Antimicrobial Drug Action

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Preface

While teaching the action of antimicrobial drugs to B.Sc. students studying microbiology I was struck by the absence of an adequate text which included a general review of the principles of drug action and their mechanisms. In writing a suitable book I have collated material which is not only relevant but which gives a suitable background to drug action. Consequently, the book may be studied in a logical sequence starting with the principles of drug action and thence progressing to the more rigorous biochemical treatment of the mechanisms of drug action.

In adopting this approach I hope that the student will realise that drugs are regarded in the context of the disease which they attempt to control and not merely as interesting problems of biochemistry and molecular biology. It should also be realised, nevertheless, that the study of such drugs has enabled significant advances to be made in biochemistry and provides a foundation upon which medicinal chemists can build to produce new and better drugs. The overall approach in preparing the book is therefore the presentation of a balanced view of drug action which encompasses both the medical and biochemical aspects. In this I hope I have succeeded and trust that students will find the book useful.

D. E.

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PART 1
GENERAL PRINCIPLES AND SELECTIVE TOXICITY

1 History of Antimicrobial Chemotherapy

1.1 INTRODUCTION

The impact that antimicrobial chemotherapy has on society affects every person, for it is unlikely that anybody will live out his or her life without receiving some form of antimicrobial drug therapy. And it is only within the last 40 years that any effective chemotherapy has developed such that few diseases nowadays can be regarded as killers.

The history of antimicrobial chemotherapy can be divided into two major phases—ancient chemotherapy which takes us to about 1600, and modern which extends into the present. The origin of chemotherapy is lost in antiquity, but has some interesting points. All ancient medicines, for example, included eating earth, the favourite one being red or yellow, having a strong smell, or being greasy. These earths would be comparatively rich in moulds and may even have had a beneficial effect. Hippocrates, in 460 B.C., was the first to realise that disease was not caused by the anger of the Gods, by evil, or by magic, but rather by miasmata—impurities in the air. From this time the importance of magic and spells waned in their use until Aristotle, 150 years later, observed that phthisis, leprosy, scabies and plague could be transmitted by contagion. This heralded the beginning of medicine as a subject which could be studied in its own right. From then until the sixteenth century little progress was made. Nature's remedies abounded on a principle that natural products were effective. Among these menstrual blood was a favourite remedy for practically everything and some of the more bizarre recipes included a bath of menstrual blood with agrimony, hyssop and ground ivy, together with an ointment of goose and chicken fat and chicken excreta, as completely effective for leprosy and venereal disease. The author of this recipe was Hildegarde von Bingen, Abbess of the Rupertsberg Nunnery during the twelth century, and seems to be one of the few privileged people to be able to put her own recipes into practice. One of the most interesting observations of the Abbess is contained in her 'Physica', where she observes that many fungi which grow on dead and living trees are good medicine and gives a remarkable list of fungi and the diseases that they cured, many of which are known today as having antimicrobial activity.

Modern antimicrobial chemotherapy developed in three eras. The first, which lasted from about 1600 to 1900, involved the use of an extract of the bark of the

cinchona tree to treat malaria successfully and the subsequent development and use of other alkaloids. The active principle of cinchona bark, quinine, was first isolated much later (in 1820) and is still in use today. Other alkaloids included extracts of the root of ipecacuanha for amoebic dysentery, a remedy widely used in Brazil and Asia and introduced into Europe early in the seventeenth century. The active constituent is the alkaloid emetine, identified in 1817 and shown to be effective against amoebic dysentery in 1891. These two alkaloid sources provided the only effective chemotherapy during this era.

