cities. “Walls and moats” make entry difficult; “roaming patrols” attack strangers; and “sentries” challenge anyone wandering about and call patrols if a proper “ID” is not presented [3, 4].

- *Walls and moats*: The outermost layer of the vertebrate body, the skin, is the first barrier to penetration by microbes. Mucous membranes in the respiratory and digestive tracts are also important barriers that protect the body from invasion [3].
- *Roaming patrols*: If the first line of defence is penetrated, the response of the body is to mount a cellular counterattack, using a battery of cells and chemicals that kill microbes. These defences act very rapidly after the onset of infection [4].

- *Sentries*: Lastly, the body is also guarded by mobile cells that patrol the bloodstream, scanning the surfaces of every cell they encounter. They are part of the immune system [3].

Cellular Counterattack: The Second Line of Defence [2]



Macrophages ("big eaters") are large, irregularly shaped cells that kill microbes by ingesting them through phagocytosis, much as an amoeba ingests a food particle [3]. Within the macrophage, the membrane-bound vacuole containing the bacterium fuses with a lysosome. Fusion activates lysosomal enzymes that kill the microbe by liberating large quantities of oxygen free-radicals. Macrophages also engulf viruses, cellular debris, and dust particles in the lungs. Macrophages circulate continuously in the extracellular fluid, and their phagocytic actions supplement those of the specialized phagocytic cells that are part of the structure of the liver, spleen, and bone marrow [4]. In response to an infection, monocytes (an undifferentiated leukocyte) found in the blood squeeze through capillaries to enter the connective tissues. There, at the site of the infection, the monocytes are transformed into additional macrophages [4].

Two major theories concerning the development and differentiation of macrophages [5]:

- The reticuloendothelial system proposed by Aschoff (1924) and
- The mononuclear phagocyte system developed by van Furth (1972).

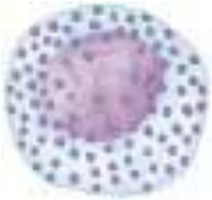
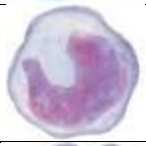
In 1924, Ludwig Aschoff determined that reticulum cells, reticuloendothelial (phagocytic endothelia), and histiocytes (tissue macrophages) show positive reactions for vital staining with lithium carmine; he regarded them as a single cell system of local tissue origin and proposed the concept of the RES [6].

In 1969, Langevoort, Cohn, Hirsh, Humphrey, Spector, van Furth rejected the concept of the RES, and selected ***mononuclear phagocytic cells*** (mononuclear phagocytes) alone as the basis for the MPS, excluding reticulum cells, fibroblasts, endothelial cells, and other non-phagocytic mesenchymal cells [7]. All macrophages are derived from monocytes, which differentiate through promonocytes from monoblasts originating in bone marrow[7]. Monocytes are the largest circulating leukocytes (diameter of 12- 20 micron), nucleus is non-lobed and ovoid to horse- shoe shaped, non-granulocyte but the cytoplasm contains many granules which are fine. Monocytes are born in the red bone marrow, from the colony forming unit, Granulocyte-Monocyte – becomes a blast cell called monoblasts and eventually becomes monocyte and enters peripheral blood [6]. In the blood it stays for 48-72 hours, then enters, the tissues where it is known as tissue macrophages where it probably remains alive for 3 months. As a phagocyte monocytes emigrates into tissues following bacterial invasion, but 24h after emigration (hence called 2nd line of defence) , engulfs and digest the bacteria by a) lethal killing agent like H2O2, b) lowering the Ph[7]. Monocytes can secrete large quantity of chemicals like- IL-1, TNF alpha, binding proteins like transferrin, lysozyme, proteases and acid hydrolases etc [7].

Neutrophils are stored in the bone marrow and move in large numbers to sites of infection, where they act and then die. After one round of ingestion and killing of bacteria, a neutrophil dies. The dead neutrophils are eventually mopped up by long-lived tissue macrophages, which break them down. The creamy material known as pus is composed of dead neutrophils [8].

Natural killer cells do not attack invading microbes directly. Instead, they kill cells of the body that have been infected with viruses. They kill not by phagocytosis, but rather by creating a hole in the plasma membrane of the target cell. Proteins, called perforins, are released from the natural killer cells and insert into

the membrane of the target cell, forming a pore [7]. This pore allows water to rush into the target cell, which then swells and bursts. Natural killer cells also attack cancer cells, often before the cancer cells have had a chance to develop into a detectable tumor. The vigilant surveillance by natural killer cells is one of the body's most potent defences against cancer [9].

