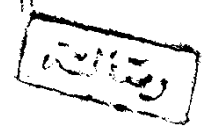
EFFECTS OF SOME NEW ANTIMICROBIAL AGENTS ON THE PHAGOCYTIC FUNCTION OF NEUTROPHIL LEUCOCYTES

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE DEGREE OF M.S. IN GENERAL MEDICINE



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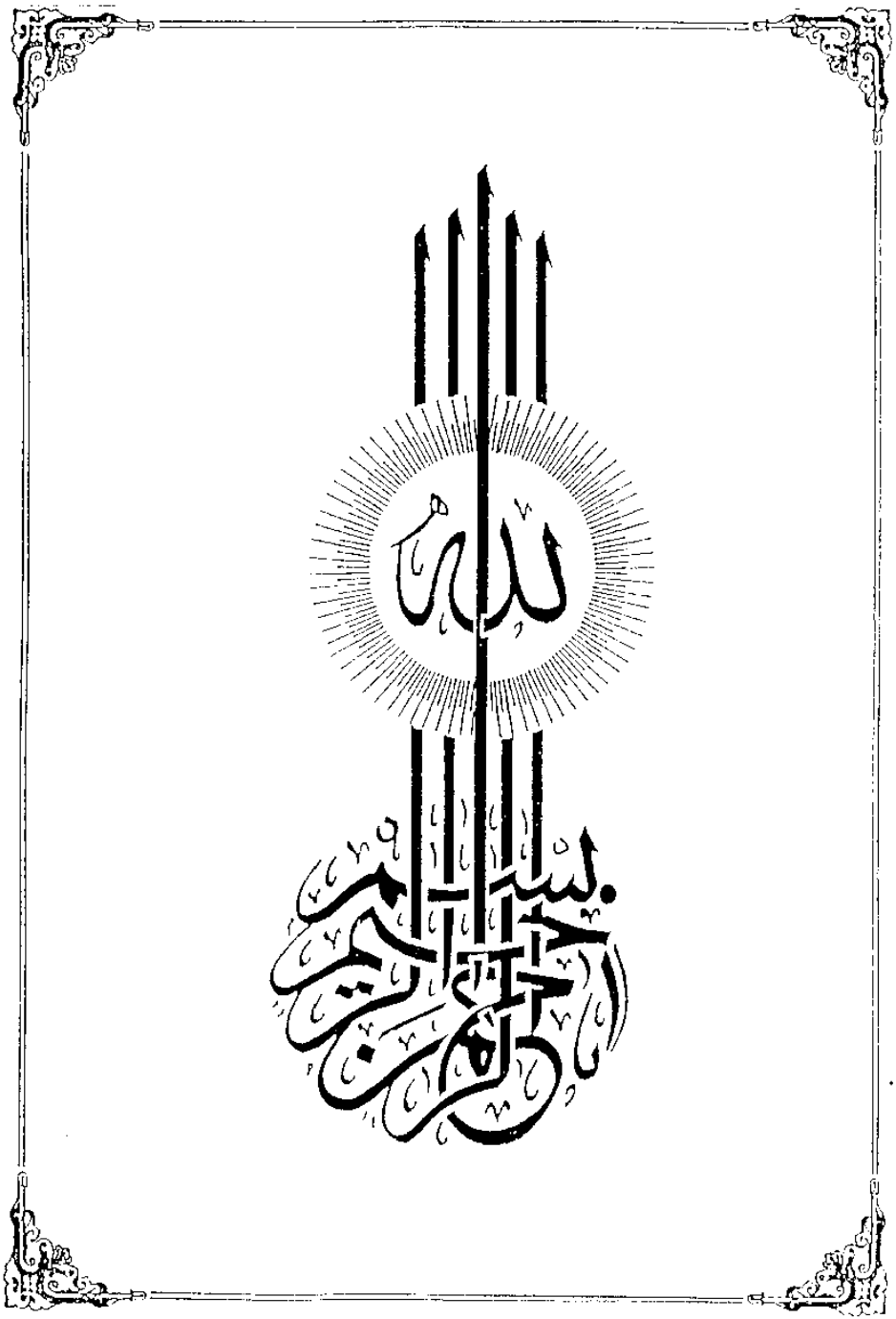

C O N T E N T S

INTRODUCTION AND AIM OF THE WORK

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New antibacterial agents are continuously being introduced for the treatment of bacterial infections , their effects are usually studied in relation to hepatotoxicity , nephrotoxicity , ototoxicity and haematotoxicity but their effects on the immune response of the host has been only sparingly touched upon . This effect on the immune response of the host is of particular importance in immunocompromised hosts and in relation to bacteriostatic agents .

