STUDY ON THE EFFECT OF SOME NEWLY INTRODUCED ANTIMICROBIAL AGENTS ON PHAGOCYTIC FUNCTION OF POLYMORPHONUCLEAR LEUCOCYTES

Thesis

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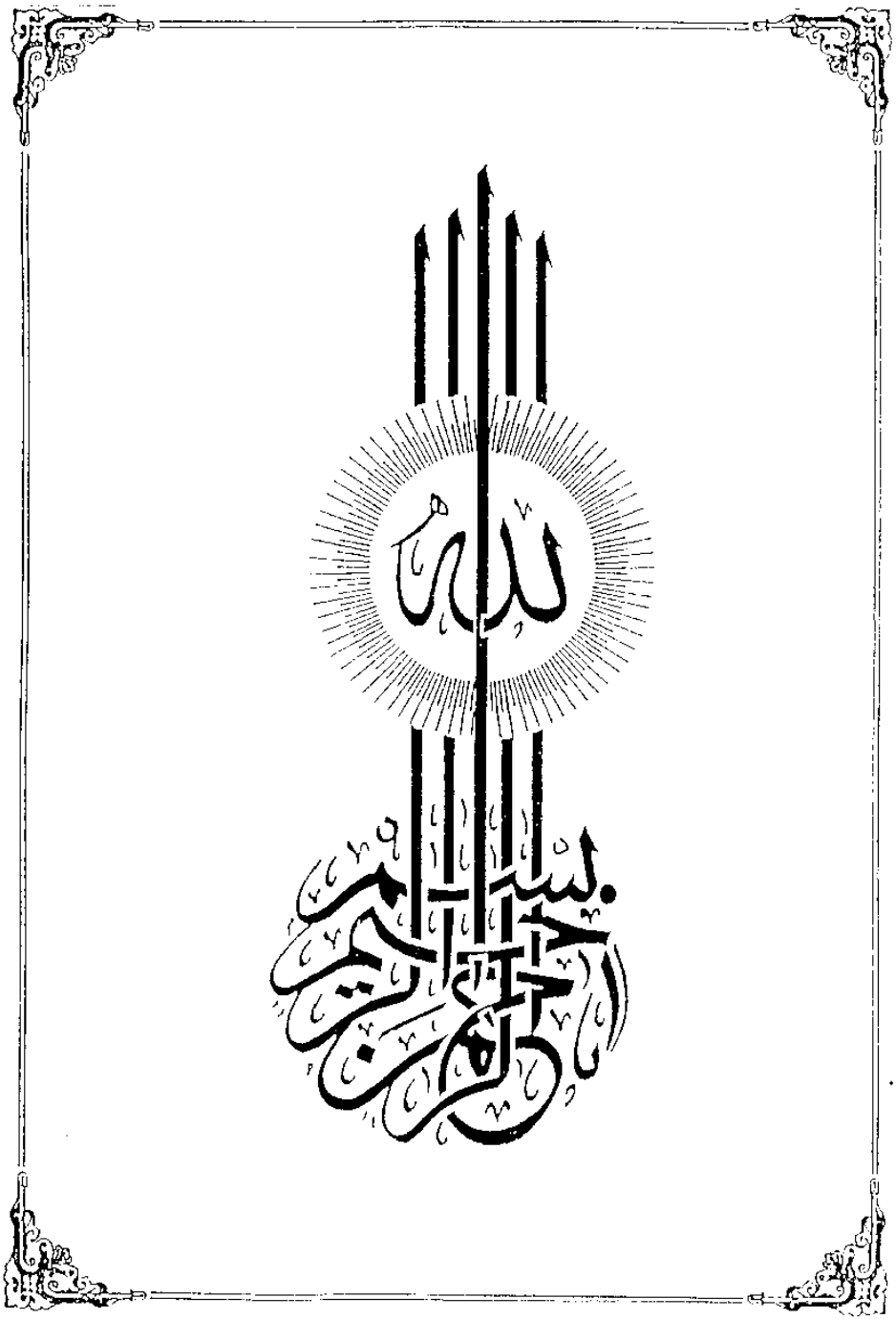

TO MY FAMILY

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Antibiotics function effectively alone as antibacterial agents in vitro. In human with bacterial infections, antibiotics presumably work in collaboration with natural defence mechanisms such as polymorphonuclear leucocytes, antibodies, and complement in order to eradicate bacterial pathogens. Since most antibiotics primarily inhibit cell wall synthesis or protein metabolism of bacteria, it is conceivable that they secondarily alter structure and function of human host cells (Faden et al., 1985).

Human polymorphonuclear leucocytes, because of their ability to phagocytose and kill micro-organisms, serve as the corner stone of defence mechanism against invading bacteria. Several antimicrobial agents have been shown to interfere with the phagocytosis process either directly by influencing the chemotaxis, phagocytic and bactericidal activity of the phagocytic cells, or indirectly by inducing changes in target micro-organisms (Hauser and Remington, 1982), but some other antimicrobial agents have shown a stimulatory effect (Milatovic, 1982).

In our department, several researches were done to investigate this point, as El-Hawary et al., 1984, studied

the effect of twelve antibiotics on phagocytic index of neutrophil leucocytes using heat killed Candida.

