Biochemical Studies On the Effect of New Biological Active Compounds On Living Cells

THESIS

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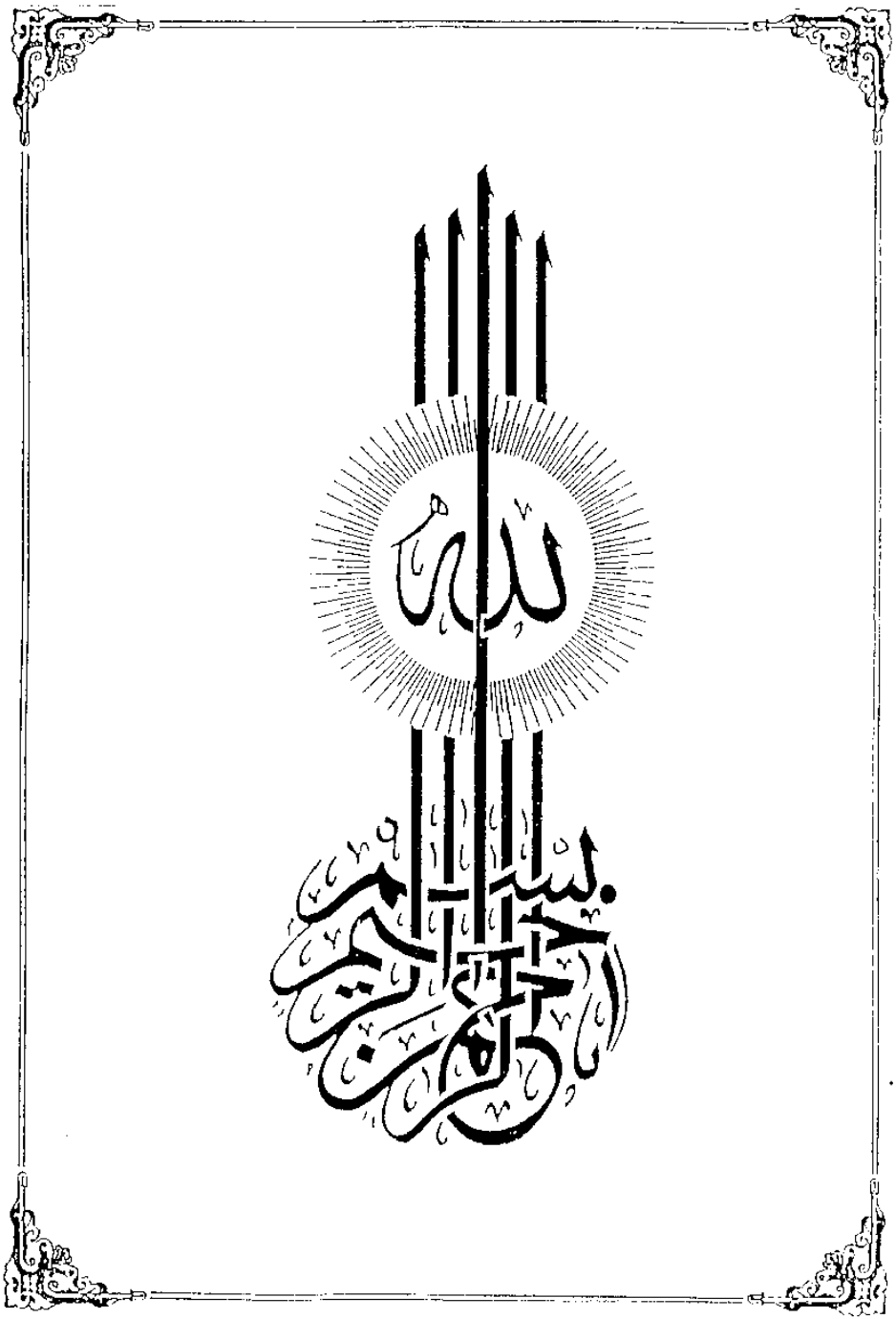

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INTRODUCTION

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Nowadays synthetic antimicrobial agents play a large part in the control of various infectious diseases. The use of these agents is an important landmark indicative of the rapid development of synthetic techniques. The main target of using chemically synthesized agents is to modify different functions and interfere with the biological functions of microorganisms.

Synthetic compounds represent the largest group of therapeutic agents, they are compounds neither occuring naturally , nor derived from natural products. Many drug resembling agents are manufactured synthetically rather than by extraction from tissues ***(Briggs, 1974).***

Some microbes are gradually developing resistance against antimicrobial drugs in common use implies continuous search for new effective compounds which are able to circumvent the acquired resistance of organisms . Several research centers around the world are now involved in such efforts which resulted in the production of several new members of synthetic compounds such as quinolones ***(Lendnicer and Mitscher, 1990),*** nitrofurans, semi-synthetic penicillins, and novel B-lactam antibiotic ***(Betina, 1983).***

A chemotherapeutic agent may be defined as "a synthetic chemical substance designed to treat infections by destroying the infecting organisms when administered to the host without injuring the tissue of the host" .The range therefore, of these agents effect extends from that on multicellular forms (as moulds and malignant tumors) to unicellular bacteria and viruses ***(Busch and Lane, 1967).***

In ***Goldestein et al. 1968*** stated that the ideal antimicrobial agent can be considered under the following headings:-

(1) Activity :-

The ideal antimicrobial agent should be effective against a wide range of microorganisms, that is , it should have a broad spectrum of activity against pathological organisms without significantly affecting commensal organisms . In addition, it should be rapidly, bactericidal and generates no resistant organisms during therapy ***(Sollman, 1975).***

(2) Toxicity :-

A low toxicity is essential, whether antimicrobial agent is used for short term or prolonged therapy. The ideal agent should not act as a sensitizing or a photosensitizing agent

and if it is to be applied topically it should not act a primary irritant.