Aim of the work :

The phagocytic function of neutrophil leucocytes is probably one of the main mechanisms by which the body can control an invading organism, the aim of the work is :

1. To review the phagocytic function of neutrophil leucocytes and the various methods to test this function .

2. To study the effects of some newly introduced antimicrobial agents on the phagocytic function of neutrophil leucocytes .

REVIEW OF LITERATURE

How Can The Body Combat Infection ?

The numerous host defense mechanisms protect man from onslaught of surrounding microbes and the resulting infectious diseases that may be precipitated . The integrity of this complex but highly integrated system includes relatively simple , non specific physical barriers provided by the skin and mucous membranes and the more complex mechanisms such as the involved metabolic events associated with ingestion of micro-organisms by phagocytic cells .

This marvelous system also produces the intricate cellular interactions of the immune response and the activation of the complement cascade .

Each system or mechanism performs specific, vital functions in host defense . For instance the phenomena of phagocytosis and microbial killing involve numerous diverse metabolic processes , many of which are dependent upon precise immune responses , such as opsonization .

We know that host defences can be compromised into two basic ways : the naturally occurring disease states and iatrogenically by various cytotoxic or immuno suppressive regimens . When this happens, the risk of infection increases, usually by those organisms arising from the particular area of defense that has been disrupted .

Therefore , a better understanding of the intricate and varied host-defense mechanisms will be of major importance to our knowledge of how diseases develop and, in turn , the implications for successful therapy .

(A) Non specific host-defence mechanisms :

Mechanical Barriers :

1. Skin :

A primary function of the epidermis , or external skin layer , is to provide a tough , resilient , protective barrier over the entire surface of the body (Rushmer , Buettner , Short et al. 1966). This is accomplished by the stratum corneum , which is a laminated epidermal layer of anucleate cornified cells . (Odland , Short et al; 1971). The stratum corneum is an unfavorable environment for most microorganisms other than the members of the normal flora (Pillsbury , Kilgman 1954) . There are several factors that prevent other potentially pathogenic organisms from actively multipling on the skin and assuming " normal flora " status . Two important factors are the low moisture content of the stratum corneum and the presence of naturally produced antimicrobial substances on the skin surface (Blank , 1959) . These antimicrobial substances are contained in a skin film of emulsified material contributed by sebaceous and sweat glands and products of cornification . Among the contents of the surface film are : (a) Lactic acid, amino acids , uric acid and ammonia derived from sweat glands ; (b) triglycerides , free fatty acids and wax alcohols from sebaceous glands ; and (c) sterols , amino acids , pentoses , phospholipids and complex polypeptides derived from the cornification process (Stoughton , 1959) .

The human body is constantly exposed to minor trauma , which produces many small defects in the skin barrier , however , this rarely lead to infection because of the complex systemic host-defense mechanisms beneath the skin . But major defects can change this situation , because sufficient numbers of micro-organisms can then invade and overwhelm the systemic defences , this can take place in pateints with extensive burns (Lowbury ; 1972) .

2. Mucous Membranes :

Like the skin , the mucous membranes of the respiratory and gastro_intestinal tracts are important elements in host defense. During normal breathing process numerous microorganisms are inhaled from the environment . Usually , the Upper airways and trachea deny entery of these microorganisms , or neutralize and remove them . These protective mechanisms are so extra ordinary efficient that the lung is normally sterile from the first bronchial division to the alveoli (Newhouse , Sanchis and Bienenstock ; 1976) . Tracheobronchial secretions and mucociliary transport are of prime importance in the barrier concept of the airway's surface .

Histologically , the respiratory tract mucosa is composed of densely ciliated , pseudo stratified epitheluim in which airway secretions are produced by both goblet cells and mucous secreting glands . (Rhodin ; 1966). The mucous itself provides a highly

effective barrier and trapping mechanism . In addition, airway secretions contain specific soluble factors such as secretory immuno globulin (I g A), and non specific factors , such as lysozyme, lactoferrin , and alpha$_1$-antitrypsin which possess bactericidal activity (Newhouse, Sanchis, 1976). An intact mucociliary transport mechanism moves the mucous blanket cephalad. This activity is essential for clearance and removal of foreign materials , including micro-organisms deposited in the respiratory tract . Various physical , chemical or biological agents can be toxic to cilia . They impede mucociliary transport , resulting in suppression of this aspect of pulmonary host defense . (Rhodin; 1966).