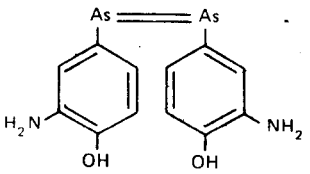
The second era is that of synthetic compounds which began around 1900. The first success came from Germany, where Ehrlich's work laid the foundations upon which all antimicrobial chemotherapy is built. Ehrlich began his scientific career in Koch's laboratory (the founder of modern bacteriology). In 1906, in a speech at the opening of the Institute he was to direct, he first described precisely this theory of substances which would seek out and destroy microbes—the *magic bullets*—and he coined the word 'chemotherapy' to describe his work. A turning point came when it became possible to infect mice with trypanosomes and he quickly discovered several dyes, including trypan red, which cured infected mice. Later, in 1909, when Hata demonstrated in Ehrlich's institute that syphilis could be made to infect rabbits, work to find a cure was intensified. At that time 10 per cent of the French population died of syphilis and 6 per cent in Germany. The effectiveness of salvarsan in treating syphilis was a milestone in chemotherapy. Because of some unpleasant side effects, a derivative—neosalvarsan—was introduced in 1912. Subsequently, more drugs were developed as an extension of Ehrlich's work, the most notable being suramin, introduced in 1920, developed from trypan red and having useful activity against trypanosomiasis, and mepacrine (quinacrine, atebrine), first introduced in 1933, developed from methylene blue, as an effective antimalarial agent of particular value in the Second World War.

The next major step forward came in 1935 when Domagk in Germany began work on the effect of a number of dyes on mice infected with streptococci. One compound, prontosil, was effective and Domagk even had the courage to use it on his daughter, who was desperately ill from a streptococcal infection, before the drug had been tested in humans. The girl recovered dramatically. Prontosil was the first of the sulphonamides. The observation by the husband and wife team, the Trefouëls, in the Pasteur Institute that prontosil was ineffective *in vitro* indicated that animals and humans converted the drug to an active component which was the agent lethal to the bacteria. Domagk quickly discovered that the drug hydrolysed to give sulphanilamide.

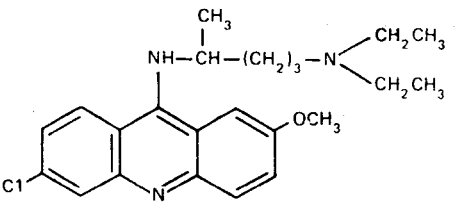
In 1938 another sulphonamide, sulphapyridine, was produced by May and Baker Ltd, Dagenham, and became famous as M&B 693. This drug was spectacularly successful against pneumonia, meningitis, staphylococci and gonorrhoea. The synthetic era of chemotherapy continues apace and in parallel with the antibiotic era. Indeed there is every reason to suppose that synthetic drugs will be produced long after antibiotics have been discarded because of problems of microbial resistance. Notable achievements of synthetic antimicrobial agents since 1935 include

isoniazid, *p*-aminosalicylic acid and ethionamide for tuberculosis and the nitroimidazole drugs for infections by anaerobes, amoebic dysentery, trichomoniasis and radiosensitisation of hypoxic tumours.

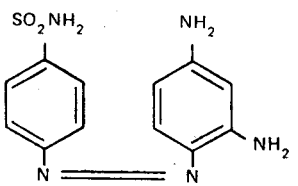
Although it is widely regarded that the antibiotic era began in 1929 with Fleming's discovery of penicillin, the real beginning was the recognition by Florey and his team of the chemotherapeutic potential and potency of the drug. The