Antimicrobial agents should not affect the metabolic actions or functions of vital organs, and an ideal agent in general should have no contraindications, such contra-indications should not be limited to the absence of immediate toxic effects.

3- Chemical and Physical Properties:

Such properties are important in determining the mode of administration and keeping properties (stability) of a particular antimicrobial agent .Ideally, the antimicrobial agent should be stable in the dry state and in solution over a reasonably long period of time (two years), preferably water soluble and not destroyed by digestive juices,so that it can be administered orally and also, if needed parenterally.

The physical form is also important, micronization of particles for example , has produced better absorption .

4- Pharmacology :

The absorption, distribution in body tissues and fluids, metabolism and excretion should be such that an

adequate concentration can be rapidly reached in the environment of the infecting organisms and maintained there for several hours. The antimicrobial agent which is quickly metabolized and excreted will result in the inconvenience of very frequent or even continuous administration . It is essential that the drug reaches therapeutic levels in serum and particularly at the site of the infection . In addition, under normal circumstances, the mean agent level attained must exceed the minimum inhibitory concentration (MIC) for the particular infecting organism. The activity of the antimicrobial agent should not be appreciably reduced by many of the body fluids or exudates ***(Binns and Dodds, 1964)***,.

5- Interactions :

The ideal antimicrobial agent should not interact with other substances in the environment .

6- Cost :

It is important that an antimicrobial agent should be reasonably cheap so that social , domestic, or political directives do not interfer with its choice or use.

SELECTIVITY OF ACTION OF ANTIMICROBIAL AGENTS

In the study of any useful antimicrobial agent it is not sufficient just to explain its action on the metabolism of the microorganism, but it is necessary to study the action of the compound on the biochemistry of the host cell as well as of the parasite. The basis of selectivity varies from one drug to another. The process inhibited may occur only in the microbial cell, so there is no reaction for the host cell to be affected. Other agents act on biochemical mechanisms found in both microbial and animal cells, but for some reasons affect only the former . In such cases the reason for this differential action is still obscure and evidently reqired further study ***(Franklin and Snow, 1989).*** Yet another type of selectivity depends on the concentration of antimicrobial agent within microbial cell, but not in the host cell Thus even though at the ultimate site of action of the drug is equally inhibitory to both ,its greater concentration in the microorganism ensures the necessary selectivity. Here the question shifts to the reason for the selective concentration, and understanding of these mechanisms at the molecular level is still limited.

THE BIOCHEMISTRY OF MICROBIAL RESISTANCE

The therapeutic value of an antimicrobial agent often declines after prolonged use through the emergence of organisms which are no longer sensitive to the compound . This problem of expanding practical importance has been studied by microbiological, biochemical and molecular genetic methods . Such studies will usually show the means by which resistance has been acquired, either by selection or by genetic transfer through a plasmid or by phage infection ***(Eriksson and Grennberg, 1968).*** The resistance mechanism of some forms still need further study and there is obviously great practical interest in methods of preventing the acquisition of resistance or of combating resistance once it has arisen.

The practical value of resistance studies has already been proved by the development of successful antibacterials, in which the original molecules have been chemically modified to render them insusceptible to bacterial enzymes responsible for important types of resistance ***(Gale et al., 1981).***

Bacterial species in which most strains are sensitive to a newly introduced antimicrobial agent, we find that a few strains are already resistant at the time the drug is introduced.The

classic example of pre-existenting resistance is *staphylococcus aureus* and penicillin as described by ***George and levy (1983).***

Mechanism of Resistance

Bacteria have inventive and versatile ways to resist antibiotics and other toxic elements ***(Levy, 1992).*** It was formerly usual to classify resistant bacteria into two groups : those able to grow in the presence of different unchanged levels of the antibiotic which are lethal to sensitive cells, and those able to destroy the drugs. In the light of recent discoveries it is more useful to consider four mechanisms by which resistance can arise. These are:

1. Alteration of target site to reduce or eliminate binding of the drug into the target.
2. Blockage of transport of the agent into the cell.
3. Destruction or inactivation of the antibiotic.
4. Metabolic by pass-providing the cell with a replacement for the metabolic step inhibited by the drug ***(Greenwood, 1989).***

MISUSE OF ANTIMICROBIAL AGENTS AND CAUSES OF FAILURE IN ANTIMICROBIAL THERAPY

There are still some infections that do not respond to any of the currently available antimicrobial agents. It is therefore useless to treat such infections with any antimicrobial agent or antibiotic. However, some infections due to large viruses respond to treatment with suitable antimicrobial agents , especially the broad spectrum type and also to certain chemotherapeutic agents such as amantadine.

Antimicrobial agent or antibiotic therapy may fail because of incorrect dosage. The dosage may be too small or the correct dose may be given for too short time or by the wrong route . The dose will depend on the severity of the infection. Resistance to antimicrobial agents may be also a cause of therapy failure.

Generally , failure following antimicrobial therapy may be due to :

1. The organism is not susceptible to the action of the antimicrobial agent used.
2. Although originally susceptible, the organism may have become resistant.