The Biochemistry and Pharmacology of Antibacterial Agents

R. A. D. Williams and Z. L. Kruk

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FOREWORD

Antibiotics are amongst the most widely used of drugs and the effectiveness of the multitude of agents available in curing fatal and severely disabling illness places them in the highest category of pharmaceuticals in terms of benefit to man. Infections, unlike many of the other major categories of diseases, can attack the person who is otherwise perfectly normal and curing of the infection can restore the patient to his original state of health. Many of the early studies on penicillin lay emphasis on its almost miraculous effects on previously fatal diseases.

The wide range of infecting agents in man determines the need for a wide range of substances with which to combat the infections, agents which can attack the differing vulnerable sites on the microbial cells. A much clearer concept of how to use antibiotics clinically is obtained if there is an understanding of the way the substances work, an understanding of what are the targets of antimicrobial action and how available are the targets of the different cells to the antibiotic. Without this basic knowledge, use of antibiotics clinically can become a speculative exercise in which we merely hope we have chosen the most appropriate of the array of substances for a particular patient. In this book the authors explain the ways in which antibiotics can disrupt the normal processes of bacterial growth, metabolism or replication, leading either to death of the microbial cell or to an inhibition of its processes to such an extent that the defence mechanisms of the host are able to overcome the invader. This small monograph should do much to provide the future prescriber of antibiotics and others whose work involves antibiotic use with a clear picture of the intricate mechanisms which are the focus of antibiotic action and the ways in which the antibiotics can alter the mechanisms. Antibiotics are so valuable it is impossible to learn too much about them.

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PREFACE

Antimicrobial drugs are amongst the most important compounds in medicine and by their use infectious bacterial diseases have been largely abolished as a major cause of loss of life in more affluent countries. These substances are often dealt with in the traditional medical curriculum at various times by different specialists. Biochemists are concerned with the basic cellular processes against which the antimicrobial agents are effective, and often introduce the teaching of the subject by referring to the more important drugs when describing the metabolic process that they affect. Pharmacologists are concerned with the absorption, distribution, metabolic transformation and untoward effects of the antimicrobial agents, amongst many other drugs. Later in the curriculum medical microbiologists describe the types of microorganisms against which the compounds are particularly effective, the testing of clinical samples for their sensitivities, and the important problems associated with resistant strains. In integrated curricula a more satisfactory unified approach to the subject may be possible, but one problem for the student that remains is that of availability of information, which is often scattered. The objective of this book is to unite the biochemical and pharmacological aspects of the use of common antimicrobials in a brief book suitable for the preclinical medical course, for medical microbiology units of science degrees and for some postgraduate courses.

1 INTRODUCTION

1.1 Historical Introduction

The earliest chemotherapeutic agents known to man were of plant origin. The Greeks used extract of male fern to treat infestation by worms, and extracts of cinchona bark were used in South America to treat malaria. Mercury, which was used to treat syphilis, was the first substance not of plant origin to be used chemotherapeutically. Until the beginning of the twentieth century preparations such as these were the only chemotherapeutic agents available.

At about this time, as an extension of his work on dyes and differential staining of tissues, Ehrlich developed the concept of cell surface *receptors*. These were defined as sites which were recognised by chemicals of a particular structure and to which the chemical became attached. Ehrlich considered that different cells might have different receptors to which chemicals could bind selectively. He reasoned that chemicals which bound to and were toxic towards pathogenic cells or organisms (but which did not bind to and therefore were not toxic to the host's cells) would be ideal drugs to treat infections. In the event, Ehrlich discovered arsphenamine (Salvarsan), an arsenical drug which was used to treat syphilis until it was superseded by penicillin in the 1940s. Work on dyes as chemotherapeutic agents continued, leading to the development of sulphonamides (see Chapter 2).

In 1928, Fleming observed that extracts from *Penicillium* could inhibit the growth of certain bacteria. Ten years later, Chain and Florey proved that such extracts could inhibit bacterial growth in mice as well as in cultures, and when in 1941 Abraham demonstrated the effectiveness of penicillin in man the era of antibiotic chemotherapy had begun. The search for other antibiotics was undertaken in many centres and to date about 5000 different substances have been discovered, many of which have found a use in chemotherapy of human infection.

1.2 Some Definitions

Chemotherapy is the study and practice of the use of drugs to damage an invading species without damage to the host. Since the time this definition was made by Ehrlich, the term chemotherapy has been applied not only to drug treatment of parasitic infestation by unicellular and multicellular organisms, but also to drug treatment of cancer. Whereas only those chemotherapeutic agents which are active against bacteria will be considered in this book, the principle of *selective toxicity* is the basis of all chemotherapy. The selective toxicity of chemotherapeutic agents aims to exploit differences in the biochemistry of host and parasite, or differences between normal and cancer cells, thus causing damage to the microorganisms or tumour cells while leaving the host's biochemistry undamaged.

Antimicrobial agents are those chemotherapeutic compounds which are toxic to microorganisms. Antimicrobial agents may be used outside the body, on the surface of the body, or systemically. *Sterilisation* is the destruction of all microbial life by chemical or physical means. Thus *disinfectants* such as phenols, 'Lysol' and sodium hypochlorite are caustic or toxic chemicals which are used in drains and places with heavy microbial populations. Heat and radiation are alternative methods of sterilisation. *Sanitising agents*, *antiseptics* or *germicides* (these terms are used interchangeably) do not sterilise completely, but they reduce the microbial population to acceptable levels. These substances are milder than disinfectants, may be suitable for use on living tissues and include, for example, dilute solutions of chlorinated phenols and acriflavine in wound dressings.

Antibiotics are chemicals produced by microorganisms (bacteria, fungi and actinomycetes) which are highly toxic to other microorganisms when the chemical is present in very low concentrations. Some antibiotics can be chemically synthesised, but most are made by culturing microorganisms under closely-controlled conditions. Whereas some antimicrobials are *bactericidal*, i.e. they kill the bacteria, in the treatment of disease it is frequently not necessary to kill all the infective microorganisms. A compound which is *bacteristatic*, i.e. it prevents further growth of the bacteria, allows the host's normal defence mechanisms to clear up the infection. The two types of action are not clearly distinguishable because the only test of whether bacteria are alive is their successful growth. It is important to remember that most chemotherapeutic agents *do not* eradicate all the infective