INTRODUCTION
AND
REVIEW OF LITERATURE

IN THE NAME OF THE GOD THE MARCEFUL THE WHOLE MARCEFUL

IMMUNITY

Historical preface

The word of immunity is derived from its earlier usage refering to exemption from militry service or paying taxes. It has been recognized that those who recovered from epidemic diseases such as small box and plague were exempted from further attack and such immune individuals used in an epidemic to nurse those suffering from active disease. Imunology as a science began with the demonstation by Von Behring and Kitasto at koch institute in Brelin in 1890 of antibacterial substances or factors in the blood of animals immunized against tetanus and diphtheria organisms.

The neutralizing ability of such blood serum for bacterial toxins was the first demonsteration of the effect of what is now known as antibody globulin.

The part played by phagocytic cells in clearing away and destroying bacteria was recognized by Metchnikoff a russian biologist working in France, later the helpful effect of antibody called opsonin in enhancing phagocytosis became apparent lby Almiroth Wright .

Thus there are two different schools of thought on immune mechanisms, one beleaving the process to be brought completely by blood factors and others upholding an entirely cellular viewpoint. (D.M. Weir, 1983).

Immune response :

All vertebtrates possess an immunity system which is concerned firstly with the recognition of any foreign material introduced in the body and secondly with the rejection of this material.

The immune response covers all the activities which lead at the end to the elimination of the foreign material intorudced. (M.M. Sherif, 1984).

Types of immunity :

(I) Innate immunity (non specific defense mechanism)

The healthy individual is able to protect himself from potentially harmful micro-organisms in the environment by a number of very effective mechanisms, present from birth, which do not depend upon having previous experience of any particular micro-organism.

The innate immune mechanisms are non specific in the sense that they are effective against a wide range of potentially infective agents.

II. Acquired immunity :

can be classified into :

(a) Humoral immunity :

Means the production of antibodies (immunoglubulins) by special cells which derived from lymphocuytes.

(b) Cell mediated immunity.

Means tissue reactions by specifically sensitizal lymphocytes.

Mechanisms of innate immunity :

(1) Mechanical barrier and surface secretions.

(2) Bactincidal substances of the tissues and body fluids.

(3) Normal bacterial flara.

(4) Temperature.

(5) Humoral factors and phogocytes :

The acute phase materials are present in the blood and increase in level in inflammatory response, appears to be mediated by a protein termed "leucocyteic endogenous mediator that is released by phsyocytes.

(6) Complement system.

Phagocytosis and inflammatory response

Two types of phagocytic cells are recognized in the body

(1) Polymorphnuclear phagocytes (leucocytes) of the blood or microphages.

(2) Mononuclear phagocytic system or macrophages which are both circulating in the blood and fixed in the tissues (previously known as R.E.S.).

The three essential features of these phagocytic cells are :

(a) that they are actively phagocytic.

(b) that they contain digestive enzymes to degrade ingested material.

(c) the macrophages are an important link between the innate and acquired immune mechanisms, partially by passing on antigens or their products to lymphoid cells, and partially by retining antigens to ensure that lymphoid cells are not overhelmed by excess antigens.

Phagocytois by nutrophils is composed of four interrelated phases:

They are chemotaxsis, opsnization, ingestion and killing.

I. Chemotaxis : defined as the ability of motile cells to recognize and respond to a suitable chemical gradient with directional migration.

Chemotactic factors include:

a) Chemotoxins from invading micro-organisms eg. N-formyl methione.

b) Crystal induced chemotactic factors result from interaction of monosodium urate or calcium pirophosphate crystals with neutrophils.

c) Chemotactic factors produced through the mediation of the complement system following classical or alternative pathway activation eg. C_{5a} , products of complex $C_{5,6,7}$ through trypsin digestion.

d) Protein systems eg. kalikrin system and fibrinolysis system have a leucotactic activity.

e) Chemotactic lipids including prostaglandins

f) Factors inside leukcytes following contact with antigen.

II. Opsonization : The function of serum opsonins is to react with micro-organisms and make them more susceptible to ingestion by phagocytes.

Van oss (1983) postulated that non virulent bacteria possess relatively hydrophobic surfaces that favor phagocytosis ; while virulent bacteria have hydrophilic surface that retard phagocytosis.

According to this view, the purpose of opsonization is to increase hydrophobicity, there by reducing the charge repulsion between bacteria and neutrophils.

Three mechanisms are present during opsonization.

a) Specific antibody (subclasses of IgG and IgG may act as an opsonin.

Specific anticapsular antibody compined with surface antigen of bacteria through its F_{ab} portion and other F_c portion of antibody attach to F_c receptor jof phagocyte thus completing a bridge between bacteria and phagocytic cells.

b) Activated complement via classical C_1, C_4, C_2 pathway :

It requires specific antibody-antigen reaction. The receptor sites for activated C3 (C3b) are present on the surface of phagocytes and the activated C_3 on the bacterial surface serves as a bridge between bacteria and phagocytes promoting ingestion.

c) Activated complement via alternative pathway:

It does not require specific antibody-antigen interaction. It's activated directly by bacterial or fungal polysaccharides resulting in fixation of C_3 to the surface of the micro-organism, phagocytosis is mediated by cellular receptor for activated C3.