Cell Type [10]	**Image**	**Function**
Helper T cell		Commander of the immune response; detects infection and sounds the alarm, initiating both T cell and B cell responses
Inducer T cell		Not involved in the immediate response to infection; mediates the maturation of other T cells in the thymus
Cytotoxic T cell		Detects and kills infected body cells; recruited by helper T cells
Suppressor T cell		Dampens the activity of T and B cells, scaling back the defense after the infection has been checked
B cell		Precursor of plasma cell; specialized to recognize specific foreign antigens
Plasma cell		Biochemical factory devoted to the production of antibodies directed against specific foreign antigens
Mast cell		Initiator of the inflammatory response, which aids the arrival of leukocytes at a site of infection; secretes histamine and is important in allergic responses
Monocyte		Precursor of macrophage
Macrophage		The body's first cellular line of defense; also serves as antigen-presenting cell to B and T cells and engulfs antibody covered Cells
Natural killer cell		Recognizes and kills infected body cells; natural killer (NK) cell detects and kills cells infected by a broad range of invaders; killer (K) cell attacks only antibody-coated cells

Cytokines

Cytokines are the proteins made by cells that are able to affect the behaviour of other cells. Different cytokines have different function [9].

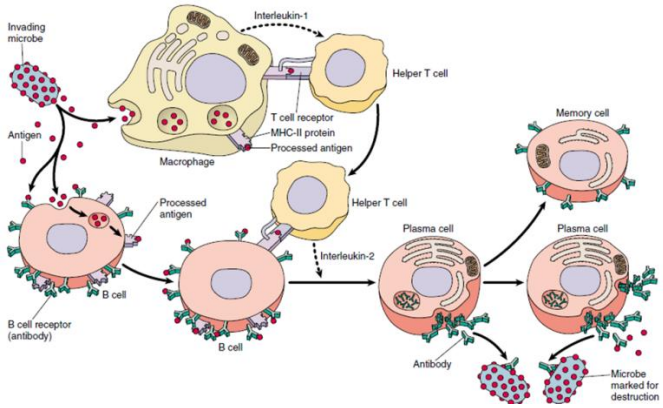
CYTOKINE	FUNCTION
Interleukins	Stimulates leukocyte proliferation and other function
Macrophage chemotactic factor	Stimulatesmacrophage emigration
Migration inhibitory factor	Inhibits macrophage activity
Macrophage activating factor	Activates macrophages to produce and secrete lysosomal enzymes
Lymphotoxins	Destroys fibroblasts
Interferons	Various functions involving leukocytes, fibroblasts and endothelial cells
Tumor necrosis factor	Various functions involving leukocytes and fibroblasts.

Pro-inflammatory cytokines like INF ϒ, TNF-α, IL-2, 6, 12 stimulate immune system. Anti-inflammatory cytokines like IL-4, 5, 10 and TGF-β suppress immune system [10].

Cells of the Specific Immune System [11]

Leukocytes include neutrophils, eosinophil, basophils, and monocytes, All of which are phagocytic and are involved in the second line of defence, as well as two types of lymphocytes (T cells and B cells), which are not phagocytic but are critical to the specific immune response. After their origin in the bone marrow, T cells migrate to the thymus [11].

There are four principal kinds of T cell: (1) inducer T cells oversee the development of T cells in the thymus; (2) helper T cells (often symbolized TH) initiate the immune response; (3) cytotoxic ("cell-poisoning") T cells (often symbolized TC) lyse cells that have been infected by viruses; and (4) suppressor T cells terminate the immune response [12]. B cells do not travel to the thymus; they complete their maturation in the bone marrow. When a B cell encounters the antigen to which it is targeted, it begins to divide rapidly, and its progeny differentiate into plasma cells and memory cells. Each plasma cell is a miniature factory producing antibodies that stick like flags to that antigen wherever it occurs in the body, marking any cell bearing the antigen for destruction. The immunity that Pasteur observed resulted from such antibodies and from the continued presence of the B cells that produced them[10]. In B cells immune defence invading particles are bound by B cells, which interact with helper T cells and are activated to divide. The multiplying B cells produce either memory B cells or plasma cells that secrete antibodies which bind to invading microbes and tag them for destruction by macrophages.

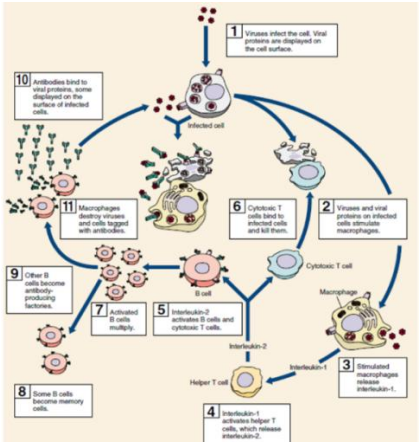


(Barrett, J.J. 1988, TEXTBOOK OF IMMUNOLOGY, 5th ed St. Louis, Miss C.V. Mosby)