The gastrointestinal mucosal barrier is quite similar to that of the respiratory tract except that it does not have true cilia . However most of the tract is covered with a fine layer of mucous , which serves a similar function . In normal subjects , the stomach and proximal small bowel contain relatively small numbers of bacteria.

Proceeding distally, the numbers increase dramatically, and populations of resident bacteria change . The acid contents of the stomach destroy most ingested bacteria . Those that pass into the small bowel and remain viable are swept into the colon where they tend to concentrate in the sticky mucous lining the digestive mucosa (Gorback et al; 1967).

The cleansing effects of peristalsis and evacuation prevent unchecked growth of microorganisms . This is illustrated by the fact that bacterial overgrowth usually follows slowing or interruption of normal intestinal motility . An intact mucosal barrier is a biological necessity . When the barrier is compromised , as by cytotoxic chemotherapy for neoplastic diseases , leakage of microorganisms will occur . The result is often a devastating infectious disease complication (Donaldson, 1973) .

Phagocytic cells :

There are two major categories of phagocytic cells in man : (a) The circulating phagocytes of the blood which include the granulocytes (neutrophils , eosinophils and to a much lesser extent the basophils) and the monocytes , and (b) the fixed phagocytes or macrophages of the tissues , particularly the reticuloendothelial system , (R.E.S.) .

In the past phagocytosis seemed a simple matter of ingesting and feeding . But more recent research has shown that the process involves numerous complex and sophisticated mechanisms . These include a delicately balanced interrelationship among kinetics , circulatory capabilities , chemotaxis , phagocytosis ; intra - cellular killing and digestion , and even cell mediated cytotoxicity . (Metchnikoff , 1887).

Phagocytic cells and phagocytosis will be discussed in details in the next chapter .

Other Nonspecific Factors of Host Defense :

1. Fever :

Fever is a non specific factor that accompanies most infectious diseases . Its exact function , if any , in host defences is still not under stood . The pathogensis of fever has long been the subject of intensive study (Wood ; 1958) .

It has now been demonstrated that the final common mediators of fever are endogenous pyrogens . These proteins, which are synthesized by the phagocytic cells of the host, act on specific neurons of the anterior hypothalamus preoptic region of the brain (Dinarello , Wolff , 1976) .

An interesting data have emerged from animal studies showing that temperature elevation may indeed have a beneficial effect on the host incertain infections (Kluger, Ringler & Anver, 1975). Subsequent studies by other authers demonstrated that artificial temperature elevation markedly facilitated the early local inflammatory response to subcutaneously injected organisms . (Berheim; 1977).

2. Interferons :

They are low molecular-weight proteins produced by viral-infected host cells . Most interferons are manufactured by monocyte-macrophages

and lymphocytes , although other cell types can produce them . The primary function of interferons is to limit the spread of viral infection . They act on the host cell by inducing the synthesis of translational inhibitory proteins . These block the replication of invading viruses , and thereby protect noninfected cells from virus released from already infected cells (Grossberg , 1972 ; Baron et al. 1966 ; DeClercq , Stewart, 1973) . Interferons are relatively spieces specific, although they display a wide range of non specific antiviral activity (Hoeprich , 1972) . In addition to viruses , a variety of other agents can induce interferon production. These include other microorganisms such as bacteria , rickettsia , fungi , and protozoa , as well as plant lectins , bacterial endotoxins, double-stranded RNA and synthetic polymers . (Grossberg , 1972).

3. Nutrition :

Adequate nutrition is also obviously important in host resistance to infection . From epidemiological and historical view points , malnourished individuals are more susceptible to infection . This can be documented in animals, but controlled studies in humans are obviously not feasible . However , there are data from studies in severaly malnourished individuals . These indicate that a variety of host-defense defects exist, including those related to phagocytosis and chemotaxis (Wolfsdrof , Nolan, 1974 - Chandra , Chandra , Chai, 1976).

4. Other, less well defined, nonspecific elements such as heridity , hormonal factors and others play a part in host defense against infection . (Hoeprich , 1972).