III. Ingestion :

Once a micro organism has been opsonised, the machinery of membrane locomtion is activated resulting in circumferntialflow of phagocyte membrane towards the particle, zipping up the particle into the formed phagosome.

(3) Myeloperoxidase (MPO) is deposited by degranulation into phagocytic vacuoles, where, in the presence of (H_2O_2) and halide it catalyzes microbicidal reactions. (4) Superoxide that escapes from the phagocytic vacuole is reduced by (H_2O_2) at an enhanced rate by superoxide of dismulase (SOD). Cytoplasmic (H_2O_2) is detoxified by the catalase and glutathione peroxidase gluthaione reductase systems. Both the superoxide forming NADPH oxidase and the glutathione systems generate $NADP^+$ in the course of their activity. This $NADP^+$ is converted back to NADPH by hexose monophosphate shunt.

(B) Degranulation :

Mean release of neutrophil contents of granules into phagosome, and into cell exterior.

a) **Primary granules :** Contain abundant lysosomal enzyme, large amount of myeloperoxidase, elastase and cationic proteins.

b) **Secondary granules :** Contain lactoferrin and lysozyme. The destruction of susceptible organisms within neutrophil is intimately associated with and affected by substances of degranulation. (D.M. Weir, 1983).

IV. Killing :

Phagocytes can bind microorganisms by various membrane receptors. The organism is phagocytosed and taken into

a phagocytic vacule (a phagosome) that then fuses with an enzyme containing lysosomal granule.

The formation of this phago-lysosome usually results in the destruction of the microorganism.

There are 2 main systems involved in this killing process:

I. **The oxygen dependent system** (peroxidase-myeloperoxidase halide system).

In oxygen dependent system phagocytosis is followed by an increase in hexose monophosphate shunt activity. This leads to conversion of oxygen to superoxide anion, hydrogen peroxide, singlet oxygen and hydroxyl radicals. These are all able to destroy microorganisms.

Myeloperoxidase generates free halide ions that have powerful bactericidal and vircidal activities, microorganisms can be classified according to their sensitivity to be killed by oxidant radical of oxygen dependent system into 2 groups :

a) Catalase-positive organisms : which require intracellular produciton of oxidant radicals for their destruction e.g. staphylococcus aureus 502A, Candida albicans.

b) Catalase-negative microorganisms : which do not require intracellular production of oxidant radicals for their destruction e.g. Streptococcus pneumoniae and Salmonella typhi-murium. (Moore L.C. 1984).

II. **Oxygen independent system :**

It includes low PH, lysozyme, lactoferrin, cationic proteins (leukin and phagocytin) and a variety of hydrolytic enzymes that damage bacterial cell wall and result in digestion of the organism.

The oxygen dependent system is further subdivided into :

1. **Myeloperoxidase mediated system** : components of this system include the following :-
   a) Myeloperoxidase.
   b) H_2O_2.
   c) Oxidizable factor (usually halide).
   d) Acid.
   e) Singlet oxigen.

2. **Myeloparoxidase independent system** : its components include the following :-
   a) H_2O_2.
   b) Superoxide anion.
   c) Singlet oxygen.
   d) Hydroxyl radical. (Zena Werb P.H.D., 1982).

a) **Myeloperoxidase** : found in the primary granules.

In conjucation with H_2O_2, oxidizable halide factor, and an acid PH, a potent antimicrobial system is developed in the phagolysosome which has antibacterial, antifungal, antiviral and antimycoplasma capabilities.

b. H_2O_2 : arise from the respiratory burst.

With deficient H_2O_2 production eg. in chronic granulomatous disease, certain micro-organisms may paradoxically provide the H_2O_2 which mediates their own destruction e.g. pneumococci & streptococci.

This may explain why patients with chronic granulomatous disease show no particular predisposition to streptococcal infection. (John Mills, M.D. 1983).

c. **Halide** : might damage micro-organisms by halogenation of bacterial cell wall, decarboxylation of amino acids with release of toxic aldehydes and production of singlet oxygen.

d. **Acid** : the MPO-mediated system has an acid PH optimum, a condition which is met in phagocytic vacule.

e. **Singlet oxygen** (O_2^1) : termed singlet oxygen because its emission lines remain unsplit in a magnetic field. It has the same molecular formula as atmospheric oxygen (O_2) but differ in destribution of electrons around the two oxygen nuclei.

It arises during the respiratory burst with particular propenisty to react with double bonds of biological systems and would be lethal to any micro-organism has these systems in its structure.

2. Myeloperoxidase independent system :

Its components H_2O_2, superoxide anion, singlet oxygen and hydroxyl radical (formed by itneraction between H_2O_2 and and superoxide anion) all may have a direct bactericidal effect independent of interaction or presence of myeloperoxidase. (David J. Drutz, M.D., 1982).