Innate immune mechanisms establish a state of inflammation at sites of infection. **INNATE**" refers to the fact that they are all determined entirely by the genes a person inherits from their parents [13]. The overall effect of the innate immune response is to induce a state of inflammation in the infected tissue. Secondary immune response- All adaptive immune responses are contingent upon an innate immune response, vaccines must induce both innate and adaptive immune responses. The first time that an adaptive immune response is made to a given pathogen it is called the *Primary immune response*. Circulating lymphocytes meet lymph-borne pathogens in draining lymph nodes [12]. Lymphocytes leave the blood and enter lymph nodes, where they can be activated by pathogens in the afferent lymph draining from a site of infection. When activated by pathogens, lymphocytes stay in the node to divide and differentiate into effector cells. If lymphocytes are not activated, they leave the

node in the efferent lymph and are carried by the lymphatics to the thoracic duct [12, 13].

The acceptance of self-cells is known as immunological tolerance. Immunological tolerance sometimes breaks down, causing either B cells or T cells (or both) to recognize their own tissue antigens [14]. This loss of immune tolerance results in autoimmune disease. There are two general mechanisms for immunological tolerance: clonal deletion and clonal suppression[15]. During the normal maturation of hemopoietic stem cells in an embryo, foetus, or new born, most lymphocyte clones that have receptors for self-antigens are either eliminated (clonal deletion) or suppressed (clonal suppression. First immunological tolerance was the observation by Owen (1945). Tolerance can be overcome spontaneously or by an injection of cross reacting immunogens [15, 16].



(Stites, D.P. and TERR, A.I. 1991. Basic and clinical immunology, 7th ed., Norwalk: Prentice Hall)

Disorders Of Immune System [17]

- Hypersensitivity reactions
- Autoimmune disease
- Immunologic deficiencies

Immunodeficiency is state in which the immune system's ability to infectious disease is either compromised or completely absent [18].

Two types of immunodeficiency [18]—

Primary Immunodeficiency- Congenital, resulting from genetic defects in some components of the immune system. Manifests in early age. Otherwise called intrinsic immunodeficiency that affects <10% population. Etiological factors can be missing enzyme (ADA), missing cell type (Ig CD40), and non-functioning component.

Secondary Immunodeficiency- as a result of other diseases or conditions such as: immunosuppressant drugs, HIV infections, malnutrition, lymphoid malignancy acquired so manifest in any age.

Primary immunodeficiency

a) Immunodeficiency disease with primary defective humoral immunity
- X-linked agammaglobulinemia
- Selective immunoglobulin deficiencies
- Common variable immunodeficiency

b) Immunodeficiency with primary defect in cellular immunity
- DiGeorge syndrome
- Severe combined immunodeficiency (SCID)
- Partial combined immunodeficiency
- Ataxia telangiectasia
- Wiskott-Aldrich syndrome

SECONDARY IMMUNODEFICIENCIES

- Leukaemia
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Nephrotic syndrome
- Multiple myeloma
- Sarcoidosis

CONNECTIVE TISSUE DISORDER

- Systemic lupus erythematosus(SLE)
- Scleroderma
- Dermatomyositis
- Rheumatoid arthritis

ALLERGY

- Localized anaphylaxis
- Serum sickness
- Latex allergy

PRIMARY IMMUNODEFICIENCY CLASSIFICATION: 2011- IUIS INTERNATIONAL UNION OF IMMUNOLOGICAL SOCIETIES, NEW YORK CITY, MAY31-JUNE 1, 2011

1. Combined immunodeficiency
2. Well defined syndromes with immunodeficiency
3. Predominantly antibody deficiencies
4. Diseases of immune dysreguation

5. Congenital defects of phagocyte number, function or both.
6. Defects in innate immunity
7. Auto-inflammatory disorders
8. Complement deficiencies

AUTOIMMUNITY [20]

Autoimmunization is the effect of immune system on self−antigens, and develops in the situation of overcoming self−tolerance mechanisms protecting from not distinguishing self-components of body tissues from foreign antigens. In these processes participate auto antigens, auto reactive lymphocytes T (especially helpers CD4+), auto reactive lymphocytes B and their products, autoantibodies. Autoantibodies after binding auto antigens activate different immunological mechanisms (complement, opsonisation, antibody−dependent cell−mediated cytotoxicity, and deposition of complexes) and can destroy tissues and organs [21].

CAUSES OF AUTOIMMUNITY [20]

Sequestered or hidden changes: Ag in the secluded places are not accessible to the immune system. Ex- lens Ag, sperm Ag, thyroglobulin.

Neo antigens or altered antigens: by physical (irradiation), chemical (drugs), microbial (intracellular viruses)

Cessation of tolerance: it may result when tolerance to self-antigen is abrogated

Cross reacting antigens: a foreign antigen resembles a self-antigen. Ex- Ag of human brain and Ag of sheep, streptococcal M protein and heart muscles, nephritogenic strains of streptococci and renal glomeruli.