These antibiotics were gentamicin, tobramycin, netilmicin, amikacin, aztreonam, cephradine, cefamandole, ticarcillin, spectinomycin, amoxycillin, clavulanic acid, and augmentin. The concentrations of these antibiotics were adjusted to be the same as their average therapeutic serum levels. Their results showed that eleven of the tested antibiotics showed slight statistically significant inhibitory effect, while amoxycillin showed no statistically significant inhibitory effect.

Hemida et al., 1988, studied the effect of 5 antimicrobial agents namely clindamycin, ofloxacin, norfloxacin, ceftriaxone and cefodizime on leucocyte phagocytosis of heat killed *Candida albicans*, living *Staph aureus* and *Pseudomonas aeruginosa*, employing the usual and half the usual therapeutic concentrations. They showed that clindamycin in its small dose had a highly significant stimulatory effect on phagocytosis of killed Candida and significant for both Staph and Pseudomonas leucocyte phagocytosis also. The usual therapeutic dose was inhibitory. Regarding ofloxacin, the small dose was observed to be significantly stimulatory and the usual therapeutic dose was non significantly inhibitory for phagocytosis of the three organisms. Regarding norfloxacin and Ceftriaxone,

it was also noticed that both had non significant inhibitory effect on phagocytic index of the three tested organisms in both concentrations used. With the small concentration of cefodizime, it was observed to have a highly significant stimulatory effect on phagocytosis of killed Candida, a significant stimulatory effect on Pseudomonas phagocytosis, and a non significant inhibitory effect on Staph phagocytosis. The large dose was non significantly inhibitory for phagocytosis of the three tested organisms.

All the previous studies had been done in vitro that is why, this thesis was carried out to study the in-vivo effects of some newly introduced antimicrobial agents on one aspect of the immune system that is the phagocytic function of the human polymorphonuclear leucocytes in a trial to correlate their effects with the clinical response of the patients and to compare the results with those of in-vitro studies.

REVIEW OF LITERATURE

MECHANISM OF RESISTANCE TO INFECTION

The immune response is made up of a complex sequence of events; it is triggered by the introduction of a stimulus (antigen) and usually culminates in the elimination of the provoking agent. Indeed, the primary function of the immune response is to discriminate between self and non self and thereby to eliminate the letter. There are 2 levels of defence against invasion by external agents: innate immunity and adaptive immunity.

Innate Immunity:

Sometimes called natural immunity, is present from birth and includes numerous non specific elements.

1- Body surface, especially skin, forms the first line of defense against penetration by microorganisms (Goodman, 1991).

There are several factors that prevent pathogenic microorganisms; two important factors are the low moisture content of stratum corneum and the presence of naturally produced antimicrobial substances on the skin surface (Blank, 1959).

Mucous Membrane: there are several protective factors for the mucous membrane including:

1) A resident bacterial flora that inhibits the growth of potential pathogens.

2) Mucosal motor activity (peristalsis and ciliary function) that maintains the flow of mucosal constituents, reducing the interaction of pathogens with epithelial cells.

3) Substances such as gastric acid and intestinal bile salts that create a mucosal environment unfavorable to the growth of pathogens.

4) Mucus secretions that form a barrier between potential pathogen and the epithelial surfaces (Strober and James, 1991).

When penetration does occur, the invading organisms initially encounter other elements of innate immune system; the enzyme lysozyme is widely distributed in secretions and can damage the cell walls of many bacteria. Similarly, the alternative complement pathway is directly activated by a variety of bacteria; this may result in clearance of the bacteria via lysis or via facilitation of phagocytosis by macrophage, which posses receptors for certain components of the complement system, and by polymorphonuclear neutrophils,

for which activated complement components are chemotactic (Goodman, 1991).

Phagocytosis is the most important activity in the natural defence against microbial diseases. It is the process by which cells internalize particulate material from the extracellular environment (Sheterline et al., 1984).

Interferons:

They are low molecular-weight proteins produced by viral-infected host cells. Most interferons are manufactured by monocytes and lymphocytes. The primary function of interferons is to limit the spread of viral infection. They act on the host cell by inducing the synthesis of inhibitory proteins. These block the replication of invading viruses, and thereby, protect non infected cells from virus released from already infected cells (Grossberg, 1972).

Adaptive Immunity:

The adaptive immune response is triggered by the presence of a foreign agent that escape early elimination by the innate immune system and is distinguished by a remarkable specificity for the offending immunogen and by its memory. The principal players in the adaptive immunity are antigen-presenting cells (APC), thymus-derived lymphocytes (T.cells), and bone marrow-derived lymphocytes (B cells). T cells produce soluble molecules with many

effects, and B-cells eventually result in antibodies formation. So in adaptive immune response antigen is initially taken up and processed by antigen processing cells, which express fragments of it called immunogenic epitopes to helper T-cells. Activated helper T-cells regulate the activities of other lymphocytes in a positive fashion through the secretion of soluble factors called lymphokines. One of these, interleukin-II an activating signal for cytotoxic T-cells, which recognize antigens on the target cells. helper T cells also furnish growth and differentiation signals to B-cells, which then differentiate into antibody-secreting plasma cells. The basis for memory in the immune response is the generation of antigen-specific helper T-cells and B-cells, those memory cells are regarded to make amplified responses upon subsequent encounters with the some antigen in secondary responses (Goodman, 1991).