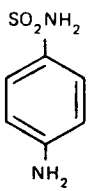
Salvarsan



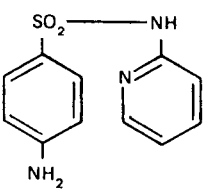
Mepacrine



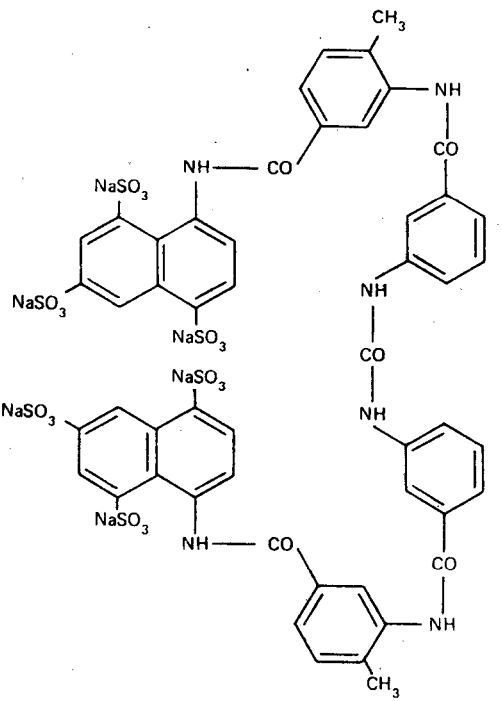
Prontosil



Sulphanilamide



Sulphapyridine (M&B 693)



Suramin

Figure 1.1 The structures of some antimicrobial drugs

announcement in 1940 marks the beginning of the antibiotic revolution which still continues today. Penicillin was used in the 1940s with enormous success against gonorrhoea, scarlet fever, pneumonia and meningitis, and began to replace sulphonamides in the treatment of puerperal fever, and neosalvarsan for the treatment of syphilis. The formulae of some of these agents are shown in figure 1.1.

The discovery and origin of antibiotics is discussed in chapter 2.

1.2 THE FUTURE

There is evidence that the antibiotic era may have reached its peak, but certainly no visible decline in antibiotic usage is predictable within the next 10 years. Instead, with increased drug legislation it is becoming increasingly difficult to produce a drug that will pass all the tests and regulations of the major countries of the world. As a result, with fewer new drugs becoming available and the ever-increasing threat of microbial drug resistance growing, there are three basic lines of research and development on which the future of antimicrobial chemotherapy depends. The first is an obvious corollary of any drug design programme—that of designing derivatives or structural analogues of existing drugs with a view to increasing their efficacy and/or decreasing their existing toxicity. Whilst this approach has been successful in some respects—the penicillins are a notable example in which synthetic manipulation of the basic molecule has produced drugs which are resistant to hydrolysis by acid or by penicillinase, and a few even show good activity against Gram-negative organisms—it has also resulted in an *embarasse des riches* in so far as so many antibiotic preparations are now available for treatment of certain diseases that the rational choice of one for chemotherapy is proving very complex, and long discussions on this very point were a feature of a recent international congress in chemotherapy.

The second approach is to increase the effort put into the synthesis and development of novel synthetic agents. In recent years this has proved very successful in some respects, particularly for some aspects of antifungal chemotherapy (for example clotrimazole), for widespread venereal infections caused by the protozoa *Trichomonas vaginalis*, and for post-surgical and gynaecological infections by anaerobes (for example nitroimidazoles). Synthetic agents have always been employed in the field of antiviral and antifungal chemotherapy since antibiotics are generally ineffective against these agents.

The third approach is to discover a new source of antimicrobial agents since it appears that diminishing returns may be expected from continued screening of soil samples—the traditional source of modern antibiotics. In this respect it is not without significance that antibiotics and other agents from the sea are being regarded by some workers as a feasible possibility. Indeed one large pharmaceutical company has set up an Institute of Marine Pharmacology in Australia to develop just these ideas.

It is known, for example, that many marine bacteria, fungi and algae, including

phytoplankton, produce antibacterial, antifungal and antiviral substances. (For a recent review see Ruggieri, 1976, and Grant and Mackie, 1977.) Many of these are admittedly not substances suitable for chemotherapy since acrylic acid and chlorinated and brominated phenols abound. However, the potential of the marine environment as a source of antibiotics is illustrated by the fact that cephalosporin was originally derived from an organism obtained from a sewage outfall (into the sea) in Sardinia. Similarly thelepin obtained from a marine polychaete is an antifungal agent analogous both in structure and potency to griseofulvin, and kaimic acid—used in Japan to eliminate intestinal worms—is derived from the red alga *Digenia simplex*. As with any new and highly speculative venture, considerable money and effort will be needed before any commercial returns occur.

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