Loss of immunoregulation: loss of self-tolerance- caused by over or under activity of T- and B lymphocytes.

CLASSIFICATION OF AUTOIMMUNITY [20, 21]

Classified into three groups:

Haemolytic autoimmune diseases

Clinical disorder due to destruction of blood components. Autoantibodies are formed against one's own RBCs, platelets, leucocytes. Ex- haemolytic anaemia, leukopenia, thrombocytopenia.

Localised or organ specific autoimmune diseases

A particular organ is affected due to autoantibodies. Ex- thyroiditis (attacks thyroid), Multiple sclerosis (attacks the myelin coating of nerve axon), Myasthenia gravis (attacks the nerve- muscle junction), Juvenile or type I diabetes mellitus (attacks insulin producing cells)

Systemic or non – organ specific autoimmune diseases

Immune complexes accumulate in many tissues and cause inflammation and damage. Affects many organs or whole body. Ex-

Systemic lupus erythematosus (anti-nuclear Ab) - harms kidney, heart, lungs, brain, skin etc.

Rheumatoid arthritis (anti- Ig G Ab) - joints, heart, lungs, nervous system etc.

Rheumatic fever- cross- reaction between antibodies to streptococcus and auto-antibodies.

AUTOIMMUNE DISEASES CLASSIFICATION: Based on site of involvement and nature of lesions:

A) ORGAN SPECIFIC/ LOCALISED

THYROID: Hashimoto's thyroiditis
Thyrotoxicosis
GIT: Ulcerative colitis
Crohn's disease
ADRENALS: Addison's disease
Idiopathic hyperparathyroidism
PANCREAS: Juvenile diabetes
MUSCLES: Myasthenia gravis
EYE: After cataract surgery
CNS: After rabies infection
SEMINIFEROUS TUBULES: Orchitis
SKIN AND ORAL MUCOUS MEMBRANE:

- Bullous Pemphigoid
- Pemphigus vulgaris
- Lichen planus
- Aphthous stomatitis
- Desquamative gingivitis
- OSMF

GASTRIC MUCOSA: Pernicious anaemia (intrinsic factor)

B) **NON-ORGAN SPECIFIC/ SYSTEMIC:**

RA, SLE, Polyarthritis nodosa, Sjogren's syndrome, Scleroderma, Behcet's syndrome, Dermatomyositis.

C) **HEMOCYTOLYTIC**:

- Haemolytic anaemia
- Autoimmune thrombocytopenia
- Autoimmune leucopenia

D) TRANSITORY:

Occurs secondary to infections or drugs. Spontaneous cure on removal of primary factors: Anaemia, Thrombocytopenia, Leucopenia, Nephritis, Contact dermatitis.

E) COLLAGEN DISORDERS:

- Scleroderma
- SLE, OSMF
- Scurvy, Osteogenesis imperfecta
- Dentinogenesis imperfect, Marfan-Syndrome
- Ehlers Danlos syndrome, RA
- Polyarteritis nodosa, Sjogren's syndrome
- Dermatomyositis, Behcet's syndrome
- Rheumatic fever.

ANOTHER CLASSIFICATION [24]

(2012 International Journal of Oral and Maxillofacial Pathology Oral Manifestations of Autoimmune Diseases, SRIDEVI ET AL)

Organ-Specific Autoimmune Diseases

Haematological disorders: Autoimmune Haemolytic Anaemia (AIHA), Immune Thrombocytopenic Purpura (ITP)

Gastrointestinal diseases-- Pernicious anaemia

Dermatologic diseases-- Pemphigus Vulgaris, Bullous Pemphigoid, Cicatricial Pemphigoid (CP) or mucous membrane Pemphigoid (MMP), Psoriasis, Epidermolysis Bullosa Acquisita, Oral Lichen Planus, Erythema Multiforme.

Systemic Autoimmune Diseases

Systemic lupus erythematous, Rheumatoid Arthritis, Sjogren syndrome, Scleroderma, Reiter's Syndrome, Behcet's disease, recurrent aphthous stomatitis.

CONCLUSION

Immune system is a sophisticated defence system to protect from invading pathogens. The immune system is able to generate variety of cells and molecules capable of recognising and eliminating limitless varieties of foreign molecules. Organ and the tissues of the immune system dot the body in a protective network of barrier to infection. Innate and adaptive immunity depends on the activity of white blood cells. Innate immunity largely depends upon granulocyte and macrophages, while adaptive immune response depends upon lymphocytes. Immunodeficiencies occur when one or more of the components of the immune system are inactive. Immunology is the most rapidly developing area of medical biotechnology research and provides great challenges with regard to the prevention and treatment of immunological diseases and autoimmune disorders.

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